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Review

Unity in diversity: A systematic review on the GHB using population

B.A.G. Dijkstra[a,b,c,*], H. Beurmanjer[a,c], A.E. Goudriaan[d,e], A.F.A. Schellekens[a,b], E.A.G. Joosten[a,b]

[a] Nijmegen Institute for Scientist-Practitioner in Addiction (NISPA), Radboud University, Nijmegen, the Netherlands
[b] Radboudumc, Department of Psychiatry, Nijmegen, the Netherlands
[c] Novadic-Kentron Addiction Treatment Center, Vught, the Netherlands
[d] Jellinek and Arkin, Amsterdam, the Netherlands
[e] Amsterdam University Medical Center, Department of Psychiatry, University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Background: Over the past decades gamma-hydroxybutyrate (GHB) has emerged as a popular drug with high potential of (ab)use due to its euphoric and relaxing effects. An overview of different populations using GHB is urgently needed, since this would enable development of adequate prevention and treatment policies to diminish the risks associated with GHB use. We systematically reviewed literature on different GHB using populations, comparing demographic characteristics, GHB use patterns, psychosocial aspects and psychiatric comorbidity.

Methods: We conducted a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using Rayyan software. Original studies published from January 1997 up to October 2019 on GHB use were included. Out of 80 full-text articles, 60 articles of 51 unique studies were included. Most studies included people using GHB 1) presenting at emergency departments ($n = 22$), 2) recruited from the general population ($n = 11$), or 3) presenting at addiction care ($n = 8$).

Results: Three main sub-populations of people using GHB are described in the literature: people using GHB recreationally without adverse effects; people using GHB recreationally with adverse effects, and people with dependence on GHB. These groups show considerable overlap in gender, age range, and comorbid substance use, as well as amount of GHB use per occasion. Differences are related to frequency and function of GHB use, the number of comas experienced, as well as work status, and psychiatric comorbidity.

Conclusion: Policy interventions should aim at preventing the transition from recreational substance use to GHB use, as most users are experienced recreational substance users prior to starting GHB use. When people use GHB regularly, interventions should aim at reducing the level of GHB use and preventing GHB use-related harm. Longitudinal studies and population-based probability sampling are required for more insight in the dynamics of GHB use in different sub-populations, and the transition from one group to the other, ultimately leading to dependence on GHB.

Introduction

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid derived from the inhibitory neurotransmitter gamma-aminobutric acid (GABA) (Snead & Gibson, 2005). GHB can cross the blood brain barrier, where it modifies GABA-ergic activity in the central nervous system, as it binds to GHB, GABA-B, and to a lesser extent also to GABA-A receptors (Bay, Eghorn, Klein, & Wellendorph, 2014; Carter, Koek, & France, 2009; Snead & Gibson, 2005; Xie & Smart, 1992). While GABA-A and GABA-B receptors are widely distributed across the brain, GHB receptors mainly occur in the hippocampus, cortex, thalamus, and amygdala (Bessman & Fishbein, 1963; Schep, Knudsen, Slaughter, Vale, & Megarbane, 2012; Snead & Morley, 1981).

GHB was first studied in the 1960s as an anesthetic but use in anesthesia remained limited due to a high occurrence of adverse effects, mainly vomiting and seizures (Kam & Yoong, 1998). Currently, GHB is medically mostly used in the treatment of narcolepsy (Xyrem®, sodium oxybate) (Boscolo-Berto et al., 2012). Over the past decades GHB has emerged as a popular and addictive party drug with a high potential of (ab)use due to its euphoric, relaxing and sexually stimulating effects (Degenhardt, Darke & Dillon, 2002; European Monitoring Centre for Drugs & Drug Addiction, 2018; Nicholson & Balster, 2001). Use of GHB, and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol, is particularly popular in some parts of Europe, the United States, and Australia. In Australia, United Kingdom, The Netherlands and United States the estimated prevalence of current GHB use in the general adult population (>18 years of age) ranges from 0.1% to 1.3%, whereas rates among

* Corresponding author.
E-mail address: Boukje.dijkstra@outlook.com (B.A.G. Dijkstra).

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partygoers are considerably higher (Center for Behavioral Health Statistics & Quality, 2016; Corkery et al., 2015; Degenhardt & Dunn, 2008; European Monitoring Centre for Drugs & Drug Addiction, 2008; van Amsterdam, van Laar, Brunt, & van den Brink, 2012).

Despite the low prevalence of GHB use in the general population, GHB was number 4 in the top 20 drug-recorded emergency department (ED) presentations in Europe in 2017 (European Monitoring Centre for Drugs & Drug Addiction, 2018). GHB is associated with a high risk of overdose, due to a narrow window between recreational dose and overdose (Abanades et al., 2007, 2006; Miotto et al., 2001). Importantly, repeated GHB-induced comas have been associated with diminished neurocognitive functions and altered hippocampal functioning (Raposo Pereira et al., 2018a, 2018b, 2019). However, GHB-induced comas are not perceived to be harmful by GHB-users, who mainly emphasize the positive effects of the substance (Beurmanjer et al., 2019; Miotto et al., 2001; Raposo Pereira et al., 2019).

Since the early 2000s, there has been a rise in studies reporting people with substance use disorders (SUD) in relation to GHB, in this article referred to GHB use disorder (GUD). Though GUD is not a formal DSM-5 diagnosis, patients with GUD commonly fulfill general criteria for SUD according to DSM-5. A DSM-5 SUD diagnