

ACMD

Advisory Council on the Misuse of Drugs

An assessment of the harms of gamma-hydroxybutyric acid (GHB), gamma-butyrolactone (GBL), and closely related compounds

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1. Introduction

- 1.1. In January 2020 the Home Secretary commissioned the Advisory Council on the Misuse of Drugs (ACMD) to review the evidence for the classification of gamma-hydroxybutyric acid (GHB), gamma-butyrolactone (GBL) and related compounds under the Misuse of Drugs Act 1971 (MDA), and the scheduling of these compounds under the Misuse of Drugs Regulations 2001 (MDR).
- 1.2. In February 2020 the ACMD notified the Home Secretary that it would expect to provide initial advice by autumn 2020 and would also provide advice on other approaches that the available evidence suggests would be of value in reducing the availability, demand, and harms of GHB, GBL and closely related compounds.
- 1.3. The Home Secretary's commission had been prompted by the suspected usage of GHB or a closely related compound in the criminal cases of Reynard Sinaga, and (separately) Stephen Port and Gerald Matovu.
- 1.4. This report reviews the evidence of harms of GHB and related compounds that have emerged since the ACMD's last significant assessment of the risks of GHB and its prodrugs, GBL and 1,4-butanediol (1,4-BD) in [ACMD, 2008a]. The aim is to enable the ACMD to assess the level of harms associated with these compounds and to make recommendations to mitigate these harms – including (but not limited to) recommendations on the most appropriate classification and scheduling of these compounds under the MDA and MDR respectively.
- 1.5. For the purposes of this report, the closely related compounds to be considered in addition to GHB by the ACMD in response to the Home Secretary's commission are:
 - GBL;
 - 1,4-BD;
 - gamma-hydroxyvaleric acid (GHV); and
 - gamma-valerolactone (GVL).

2. Previous ACMD advice and legal status of GHBRs- UK

- 2.1. In the UK, drugs deemed suitable for control under the Misuse of Drugs Act 1971 (MDA) are designated as either Class A, B or C substances and typically placed in any of Schedules 1 to 5 of the Misuse of Drugs Regulations 2001 (MDR) to enable their legitimate use. The current legal status in the UK of the compounds being considered by the Advisory Council on the Misuse of Drugs (ACMD) in this report (gamma-hydroxybutyric acid [GHB], gamma-butyrolactone [GBL], 1,4-butanediol [1,4-BD], gamma-hydroxyvaleric acid [GHV] and gamma-valerolactone [GVL]) is given in Table 1. The chemical structures of the compounds being considered in this report are given in Annex A.

Table 1: The current legal status of the compounds being considered in this report

Compound name	Classification under the MDA	Schedule under the MDR
GHB	C	2
GBL	C	Unscheduled (regulation 4B of the MDR makes it lawful to import, export, produce, supply, offer to supply or possess these substances except where a person does so knowingly or believing that they will be used for the purpose of human ingestion)
1,4-BD	C	Unscheduled (regulation 4B of the MDR makes it lawful to import, export, produce, supply, offer to supply or possess these substances except where a person does so knowingly or believing that they will be used for the purpose of human ingestion)
GHV	Unclassified	Unscheduled
GVL	Unclassified	Unscheduled

- 2.2. Since 2003 GHB has been controlled as a Class C drug under the MDA. At this time GHB was also placed in Schedule 4, Part 1 of the MDR since a GHB-based medicine (Xyrem®) is used in the treatment of narcolepsy and prescribed at low levels in the UK. GBL and 1,4-BD remained uncontrolled until an ACMD report was initiated in 2008 by concerns that users of GHB may have switched to using GBL and 1,4-BD (since they rapidly convert in the body to the intoxicant GHB) [Wood *et al.*, 2008; US Department of Justice 2002], with further evidence of switching reported subsequently [Anderson *et al.*, 2011; Corkery *et al.*, 2015; van Amsterdam *et al.*, 2015; Busardò *et al.*, 2018].
- 2.3. The report [ACMD, 2008a] provisionally recommended that GBL and 1,4-BD should be controlled under Class C of the MDA and Schedule 1 of the MDR (having no recognised medical use), with licensing arrangements to allow their legitimate industrial use (they are used in large quantities in the chemical industry) [ACMD,

[2008a](#)]. However, the report also recommended a government consultation specifically on the impact of control on the legitimate use of GBL and 1,4-BD in the chemical industry. Responding after the consultation, the ACMD advised that it would be disproportionate to recommend control of GBL and 1,4-BD with no concession to the legitimate uses of the substances [[ACMD 2008b](#)]. The ACMD recommended prohibiting the possession, supply, production and importation/exportation for GBL and 1,4-BD, with the inclusion of a licensing regimen for industrial use. However, the approach taken by the Government was to regulate and limit the offences to where these substances are possessed or supplied for human consumption. In December 2009 GBL and 1,4-BD were classified as Class C drugs under the MDA [Home Office, 2009]. Although they were not placed into a Schedule of the MDR, Regulation 4B of the MDR makes it lawful to import, export, produce, supply, offer to supply or possess these substances except where a person does so knowingly or believing that they will be used for the purpose of human consumption. This aimed to allow the legitimate use by the chemical industry, whilst regulating use for human consumption.

- 2.4. In 2013 the Home Office requested updated advice from the ACMD regarding the scheduling of GHB following the World Health Organisation (WHO) rescheduling GHB from Schedule IV (drugs presenting a risk of abuse, posing a minor threat to public health, with a high therapeutic value) to Schedule II (drugs presenting a risk of abuse, posing a serious threat to public health, with a low or moderate therapeutic value) of the Convention on Psychotropic Substances of 1971. GHB was, at the time, in Schedule 4, Part 1 of the MDR.
- 2.5. In the light of the WHO decision, the ACMD reviewed the evidence and agreed that the abuse liability of GHB is substantial whereas the therapeutic use is little to moderate in the UK [ACMD, 2013]. The ACMD therefore recommended that GHB should be rescheduled under the MDR to Schedule 2, which was brought into law in 2014.
- 2.6. Given that GBL and 1,4-BD are converted in the body to GHB upon ingestion, GHB, GBL and 1,4-BD all display very similar psychoactive effects – and are also considered synonymous by users. Therefore, for the majority of this report, evidence of GHB harm can be assumed to be equivalent to GBL and 1,4-BD harm unless otherwise stated. When referring to GHB, GBL and 1,4-BD in this report, the abbreviation for GHB and related substances (GHBRs) will be used.
- 2.7. GHB can be easily manufactured from GBL and 1,4-BD. Therefore, some countries (Italy, Latvia, Sweden) have chosen to control one or both precursors under drug control or equivalent legislation [EMCDDA, 2008].
- 2.8. Unlike GBL and 1,4-BD, GVL is not metabolised to GHB in the body but is instead metabolised to GHV. Because of its activation of the gamma-aminobutyric acid system, GHV reveals similar effects to GHB, but it is less potent – therefore, for the purposes of this report, evidence of GHB harms are not considered to be equivalent to that of GHV or GVL harms.

3. Chemistry and pharmacology

- 3.1. Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are structurally related to gamma-hydroxybutyric acid (GHB) and both are converted within the body to GHB [Roth and Giarman, 1966; Busardò *et al.*, 2018]. Therefore, all three substances have similar psychoactive effects [Wong *et al.*, 2004; Fjeld *et al.*, 2012; Castro *et al.*, 2014; Busardò and Jones, 2015]. All three substances are considered to have the same withdrawal syndrome [Lingford-Hughes *et al.*, 2016; Floyd *et al.*, 2018] and withdrawal has been observed in individuals with dependence for GHB, GHB/GBL co-ingestion, GBL, and 1,4-BD [Catalano *et al.*, 2001; Wojtowicz *et al.*, 2008; Zvosec *et al.*, 2011; Evans and Sayal, 2012; Corkery *et al.*, 2015].
- 3.2. The National Drug Intelligence Centre (NDIC) in the USA considers GHB analogues to be GBL, 1,4-BD, gamma-hydroxyvaleric acid (GHV) and gamma-valerolactone (GVL) [US Department of Justice, 2002], as they produce similar effects to GHB. GVL is a substance that metabolises into GHV, which has similar effects to GHB [Bourguignon *et al.*, 1988; Carter *et al.*, 2005].

GHB

- 3.3. GHB occurs naturally in the brain [Bessman and Fishbein, 1963; Snead and Morley, 1981] and is both a precursor for and a breakdown product of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) [Vayer *et al.*, 1985; Busardò and Jones, 2015]. GHB acts as a neuromodulator in the brain promoting relaxation and sleep. The effects of GHB are similar to alcohol in that they can both cause euphoric effects in small doses and sedative effects in larger doses [Miotto, 2001; Zvosec and Smith, 2005; Oliveto *et al.*, 2010; Bay *et al.*, 2014; Neptune, 2015]. However, one of the major differences between GHB and other drugs, including alcohol, is that it has a very steep dose-response curve [Gable, 2004; van Amsterdam *et al.*, 2012; Korf *et al.*, 2014]. This means there is a narrow margin between a dose that results in desired effects, and a dose that results in adverse effects. For GHB this margin can be in the magnitude of a few grams, discussed more in chapter 6.
- 3.4. The mechanism(s) of action of GHB are still a matter of debate. There is literature suggesting that there is a high affinity binding site for GHB in the brain, sometimes referred to as the 'GHB receptor' [Laborit, 1964], but the existence of a specific receptor is still not generally accepted. It has been proposed that GHB may activate subtypes of the GABA-A receptors and be a partial agonist at GABA-B receptors [Szabadi, 2015; Venzi *et al.*, 2015; Ritter *et al.*, 2020]. The interaction with GABA-A receptors may result in euphoria, increased libido and sociability whereas interaction with inhibitory GABA-B receptors may result in sedation, respiratory depression and hypotension [Bay *et al.*, 2014].
- 3.5. Several early studies researching the pharmacokinetics of GHB in healthy volunteers [Palatini *et al.*, 1993; Borgen *et al.*, 2003; Brenneisen *et al.*, 2004; Abanades *et al.*, 2006; Helrich *et al.*, 2008] showed that GHB is rapidly absorbed, metabolised to carbon dioxide, and rapidly eliminated [Brailsford *et al.*, 2012]. There

are numerous routes of administration (see chapter 5), but when GHB is ingested the effects usually occur 15 to 20 minutes after ingestion and can last for up to 3 or 4 hours [Gonzalez and Nutt, 2005], with peak effects 30 to 60 minutes after ingestion [Schep *et al.*, 2012]. GHB is rapidly eliminated, demonstrated by a half-life of 20 to 30 minutes [ibid.]. Elimination is mainly through the lungs, with less than 5% of GHB excreted in urine [Neptune, 2015]. GHB is undetectable in urine after approximately 12 hours [EMCDDA, 2002].

GBL

- 3.6. GBL is a precursor of GHB and is non-enzymatically converted in the body into GHB. On ingestion GBL is converted to GHB with faster acting but identical psychoactive effects [Wood *et al.*, 2008; Busardò and Jones 2015; Veerman *et al.*, 2019].
- 3.7. GBL is more potent than GHB because of higher lipid solubility, which facilitates rapid passage across the blood-brain barrier to achieve high concentrations at its site of action in the brain [Palatini *et al.*, 1993; Brunt *et al.*, 2014]. It also has longer duration of action [EMCDDA, 2002].
- 3.8. GBL is a colourless, odourless liquid and is approved for use in the chemical industry (see chapter 4). It is also available as a common solvent for several products, including nail polish remover and cleaning products. It can be relatively easily bought over the internet [Veerman *et al.*, 2019] for either legitimate or illicit use. GBL can be used as a precursor to GHB, and GHB synthesised illicitly is most commonly produced using GBL as a starting reagent [EMCDDA, 2008; Giorgetti *et al.*, 2017; Veerman *et al.*, 2019].
- 3.9. GHB synthesised illicitly could contain cutting agents that could also be harmful, or cause a harmful drug interaction; however evidence of this is limited. One study reports sildenafil (Viagra) as an adulterant systematically added to GHB, which caused additional harm to the user (see chapter 7) [Pichini *et al.*, 2016].

1,4-BD

- 3.10. 1,4-BD is a precursor to GHB and converts into GHB in a two-stage conversion in the liver through enzymatic biotransformation [Corkery *et al.*, 2015; Castro *et al.*, 2019]. The distribution and rate of conversion of 1,4-BD to GHB influence the desired/undesired pharmacological actions [Bosch and Seifritz, 2016]. 1,4-BD has a similarly steep dose-response curve to GHB, with a narrow safety window [Stefani and Roberts, 2020]. There is evidence of inter-individual variability of 1,4-BD pharmacokinetics, so there is variation in an individual's susceptibility to overdose due to different absorption and conversion rates [Thai *et al.*, 2007].
- 3.11. Recent literature has shown that 1,4-BD intoxication causes coma and recovery symptoms similar to those seen with GHB [Nunez *et al.*, 2018]. However, more recent literature has revealed that a 1,4-BD-induced coma can last longer than those associated with GHB, with patients recovering more slowly due to more prolonged central nervous system (CNS) depression [Stefani and Roberts, 2020].

The first case report of a confirmed 1,4-BD intoxication in Portugal provides additional evidence that 1,4-BD induces a profound coma and can be abused in place of GHB [Castro *et al.*, 2019].

- 3.12. The major difference between GHB and 1,4-BD is the rate of elimination in the body, with 1,4-BD elimination/metabolism being slower than that of GHB, meaning its effects last longer [Corkery *et al.*, 2015; Stefani and Roberts, 2020].

GHV/GVL

- 3.13. GVL is a drug that can be ingested and is metabolised into GHV. GHV has similar psychoactive effects as GHB, as it has an affinity for the same receptors as GHB [Bourguignon *et al.*, 1988]. However, this affinity is approximately half that of GHB, as determined by rat brain preparations [Carter *et al.*, 2005]. Therefore, it would be expected that GHV/GVL would have similar effects on behaviour as GHB but be less pronounced (at the same dose).
- 3.14. In an early animal study, the administration of GVL produced muscular weakness, mild anaesthesia and an increase in respiration rate. These signs were followed by dyspnoea, mild asphyxia convulsions and death at higher doses [Deichmann *et al.*, 1945]. More recently, GHV has been shown to have similar effects as GHB in rat brains, causing sedation, catalepsy and ataxia, although larger doses of GHV were required to produce these effects [Carter *et al.*, 2005].
- 3.15. GHV exists as a mono-sodium crystalline salt but is often mixed in a liquid where it is colourless and cannot be identified [US Department of Justice, 2002]. GVL exists as a colourless liquid at room temperature.

4. Therapeutic and other legitimate uses of GHBRs

- 4.1. The Advisory Council on the Misuse of Drugs (ACMD) has consulted with the Medicines and Healthcare products Regulatory Agency (MHRA) in establishing whether there are any withdrawn, current or pending licences for any products containing the compounds being investigated in this report to identify therapeutic uses. The ACMD has also consulted with the Department for Business, Energy and Industrial Strategy (BEIS) and stakeholders within the chemical industry to establish the extent of the legitimate industrial uses of the compounds being investigated in this report.

Therapeutic uses

- 4.2. A gamma-hydroxybutyric acid- (GHB)-based medicine (Xyrem®) is used in the treatment of narcolepsy and is effective in improving narcolepsy-cataplexy related symptoms [Xu, 2019]; it is prescribed at low levels in the UK. Figures for England from the NHS Business Service Authority (NHSBSA) show 1,711 items of sodium oxybate (Xyrem® or GHB) 500mg/ml oral solution were dispensed in primary care in 2019 [NHSBSA, 2020]. These figures are only from primary care settings, so do not reflect prescribing in other settings for example, hospitals, and are therefore likely to be an underestimate of the total prescribing level in the UK.
- 4.3. Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are prodrugs for GHB, but the MHRA has confirmed they are not themselves found in any medicinal products with withdrawn, current or pending licences. The MHRA has also confirmed that there are no withdrawn, current or pending licences for any products containing gamma-hydroxyvaleric acid (GHV) or gamma-valerolactone (GVL) so consider there to be no legitimate medicinal uses of these compounds that it is aware of.

Industrial/commercial uses

- 4.4. In its 2008 report on GBL and 1,4-BD, the ACMD reported extensively on the legitimate industrial uses of those two compounds [ACMD, 2008a]. GBL and 1,4-BD were then, and still are, widely used in UK industry. Both chemicals are imported and utilised in significant volumes in a wide variety of processes by the chemical industry and are distributed by chemical distribution companies. There is no authorised UK manufacture of GBL or 1,4-BD, as such these compounds are imported in large volumes to the UK for industrial use. GBL and 1,4-BD imports are typically from non-EU countries.
- 4.5. Many of the companies that handle GBL and 1,4-BD in the UK are members of the Chemical Business Association (CBA), which represents members' interests in the UK and Europe and promotes industry standards. The CBA reported that these compounds are primarily imported and/or sold for industrial applications – with a small volume going into consumer market materials. In 2019 the volume of GBL and 1,4-BD sold by CBA members was in excess of 300,000kg and 500,000kg respectively.

- 4.6. The main use of GBL is as an intermediate in the synthesis of n-methyl-pyrrolidone (NMP), pyrrolidone, herbicides (for example, MCPB = γ -2-methyl-4-chlorophenoxybutyric acid), growth regulators (for example, α -(4-methylbenzylidene)- γ -butyrolactone [5418-24-6]), α -acetobutyrolactone (a vitamin B intermediate), and the rubber additive thiodibutyric acid. GBL is used as a solvent for polymers and as a polymerization catalyst; in hair-wave compositions and sun lotions; and in pharmaceuticals. It is also used in printing inks, for example, for ink-jet printing; as an extractant in the petroleum industry; as a stabilizer for chlorohydrocarbons and phosphorus-based pesticides; and as a nematocide. More recent applications are in the electronics field as a cosolvent for capacitor electrolytes and as a cosolvent for photoresists.
- 4.7. 1,4-BD is a versatile intermediate for the chemical industry and an intermediate for GBL and tetrahydrofuran. The most important application is the production of polyurethanes and polyesters, for example, poly (butylene terephthalate). Among the polyurethanes produced from 1,4-BD, cellular and compact elastomers are of prime importance. Polybutylene terephthalate is processed particularly to plastic materials and hot-melt adhesives but is used also for the production of plastic films and fibres.
- 4.8. After consultation with stakeholders from the chemical industry and BEIS, the ACMD has not identified any significant industrial uses of GHB, GHV or GVL in the UK.

5. Recreational use

- 5.1. Gamma-hydroxybutyric acid (GHB) acts mainly as a central nervous system depressant, however different doses can give varying effects. At low doses GHB can give euphoric and stimulant-like effects, but at higher doses it can be sedative. GHB/gamma-butyrolactone (GBL) also affects people in different ways, and a euphoric dose for one person may be a sedative dose for another [Kam and Yoong, 1998]. Therefore, recreational users of GHB should not assume that a dosage that gives them a desired effect would be the same for another individual.
- 5.2. The desirable effects of GHB include relaxation, euphoria, confidence boosting, disinhibition, increased sociability, social and sexual disinhibition, enhanced libido, increased sexual arousal and enhancement of sexual encounters, with effects being dose-dependent [Luby *et al.*, 1992; Henderson and Ginsberg, 2008; Galicia *et al.*, 2011; Schep *et al.*, 2012].
- 5.3. GHB is used recreationally as a club drug, as the desirable effects tend to be produced without hangover [Palatini *et al.*, 1993; Abanades *et al.*, 2007]. Some people also use GHB after using other drugs, such as stimulants, to enhance or modify their effect [Miotto *et al.*, 2001], or to help their 'come down' [Degenhardt *et al.*, 2002] after the initial high.
- 5.4. GHB and related substances (GHBRs) are also used to self-medicate for anxiety and/or sleep problems. It is also used in the hope that it will reduce the effects of ageing, improve cognitive ability, reduce depression, and boost energy levels [Stein *et al.*, 2011]. Previously GHB was also used in bodybuilding; however, its anabolic effects are unproven [Nicholson and Balster, 2001], and recent literature does not appear to support use in this context.

Routes of administration of GHB and related compounds

- 5.5. GHB is a solid white compound that has a high solubility in aqueous solvents where it is colourless and odourless. It has a slight salty-bitter taste but is often difficult to detect in flavoured beverages [Veerman *et al.*, 2019]. For recreational purposes GHB is most commonly sold as a colourless liquid in the UK, usually in bottles or vials. It can also be sold as powder, usually GHB sodium salt (capsules or loose) or a waxy substance/paste to which water can be added [EMCDDA, 2008].
- 5.6. GBL and 1,4-butanediol (1,4-BD) exist as colourless liquids, so are sold for recreational purposes as such, usually in bottles or vials.
- 5.7. There are a number of different administration routes for GHBRs, however oral ingestion is by far the most common. Outside oral ingestion there is a lack of evidence on the mode of administration.
 - Oral ingestion usually involves dilution of GHB, GBL or 1,4-BD in a beverage for drinking. The beverage masks their unpleasant salty taste. Although uncommon,

swallowing GHB capsules has also been reported [Evans and Sayal, 2012]. GHB has irritant properties, so it is thought capsules may be easier to ingest.

- Insufflation (snorting) is uncommon for GHB and not possible for GBL or 1,4-BD due to their liquid state.
- Mucosal is, again, relatively uncommon, but possible for GHB, GBL and 1,4-BD.
 - i. Rectal insertion of these drugs has been reported by mixing or dissolving the drug in a small amount of water and inserting into the anal passage using a wide-bore oral syringe. The drugs pass through rectal membranes and are absorbed. This technique is sometimes referred to as 'plugging' and was a route of administration used by Stephen Port on a number of his victims under the pretext of administering lube [Pettigrew, 2019]. It is thought this was done to see if this method would result in faster onset of action.
 - ii. Another example of mucosal administration is absorption of GBL contained in nail polish remover pads when held against the gum.

5.8. Injection of liquid GHB, GBL or 1,4-BD is very uncommon.

5.9. The GHB/GBL dose is often measured by users in imprecise 'capfuls', teaspoons, eye droppers, vials, or the sushi fish shaped plastic containers. This imprecise dose measurement is considered to be one of the main reasons for acute GHB/GBL-related harms, as users risk overdose because of its steep dose-response curve [Neptune, 2015].

5.10. Although purity and concentration of GHB and GBL vary, typically 1mL of liquid contains 1g of GHB [Miotto *et al.*, 2001; EMCDDA, 2008; de Jong *et al.*, 2012]. The size of a single GHB dose also varies depending on the individual and can range from 0.5g to 5g (0.5ml to 5ml for a typical concentration). The typical size of a single GBL dose varies between 0.5ml and 1.5ml, but individual responses vary. Even a very small dose, below 1ml, could lead to overdose without warning [NHS, 2020].

5.11. Recreational users typically take small doses frequently in the context of binges, or sometimes at night to help them sleep [Neptune, 2015]. Dependent users ingest GHB/GBL more frequently, at regular intervals, and over prolonged periods, including throughout the night [Miotto *et al.*, 2001]. Anecdotal evidence was reported from a GHB-dependent user who took 2ml doses every hour during the day and 3ml every 2 hours at night. A wide range of dosing intervals have been reported [Sivilotti *et al.*, 2001; Chew and Fernando, 2004; de Jong *et al.*, 2012], with an average of 4.4 hours between doses for dependent users [McDonough *et al.*, 2004]. People who have developed dependence report using more than 25g of GHB in a single day [Miotto *et al.*, 2001].

5.12. As GBL is more lipophilic, and therefore more potent than GHB, the doses are smaller and 1.5g is typically considered a single dose [Couper and Marinetti, 2002].

Availability of GHB and related compounds

- 5.13. GHB retailers are easy to find on the internet, as are instructions for making GHB [Sanguinetti *et al.*, 1997; EMCDDA, 2002; 2008]. Individuals can use these recipes to manufacture GHB themselves after easily obtaining precursors such as GBL [Brunt, *et al.*, 2014].
- 5.14. GBL for recreational use in the UK is usually bought from street dealers or via the internet in amounts ranging from 125mL to 10L [Neptune, 2015]. According to anecdotal reports from a GHB user who underwent detoxification two months prior to commenting, GHB/GBL dealers typically buy the substances online and users purchase them face to face. The same GHB user reported in June 2020 that the approximate street value for GHB/GBL is £50 per 100ml (in Manchester). Assuming a recreational dose of 2ml (although this varies) this equates to GHB/GBL costing £1 per recreational dose. A news report from Manchester also reported the cost of GHB/GBL to be £1 per recreational dose [*Manchester Evening News*, 2020]. It should be noted that it has previously been reported that the price of GHB differs depending on locality [ACMD, 2008a]. However, the [Bristol Drugs Project](#) reported that 1ml of GHB or GBL costs £1 in Bristol too, regardless of the volume bought. Online searches indicate that this is generally the case across the UK, with the drugs costing under £1 per 1ml (so under £2 per average recreational dose) even when buying at the lowest volume.

6. Prevalence and patterns of GHBRs use

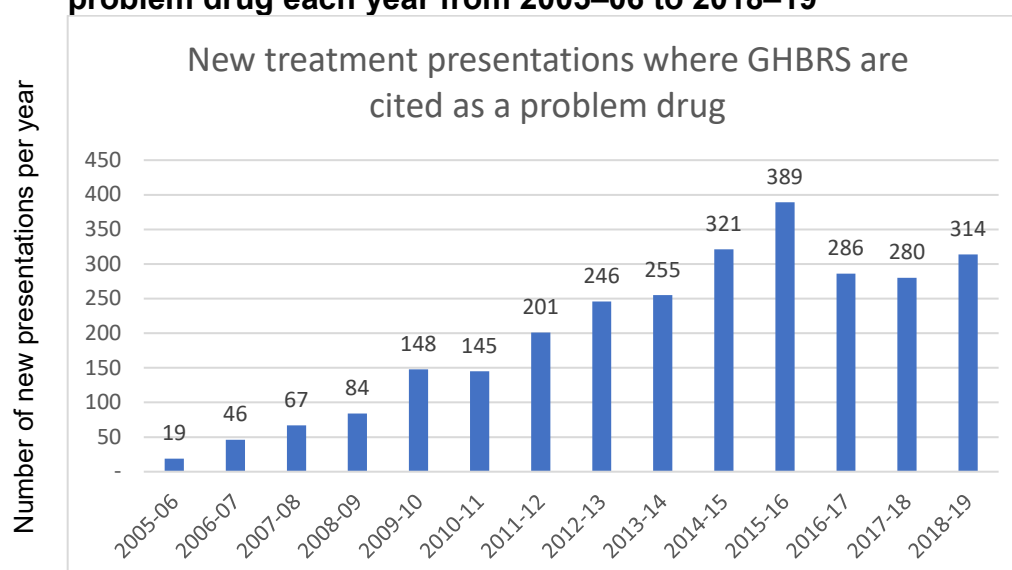
- 6.1. General population use of gamma-hydroxybutyric acid and related substances (GHBRs) in the UK has typically been low. The use of GHB appears to be concentrated among certain groups, such as men who have sex with men (MSM), or in specific contexts such as nightclubs [Neptune, 2015]. There was a steep increase in GHBRs use in the UK, specifically in England, from 2005 to 2015. Since then the evidence suggests a plateauing in use, but a small and steady pattern of use and harm. It is suspected that general population prevalence is still relatively low, but this is difficult to determine due to lack of systematic data collection [Brunt *et al.*, 2014; van Mechelen *et al.*, 2019].
- 6.2. In the absence of general population data in the UK, sources of evidence outlined in this chapter include:
 - National Drug Treatment Monitoring System (NDTMS) data;
 - presentations with acute GHBRs toxicity to emergency departments (EDs);
 - addiction service access data;
 - National Poisons Information Service (NPIS) data;
 - Independent Drug Monitoring Unit; and
 - drug seizures data.
- 6.3. These sources of evidence are not all available across the UK and additional evidence specific to devolved administrations are also included.

England, Wales, Scotland and Northern Ireland

England

- 6.4. The NDTMS collects data from statutory drug treatment services in England. Its annual reports reveal an increase of new presentations to treatment services with GHB/gamma-butyrolactone (GBL) related problems, as shown in Figure 1. Whilst there is a general increase in the number of new treatment presentations citing GHBRs as a problem drug, the peak appears to be in 2015/16, and after that a plateau to approximately 2014/15 levels.

Figure 1: The number of new treatment presentations citing GHBRs as a problem drug each year from 2005–06 to 2018–19



Source: Public Health England 2019 data tables [PHE, 2019, Table 11.5].

- 6.5. When data from Figure 1 are considered as a proportion of new presentations involving ‘club drugs’ for that year, there is an increase from 1% in 2005–06; 6% in 2013–14; to GHB/GBL related problems representing 8% of new club drug treatment presentations in 2018–19.
- 6.6. The PHE-NDTMS data also present a breakdown of all clients in treatment and their associated problem drugs. In 2016 there were 553 people in treatment services citing GHBRs as a problem drug, equivalent to 0.2% of people in drug treatment services in England [PHE, 2016]. In 2018–19, this number decreased to 454; however, this still represented 0.2% of the treatment population [PHE, 2019]. Therefore, for those in treatment services, the proportion of GHBRs related addiction has remained fairly constant in recent years. In comparison to other drugs the number of GHB presentations to treatment is low.
- 6.7. Presentations with acute GHB/GBL toxicity to the ED and clinical toxicology service at London Guy’s and St Thomas’s Hospital increased from 158 in 2006, to 270 in 2010 [Wood *et al.*, 2013]. The European Drug Emergencies Network (Euro-DEN) reported equally high number of ED presentations at the same hospital in [EMCDDA, 2015], evidencing 293 GHB/GBL-related presentations over the course of 2013–14, accounting for 31% of all drug-related ED presentations, beating cocaine (n=171), mephedrone (n=126) and heroin (n=111). The same study revealed, however, that two other UK EDs did not report the same high proportions of GHB/GBL-related presentations (as shown in Table 2).
- 6.8. The high rate of GHB/GBL representation is only seen in the London hospitals in the EuroDEN data, with York reporting zero presentations. Localised prevalence can be linked to Guy’s and St Thomas’s Hospital proximity to Vauxhall, a well-established and popular night time economy for the LGBT community. York hospital may be more representative of the picture nationally, but this is difficult to determine without data from other UK hospitals being included in the EuroDEN data collection.

Table 2: UK data extracted from the 2015 Euro-DEN data set, data collected for a 12-month period, October 2013 to September 2014

	Number of drug-related presentations	GHB/GBL	Cocaine	Heroin	Cannabis	Mephedrone
London Guy's and St Thomas's Hospital	956	293	171	111	96	126
London King's College Hospital	422	87	90	72	77	27
York Hospital	202	0	16	91	27	23
Total	1,580	380	277	274	200	176

Source: [EMCDDA, 2015]

- 6.9. The numbers of individuals seeking help from services such as Antidote (substance misuse service provided for the lesbian, gay, bisexual and trans-gender [LGBT] community by the non-governmental organisation London Friend) and the Club Drug Clinic, Central North West London NHS Foundation Trust (CNWL) for GHB-related problems has increased.
- 6.10. Antidotes report an increase in the proportion of individuals presenting with GHB-related problems from 1.7% (n=3) of total referrals in 2005, to 57% (n=317) in 2010; this subsequently fell to 44% (n=334) in 2013–14 [Lingford-Hughes *et al.*, 2016].
- 6.11. It is possible that the steep increase in GHBRs-related hospital presentations and service access from 2005 to 2015 may be due to an increase in problematic use amongst those who already use GHB, or an increase in the strength of available GHBRs. However, from the literature reviewed, it is thought that this is marginally more likely to be due to an increase in prevalence of GHBRs use. Therefore, it can be inferred from the data that GHB use increased in the UK population until 2015. Since then, the evidence suggests a plateauing in use, but a small and steady pattern of use and harm.

Wales

- 6.12. The Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) project received 18 samples submitted as, or found to contain, GHB between May 2014 and August 2020. Of the 18 samples submitted, only 7 met the project's acceptability criteria and were analysed (five from Wales, one from England and one from Scotland). One contained GHB, five GBL, one 1,4-BD and one was found to have no active compounds present. This is evidence that all three compounds are used in Wales, with an initial indication that GBL is the most prevalent [WEDINOS, 2020, data request].
- 6.13. The Welsh National Database for Substance Misuse (WNDSM), collected by NHS Wales, collects treatment reports across primary, secondary and tertiary care settings. These data report low prevalence with between 4 and 12 individuals in treatment per annum from 2014 to 2020 [Welsh Government, 2019]

- 6.14. Over the last five years in Wales there have been three deaths where GHB was mentioned on the death certification. One in each of 2015, 2017 and 2018. This again indicates low prevalence of GHBRs use in Wales.

Scotland

- 6.15. There appears to be limited evidence of use of GHB or GBL in Scotland. The Scottish Drug Misuse Database (SDMD) assessed the number of individuals at specialist drug treatment services in Scotland who had reported use of GHB in the previous 30 days. In every year between the financial years 2006/07 to 2018/19, under seven cases were reported per year as using GHB as their main drug. In the same period, under 10 cases were reported per year as using GHB at all within the last 30 days [Public Health Scotland, 2019].
- 6.16. Summary reports prepared by consultant Dr Richard Kennedy (Sandyford Sexual Health Services, NHS Greater Glasgow and Clyde) and the ‘Social Media, Men Who Have Sex With men, Sexual and Holistic Health Study (SMMASH)’ which is undertaken by Glasgow Caledonian University (and covers Scotland, Wales, Northern Ireland and the Republic of Ireland), both indicate a low incidence of disclosed GHB within sexual health settings in Scotland, with those disclosures recorded primarily being experienced by gay, bisexual, and MSM (GBMSM) within the context of chemsex [Strongylyou and Frankis, 2020]. However, the true levels of GHBRs use within these settings may be higher.
- 6.17. Between the years 2000 and 2018, GHB was ‘implicated in, or potentially contributed to, the cause of death’ in 26 cases. GHB was ‘present in the body but not considered to have had any direct contribution to the death’ in a further 13 cases. No deaths involving GBL, 1-4 BD, gamma-hydroxyvaleric acid (GHV) or gamma-valerolactone (GVL) were reported between the years 2000 and 2018. Data have not yet been published for the year 2019 [National Records of Scotland, 2018]. The information suggests that GHB is a relatively minor problem when it comes to drug deaths in Scotland – pathologists report that it is involved in only a few deaths per year, and that it is usually jointly implicated as the cause of death with other substances.
- 6.18. Statistics on drug seizures made by Police Scotland show there have only been two confirmed seizures of GHB between the years 2014 and 2018, both of which were in 2015 and 2016 [Police Scotland, 2018]. This represented 0.5% of Class C drug seizures in 2015–16. GHB and GBL are not frequently recovered by the police in Scotland (four cases of GBL in 2019). Scotland has confirmed that there is an increasing awareness of GHB and GBL use within the police force. It is suspected that there are many more people consuming GBL than the data indicate, but it is difficult to identify as its status as a wheel cleaning product means that those in possession of GBL are less likely to come to the attention of the police.

Northern Ireland

- 6.19. There is an absence of data on prevalence and harms from GHBRs in Northern Ireland and GHBRs are not routinely appearing in surveys, seizures, treatment or

other datasets. It is unclear to what extent this reflects prevalence or data reporting systems.

UK

- 6.20. Overall reported population prevalence was low in England and Wales in 2011/2012; 0.13% in the Crime Survey for England and Wales (CSEW) [Home Office, 2012], an increase from 0.04% the previous year. Unfortunately, data on GHB/GBL use were not collected in later CSEW surveys, so more recent general prevalence data are not available.
- 6.21. The NPIS reports data on access activity on its online poisons information database TOXBASE® and details of telephone enquiries by health professionals. These data reflect (but do not measure directly) the frequency of contacts from health professionals and patients following suspected exposure.
- 6.22. TOXBASE® is an online portal for clinicians holding information on diagnosis, treatment and management of acute poisoning from many substances, including GHBRS. Data pooled from four service units (Birmingham, Cardiff, Edinburgh and Newcastle) over the last 5 years, show that GHB, GBL, 1,4-BD and GHV account for 4.3% of all TOXBASE® accesses relating to drugs of misuse (see Table 3). Since 2016/17 there has been a small overall reduction in TOXBASE® accesses relating to these four compounds, with a slight uptake reported in 2019/20. In 2018/19 GHB was the tenth most common substance of misuse involved in online TOXBASE® accesses. There has also been an increase in TOXBASE® access to information on GHV since 2017/18.

Table 3: Data showing the TOXBASE® accesses and telephone call data relating to GHBRs from 2015/16 to 2019/20

	2015/16	2016/17	2017/18	2018/19	2019/20	5-year totals
TOXBASE® accesses for GHB, GBL, 1,4-BD and GHV	3,322	3,529	2,692	2,137	2,418	14,098
% relating to GHB, GBL, 1,4-BD and GHV	4.9%	5.5%	4.2%	3.2%	3.5%	4.3%
All drugs of misuse TOXBASE® accesses	67,228	64,015	63,373	66,227	68,195	329,038
Telephone calls GHB and GBL	24	18	24	28	31	125
% of calls relating to GHB and GBL	1.5%	1.5%	1.9%	2.3%	2.3%	2.0%
All drugs of misuse telephone calls	1,613	1,210	1,245	1,220	1,112	6,400

Source: NPIS, 2020. The TOXBASE® data include GHB, GBL, 1,4-BD, and GHV. The telephone call data include GHB and GBL. The 2019/20 data have been shared ahead of publication

- 6.23. The NPIS provides a national telephone service to advise clinicians in cases of acute poisoning, including toxicity relating to drug misuse. Over the last 5 years GHB and GBL have accounted for 2.0% of telephone enquiries that relate to substances of misuse with no material increase during this time (evident from Table 3). Neither GHB nor GBL featured in the top ten drug misuse telephone enquiries in 2018/19 [NPIS, 2019].
- 6.24. In 2016 less than 3% of festival goers reported ever using GHB [Independent Drug Monitoring Unit, 2016] In 2018/19 there were 68 seizures of GHB by police forces in England and Wales, weighing a total of 0.72 kg (CSEW presentation to ACMD, PHE Drugs and Alcohol Unit).

Globally

- 6.25. A comprehensive overview of the prevalence of GHB/GBL usage globally is hindered because there are no comparable systematic data collections at an international level, along with many countries having different user populations and patterns of use [van Mechelen *et al.*, 2019]. This has been known for a number of years, with previous studies concluding that overall prevalence cannot be determined due to lack of systematic surveillance [Brunt, *et al.*, 2014]. Whilst population-level analysis is missing, there are other pieces of evidence indicating increased use in a number of countries.

- 6.26. In the 2014 Global Drug Survey GHB/GBL did not appear in the top 20 drugs ranked by last year's proportional prevalence use for any of the countries taking part (of which there were 18: Australia, Belgium, Brazil, Denmark, France, Germany, Hungary, Mexico, New Zealand, Portugal, Republic of Ireland, Scotland, Spain, Slovenia, Switzerland, The Netherlands, UK and USA), with the exception of The Netherlands where it ranked 15th at 7.2% [Winstock, 2014].
- 6.27. According to previous European drug reports, the prevalence of non-medical use of GHB is low in the general population [EMCDDA, 2008; 2015; 2017a], but is higher in LGBT and MSM [Miró *et al.*, 2017]. According to the EMCDDA's most recent 2019 report, whilst there has been reported use of GHB and its prodrug GBL among some drug users in Europe for the last two decades, where national estimates exist, current prevalence still appears to be low. For example, in its 2017 survey the last year prevalence among adults in Norway (aged 16 to 64 years) was 0.1% [EMCDDA, 2019].
- 6.28. In 2015 and 2017 seizures of GHB or GBL were reported by 16 European countries [EMCDDA, 2017a; 2019]. There was an estimated total of 1,300 seizures (of GHB or GBL) across these countries in 2015 and 1,600 seizures in 2017. These seizures amounted to 320kg and over 1,500 litres in 2015, compared with 127kg and 1,300 litres in 2017 [*ibid.*]. For the 2017 data, Belgium seized almost half of the total quantity, mainly as GBL [EMCDDA, 2019].
- 6.29. GHB was reported as the fourth most common recreational drug implicated in intoxication presentations in EDs in Europe in 2015 and in 2019, after heroin, cocaine and cannabis [EMCDDA, 2015; 2019; Dines *et al.*, 2015]. This is strong evidence of GHBRs use, and harm, across Europe. However, 85% of presentations associated with GHB/GBL were from London (UK), Oslo (Norway) and Barcelona (Spain), demonstrating that GHBRs use is particularly localised and that these cities have a high prevalence [EMCDDA, 2015].
- 6.30. There is particular evidence of GHBRs use in The Netherlands. As discussed above it was the only country in the 2014 Global Drug Survey where GHB/GBL featured on its top 20 drug ranking by prevalence. In addition, a web survey in 2013 showed that 21.8% of regular nightlife participants aged 15 to 35 years had ever used GHB and 5.1% did so in the last year [Goossens *et al.*, 2014]. GHB accounted for the largest proportion of non-fatal overdoses reported by Dutch emergency services in 2013 [Vogels *et al.*, 2013], and in 2017 almost a third of drug-related ambulance call outs in The Netherlands were linked to GHB use [EMCDDA, 2019].
- 6.31. In Asia prevalence is thought to be low, but there are indications that GHB usage has increased, particularly among MSM [Wei *et al.*, 2012].
- 6.32. It should be noted that most literature does not differentiate between GHB, GBL and 1,4-BD in terms of prevalence of use. For the most part literature rarely includes GHV/GVL as part of this group of drugs; this may be because evidence of use is new and limited, or because their use is low.

- 6.33. GHV/GVL was detected in humans for the first time in 2013 in three individuals through toxicology analysis [Andresen-Streichert *et al.*, 2013]. One of the individuals was suspected to be the victim of a drug-facilitated sexual assault (DFSA) and the other two individuals were suspected to be regular GHV/GVL users. The reason for the low number of GHV/GVL identifications in literature may be due to low levels of use, but the case report authors comment that it is more likely because toxicology laboratories do not routinely test for GHV or GVL [*ibid.*]. Prior to this case, authors have reported anecdotal evidence that GVL is used as a legal alternative to GHB/GBL [US Department of Justice, 2002; Palmer, 2004; Carter *et al.*, 2005], however this is the first case report confirming presence by toxicology.

Pharmacosex and chemsex

Pharmacosex

- 6.34. 'Pharmacosex' is a phrase coined for a broad discourse on the creative ways that wider populations (than the typically considered LGBT and MSM populations) experiment with a range of different drugs that modify and enhance their sex lives [Moyle *et al.*, pre-publication]. Pharmacosex considered the duality of sex and drugs, where sometimes sex is used to enhance, disinhibit or mitigate drug experiences, just as drugs are used to enhance and disinhibit sexual experiences [*ibid.*]. The authors drew on qualitative data from two separate studies conducted between 2018 and 2019. Participants of both studies identified across a range of sexual orientations. GHB/GBL was used in combination with sex in 27% of the total number of interview participants, showing that people with a wide range of sexual orientations combine GHBRS and sex.
- 6.35. 'Chemsex' (see below) is considered a specific form of 'pharmacosex'.

Chemsex

- 6.36. Within UK and global prevalence trends, there is evidence to suggest that certain population sub-groups use the drug more than others. This is particularly true for MSM in the context of chemsex.
- 6.37. 'Chemsex' is a colloquial term used to describe sex between MSM that occurs under the influence of drugs, which are taken immediately preceding and/or during the sexual session for the purpose of enhancing the sexual experience. Chemsex is often higher risk, with more partners, not using barrier protection such as condoms and of longer duration than other sex [Bourne, 2015a]; group sex is common. GHBRS is one of a number of drugs used in chemsex (either in combination or alone), as it has been found to enhance sexual experience, prolong the length of intercourse and make people more attracted to their partner [Kapitány-Fövényi *et al.*, 2015; Hibbert *et al.*, 2019].
- 6.38. When considering GHB-specific chemsex, again prevalence is hard to determine. Data from 1,472 attendees at two London sexual health clinics reported lifetime prevalence of use of GHB at 19% and GBL at 13% [Thurtle *et al.*, 2015].
- 6.39. There is evidence in the UK that engaging in GHB-related chemsex is more prevalent amongst LGBT and MSM sub-groups compared with heterosexual chemsex [Bourne *et al.*, 2014; Mohammed *et al.*, 2016; PHE, 2020b].

- 6.40. PHE-NDTMS data hold information on both GHB prevalence in new treatment presentations, and on the sexual orientation of those receiving treatment, but these two pieces of data are not presented together in PHE-NDTMS tables – i.e. the relative proportions of different sexual orientations within the cohort who cite GHB as a problem drug in the treatment data set. However, PHE-NDTMS data provided information to the ACMD that 12% of all gay/bisexual clients presenting to treatment services in 2019 had cited GHB use, compared to less than 0.1% for heterosexual men [PHE, 2020b]. Of all 502 clients presenting to treatment in 2019 citing GHB, the vast majority (75%) were gay/bisexual men (16% were heterosexual men, 7% were heterosexual women and 2% gay/bisexual women) [*ibid.*]. It is important to note that whilst the prevalence of GHB chemsex use is higher amongst MSM compared to other groups, a minority of MSM engage in the practice; with only a proportion of these reporting associated harms [Hibbert *et al.*, 2019].
- 6.41. There is also research showing that men who are living with HIV more commonly use chemsex drugs than those who are HIV negative or of unknown status [EMIS, 2013; Kirby and Thornber-Dunwell, 2013; Hunter *et al.*, 2014; Theodore *et al.*, 2014; Bourne, 2018; Frankis *et al.*, 2018; Hammoud *et al.*, 2018; O'Reilly, 2018; PHE, 2020a].

In conclusion, whilst exact prevalence data are unknown, it is predicted that overall use in the UK and in each devolved administration is low, with more evidence of use in England than in other devolved nations. There is also consensus across literature that:

- **there was a steep increase in GHBRs use in the UK, specifically in England, from 2005 to 2015;**
- **since 2015 the evidence suggests a plateauing in use, but a small and steady pattern of use and harm;**
- **use is higher amongst LGBT groups, particularly gay and bisexual men; and**
- **in the UK there is higher use within specific contexts, for example, chemsex.**

7. Physical health harms

- 7.1. Gamma-hydroxybutyric acid (GHB) has a steep dose-response curve, meaning there is a narrow dose margin between the desired and adverse effects [Gable, 2004; van Amsterdam *et al.*, 2012; Korf *et al.*, 2014]. Even a small increase in dose can cause serious toxic effects such as impaired consciousness, coma, and death. GHB use frequently causes comas lasting between one and four hours, which often score the most critical classification on the Glasgow coma scale (GCS) [Abanades *et al.*, 2006; Schep *et al.*, 2012; van Amsterdam *et al.*, 2012; Korf *et al.*, 2014; Busardò and Jones, 2015; Miró *et al.*, 2017]. The steep dose-response curve of GHB differentiates it from other drugs, and significantly increases risk of harm [Neptune, 2015].
- 7.2. In addition, the narrow safe dose range for GHB varies between individuals, and adverse effects occur at a variety of doses [Chin *et al.*, 1998; Kam and Yoong, 1998]. Imprecise dosing of illicit GHBRs as described in chapter 5 further increases the risk of harm. Therefore, alongside the intrinsic toxicity of the substance, the hazard profile of GHB is considered more harmful than many other psychoactive substances. The severity of adverse effects is influenced by:
 - the dose ingested (which is difficult to measure);
 - individual variation in response; and
 - whether other substances have been co-ingested [Neptune, 2015].
- 7.3. This chapter outlines the physical harms from GHB and related substances (GHBRs) use including:
 - mortality; neurological;
 - cardiovascular;
 - respiratory;
 - gastroenterological;
 - physiological and psychological dependence;
 - physical harms from polydrug use with GHBRs; and
 - physical harms from GHBRs use in chemsex.

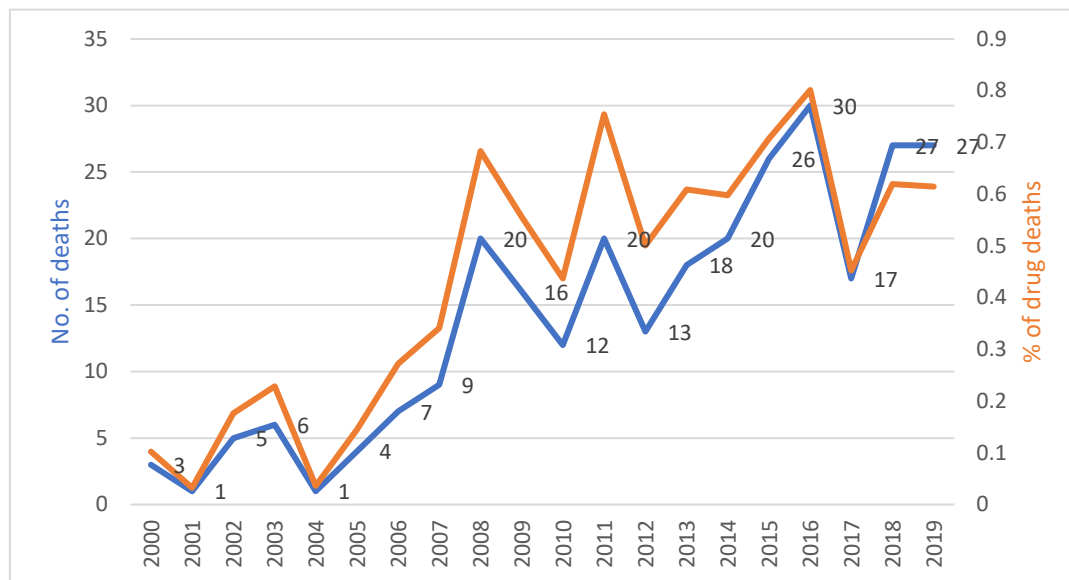
Mortality

- 7.4. Due to the GHBRs steep dose-response curve, there is a narrow dose margin between the desired and adverse effects. Therefore, overdose is a significant risk, which can result in death.
- 7.5. Literature reports increasing number of deaths attributed to GHB since the 1990s in Australasia, the UK, the USA, western Europe, and other developed countries [Caldicott *et al.*, 2004; EMCDDA, 2008; Zvosec *et al.*, 2011; Corkery *et al.*, 2015]. More recent studies show that this trend is continuing; furthermore these numbers are likely to be an underestimate because GHB and analogues are not routinely included in toxicology post-mortem investigations and can be difficult to detect.

UK

- 7.6. The Office for National Statistics (ONS) collects data on drug poisoning and deaths. The figure below shows the number of drug-related poisonings where GHB was mentioned on the death certificate [ONS, 2019]. These data relate specifically to 'GHB' being mentioned on the death certificate and does not capture GBL, 1,4-BD or other related drugs. The data are for England and Wales combined and include GHB used in isolation, GHB taken with alcohol, and GHB taken with other drugs.

Figure 2: Data on deaths where GHB is mentioned on the death certificate



[Source: [ONS, 2019](#)]

- 7.7. The ONS data show an increasing trend for GHB deaths in England and Wales over the last 18 years. However, overall, they still represent a small proportion of all drug-related deaths with the 27 deaths recorded in 2018 representing only 0.6% of all reported drug-related deaths (4,393). This is supported by analysis of data from the UK's [National Programme of Substance Abuse Deaths](#) (NPSAD) database, which showed that there were 159 GHB-related deaths in the UK in the 17 years between 1995 and 2012 [Corkery *et al.*, 2015], corresponding to approximately 0.5% of drug-related deaths ($\approx 32,000$). Both the ONS data and NPSAD data are likely to be underestimates due to challenges in post-mortem toxicology and the voluntary nature of coroners contributing to the NPSAD.
- 7.8. Of the 159 deaths reported in NPSAD, 21 were lesbian, gay, bisexual and transgender (LGBT) individuals. These 21 deaths were analysed in more detail, revealing GHB was implicated in 11 and the remaining 10 cases involved gamma-butyrolactone (GBL); none were attributed to 1,4-butanediol (1,4-BD) [Corkery *et al.*, 2018].

London

- 7.9. A more recent study concluded that the number of deaths associated with GHB have increased in London in recent years, with an 119% increase in GHB-associated deaths in 2015 compared with 2014 [Hockenull *et al.*, 2017]. Between

2011 and 2015 the study reported there were 61 deaths associated with GHB (0.92%) out of the 6,633 deaths referred to a coroner that underwent toxicology analysis [*ibid.*]. It is important to note that the Hockenhull study reports *GHB associated* deaths, meaning that GHB was present in some form; however the Corkery studies report *GHB-related* deaths, meaning the GHB was considered to contribute to the death.

Globally

- 7.10. Global mortality trends are difficult to determine due to lack of comparable data. However, there is evidence of GHB-associated deaths in Australia, Canada, and USA. [Zvosec *et al.*, 2011; Darke *et al.*, 2020].

Post-mortem GHB analysis

- 7.11. Interpretation of post-mortem GHB toxicology results (where available) can be challenging as GHB is an endogenous substance and can be naturally present as a metabolite. Additionally, levels increase post-mortem even during sample storage, for both blood and urine samples [Busardò *et al.*, 2014].
- 7.12. Different studies use different definitions and methodologies for identifying a GHB-related fatality, making cross study comparisons difficult. There is a lack of consensus on the fatal GHB concentration [Hockenhull *et al.*, 2017]. The majority of papers use post-mortem blood levels of 50mg/L as the minimum threshold to indicate GHB/GBL ingestion rather than endogenous production [Kugelberg *et al.*, 2010; Zvosec *et al.*, 2011; Corkery *et al.*, 2015], and hence cause of death; other authors use a cut-off of 30mg/L. However, some research reports GHB blood concentrations in excess of 50mg/L, and up to 193mg/L, for deaths unrelated to GHB use [Korb and Cooper, 2014].
- 7.13. In addition, the short half-life of GHB means the peak concentration may be missed on post-mortem measurement, which presents further difficulty in identifying the cause of death. In a recent study, 12 cases had GHB concentrations below 50mg/L, the generally accepted threshold, and 4 had no detectable blood GHB, but all were confirmed as death due to GHB from detection of GHB in ingested substances [Darke *et al.*, 2020]. A large range of GHB concentrations are observed in post-mortem blood samples for GHB-associated deaths: 0 – 6,500mg/L [Corkery *et al.*, 2015], 108–2,444mg/L [Hockenhull *et al.*, 2017], 13–1,350mg/L [Darke *et al.*, 2020].
- 7.14. Due to the challenges in interpreting GHB concentration post-mortem, some researchers cite the need for evidence of proximity of consumption, for example, detection in a drink rather than using a threshold concentration [Kintz *et al.*, 2004; Busardò and Pichini, 2017; Darke *et al.*, 2020]. In some toxicology laboratories GHB would need to be confirmed in more than one sample type, for example, in post-mortem blood and urine before a GHB-related death is considered. This is not always possible because of limited sample volumes and the availability of specimens at autopsy. Another problem in identifying deaths caused by GHB is polydrug use, as it may be difficult to describe a death as purely GHB-related if other drugs are also detected or reported.

Demographics and cause of deaths

- 7.15. The manner of death reported in the literature is mainly accidental drug toxicity [Caldicott *et al.*, 2004; Knudsen *et al.*, 2010; Kugelberg *et al.*, 2010; Corkery *et al.*, 2015; Hockenhull *et al.*, 2017], with a notable minority due to trauma or suicide [Hockenhull *et al.*, 2017; Corkery *et al.*, 2015; Zvosec *et al.*, 2011].
- 7.16. Deaths from GHB and related substances (GHBRs) have occurred mostly in men, accounting for 70% to 98% of deaths in recent studies [Hockenhull *et al.*, 2017; Darke *et al.*, 2020]. Most deaths are reported in young people, typically those in their 30s [Caldicott *et al.*, 2004; Zvosec *et al.*, 2011; Corkery *et al.*, 2015; Hockenhull *et al.*, 2017; Darke *et al.*, 2020]. A history of drug use is also common, with prevalence ranging from 57% to 81% [Hockenhull *et al.*, 2017; Corkery *et al.*, 2018]. In addition, GHB was taken in combination with other drugs in 92% of deaths [Darke *et al.*, 2020], highlighting the dangers of polydrug use for GHB. Alcohol was found to be a fairly common co-ingestant and was present in 20% to 25% of deaths, but the most common co-usage was stimulants, for example, cocaine or methamphetamine, which were present in 64% to 72% of deaths [Hockenhull *et al.*, 2017; Darke *et al.*, 2020]. This is additional evidence, alongside that in this chapter relating to overdose and drug co-ingestion, demonstrating that the presence of alcohol or other substances increases the risk of harm from GHB [Gonzalez and Nutt, 2005; Liechti *et al.*, 2006; Galicia *et al.*, 2011; Department of Health, 2011; Miró *et al.*, 2017].
- 7.17. Deaths occurred mainly in the home of the deceased or their friends and was more likely to occur at the weekend [Corkery *et al.*, 2015; Hockenhull *et al.*, 2017; Darke *et al.*, 2020].
- 7.18. In [Corkery *et al.*, 2015] 21 out of 159 GHB-related deaths (13%) were LGBT individuals. As discussed in chapter 6, there is evidence that prevalence of GHBRs use is significantly higher amongst LGBT individuals than in the general population. Therefore, it is striking that 87% of deaths are not LGBT. This could be because use is higher amongst other groups in the population than has been identified in the literature thus far, or it could be that in the mortality data sexuality is not always captured or reported. Three London boroughs accounted for 62% of the GHB-related deaths in LGBT individuals; considered to reflect the concentration of resident and visiting gay individuals [Corkery *et al.*, 2018]. In addition, of the individuals who died from GHB (n=61) in [Hockenhull *et al.*, 2017], 33% (n=21) had been living with HIV, significantly higher than observed in other drug-related deaths (8% for ecstasy-related deaths and 3% cocaine).

Deaths involving GBL and the GHB/GBL equilibrium

- 7.19. The literature relating specifically to GBL related deaths, where GHB is not also present, is sparse, with only five reports globally between 2001 and 2019 [Duer *et al.*, 2001; Lenz *et al.*, 2008; Dargan *et al.*, 2009; Küting *et al.*, 2019]. However, there is evidence of GHB-related deaths involving GBL in addition to GHB, with 55 (34.6%) of the 159 GHB-related deaths in the UK between 1995 and 2012 involving GBL as well as GHB [Corkery *et al.*, 2015].
- 7.20. GHB and GBL have previously been found to be in equilibrium with one another in aqueous solutions [Ciolino *et al.*, 2001; Dahlén *et al.*, 2011]. In a case report of a man who died after ingesting GHB, the concentration of GHB in the beverage he

ingested increased significantly over a 16-month period [Küting *et al.*, 2019]. This demonstrated that GBL was present and had established an equilibrium with GHB. The GHB/GBL equilibrium means that identifying the presence of GBL is difficult in toxicology analysis [*ibid.*]. In addition, some laboratory methods require the conversion of any GHB in the sample to GBL before it can be analysed [Ingels *et al.*, 2014], adding additional challenge. Therefore, the prevalence of GBL-related deaths within the GHB reported deaths is unknown.

Relative harm

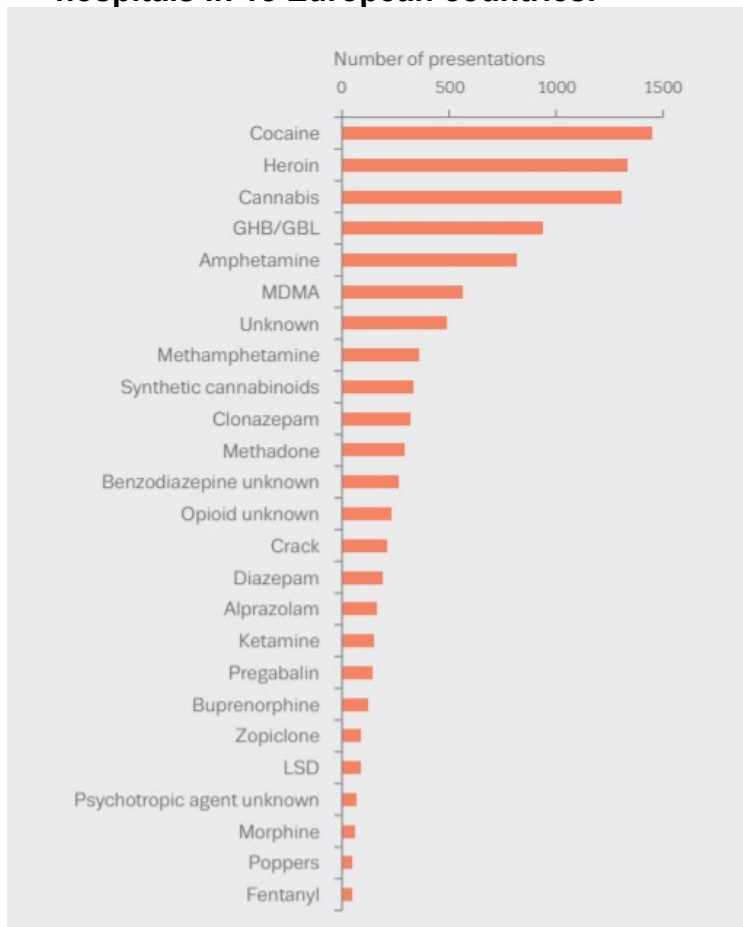
- 7.21. A publication in 2018 calculated the fatal toxicity index for new psychoactive substances (NPS) including GHB/GBL [King and Corkery, 2018]. The toxicity index was developed based on data from death certificates by calculating the ratio of deaths to prevalence and seizures. The research also showed that calculating the number of deaths from sole use of a particular drug, divided by the number of deaths where that drug was listed alongside others on the death certificate, is also a measure for the fatal toxicity potential of a substance. A significant finding was that GHB (alongside other drugs such as methyltryptamine, synthetic cannabinoid receptor agonists and benzofurans) had a higher fatal toxicity than other NPS, whilst benzodiazepines analogues had a particularly low fatal toxicity index [*ibid.*].

In conclusion, there is evidence of increasing deaths associated with GHBRs since the Advisory Council on the Misuse of Drugs last considered the harms of GHB in 2003, and GBL and 1,4-BD in 2008. Although overall mortality numbers are low, there has been a marked increase in deaths between 2008 and 2018. Mortality figures are likely to be an underestimate due to the challenges in testing for and identifying GHBRs post-mortem. When GHBRs mortality is compared with other NPS drugs, there is evidence that they have a higher risk of fatality.

Emergency department presentations and hospital admissions

- 7.22. GHB was reported as the 4th most common recreational drug implicated in intoxication presentations in emergency departments (EDs) in Europe in 2015 after heroin, cocaine and cannabis, with 711 reports of GHB across Europe in 12 months, out of a total of 5,529 presentations involving 8,709 drugs in drug-related hospital presentations [Dines *et al.*, 2015; EMCDDA, 2015]. This was supported by the 2019 report with GHB being the 4th most common again, representing over 10% of intoxication presentations across Europe [EMCDDA, 2019]. This provides evidence that despite low levels of use (see chapter 6), there appears to be high levels of morbidity associated with GHBRs use.

Figure 3: The top 25 drugs recorded in emergency presentations in sentinel hospitals, 2017: Results of 7,267 presentations in 26 Euro-DEN plus (sentinel) hospitals in 18 European countries.



Source: European Drug Emergencies Network (Euro-DEN) Report, [EMCDDA, 2019].

- 7.23. GHB accounts for the largest proportion of non-fatal overdoses reported by Dutch emergency services [Vogels *et al.*, 2013], and in 2017 almost a third of drug-related ambulance call outs in The Netherlands were linked to GHB use [EMCDDA, 2019]. A review of ambulance records on pre-hospital treatment of overdoses in Norway between 2009 and 2015 showed 1,112 cases of GHB and GBL poisoning, with GHB suspected for 89% of patients [Madah-Amiri *et al.*, 2017]. This again demonstrated that despite the low prevalence of use, morbidity associated with GHBRs use is high.
- 7.24. To view England and UK ED presentation data, please see EuroDEN statistics presented in chapter 6.
- 7.25. In 2019, 133 Freedom of Information requests were submitted by BuzzFeed News and Channel 4 Dispatches to NHS trusts across England and Wales. They found that most hospitals do not test specifically for GHB/GBL in overdose patients. Some hospitals do record the number of admissions related to GHB/GBL and in the year to November 2018, four hospitals (Blackpool, Portsmouth, and London – King’s College Hospital and Guy’s and St. Thomas’) reported that they had 700

presentations where GHB/GBL had been used. Unfortunately there is no more granularity presented in these data.

- 7.26. The evidence given here demonstrates that GHBRs toxicity is significantly represented in hospitals and clinical care settings in Europe [Vogels *et al.*, 2013; Dines *et al.*, 2015; Madah-Amiri *et al.*, 2017; EMCDDA, 2015; 2019].

Neurological, cardiovascular and respiratory harms

- 7.27. Symptoms of GHBRs toxicity span neurological, cardiovascular and respiratory harms.

Symptoms of acute toxicity

- 7.28. *Mild/moderate symptoms:* Shortly after ingestion of GHB or its analogues, individuals may experience drowsiness, dizziness, shallow breathing, slow heart rate, low blood pressure, nausea or vomiting, muscle spasms and seizures (myoclonus), and hypersalivation [Chin *et al.*, 1992; Li *et al.*, 1998; Thai *et al.*, 2006; Schep *et al.*, 2012; Korf *et al.*, 2014; Neptune, 2015].
- 7.29. *More severe symptoms:* the hallmark of GHB intoxication is a rapid and profound coma that is usually associated with slow heart rate (bradycardia), slow breathing (hypoventilation), and respiratory depression, followed by a full recovery within four to eight hours, often requiring supportive care for survival. The coma is accompanied by loss of bowel/bladder control, headaches, amnesia and convulsions, respiratory arrest, and in some cases cardiac arrest. More recent literature supports this evidence with coma leading to the characterisation of intoxication as severe and an intensive care setting advised [Chin *et al.*, 1992; Miró *et al.*, 2002; Couper *et al.*, 2004; Snead and Gibson, 2005; Liechti *et al.*, 2006; Thai *et al.*, 2006; Knudsen *et al.*, 2008; Munir *et al.*, 2008; Wood *et al.*, 2008; Galicia *et al.*, 2011; Schep *et al.*, 2012; Dietze *et al.*, 2014; Dines *et al.*, 2015; Neptune, 2015; Madah-Amiri *et al.*, 2017].

Single dose and chronic use toxicity

- 7.30. There are harms associated with any use of GHB, whether this is one-off, binge or dependent use. All users risk acute toxicity and overdose, and tolerance for GHB does not protect a user from harm.
- 7.31. In terms of single-dose toxicity, GHBRs appear to be the most toxic club drug [Neptune, 2015]. Overdoses typically occur as a result of taking large doses in a short period of time, or when taken in combination with other central nervous system (CNS) depressants, such as alcohol or benzodiazepines [Gonzalez and Nutt, 2005]. One study in mice suggests that whilst tolerance is reported for GHB sedative effects, this is not the case for respiratory depression [Morse *et al.*, 2017]. Therefore, taking a single dose of GHB has same risk of respiratory arrest in GHB overdose for chronic users as for binge or one-off users.
- 7.32. For chronic or dependent users, non-lethal overdose causing coma or blackout has been recognised as a common occurrence for some time [Chin *et al.*, 1992; Duff 2005; Degenhardt and Dunn, 2008]. Recent literature further supports this finding.

- 7.33. In The Netherlands a recent survey of 146 GHB users found more than 9 in 10 respondents had ever slipped into a light sleep, referred to as 'G-napping', often more than once. Over two thirds (69%) reported having been in a drug-related coma at least once; 14% experiencing a coma in the last month. About 10% had experienced coma extremely often (more than 100 times), including 9 respondents who reported over 250 comas, with a maximum of 1,800 comas reported for one individual [Grund *et al.*, 2018]. The average number of comas experienced was 81, with a median of 6 [*ibid.*].
- 7.34. In Switzerland it was found that 64% of GHB-related ED presentations were comatose [Liakoni *et al.*, 2016].
- 7.35. In Australia, 14.7% of GHB users had experienced coma at least once [Hammoud *et al.*, 2018].
- 7.36. In a case series of GHBRs presentations to a London ED in 2006, there were 158 GHBRs presentations in total. Of these 158, 24 (around 16%) had a Glasgow Coma Scale (GCS) score of 3, meaning severe coma on presentation and 72 (around 48%) had a GCS score of less than or equal to 8, which is the usual cut-off for intubation [Wood *et al.*, 2008].
- 7.37. A higher lifetime use of GHB consumption increases the likelihood of coma, as does 'stacking', which is the cumulative number of GHB doses taken in an episode of drug taking, with more stacking increasing the likelihood of coma [Grund *et al.*, 2018].
- 7.38. The circumstances of the overdose are typically accidental overdoses in night clubs [EMCDDA, 2002]. ED admissions for GHB use were mostly young males [Madah-Amiri *et al.*, 2017; Miró *et al.*, 2017], consistent with the prevalence of use data.
- 7.39. Recent literature has shown that 1,4-butanediol (1,4-BD) intoxication has coma and recovery symptoms similar to that seen with GHB [Nunez *et al.*, 2018]. However, more recent literature has revealed that a 1,4-BD-induced coma can last longer than those due to GHB, with patients recovering more slowly due to more prolonged CNS depression [Stefani and Roberts, 2020]. The first case report of confirmed 1,4-BD intoxication in Portugal provides additional evidence that 1,4-BD can also induce a profound coma [Castro *et al.*, 2019].
- 7.40. Acute GHBRs toxicity can also cause amnesia, which increases the risk of relapse as users do not recall the experience of acute intoxication and overdose [Doyon, 2001].

Management

- 7.41. Current treatment for GHB/GBL overdose is limited to supportive care, as antidotes that are available for other substance groups (for example, naloxone and flumazenil) have no beneficial effect in the treatment of GHB intoxication [Nunez *et al.*, 2018].
- 7.42. There is new evidence showing that specific monocarboxylate transporter 1 (MCT1) inhibitors enhance GHB renal excretion and reduce respiratory depression after oral

GHB or GBL overdose in rats [Follman and Morris, 2019]. This updates previous evidence that suggested that MCT1 inhibitors might be useful treatments [Vijay *et al.*, 2015] because MCT1 mediates the brain uptake of GHB [Kaupmann *et al.*, 2003; Goodwin *et al.*, 2005; 2009]. However, this is very early stage research and is only likely to be effective if administered one to two hours after GHB/GBL ingestion [Follman and Morris, 2019], so is currently (2020) not an approved antidote to GHB or GBL overdose.

Long-term toxicity effects

- 7.43. Comas have previously been weakly associated with hypoxia (oxygen deprivation) and may lead to oxidative stress in the brain [Nayak *et al.*, 2006; Perouansky and Hemmings, 2009; Snyder *et al.*, 2017]. Recent evidence shows that in addition to the immediate effects of the coma, there are long-term negative effects of GHB-induced coma on memory [Pereira *et al.*, 2018] and emotional processing [Pereira 2019a; 2019b].

Gastroenterological symptoms

- 7.44. Vomiting in acute intoxication is common; literature reports range from 17% to over 50% of GHB overdoses being accompanied by vomiting [Garrison and Mueller, 1998; Degenhardt *et al.*, 2002; Wood *et al.*, 2008]. Vomiting in individuals with reduced consciousness increases the risk of aspiration), especially when the GCS score is less than 8 out of 15. Therefore, aspiration in patients intoxicated with GHB/GBL needs to be considered a significant risk, particularly in those with reduced consciousness.

In summary, GHB can cause profound unconsciousness and the steep dose-response curve puts the user at risk of overdose and death. The co-ingestion of alcohol, and other depressants such as benzodiazepines, is a significant additional risk factor. The high number of GHB emergency department presentations in Europe, alongside the fact that GHB use at a population level is estimated to be low, may indicate that GHB harms are over-represented in hospitals and clinical settings, thus suggesting harm from GHB may be higher than other drugs. However, the evidence of both prevalence and emergency department presentations is stronger in The Netherlands and London than in other regions in Europe where there is an absence of evidence.

Withdrawal syndrome (physiological and psychological dependence)

Tolerance, dependence and withdrawal

- 7.45. Tolerance to GHB, GBL and 1,4-BD develops, so larger doses are needed over time to produce the same psychoactive effects. Therefore, long-term GHB users typically take higher doses than naïve users [EMCDDA, 2002]. Users who have developed tolerance to GHB report taking larger doses just 'to normalise' themselves rather than achieve euphoric effects as before [Chew and Fernando, 2004]. The fact that tolerance develops suggests that GHB, GBL and 1,4-BD are psychologically and physically addictive with high abuse potential [Corkery *et al.*, 2018].

- 7.46. Tolerance and physical dependence can develop when GHBRs are used regularly within weeks to months, especially if use is daily [McDaniel and Miotto, 2001; van Noorden *et al.*, 2010; 2017]. A distinctive feature of GHBRs is the rapid onset of withdrawal symptoms. The short half-life of GHB (around 30 minutes) means those with GHB/GBL dependence need to take every few hours, typically between 1 and 4 hours, to prevent withdrawal symptoms developing [Galloway *et al.*, 1997; Gonzalez and Nutt, 2005; Bell and Collins, 2011; Wood *et al.*, 2011; Choudhuri *et al.*, 2013; Liechti *et al.*, 2016]. Withdrawal may also occur during recovery from acute intoxication (overdose) [Wojtowicz *et al.*, 2008; Bell and Collins, 2011; PHE, 2014; Busardò and Jones, 2015].
- 7.47. All three drugs are considered to have the same withdrawal syndrome [Lingford-Hughes *et al.*, 2016; Floyd *et al.*, 2018] and it has been observed in individuals with dependence for GHB, GHB/GBL co-ingestion, GBL, and 1,4-BD [Catalano *et al.*, 2001; Wojtowicz *et al.*, 2008; Zvosec *et al.*, 2011; Evans and Sayal, 2012; Corkery *et al.*, 2015]. GHBRs withdrawal symptoms have been reported to last between 3 to 21 days [McDonough *et al.*, 2004; Schep *et al.*, 2012], with a mean of 9 days [McDonough *et al.*, 2004].
- 7.48. Early withdrawal symptoms from GHB typically include tremor, insomnia, confusion, nausea and vomiting [Liao *et al.*, 2018]. After 12–48 hours, anxiety, tachycardia, hypertension, agitation and hallucinations may develop [Neptune, 2015]. Severe withdrawal may include delirium, seizures, psychosis with delusions, autonomic instability with tachycardia, and rhabdomyolysis [McDaniel and Miotto, 2001; Wojtowicz *et al.*, 2008; Veerman *et al.*, 2010; Ghio *et al.*, 2014; Neptune, 2015; van Noorden *et al.*, 2010; 2017;]. Severe withdrawal can be fatal; clinical management is supportive.

Pharmacological management of GHB withdrawal (detoxification)

- 7.49. Clinical management of GHB/GBL withdrawal (detoxification), presents the following specific challenges.
- The onset of the withdrawal is rapid, and the symptoms are life threatening [Kamal *et al.*, 2014; Lingford-Hughes *et al.*, 2016].
 - Identification as GHB withdrawal is challenging due to the fast elimination of GHB from the body and the overlap of symptoms with other conditions, such as alcohol withdrawal [Bell and Collins, 2011; Wood *et al.*, 2011; Busardò and Jones, 2015].
 - Lack of awareness in non-specialist healthcare settings, particularly in EDs [van Noorden *et al.*, 2009; Lingford-Hughes *et al.*, 2016].
 - Lack of well evidenced, effective pharmacotherapy interventions [Roth and Giarman, 1966; Miotto, 2001; Kamal *et al.*, 2017a; Floyd *et al.*, 2018].
- 7.50. High-dose benzodiazepines, such as diazepam, have been the standard treatment employed for detoxification [Bell and Collins, 2011, Kamal *et al.*, 2017a], however this treatment is sometimes ineffective as the GHB withdrawal syndrome may be resistant to benzodiazepines [McDaniel and Miotto, 2001; Sivilotti *et al.*, 2001;

McDonough *et al.*, 2004; LeTourneau *et al.*, 2008; Wojtowicz *et al.*, 2008; Acciani and Kao, 2010; de Jong *et al.*, 2012; van Noorden *et al.*, 2014; Kamal *et al.*, 2017a].

- 7.51. Benzodiazepine-resistant withdrawal needs to be managed in an inpatient setting, as patients may require intubation and critical care admission. Benzodiazepine-resistant withdrawal tends to be treated by either barbiturates or more recently pharmaceutical grade GHB or baclofen [Boukje *et al.*, 2017; Kamal *et al.*, 2017a]. Whilst baclofen, either in combination with benzodiazepines [LeTourneau *et al.*, 2008; Bell and Collins, 2011; Kamal *et al.*, 2015a; 2015b; 2015c; Lingford-Hughes *et al.*, 2016; Floyd *et al.*, 2018], or more recently as a stand-alone treatment [Habibian *et al.*, 2019] offers promising early findings for managing withdrawal, it is currently unlicensed for this use and the reported successes are largely case studies or anecdotal. Services/individual clinicians prescribing baclofen need to follow local processes for using medicines for off-label indications.
- 7.52. In addition, GHB detoxification is of higher intensity and duration than for other substances, with more contacts required and the highest frequency of associated hospital admissions [van Noorden *et al.*, 2017].
- 7.53. In terms of acute presentation for both intoxication and withdrawal, TOXBASE® has clear clinical guidelines, which are used by ED (A&E) staff. However, there are no specific guidelines for non-acute presentations to support services, such as elective detoxification.

Relapse and recovery

- 7.54. Amnesia, including retrograde amnesia, is often caused by GHBRs. This means people who experience intoxication, overdose or develop withdrawal syndrome may recover with no recall of the episode [Miotto *et al.*, 2001]. In a small study 13% of participants experienced amnesia with GHB use, and 45% experienced amnesia after GBL use [*ibid.*]. It is thought that amnesia may increase the risk of relapse in this situation, as individuals do not remember their overdose, so it does not act as a deterrent [Doyon, 2001].
- 7.55. Relapse rates for GHB dependence have been shown to be particularly high, with a 69% relapse rate after three months (following DiTiTap® tapering detoxification), with relapse occurring immediately after detoxification in 27% [Boukje *et al.*, 2017]. A large cohort study showed that, compared with other addictive substances, GHB has a two to five times higher re-enrolment rate in addiction treatment [van Noorden *et al.*, 2017]. In the van Noorden paper re-enrolment was taken as a sign of relapse, however it could also be considered to be evidence of GHB users having greater motivation to seek help and undertake detoxification. As re-enrolment signifies that the user has both relapsed and then re-sought detoxification, re-enrolment rate is considered a reasonable measure of relapse; although it may not be an appropriate measure to compare between substances. This was a large study with over 17,000 patients in Dutch addiction treatment centres between 2008 and 2011, 0.9% of whom had GHB dependence (n=596).
- 7.56. There are some indications that baclofen may be effective in preventing GHB relapse, by increasing the likelihood of a patient completing their recovery treatment. However more research is needed to assess the safety of baclofen at higher doses.

Several baclofen relapse prevention trials are being conducted [Kamal *et al.*, 2015a; 2015b; 2015c; Lingford-Hughes *et al.*, 2016].

In conclusion, the harms from GHB withdrawal syndrome are significant and sometimes life-threatening. It is considered a particularly severe withdrawal syndrome compared with other drugs. Effective clinical management is challenging due to the inherently complex syndrome and the intensity of detoxification treatment (treatment contacts and duration), making reducing harms from GHB withdrawal challenging for clinicians. There is also a high rate of relapse reported, and more research is needed to investigate relapse prevention treatment.

Polydrug use with GHBRs

- 7.57. Little information is known about the behaviour of using GHB in combination with other drugs, but symptoms have been found to be more severe when GHB is taken in combination with other substances of abuse [Giorgetti *et al.*, 2017].
- 7.58. A study collected data on all patients attending EDs of the Euro-DEN network over a 12-month period in 2013/14, recording a total of 710 cases of GHB-related presentations [EMCDDA, 2015]. Almost 72% consumed GHB/GBL in combination with other substances of abuse [Miró *et al.*, 2017]. In comparison with GHB/GBL-only consumption, patients consuming GHB/GBL with co-intoxicants presented with more vomiting and cardiovascular symptoms, a greater need for treatment and a longer ED stay [*ibid.*].

Alcohol and other CNS depressants

- 7.59. Cross tolerance may occur between GHB and alcohol [EMCDDA, 2008] and both alcohol and GHB/GBL can cause changes in behaviour and induce aggression [Neptune, 2015]. Patients who use alcohol are, like GHB/GBL users, also more likely to vomit [Liechti *et al.*, 2006].
- 7.60. More recent evidence has shown that coma occurred in 77% of alcohol and GHB co-ingestion presentations in Swiss EDs, compared to 62% of non-alcohol users. The percentages did not reach statistical significance but were considered to be clinically relevant [Liakoni *et al.*, 2016].
- 7.61. Subsequently alcohol has been shown to be the most common substance consumed with GHB/GBL that results in presentation to EDs [Miró *et al.*, 2017]. However, it was unclear whether this was due to alcohol causing additional harm, or from alcohol often being present in the context of GHB use (for example, in night clubs). A subsequent study in 2017 showed that comas occurring when GHB or GBL was combined with alcohol were more life threatening because the alcohol increased CNS inhibition, resulting in more pronounced respiratory depression, hypotension and bradycardia [Madah-Amiri *et al.*, 2017]. This supports previous evidence that when GHB/GBL is taken in combination with other drugs (including alcohol or stimulants), the duration and depth of coma are greater than when it is taken alone, and recovery times are longer [Liechti *et al.*, 2006; Department of Health, 2011; Galicia *et al.*, 2011; Neptune, 2015].

- 7.62. More recent literature provides strong evidence that significant caution is needed when taking GHB or precursors in combination with other CNS depressants, such as alcohol, as it increases risk of death [Corkery *et al.*, 2018].

HIV antiretroviral agents

- 7.63. HIV antiretroviral agents in combination with GHBRs is of concern because there is evidence to suggest that the drug-drug interactions may increase the risk of GHBRs-related toxicity and seizures and may lower adherence to HIV therapy. Literature is limited and more research is needed on drug-drug interactions between GHB and HIV medication.
- 7.64. Elimination of GHB from systemic circulation occurs rapidly by oxidation [Lettieri and Fung, 1976; Harrington *et al.*, 1999], but animal data suggest that GHB undergoes substantial first pass metabolism (when the concentration of the drug is reduced before it reaches systemic circulation). First pass metabolism of GHB may involve the enzymes CYP2D6 and CYP3A4, however this is not proven. If the first pass does involve these enzymes, then administration of GHB alongside CYP3A4 inhibitors such as the HIV medicines ritonavir and cobicistat, may lead to raised concentrations of systemic circulation of GHB and increased toxicity [Neptune, 2015]. Therefore, HIV doctors should be made aware of this when changing HIV medication and advise patients of the potential risks.
- 7.65. GHB may precipitate seizure-like activity. Therefore, caution should be exercised by people living with HIV who have predisposing seizure disorders or opportunistic infections that may lower their seizure threshold, when taking GHB [*ibid.*].
- 7.66. Some of the side effects of GHBRs include severe nausea, vomiting and gastrointestinal tract irritation. These may adversely affect absorption of antiretroviral therapy [Romanelli *et al.*, 2003]. There are also concerns about adherence to HIV medication while intoxicated, especially during prolonged binges, which may have implications for the effectiveness and durability of HIV therapy [*ibid.*]. It should be noted that evidence for this is limited and there have been no recent studies conducted.

Erectile treatment/dysfunction drugs

- 7.67. Sildenafil (Viagra) is often reported as being used in the context of chemsex. There is little evidence of drug-drug interaction between Sildenafil and GHBRs apart from one case report, where the individual experienced symptoms such as chest pain, headache and shortness of breath not previously experienced with GHB use [Pichini *et al.*, 2016].

In conclusion, the evidence presented in this section, alongside mortality and ED data previously discussed, indicates that GHB taken in combination with other drugs either results in more severe harms or increases the risk of harm.

Chemsex and men who have sex with men

- 7.68. The prevalence of chemsex within different countries and different population groups is discussed in chapter 6, which highlights that men who have sex with men

(MSM) individuals appear to be particularly prevalent users of GHBRS for use in chemsex.

- 7.69. As already discussed, GHBRS use is particularly prevalent amongst MSM individuals within a chemsex context. This section relates to the harms experienced by this population of users. In general, most evidence in this field is of general chemsex drugs, and not specific to GHBRS. This section aims to present the evidence that is available for GHBRS-specific chemsex harms. The main harms are risk of sexually transmitted infection (STI)/HIV transmission, physical trauma, seizures, and being a victim of sexual assault or other crimes.

STI transmission and infections, including HIV and Hepatitis

- 7.70. Condomless sex increases the risk of STI/HIV transmission. Chemsex in general has a higher association with condomless sex than other sex facilitation drugs (for example, 'Poppers') [Hibbert, 2019], and there is some evidence that GHBRS use means that individuals are less likely to use condoms for anal sex [Bracchi *et al.*, 2015; Melendez-Torres *et al.*, 2017]. However, other studies report contradictory findings, concluding that chemsex drugs have a varied association with condomless sex and risk-taking behaviour, and that practices vary amongst individuals who use GHBRS [Bourne, 2015a; 2018; Graf *et al.*, 2018]. A higher number of sexual partners also increases the risk of STI/HIV transmission. Chemsex drugs have been found to facilitate a higher number of different sexual partners, [Bourne *et al.*, 2015a; Kapitány-Fövény *et al.*, 2015]. Therefore, GHBRS use in a chemsex context increases the risk of STI/HIV transmission due to higher levels of condomless sex and higher number of sexual partners.
- 7.71. In addition to STI and HIV transmission, there is also evidence that GHBRS increases risk of transmission of:
- *Shigella flexneri*, a pathogen that can cause severe dysentery in humans and is orofecally transmitted [Gilbart *et al.*, 2015]; and
 - *Lymphogranuloma venereum* (LGV), an STI caused by a strain of chlamydia. There is evidence that LGV is a significant problem amongst MSM, and that co-infection with HIV and hepatitis C is common [Ward *et al.*, 2007]. It is thought that LGV may facilitate HIV transmission [Ward *et al.*, 2007; Macdonald *et al.*, 2014].

Physical trauma

- 7.72. Rectal trauma and penile abrasions are associated with GHBRS use in chemsex [Bracchi *et al.*, 2015; Bowden-Jones, 2017] due to length of sexual encounter [Bourne, 2015a].

Seizures

- 7.73. GHB/GBL may precipitate seizure-like activity in HIV-positive patients with predisposing seizure disorder or opportunistic infections that may lower seizure threshold [Romanelli *et al.*, 2003].

Sexual assault

- 7.74. Whilst MSM who use GHBRS for chemsex do consent to the initial taking of GHBRS, the effects of the drugs (drowsiness, reduced consciousness, coma) make individuals vulnerable to sexual assault, rape, and administration of further substances, which they either may not consent to, or do not have the capacity to

consent to due to the effects of GHBRs. Therefore, those who use GHBRs in a chemsex setting may be at heightened risk of sexual assault, and the harms associated with sexual assault, including psychological harms.

In conclusion, along with the harms associated with GHBRs discussed in this chapter, GHBRs use in the context of chemsex has additional associated harms. These include STI and HIV transmission and the risks to health these pose, rectal and penile trauma, higher risk of seizures amongst HIV positive individuals with predisposed seizure disorders or opportunistic infections, and the potential for heightened risk of becoming a victim of sexual assault.

8. Mental health harms

Intoxication, delirium, psychosis, mood disorders and anxiety

- 8.1. A study conducting interviews with 146 gamma-hydroxybutyric acid (GHB) users in The Netherlands found that of those who had 'abundant' GHB experience (more than 200 lifetime episodes of GHB use, n=73), a significant minority deliberately sought near-comatose levels of intoxication on a regular basis to sleep or find self-medicated relief from mental health troubles [Grund *et al.*, 2018].
- 8.2. Regular use of GHB has been associated with persistent alterations in emotion identification, decreased social interaction, and increased social anxiety [van Nieuwenhuijzen *et al.*, 2010; Johansson, 2012; Dijkstra *et al.*, 2017]. These are negative effects regulated by a major affective network, where the amygdala and the hippocampus are central processing hubs [Adolphs 2002, Chudasama *et al.*, 2009]. Animal studies show that these are regions particularly sensitive to neurotoxic effects induced by GHB [van Nieuwenhuijzen *et al.*, 2010; Johansson 2012]. The most recent evidence of self-reported data in humans combined with functional magnetic resonance imaging (fMRI) showed that long-term exposure to GHB – particularly GHB-induced coma – has a negative effect on an individual's ability to regulate their emotions [Pereira *et al.*, 2019a; 2019b]. The study found that those who had experienced GHB coma reported higher levels of depression, anxiety and stress [Pereira *et al.*, 2019b]. All GHB users showed decreased functional connectivity in the fMRI data between the hippocampus and the amygdala in comparison with the non-GHB group, suggesting that chronic GHB use is associated with altered emotional identification and regulation [Pereira *et al.*, 2019a; 2019b].
- 8.3. GHB and related substances (GHBRS) use within the chemsex context may have additional mental health harms. As part of the Chemsex Study in 2014, some men reported problems relating to paranoia, anxiety or aggression, and a few experienced acute attacks of mania or psychotic episodes that required medical intervention [Bourne *et al.*, 2014]. In addition, the high rates of blackout and coma with GHBRS mean, taken within a chemsex contact, an individual may be less able to give consent. Within the context of a chemsex study, 3 out of 30 men reported being a victim of non-consensual sex [Bourne, 2015a; 2015b]. Another study found 17% of participants reported loss of consciousness during sex and 6% reported their partner losing consciousness during sex [Glynn *et al.*, 2017]. In addition to physical harms, there is also significant psychological distress from this type of sexual assault [Bowden-Jones, 2017].

Memory disorder

- 8.4. Human studies assessing the regular use of GHB have suggested a link between regular GHB use and reported memory complaints [Barker *et al.*, 2007; Durgahee *et al.*, 2014]. However, until recently there has been no strong neurological evidence in human studies of the long-term effects of GHB use on memory.

- 8.5. New evidence has demonstrated an association between repeated GHB-induced comas and the negative effect on associative long-term memory processing and performance [Pereira *et al.*, 2018]. The study conducted neuroimaging on three different user groups (regular GHB users with four or more coma episodes, GHB use with no coma episodes, non-GHB polydrug users) during verbal and spatial memory encoding tests. The results of the tests alongside fMRI data showed that the group of GHB users with four or more coma episodes performed worse on the verbal recognition memory test and recruited sections of the brain associated with memory (primarily the hippocampus) less during the memory encoding test than the other two groups [Pereira *et al.*, 2019a; 2019b]. This is the first evidence of the effects of GHB use on memory and is considered reasonably robust evidence due to the control groups and neuroimaging data.

Intensity of withdrawal on cessation of drug use

- 8.6. As discussed in chapter 7, the withdrawal from GHBRs on cessation is severe. Withdrawal from recreational or medical use of GHB is often associated with anxiety, stress, and sporadically depression [Johansson, 2012; Dijkstra *et al.*, 2017; Kamal *et al.*, 2017b; Miró *et al.*, 2017; UN Office on Drugs and Crime, 2017].
- 8.7. Mental health problems and cognitive disabilities are reportedly widespread among people who use GHB during and after treatment [Dijkstra *et al.*, 2013; Beurmanjer *et al.*, 2018]. Among people in treatment for GHB dependence, 74% to 96% reported sleep disturbances [Dijkstra *et al.*, 2013; Beurmanjer *et al.*, 2018; Grund *et al.*, 2018]. A Dutch study of 98 patients undergoing GHB detoxification monitoring showed a high rate of psychiatric co-morbidity (79%), which included anxiety, mood and psychiatric disorders [Kamal *et al.*, 2017b]. The level of psychological distress was significantly higher than the standard outpatient reference group. The paper concludes that GHB dependence is characterised by serious psychiatric comorbidity and psychological distress, both of which are associated with increased GHB use – creating a cycle leading to lower quality of life [*ibid.*].

In conclusion, there is a strong base of new evidence about the mental health harms caused by GHBRs since the Advisory Council on the Misuse of Drugs last considered their harms.

9. Social harms

Crimes facilitated by GHBRs

- 9.1. Crime was not part of any previous Advisory Council on the Misuse of Drugs (ACMD) considerations on gamma-hydroxybutyric acid and related substances (GHBRs). Therefore, all evidence in this chapter is evidence of new harms.
- 9.2. The table below summarises the number of different types of offences committed for both GHB and gamma-butyrolactone (GBL) in England and Wales in the last five years (2015 to 2020). The table shows that the majority of offences are for possession of a controlled drug (72% of offences).

Table 4: Number and type of offences committed relating to GHB and GBL, 2015–2020

Number of offences	Total offences (2015–20)		
	GHB	GBL	Combined total
Production of or being concerned in the production of a controlled drug	1		1
Supplying or offering to supply (or being concerned in supplying or offering to supply) a controlled drug	13	37	50
Having possession of a controlled drug	110	37	147
Having possession of a controlled drug with intent to supply	3	4	7
Grand total	127	78	205

Note: Home Office data for GHB are as of September 2019. (Data supplied from the Home Office Data Hub as of 25 March 2020. Data are provided by 38 police forces in England and Wales. Data have not been reconciled by the police forces).

- 9.3. The Metropolitan Police Service (MPS) has indicated significant concern about the emerging nature of offending behaviour within the chemsex context, and the weaponisation of ‘chems’ – crystal methamphetamine, mephedrone, GHB/GBL. The MPS has reported particular concern about GHB/GBL, as they are considered the most dangerous of these three substances to an individual [Metropolitan Police, 2020a]. The MPS also notes that the supply of GHB/GBL attracts the involvement of organised criminal networks [Metropolitan Police, 2020a; 2020b].
- 9.4. In the UK in recent years, GHBRs have been used to facilitate serious crimes, including murder, rape, sexual assault and robbery. Some of these crimes occur in a chemsex context, however this is not exclusively the case. A number of criminal UK cases are outlined below and demonstrate the extreme harm that can be inflicted on others by predators using GHBRs.

Murder

- 9.5. The cases of Stephen Port and Gerald Matovu outlined below provide evidence of GHBRs being used as a murder weapon.

Stephen Port – four counts of murder and rape

- 9.6. Stephen Port, 41 years old, was found guilty in 2016 of four counts of murder; ten counts of administering a substance with intent; four counts of rape; and four counts of assault by penetration [Pettigrew, 2018; Crown Prosecution Service, 2019]. He often met his victims, all young men, using dating websites and apps and inviting them to his house. There he surreptitiously administered GHB in its liquid form with the aim of raping them whilst in a comatose state. Four men died as a result of the GHB administration and the bodies were found in or near a graveyard close to Stephen Port's house [Pettigrew, 2018].

Gerald Matovu

- 9.7. Gerald Matovu, age 25 years, drugged men with GHB and stole from them after meeting them for sex through dating apps such as Grindr. In total there were seven victims of theft, five of whom he drugged with GHB in order to steal from them. He administered a lethal overdose to one of the five men, Eric Michels, and was convicted of murder in July 2019 [Crown Prosecution Service, 2019]. Before Mr Michels' death, Matovu had been convicted of supplying GHB to serial killer Stephen Port (above) and was aware of the danger of GHB doses. Matovu and Brandon Dunbar, a man he sometimes worked with to contact men on Grindr and steal from them and/or assault them, have not yet been sentenced [*ibid.*].

Drug-facilitated sexual assaults

- 9.8. Drug-facilitated sexual assault (DFSA) is where a victim is unable to give or rescind sexual consent due to intoxication that is either self-administered or covertly administered by the perpetrator (predatory DFSA) [[UN Office on Drugs and Crime, 2011](#)].
- 9.9. It is suggested that only 15% of all sexual assault victims (including DFSA) in England and Wales report it to the police [[Ministry of Justice, Home Office and the ONS, 2013](#)]. Victims cite feelings of shame, embarrassment, guilt, fear and denial as reasons for not reporting sexual crimes [*ibid.*; Grela *et al.*, 2018; Busardò *et al.*, 2019; Paul *et al.*, 2019]. Of the sexual assaults that are reported, the proportion that are drug-facilitated is difficult to estimate.
- 9.10. When identifying the drugs used in DFSA, consistently reported as the most common is alcohol [Bertol *et al.*, 2018; Grela *et al.*, 2018; Busardò *et al.*, 2019]. Aside from alcohol, some studies report DFSA to be most common with flunitrazepam and GHB [Marinetti and Montgomery, 2010; Busardò *et al.*, 2019; Veerman *et al.*, 2019] due to their properties of causing retrograde amnesia, sedation, ease to dissolve in drinks, rapid onset of action, and rapid elimination from the body. One study commented that GHB is one of the most commonly used substances in DFSA [Bracchi *et al.*, 2015] and another found GHB to be five times more prevalent than flunitrazepam in sexual assault [White, 2017]. However, a number of other studies contradict this and show the prevalence of GHBRs DFSA

to be low. A systemic review from 2010 reporting the rate of GHB-positive samples among victims of reported sexual assault to be between 0.2% and 4.4% [Németh *et al.*, 2010], showing relatively low prevalence. This was supported by a study in Italy where 256 sexual assaults between 2010 and 2018 were analysed to find there was only one confirmed case of GHB being used to facilitate the sexual assault [Bertol *et al.*, 2018]. This low prevalence was also confirmed by a study in Hungary, which collected questionnaire responses from 60 GHB users about their GHB use in a sexual context, with 2 subjects reporting sexual assault (3.4%) [Kapitány-Fövény *et al.*, 2015]. Due to fast elimination from the body and no common protocol for data collection (including samples collected, drugs routinely tested for, and methods of analysis), there is no accurate evidence on prevalence of DFSA or date rape under the influence of GHBRs, which may explain why literature on DFSA varies.

- 9.11. Whilst some research suggests that the frequency of GHB facilitated sexual assaults are over-estimated and recommends the term ‘alleged sexual assault’ [EISOhly and Salamone, 1999; Varela *et al.*, 2004; du Mont *et al.*, 2010; Németh *et al.*, 2010], the theme in more recent literature is that GHBRs DFSA is under-reported [Grela *et al.*, 2018; Paul and Mahesan, 2019]. This is because sexual assault in general is:
- under-reported;
 - forensic testing is needed to identify any drugs, which is challenging retrospectively; and
 - because victims often do not report the assault, and if it is reported it is not often reported immediately.
- 9.12. These last two factors are particularly problematic for GHBRs DFSA. GHB causes retrograde amnesia so victims often have large gaps in their memory, sometimes not knowing they have been assaulted when they awake from their sedated state, meaning they are less likely to report the attack. Even if the victim does report the attack, due to GHB being eliminated from the body very quickly, by the time the victim’s sample is collected, the drug is likely to have been metabolised, making it undetectable in forensic analysis [Scharf, 1998; Borgen *et al.*, 2003; Abanades *et al.*, 2006; Grela *et al.*, 2018; Busardò *et al.*, 2019]. It is widely accepted that the presence of exogenous GHB is difficult for forensic toxicologists to confirm [Brailsford *et al.*, 2012] and it is not always tested for. For these reasons, it can be reasonably concluded that GHB-facilitated DFSA is under-reported [Bertol *et al.*, 2018].
- 9.13. GBL has a faster onset of action than GHB [Wood *et al.*, 2008; Busardò and Jones 2015; Veerman *et al.*, 2019], theoretically making it a better candidate for premeditated DFSA. A recent review concludes that due to GBL having a less restricted legal status than GHB, a low cost, and being readily available to buy on the internet, this has led to GBL being the preferred DFSA drug over GHB [Veerman *et al.*, 2019].
- 9.14. A number of GHBRs suspected DFSA crimes are outlined below.

Reynhard Sinaga, UK – 159 counts of sexual offences, 136 counts of anal rape

- 9.15. In January 2020 Reynhard Sinaga, age 36 years, was found guilty and jailed for life after drugging and assaulting 48 identified men between 2015 and 2017. He was

found guilty of 159 sexual offences, including 136 condomless anal rapes. He has been described as Britain's most prolific rapist in history [Crown Prosecution Service, 2020]. Sinaga approached intoxicated young men in central Manchester and lured them back to his flat near the city's nightclubs, on the pretence of having a drink or ordering a taxi. There, Sinaga spiked his victims' drinks with sedatives, primarily suspected of using GHBRs, to make them unconscious. After that he filmed himself raping them [*ibid.*]. Although GHBRs was never forensically confirmed (due to its fast elimination from the body), it is suspected Sinaga used GHB or similar due to the observed presentation of victims in the video footage (for example, coma and vomiting). The Crown Prosecutor commented that the victims "have suffered severe and life-changing psychological trauma". This case provides strong evidence that GHBRs can and is used as a weapon for sexual assault in the UK, and demonstrated the severe harm caused to victims.

DFSA crimes involving 1,4-BD and GHV/GVL

- 9.16. Early evidence in the USA, from 2002, reported a man drugging his wife and their babysitter and sexually abusing them both, reported by the National Drug Intelligence Centre (NDIC). He added 1,4-butanediol (1,4-BD) to their drinks in order to drug them to facilitate the sexual assault [US Department of Justice, 2002]. This shows that even in 2002, 1,4-BD was being used in the same way as GHB/GBL to facilitate sexual assault.
- 9.17. Gamma-hydroxyvaleric acid/gamma-valerolactone (GHV/GVL) have been associated with (but not analytically confirmed) in one case of DFSA [Andresen-Streichert *et al.*, 2013].

Acquisitive crimes

- 9.18. As mentioned previously, the high rate of blackout amongst GHB users makes them vulnerable and susceptible to crime. In addition to DFSA, other criminal activity is also facilitated by GHB. There is emerging evidence that GHB facilitates acquisitive crimes. Acquisitive crimes are when an individual takes (acquires) something from another individual – also referred to as robbery or theft.
- 9.19. A Hungarian study that reported two cases of DFSA amongst the 60 participants (3.4%), also found that 5 participants reported acquisitive crimes (8.6%) [Kapitány-Fövény *et al.*, 2015]. A further study conducted by the same researchers considered 408 GHB intoxication cases and compared whether crimes were committed against the individuals, and how they came to ingest GHB (unintentionally or intentionally). Those who took GHB intentionally had no crimes committed against them; it was only people who took GHB unintentionally (although there may be self-reporting bias) who reported having crimes committed against them (*ibid.*). This suggests that GHB is used as an instrument in crime. The study concluded that of the total 408 GHB intoxications they reviewed, acquisitive crimes were committed against the individual in 38 cases (9.6%). In comparison, GHB sexual assault happened in 11 cases (2.8%) [Kapitány-Fövény 2017]. This is consistent with the previous smaller study in terms of prevalence of both acquisitive crime and DFSA.

- 9.20. These two papers were the first to provide evidence of acquisitive crimes facilitated by GHB and demonstrate that GHB facilitates acquisitive crimes more frequently than it facilitates DFSA [Kapitány-Fövény *et al.*, 2015; 2017].
- 9.21. The Gerald Matovu case described earlier in this chapter also highlights the use of GHB and its analogues in robbery, with the potential for even more serious harms, including death [Crown Prosecution Service, 2019].

Personal relationships

- 9.22. Five gay men and two straight women described using GHBRs daily for over a year, and for some over a two- to three-year period, as part of a small but in-depth qualitative study. Because of problematic use of GHB, the participants referred to changes in perceptions of their identity, and loss of connectivity to family, community and work roles [Joyce *et al.*, 2013].
- 9.23. There is consistent evidence that that GHBRs use is associated with isolation and loneliness [Joyce *et al.*, 2013; Zapata, 2013; Bourne, 2015a; Pollard *et al.*, 2018; Evers *et al.*, 2020]. Whilst chemsex is frequently reported as a driver behind initial GHBRs use, once the individual becomes dependent and uses daily, chemsex was no longer a significant feature and the individual generally became withdrawn from previous social settings and communities [Stuart, 2013a; Zapata, 2013; Joyce *et al.*, 2018].

Stigmatisation

- 9.24. Stigma is widely experienced by drug users from all communities, and those who use GHBRs within the lesbian, gay, bisexual and trans-gender (LGBT) community have reported multiple stigma, discriminations and oppressions [Lea *et al.*, 2013; Ahmed *et al.*, 2016]. Stigma related to use of GHB is widespread thus potentially leading to patterns of use that are 'hidden', difficult to detect, and not open to preventative or intervention approaches.
- 9.25. The stigma surrounding GHB/GBL use has been attributed in part to community members' knowledge of the high incidence of overdose and adverse effects of the drugs [Palamar and Halkitis, 2006]. In Canada, anti-GHB campaigns in the nightclub scene have commenced in response to recent overdoses [Palamar, 2018]. However, while stigma might divert people away from using GHBRs, it may lead others to hiding their use and thereby increasing risk.
- 9.26. A further level of 'in group' stigma is demarcated by how the drug is administered, with injecting drugs users who 'slam' or inject being perceived as taking greater risks than those who ingest GHB or related drugs orally [Ahmed *et al.*, 2016].
- 9.27. High-profile cases that involve the use of GHBRs in sexual assault, such as the trials of Port and Sinaga outlined earlier in this chapter, can have a negative effect on the gay and bisexual men as a community. This is because negative press linked to a group of people can cement stigma and homophobia, which is likely to increase shame for these men. This can be a major barrier to accessing substance misuse,

sexual health, and mental health support that they could benefit from [LGBT Foundation, 2020].

- 9.28. LGBT and men who have sex with men (MSM) groups have also reported perceived judgement of their sexualised chemsex behaviour by the health services [UK Drug Policy Commission, 2010], creating a major barrier to service access.

GHBRs impaired driving

- 9.29. A study was conducted with 51 current and past users of GHB who were asked about their decision making and experiences of driving under the influence of GHB. The symptoms that most commonly caused driving difficulties were rapid loss of consciousness, onset of stupor, and ante-retrograde amnesia [Barker and Karsoho, 2008]. There was consensus among participants that driving after taking GHB was risky and unsafe and could lead to injuries. Nevertheless, a minority (16%) of participants reported first-hand experience of driving under the influence of GHB [*ibid.*].
- 9.30. This has been supported by more recent studies, which found that GHB causes cognitive and psychomotor impairment and risky driving behaviour [Centola *et al.*, 2018; Darke *et al.*, 2020], with severe impairment observed in real cases of driving under the influence of GHB. In addition, a case report from Taiwan reports several traffic accidents caused from driving under the influence of GHB [Liao *et al.*, 2018].
- 9.31. Analysis for GHB was performed on samples collected from motor vehicle drivers in Australia from 2011 to 2018. Of the 15,000 blood samples collected, GHB was identified in 1.1% of them (n=160) [Griffiths and Hadley, 2019]. A significant finding in the study was that GHB was very commonly co-consumed with amphetamine-type substances (91%). This study provides the first evidence of the prevalence of GHB intoxication amongst motor vehicle drivers. However, it did not draw any conclusions on how this may relate to driving accidents.

Other

- 9.32. Adverse effects on employment were not widely acknowledged in the relevant literature, although [Bourne *et al.*, 2015a; 2015b] posited that withdrawal negatively influenced work attendance and focus, which ultimately had a negative effect on work performance.
- 9.33. The LGBT Foundation has also provided unpublished anecdotal evidence of GHBRs use leading to severe social harms, including homelessness.

In conclusion, there is strong new evidence of significant criminal harm from GHBRs, including murder, DFSA and robbery. Other evidence of social harms is sparse, but the evidence available suggests a reduction or loss of an individual's social and community networks, and a negative impact on personal relationships. There is significant evidence of stigma experienced by LGBT GHBRs users, which is a barrier to service access. There is a scarcity of information as regards the effects of GHBRs on employment, family life, education and housing.

DFSA victim support

- 9.34. Although most of this chapter relates to drug-facilitated sexual assault (DFSA) harms in general, as evidenced in chapter 9, gamma-hydroxybutyric acid and related substances (GHBRs) have been found to be used in DFSA crimes.
- 9.35. The support interventions available in the UK for individuals who experience sexual assault are outlined below.
- Rape and Serious Sexual Offences (RASSO) services provide a range of support for victims/survivors of sexual violation, ranging from peer-led interventions, group work, talking therapy and independent sexual violence advisors (ISVAs) all with the aim of supporting the individual to work through the psychological impact of the unwanted sexual experiences.
 - The National Institute for Care and Excellence (NICE) recommends that trauma-focused cognitive behavioural therapy (CBT) and eye movement desensitisation and reprocessing (EMDR) are used to treat post-traumatic stress disorder (PTSD) [NICE, 2018], which is a key impact of DFSA. However, the guidelines are focused on single incident trauma and the treatment conducted within one month of the incident. As victims of sexual assault often take years to disclose, treatment should be thought about in a wider context and focused on trauma and recovery [Herman, 2015].
 - All individuals seeking support should be offered the opportunity to be assessed by an ISVA [Home Office, 2017] to ensure that the victim understands the options available to them and give them a 'care co-ordinator', particularly if engaging in the criminal justice system and investigation process.
- 9.36. RASSO services, and specialist provision from the voluntary, community and social enterprise (VCSE) sector, has historically, and continues to, mainly provide support to women and girls, as discussed at the Women and Equalities Committee on Boys and Men [Parliament UK, Commons Select Committee, 2019].
- 9.37. Whilst RASSO services have had an awareness of the actuality of DFSA [EISohly and Salamone, 1999] the focus has been on a binary view of female victims of male perpetrated crimes and held under the umbrella of violence against women and girls (VAWG) [Home Office, 2016]. In March 2019, the Government published the first position statement on male victims of crimes considered VAWG [Ministry of Justice, 2019]. This gave formal visibility to male victims of sexual violence and highlighted the need to provide specialist quality services for males [Rape Crisis England and Wales, 2018] with the advent of the male quality standards [Male Survivors Partnerships, 2018]. In addition, whilst men who have sex with men (MSM) who use GHBRs for chemsex do consent to the initial taking of GHBRs, they may become vulnerable to additional sexual or substance abuse that they may not be capable of giving or rescinding consent for due to the effects of GHBRs, as discussed in chapter 7. It is vital that men can access specialist RASSO services and medical support, whether in relation to DFSA or chemsex-related harms. It is also vital they can have both practical assistance from an ISVA, and from mental health professionals who understand the impact of sexual violence.
- 9.38. During the Stephen Port trial (see 9.6 above), some victims experienced a fear of reporting crimes to the police for fear of prosecution in relation to GHBRs use. It is

important that users are encouraged that should they become a victim of sexual assault, they should report a crime to the police, although fear of prosecution could be a barrier for sexual assault victims to come forward. The Greater Manchester Police ran an effective community engagement exercise encouraging individuals to come forward and report sexual assault following the Sinaga case.

- 9.39. As the provision of specialist sexual violence services is weighted to supporting females, the understanding of DFSA is equally weighted towards female victims, which sets a precedent to a complex set of barriers that prevent male/trans victims from seeking support and thus, denies further understanding of the actual phenomena of DFSA.
- 9.40. However, as the 2020 Reynhard Sinaga case was identified as the 'biggest rape case in British legal history' [Crown Prosecution Service, 2020] it thrust male victims of DFSA into the spotlight with a vast amount of media interest and reporting [BBC News, 2020a; 2020b; ITV News, 2020; the *Guardian*, 2020a; 2020b; Victoria Derbyshire, 2020]. This led to an increase in contacts to victim support services and alongside it an increase in government funding for specialist support services [Ministry of Justice, 2020].

In conclusion, both men and women experience significant harm from DFSA. However, there are currently (as at 2020) more barriers to men accessing support interventions available. In addition, the provision of specialist services is weighted towards supporting female victims, meaning that support for male victims of DFSA, and particularly males who experience harms from chemsex due to decreased ability to provide consent, is not well recognised or developed nationally.

10. Conclusions and recommendations

The Advisory Council on the Misuse of Drugs (ACMD) advises that the following recommendations be considered by the Government as a package of interventions. No single recommendation among them will be sufficient to significantly reduce the harms associated with gamma-hydroxybutyric acid and related substances (GHBRs) use.

Due to the significant risk of harm from overdose and withdrawal, alongside new evidence of mental health harms and harms from DFSA crimes, and the specific needs of GHBRs users, recommendations 5, 6 and 7 relate to improving treatment services for GHBRs overdose, withdrawal, dependency, mental health and sexual health. Recommendation 9 focuses on preventing harm coming to GHBRs users by improving their understanding and awareness of the potential harms of GHBRs use.

Monitoring: surveillance and data

- 10.1. It is estimated that overall use of GHBRs in the UK, and in each devolved administration, is low – with more evidence of use in England than in the other devolved nations. There is consensus across the literature that there was a steep increase in GHBRs use in the UK, specifically in England, from 2005 to 2015. Since 2015 the evidence suggests a plateauing in use; albeit with a small and steady pattern of use and harm. However, prevalence estimates are challenging in the absence of general population data in the UK, and with no systematic data collection. There is also a likely underestimate of harm due to the fast elimination of GHBRs from the body and subsequent difficulties identifying GHBRs in:
 - post-mortem samples;
 - emergency department (ED) admissions;
 - sexual health and drug misuse services; and
 - criminal investigations.
- 10.2. Therefore, there is a need to develop systems for future monitoring of the prevalence of GHBRs use and the harms they cause.
- 10.3. The 2019 British Association for Sexual Health and HIV (BASHH) guidelines on sexual history taking now recommend obtaining a history of recreational drug use (including alcohol and chemsex) for all attendees when taking a sexual history [BASHH, 2019]. The Genitourinary Medicine Clinic Activity Dataset (GUMCAD V3), is the updated version of the mandatory data reporting by sexual health services to Public Health England (PHE). This new version is currently (2020) being rolled out across England and includes new data fields for drug use and chemsex. Therefore, ensuring that sexual health services can action the GUMCAD V3 data collection by providing IT updates or required funding, could improve data collection on GHBRs use. The recommendation here is to ensure that sexual health services respond to the GUMCAD V3 update.

- 10.4. There is a concern stemming from anecdotal clinician reporting of emerging and increasing use of GHBRs as a recreational club drug, and in other groups who use it outside of a sexual context. Therefore it is important to consider and monitor these trends.

Recommendation 1: Data collection and reporting

To improve current service level data collection and reporting in the following ways:

Part 1

- Ensure that sexual health services report relevant sections as required in GUMCAD V3, with financial support afforded to those services that require adaptation of electronic patient systems.

- For the PHE National Drug Treatment Monitoring System (NDTMS):
 - a) service reporting of sexual orientation to remain above 95% field completion; and
 - b) to make publicly available, on an annual basis, the sexual orientation for individuals in treatment for GHBRs, crystal methamphetamine, ketamine and mephedrone (note: all four relevant chemsex drugs are included to give an indication of chemsex needs and ensure that data for GHBRs does not need to be limited by PHE for the reasons of disclosure control).

• **Part 2**

For the Crime Survey for England and Wales (CSEW) to collect data frequently from all individuals on:

- a) GHBRs use; and
- b) sexual orientation.

• **Part 3**

For the UK Government to provide sufficient funding to enable provision and analysis of The Gay Men's Sex Survey (GMSS) for at least five years. As this has previously been funded as part of an EU grant this recommendation is in line with the UK Government's commitment that research in the UK will not suffer as a result of EU-exit.

Lead organisations:

Part 1: PHE; the Home Office; and British Association for Sexual Health and HIV (BASHH).

Part 2: The Home Office; and the Office for National Statistics.

Part 3: UK Government department responsible for funding research.

Measure of impact:

Part 1 of recommendation:

- for 95% reporting from all services in NDTMS;
- at least 65% improvement in services reporting via GUMCAD V3; and
- evidence of financial support where services require it.

Part 2 of recommendation:

- CSEW survey: For subsequent CSEW survey reports to demonstrate that the question has been asked and data have been collected, and that there is improvement in the data completeness over time.

Part 3 of recommendation:

- GMSS: For confirmed funding of the GMSS survey for at least the next five years.

Toxicology

10.5. There is evidence of increasing mortality associated with GHBRs use since the ACMD last considered harms of GHB in 2003, and gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in 2008. Although the overall number of deaths is relatively low there was a particularly steep rise in deaths between 2008 and 2015. There is more recent evidence that GHBRs have a higher risk of fatality when GHBRs mortality is compared with novel psychoactive substances (NPS) drugs. However, mortality figures are likely to be an underestimate due to the challenges in testing for and identifying GHBRs in post-mortem samples, due to both rapid elimination and endogenous GHB production post-mortem. Mandatory testing for GHBRs in cases of unexplained death would improve data on GHBRs mortality. Although there are several reasons why testing for GHBRs may not be possible or appropriate in all cases of unexplained death, a statement to the effect of why it has not been done, or the result of the test, would improve data on mortality associated with GHBRs.

Recommendation 2: Testing

Testing for GHBRs should be routinely undertaken in all cases of unexplained sudden death. Where testing is not possible (for example, not enough sample, financial, or other reason) then a clear statement should be included in the toxicology report stating that GHBRs testing has not been carried out. Where a blood sample is positive for GHBRs, if possible, this should be confirmed in another sample type, for example, urine.

Lead organisations: Forensic services; sexual assault referral centres (SARCs); coroners in England, Wales and Northern Ireland; and procurators fiscal in Scotland.

Measure of impact: Non-systematic toxicology screening for GHBRs hinders the capacity to measure and understand trends in GHB use and harm. If these recommendations are implemented, those agencies and researchers monitoring GHBRs involvements in deaths, will be able to report GHBRs-related deaths as a proportion of those tested for GHBRs. In cases of unexplained sudden death, impact could be measured with testing (numerator) and autopsies (denominator).

Enforcement

Classification of GHBRs under the Misuse of Drugs Act 1971 (MDA)

- GHB, GBL and 1,4-BD are currently in Class C
- Gamma-hydroxyvaleric acid (GHV)/ gamma-valerolactone (GVL) are currently uncontrolled

10.6. GBL and 1,4-BD are pro-drugs for GHB and have a similarly steep dose-response curve as GHB, meaning their physical and psychoactive effects are very similar to GHB. Although there was some evidence to suggest that GBL was slightly more

potent than GHB, the harms associated with GHB, GBL and 1,4-BD were broadly comparable – meaning that it would be appropriate to classify all three under the same class of the MDA.

- 10.7. There is increasing evidence of physical, mental and social health harms related to GHBRs. Of particular note are the new harms identified since the ACMD last considered GHBRs - severe harm from crimes facilitated by GHBRs and mental health harms associated with GHBRs use.
- 10.8. There is limited evidence of harms and prevalence of GHV and GVL misuse and therefore the control of these compounds under the MDA at this time is not recommended. These compounds should be monitored by the ACMD and considered subsequently for control, should evidence emerge of associated harms or increased prevalence of use due to a shift towards these substances as a result of the recommended re-classification of GHB, GBL and 1,4-BD.

Recommendation 3: Classification

The ACMD recommends that GHB, GBL and 1,4-BD be moved to Class B of the MDA.

Lead Department: The Home Office.

Measure of implementation: Legislative change to the MDA. This recommendation should be considered alongside recommendations 5 to 8, which will collectively provide a range of interventions to reduce the harms associated with these compounds.

Metrics for assessing the intended effect: Reduction in severe harm from crimes facilitated by GHBRs and mental health harms associated with GHBRs use

There may be unintended effects of the recommendation (see discussion in Annex E). These might be quantified and gaps in evidence could be explored further with research.

Scheduling of GHBRs under the Misuse of Drugs Regulations 2001 (MDR)

- GHB is currently in Schedule 2 of the Misuse of Drugs Regulations 2001
 - GBL and 1,4-BD are currently unscheduled in the Misuse of Drugs Regulations 2001 and are in Part 1, Schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015
- 10.9. The ACMD's 2013 advice relating to the scheduling of GHB remained current in 2020. The legitimate therapeutic use of GHB (in the GHB-based drug for narcolepsy, Xyrem®) means that it would be inappropriate to place GHB in Schedule 1 of the MDR, whilst keeping GHB in Schedule 2 of the MDR would ensure that the relevant requirements are applied to GHB, as a Schedule II drug under the Convention on Psychotropic Substances of 1971, under UK legislation.
 - 10.10. A range of options for scheduling GBL and 1,4-BD have been considered, as outlined in Annex E, balancing the restriction of the illegitimate supply of these compounds with a consideration of the legitimate large volume use of these compounds by the chemical industry.

10.11. There is a need to disrupt the unrestricted sale from suppliers of GBL and 1,4-BD on the open-web purporting to be 'cleaning materials' when clearly destined for the illicit market. While a licensing regime would 'catch out' illegitimate suppliers, large-scale legitimate chemical suppliers would most likely be able to adapt to the imposition of a licensing regime for GBL and 1,4-BD. There is limited prevalence of the utilisation of GBL and 1,4-BD among the UK chemical industry, and there is an existing framework (the controlled drug licensing regime) that can be used to control GBL and 1,4-BD. Additional controls could also mitigate the risk of diversion of GBL/1,4-BD from the chemical industry to the illicit market. Given the large volumes (multiple litres) that can often not be accounted for by the chemical industry, there is an argument that regulatory oversight could be beneficial in these settings.

10.12. As the ACMD is not recommending the control of GHV and GVL under the Misuse of Drugs Act 1971 at this time, GHV and GVL will not need to be scheduled under the Misuse of Drugs Regulations 2001.

Recommendation 4: Scheduling

The ACMD recommends that:

- i) GHB remains scheduled under Schedule 2 of the MDR (as amended).
- ii) GBL and 1,4-BD are placed under Schedule 1 of the MDR (as amended), and that their legitimate industrial uses are made subject to a Home Office controlled drugs licensing regime.

Lead Department: The Home Office.

Measure of impact: Legislative change to the MDR (as amended).

Prevention and treatment

The following conclusions are relevant to Recommendations 5, 6, 7 and 8; relating to prevention and treatment.

10.13. GHBRs can cause profound unconsciousness and its steep dose-response curve puts the user at risk of overdose and death. The harm from this is exacerbated by imprecise recreational dosing. The co-ingestion of alcohol, and other depressants such as benzodiazepines, is a significant additional risk factor for overdose and death.

10.14. GHBRs also have a particularly severe, life-threatening withdrawal syndrome. Physical dependence on GHBRs develops quickly (over a few weeks to months depending on frequency of use), and withdrawal symptoms can develop within a few hours of cessation. In addition, effective clinical management is challenging due to the difficulties identifying the withdrawal syndrome, followed by resistance to treatment (benzodiazepines) and the high intensity of detoxification (treatment contacts and duration). This makes reducing the harms from GHB withdrawal challenging for clinicians, leaving individuals more exposed to harms from withdrawal. In addition, there is consensus within the literature that GHBRs withdrawal has high relapse rates after detoxification, meaning once an individual is

addicted it is difficult for them to break the addiction cycle. The literature is also consistent in recommending that more research is needed to investigate effective clinical management of withdrawal, and effective relapse prevention.

- 10.15. There is increased evidence that GHBRs toxicity is significantly represented in hospitals and clinical care settings in London [EMCDDA, 2015]. When this is considered alongside the estimated low prevalence of GHBRs use at a population level, it suggests that GHBRs harms are over-represented in hospitals, suggesting that harm from GHBRs may be higher than other drugs.
- 10.16. In addition to harms from overdose and withdrawal, there is also new evidence of mental health harms and harm from crimes facilitated by GHBRs, both of which are newly identified since the ACMD last reviewed GHBRs and are important to consider for treatment and service provision.
- 10.17. There is evidence that GHBRs use is associated with sleep disturbances, anxiety and mood disorders. There is also new and emerging evidence of the occurrence of GHB-induced coma negatively impacting on an individual's ability to regulate emotions, and of GHBRs possibly causing negative effects on associative long-term memory processing and performance.
- 10.18. There is strong new evidence of significant harm due to the criminal use of GHBRs, including murder, drug-facilitated sexual assault (DFSA) and robbery. The harms resulting from these criminal acts are severe and include death in the most extreme instances. Survivors of DFSA may experience a complex wide-ranging combination of harms requiring support from several different services. Weaponisation of GHBRs is of particular concern because GHBRs are eliminated from the body rapidly, meaning it is very difficult to definitively pronounce in criminal cases. In addition, GHBRs cause amnesia, meaning victims of crime sometimes do not recall they have been the victim of crime, or can remember very little about it. Other evidence of social harms is sparse, but the evidence available suggests a reduction or loss of an individual's social and community networks, and a negative impact on personal relationships. There was a scarcity of information regarding the effects of GHBRs on employment, family life, education and housing.
- 10.19. GHBRs use is higher amongst the lesbian, gay, bisexual and trans-gender (LGBT) groups and particularly amongst men who have sex with men (MSM) within a sexualised context. These users are vulnerable to additional harms, including sexually transmitted infections (STI), HIV and Hepatitis transmission. MSM using GHBRs in chemsex are at risk of sexual assault due to the effects of GHBRs (reduced consciousness or coma) rendering the individual unable or less able to give or rescind consent during sex. If sexual assault does occur, there is potential for significant harm from psychological distress. Additionally, there is significant evidence of stigma experienced by LGBT GHBRs users, which is a barrier to service access. The complex harms – both physical, mental and social – experienced by MSM require specialist sexual assault support, and it is reported that users believe that current services do not meet these needs.

Treatment

- 10.20. Treatment services, including drug treatment, sexual health services and A&E, are currently under-prepared to treat people with harmful/dependent use of GHBRs due to the overlap between physical, mental and social harms from GHBRs drug use, along with the chemsex context of use and associated sexual health needs. LGBT and MSM individuals report experiencing stigma when attending treatment services for GHBRs, due to a lack of expertise or understanding of chemsex, which acts as a barrier to treatment access.
- 10.21. Therefore, there is a need for integrated and open access sexual health and substance misuse services in order to reduce harm from GHBRs.
- 10.22. There is a concern stemming from reports by clinicians of emerging and increasing use of GHBRs as a recreational club drug, and in other groups who use them outside of a sexual context. Therefore it is important to ensure that all services are equally accessible and not exclusive.

Recommendation 5: Better integration of drug treatment and sexual health services. Commissioning (including at regional/local level as indicated by need) of open access, competent, culturally appropriate, substance use and sexual health services to address the inter-related harms and psychosocial aspects of health due to GHBRs use, including in the context of sexualised drug use. Integrated treatment models currently (as at 2020) exist in the UK and these should be examined to understand best practice.

In high demand areas, the closer integration of drug treatment and sexual health services, including co-location, should be further explored for effectiveness, underpinned by models of joint funding and commissioning. In areas of lower demand/capacity, commissioners and providers should ensure expert referral pathways between services.

Further research into effective service access should be conducted, particularly in areas of high prevalence, including A&E and primary care. It is noted that this recommendation applies to GHBRs but could also apply to chemsex drugs in general.

Lead organisations: The commissioners of Sexual Health Services (SHS) and Substance Misuse Services (SMS); BASHH – in the standards for STI management; PHE Health Improvement Division, The Local Government Association (LGA); The Association of Directors of Public Health.

Measure of impact

Delivery: PHE to conduct an annual audit/questionnaire of the SHS, SMS and local government to capture presence or co-commissioning, alongside treatment numbers.

Impact: Service user feedback annually undertaken by providers and commissioners jointly of service users. Feedback should be collected on:

- accessibility;
- acceptability;
- waiting times for appointment at integrated service; and

- out of area attendances.

A surrogate marker for improvement in acceptability of the SMS could be a decrease in the proportion of people over time who decline to give their sexual orientation when specifically asked by services. These data can be found in the PHE NDTMS data tables published annually.

Staff education and training

- 10.23. Whilst a significant proportion of GHBRs users experience a range of physical, mental and social health harms, few access professional support for fear of judgement or concern about chemsex expertise. It is important not just to develop knowledge of the drug itself, but also the cultural context of use, and the ability and cultural competence of staff to create an environment where a service user can be open and honest about associated behaviours such as sexual behaviour.
- 10.24. There is a lack of available training opportunities for staff who come into contact with GHBRs users. Developing better service models (recommendation above) will only work if staff are appropriately skilled.

Recommendation 6: Education

Develop a specialist education pathway for frontline staff in the health and social care system who come into contact with GHBRs users. These staff include those within the SHS, SMS, and emergency departments (overdose and withdrawal). The specialist education pathway should provide staff with relevant training on GHBRs-related harms in order to better equip them in managing complex cases and provide essential information on drug use, cultural competence and understanding. This should help to deliver a higher quality and non-judgemental service, working towards reducing harm and alleviating some of the stigma associated with the use of GHBRs. A skilled workforce should also enable improved engagement at the first point of contact with the SHS/SMS.

To review and update the chemsex e-Learning module of the Sexual Health and HIV training to ensure that the content reflects the importance of not just drug knowledge but also covers cultural competence and creating a safe environment for open discussion about risks and sexual behaviour.

In addition, for the inclusion of GHBRs within postgraduate programmes and speciality nurse training, Diploma of genitourinary (GU) Medicine, and speciality training curricula.

Lead organisations: BASHH; SAAS Advisory Board (NHS England and PHE); the Society of Apothecaries; NEPTUNE; Health Education England (HEE); the Academy of Royal Colleges; the Royal College of Psychiatrists; the Royal College of Physicians (including the Faculty of Forensic and Legal Medicine); postgraduate programmes.

Measure of impact: Training requirements clearly stated in national standards (for example, BASHH standards for STI management, speciality training curricula and Faculty of Forensic and Legal Medicine national standards), service specifications and staff competencies monitored by commissioners and providers. Audit of relevant courses/standards for inclusion; metrics of current training courses; provider training records (staff continuing professional development (CPD) certification and e-learning completions).

Individual treatment interventions

10.25. There is a need for improved management of GHBRS-related chronic harms (sexual trauma, stigma) and non-acute GHBRS-related presentations to support services, such as elective withdrawal.

Recommendation 7: Treatment interventions

Chronic harms (sexual trauma and stigma)

Services involved in the management of people who use GHBRS should provide comprehensive assessments and evidence-based psychological and social support to individuals within a key worker/client context. These should be tailored to the individual requirements of the service user according to their specific needs, for example, issues related to age, ethnicity, cultural context, diversity and social isolation. For those individuals with more complex needs all relevant services should have commissioned, clear and timely pathways to care.

Non-acute presentations to support services (for example, elective withdrawal)

The TOXBASE[®] clinical guidelines for GHBRS intoxication and withdrawal, which are used by emergency department staff, should be emphasised to be of value for non-acute services, such as elective detoxification presentations. Support services should access TOXBASE[®] guidelines directly or adapt the content to the local service need.

Lead organisations: PHE; the voluntary sector; NHS Sexual Health and Substance Misuse treatment providers; commissioners who have responsibility for funding services relevant to the sector.

Measure of impact: Number of individuals accessing sexual health and substance misuse treatment, for example, PHE to produce reports using GUMCAD V3 and NDTMS data and to monitor an individual's engagement with the service over time and any reduction in drug and sexual risky behaviour. Improved access to and retention in relevant service provision.

Information and awareness for at risk groups

10.26. GHBRS have a unique risk profile to people who choose to use them (and to those who are given them covertly). GHBRS users can reduce their risk by being provided with accurate and timely information regarding:

- the safest way to manage doses;
- interactions with other substances;
- mental health harms from GHB-induced coma; and
- vulnerability to crimes such as DFSA and robbery.

Recommendation 8: Information and support

To ensure the availability and promotion of information and support to those who are at highest risk of harms associated with GHBRS. This should utilise reliable and up-to-date sources of information that are already available on physical, mental and social harms, including sexual harms and consent in a chemsex setting. The information should, where necessary, be individualised and accessible (for example, in appropriate languages).

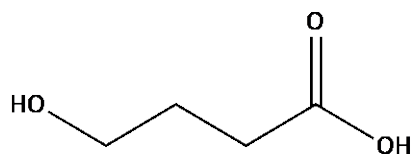
Current sources of available information include: FRANK, Antidote, [Crew](#).

Lead organisations: The Department of Health and Social Care; PHE; SAAS; NHS England, Wales, Scotland and Northern Ireland; BASHH; third-sector treatment providers; relevant non-governmental organisations active in the field.

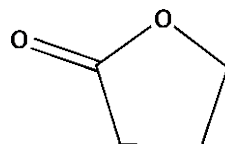
Measure of impact: Audit of advice (quality and access metrics repeated over time); research on reach and uptake of the information; organisations undertake feedback exercise with users.

Annex A: Chemical structures of the compounds being considered in this report

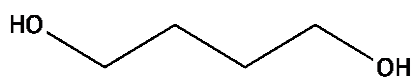
The chemical structures of the compounds considered in this report are given below.



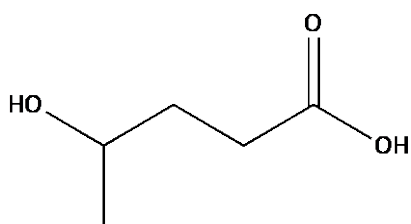
gamma-hydroxybutyric acid
(GHB)



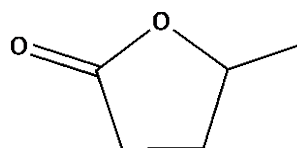
gamma-butyrolactone (GBL)



1,4-butanediol (1,4-BD)



gamma-hydroxyvaleric acid
(GHV)



gamma-valerolactone
(GVL)

Annex B: Quality of evidence

Evidence gathered was considered in line with the Advisory Council on the Misuse of Drug's (ACMD's) standard operating procedure (SOP) for using evidence in ACMD reports [ACMD, 2020].

The international evidence relating to the clinical management of gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL) overdose, withdrawal and relapse is limited as randomised control trials are notably absent. The majority of evidence came from case reports and case series, with several small observational studies, retrospective cohort studies and analysis of patient records. Despite these limitations, these sources are consistent in their reported outcomes and recommendations.

The evidence-base relating to GHB harm is substantial in volume. There is evidence of harm from official statistics of mortality and drug-related overdose in emergency departments, despite challenges in testing for GHB due to its endogenous nature and fast elimination from the body. There is also evidence of GHB harm from service treatment records, large-scale surveys, qualitative interview analysis, case reports, case series, and observational studies.

There is some evidence of harms relating to GBL, however this is limited due, again, to challenges in testing. Evidence of the harms of GBL is largely considered as an extension to the evidence of harms of GHB, with many sources referring to GHB and GBL concurrently as 'GHB/GBL' or 'G' (the general term for GHB and GBL). The evidence of harms for 1,4-butanediol (1,4-BD) specifically are limited. However, due to GBL and 1,4-BD being a prodrug for GHB all evidence of harm relating to GHB can also be considered as evidence of harm relating to GBL and 1,4-BD.

There is very limited evidence of harm relating to gamma-hydroxyvaleric acid (GHV) or gamma-valerolactone (GVL) from peer-reviewed literature (UK and international publications) or from government reports.

The ACMD has also considered international approaches to the legislative control of GHB, GBL, 1,4-BD, GHV and GVL when drafting this report (see Annex C).

Annex C: International legal status of GHBRS

United States of America

The USA drug control system is founded on the Controlled Substances Act (CSA), which lists individual substances, and the Federal Analogue Act, which enables control of materials that can be shown to be 'substantially similar' (in chemistry and effect) to a material already listed in Schedule I or II of the CSA.

Gamma-hydroxybutyric acid (GHB) is placed in Schedule I of the CSA (except if in the form of Food and Drug Administration- [FDA]-approved products – such as Xyrem® – in which case the drug is in Schedule III of the CSA). The result of this scheduling is that anyone who manufactures, distributes, dispenses, imports/exports GHB or conducts research with GHB must apply for 'Schedule I registration'.

Gamma-butyrolactone (GBL) – as a precursor to GHB – is considered a 'List I' chemical under the CSA. As a List I chemical, all distributors interested in handling GBL must comply with requirements surrounding registration, records/reports, imports/exports and administrative inspection [US Department of Justice, 2000].

Although GBL is treated as a drug precursor under US legislation for the manufacture of GHB, in accordance with the same legislation it can also be treated as an analogue of GHB under certain conditions if taken for human consumption. The definition of a 'controlled substance analogue' is covered in 21 US Code 802 Section 32 and includes a stipulation that although GBL is a listed chemical, that does not preclude a finding that the chemical is a controlled substance analogue (i.e. of GHB).

Australia

Australian legislative controls on serious drugs and precursors is split between the federal, state and territory governments. The Commonwealth is responsible for controlling the import and export of substances at the border, while the state and territory governments have their own legislative controls over the possession and use of controlled substances.

At the federal level, GHB and GBL are listed as border-controlled drugs under the Criminal Code Regulations 2019 and as prohibited imports under the Customs (Prohibited Imports) Regulations 1956. 1,4-Butanediol (1,4-BD) is not currently (as at 2020) under border control in Australia. However, the Australian Government will commence work in the latter half of 2020 to consider the regulatory impacts on legitimate industry if 1,4-BD were to come under border control.

At the state and territory level, GHB and GBL are also controlled under each jurisdiction's drug laws; 1,4-BD is also a controlled substance in all states and territories, except Tasmania.

Annex D: Anecdotal evidence

The lesbian, gay, bisexual and trans-gender (LGBT) Foundation described a case in 2018 where it supported a service user who had antisocial behaviour charges made against him when he had been found naked in the lift of an apartment block after using gamma-hydroxybutyric acid (GHB). These charges resulted in him losing his flat and having to stay with his brother. By the time he got in touch with the LGBT Foundation, he had credit card debt and a bailiff had visited his brother's house. He was considering leaving his job to qualify for debt support, as well as feeling suicidal. He was advised that his access to housing would be affected by the antisocial behaviour order, and that his mental health needs were unlikely to change this. In this scenario, criminalisation of this service user for offences caused as a result of GHB-related intoxication led to direct distress and homelessness [LGBT Foundation, 2020].

The LGBT Foundation Manchester commented that *“Callers to our helpline and people using our services tell us that for them, chemsex is ‘a way of removing emotions from sex’, or something they usually do when things are particularly bad in their personal life, highlighting the problematic use of GHBRs [GHB and related substances] in the chemsex context and its like to mental health” [ibid.]*.

From a straw poll of 11 GHB/gamma-butyrolactone (GBL) patients, treated as inpatients at the Chapman Barker Unit and/or in the community, co-morbid mental health problems were a theme for all the GHB/GBL patients (Addiction Services at Greater Manchester Mental Health NHS Foundation Trust).

There are anecdotal reports of an increase in GHBRs use in the last two to three years in clubs, particularly by straight people in London (though not exclusively). There were a number of news reports in 2018 documenting a mainstream move to using GHBRs. A *Guardian* news article focused on straight clubbers who use ‘G’ because it has *“no sugar, no calories and no hangover”* [Guardian, 2018].

Annex E: Options and views considered for classification and scheduling

a) Classification of GHB, GBL and 1,4-butanediol under the Misuse of Drugs Act 1971

Over the course of this assessment, the Advisory Council on the Misuse of Drugs' (ACMD's) Technical Committee considered two options with regard to classification.

(i) Change in classification: GHB, GBL and 1,4-butanediol to move to Class B
The majority of the ACMD's Technical Committee supported recommending the movement of GHB, GBL and 1,4-BD from Class C to Class B of the MDA. These views included:

- a significant body of new evidence of the harms of these compounds emerging since the ACMD's last review of their classification, particularly in terms of the associated levels of drug-related death and their 'weaponization' (use to facilitate robbery and sexual assault);
- the harms of these compounds being most commensurate with compounds in Class B of the MDA, and;
- providing law enforcement agencies with additional tools to tackle offences associated with these compounds.

(ii) No change in classification: GHB, GBL and 1,4-butanediol to remain in Class C

Some members of the ACMD Technical Committee did not support of recommending a movement of GHB, GBL and 1,4-BD from Class C to Class B of the MDA. These views included:

- A lack of evidence to suggest that reclassification alone would be effective in reducing the harms associated with these compounds.
- Concern of the unintended impacts of reclassification on those using these compounds – particularly those from the LGBT community and those using these compounds in the Chemsex context specifically. These already vulnerable groups could be disproportionality impacted by any changes to the criminal justice system.
- Higher offences applicable to the possession of these compounds could deter recreational users who fell victim to a drug facilitated sexual assault from reporting their assault to the police.
- Given that these compounds are often used in combination with Class B or A drugs during Chemsex, increasing the penalties for the possession of these compounds by moving them to Class B would be unlikely to significantly deter misuse or abuse.

Other possible unintended consequences of reclassification might include:

- a shift to increased use of GHV/GVL.
- it may force current GHB users to withdraw from the drug in an uncontrolled way with consequent impacts on their physical and mental health.

b) Scheduling of GBL and 1,4-butanediol under the Misuse of Drugs Regulations 2001

Over the course of this assessment, the Advisory Council on the Misuse of Drugs' (ACMD's) Technical Committee considered a range of possible options for the scheduling of gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) under the Misuse of Drugs Regulations 2001 (MDR).

These options gave due consideration to the legitimate industrial uses of GBL and 1,4-BD, while also scrutinising the feasibility of additional controls in reducing the harms associated with the illicit use of these compounds. These options included (but were not limited to):

- the scheduling of GBL and 1,4-BD under Schedule 1 of the MDR, making their legitimate industrial uses subject to a Home Office controlled drugs licensing regime;
- the creation of a new Schedule under the MDR for compounds utilised by the chemical industry but with no known medicinal use;
- the amendment of Regulation 4B of the MDR to apply additional bespoke restrictions for GBL and 1,4-BD without creating a new Schedule under the MDR; and
- making no amendments to the legislative situation with respect to the scheduling of GBL and 1,4-BD under the MDR.

On balance, a majority of the ACMD's Technical Committee were found to be in support of scheduling GBL/1,4-BD under Schedule 1 of the MDR, making their legitimate usage subject to a Home Office controlled drugs licensing regime. The Committee noted that this option would provide increased clarity for the prosecution of offences involving GBL and 1,4-BD and would disrupt the unrestricted sale from open-web suppliers of GBL and 1,4-BD purporting to be 'cleaning materials' when clearly destined for the illicit market. The Committee considered that it would be beneficial to use an existing framework (the Home Office controlled drugs licensing regime) – a regime to which it would be expected that legitimate, large-scale chemical suppliers would be able to adapt – to restrict the illegitimate uses of GBL and 1,4-BD.

It was confirmed to the ACMD by the Home Office Drugs and Firearms Licensing Unit (DFLU) that the large quantities of GBL and 1,4-BD utilised by the chemical industry would not be incompatible with a Home Office Schedule 1 licensing regime. It was acknowledged that a volume of GBL/1,4-BD might legitimately be lost at some stages or transfer processes by the chemical industry – this could be accounted for, were GBL/1,4-BD made Schedule 1 and subject to a licensing regime.

Annex F: List of abbreviations used in this report

1,4-BD	1,4-Butanediol
ACMD	Advisory Council on the Misuse of Drugs
BASHH	British Association for Sexual Health and HIV
BEIS	Department for Business, Energy and Industrial Strategy
CBA	Chemical Business Association
CBT	Cognitive behavioural therapy
CNS	Central nervous system
CPB	Chlorophenoxybutyric acid
CSA	Controlled Substances Act
CSEW	Crime Survey for England and Wales
DFSA	Drug facilitated sexual assault
ED	Emergency department
EMCDDA	European Monitoring Centre for Drug and Drug Addiction
EMDR	Eye movement desensitisation and reprocessing
EuroDEN	European Drug Emergency Network
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GBL	gamma-butyrolactone
GBMSM	gay, bisexual and men who have sex with men
GHB	gamma-hydroxybutyric acid
GHBRs	gamma-hydroxybutyric acid and related substances
GHV	gamma-hydroxyvaleric acid
GMSS	Gay Men's Sex Survey
GUMCAD	Genitourinary Medicine Clinic Activity Dataset
GVL	gamma-valerolactone
HIV	human immunodeficiency virus

ISVA	Independent Sexual Violence Adviser
LGBT	Lesbian, Gay, Bisexual and Trans-gender
LGV	Lymphogranuloma venereum
MCPB	γ -2-methyl-4-chlorophenoxybutyric acid
MCT1	monocarboxylate transporter 1
MDA	Misuse of Drugs Act 1971
MDR	Misuse of Drugs Regulations 2001
MHRA	Medicines and Healthcare products Regulatory Agency
MSM	men who have sex with men
NDIC	National Drug Intelligence Centre
NDTMS	National Drug Treatment Monitoring System
NHS	National Health Service
NHSBSA	National Health Service Business Service Authority
NICE	National Institute for Care and Excellence
NIS	National Infection Service
NMP	n-methyl-pyrrolidone
NPIS	National Poisons Information Service
NPSAD	National Programme of Substance Abuse Deaths
ONS	Office for National Statistics
PHE	Public Health England
PTSD	post-traumatic stress disorder
RASSO	Rape and Serious Sexual Offences
SARCS	sexual assault referral centres
SDMD	Scottish Drug Misuse Database
SHS	Sexual Health Services
SMMASH	Social Media, Men Who Have Sex With men, Sexual and Holistic Health Study
SMS	Substance Misuse Services

STI	sexually transmitted infection
VAWG	violence against women and girls
VCSE	voluntary, community and social enterprise
WEDINOS	Welsh Emerging Drugs and Identification of Novel Substances
WHO	World Health Organization
WNDSM	Welsh National Database for Substance Misuse

Annex G: ACMD membership, at time of publication

ACMD membership, at time of publication	
Professor Judith Aldridge	Professor of Criminology, University of Manchester
Dr Kostas Agath	Consultant Psychiatrist (addictions), Change Grow Live Southwark
Professor Owen Bowden-Jones	Chair of ACMD, Consultant psychiatrist, Central North West London NHS Foundation Trust
Dr Anne Campbell	Lecturer in social work, Queens University Belfast
Mr Mohammed Fessal	Chief Pharmacist, Change Grow Live
Dr Emily Finch	Clinical Director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Professor Sarah Galvani	Professor of Social Research and Substance Use, Manchester Metropolitan University
Lawrence Gibbons	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Professor Graeme Henderson	Professor of Pharmacology, University of Bristol
Dr Hilary Hamnett	Senior Lecturer in Forensic Science, University of Lincoln
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services, NHS Greater Glasgow and Clyde
Professor Roger Knaggs	Associate Professor in Clinical Pharmacy Practice, University of Nottingham
Professor Tim Millar	Professor of Substance Use and Addiction Research Strategy Lead, University of Manchester
Mr Rob Phipps	Former Head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Harry Shapiro	Director, DrugWise
Dr Richard Stevenson	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Paul Stokes	Reader in Mood Disorders and Psychopharmacology, King's College London
Dr Ann Sullivan	Consultant physician in HIV and Sexual health and National co-lead for HIV Surveillance, PHE
Professor Matthew Sutton	Chair in Health Economics, University of Manchester
Professor David Taylor	Professor of Psychopharmacology, King's College, London and Director of Pharmacy and Pathology, South London and Maudsley NHS Foundation Trust

ACMD membership, at time of publication

Professor Simon Thomas	Consultant physician and clinical pharmacologist, Newcastle Hospitals NHS Foundation Trust and Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Dr Derek Tracy	Consultant Psychiatrist and Clinical Director, Oxleas NHS Foundation Trust
Ms Rosalie Weetman	Public Health Lead (Alcohol, Drugs and Tobacco), Derbyshire County Council
Dr David Wood	Consultant physician and clinical toxicologist, Guys and St Thomas' NHS Trust

Annex H: Membership of the ACMD's Drug use in the Lesbian, Gay Bisexual and Trans-gender (LGBT) Community Working Group

The table below gives the membership of the Drug Use in the Lesbian, Gay, Bisexual and Trans-gender (LGBT) Community Working Group. This report has been produced by the Working Group, with support from the Advisory Council on the Misuse of Drugs (ACMD) Secretariat.

Member	ACMD position	Professional role
Dr Ann Sullivan	ACMD member, Working Group Chair	Consultant in HIV Medicine, Chelsea and Westminster Hospital Foundation Trust and National co-lead for HIV Surveillance, Public Health England
Dr Richard Stevenson	ACMD member	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Emily Finch	ACMD member	Clinical Director, Southwark, Central Acute and Addictions Directorate
Dr Anne Campbell	ACMD member	Programme Director, Masters in Substance Use and Substance Use Disorders; Co-Director, Drug and Alcohol Network @QUB, Senior Lecturer in Social Work, Queen's University Belfast
Lawrence Gibbons	ACMD member	Head of Drug Threat (Intelligence Directorate, Commodities), National Crime Agency
Dr Hilary Hamnett	ACMD member	Senior Lecturer in Forensic Science, University of Lincoln
Paul Steinberg	Co-opted member	Lead Commissioner, Head of Programme and Communications, London HIV Prevention Programme
Dr Michael Brady	Co-opted member	National Advisor for LGBT Health, NHS England
Monty Moncrieff MBE	Co-opted member	Chief Executive, London Friend
Dr Dima Abdulrahim	Co-opted member	NEPTUNE (Novel Psychoactive Treatment UK Network), ATOMIC (Addiction to Medication: Improving Care) Lead Researcher and Programme Manager
Dr David Wood	ACMD member	Consultant Physician and Clinical Toxicologist, Guy's and St Thomas' NHS Foundation Trust
Saye Khoo	Co-opted member	Professor in Pharmacology, University of Liverpool and Hon Consultant Physician in Infectious Diseases, Liverpool University Hospitals NHS Foundation Trust.

Dr Jonathan Dewhurst	Co-opted member	Clinical Lead Consultant, Addiction Psychiatrist, Greater Manchester Mental Health NHS Foundation Trust
Duncan Craig OBE	Co-opted member	Chief Executive Officer, Survivors Manchester
Gaynor Driscoll	Co-opted member	Head of Commissioning (ASC/PH), Integrated Commissioning (Royal Borough of Kensington and Chelsea and Westminster City Council)
Dr Seán Cassidy	Co-opted member	Specialty Registrar in Genitourinary Medicine 56 Dean Street

References

The references from 2015 onwards are given below, with older literature references provided under the subheading 'References prior to 2015' below.

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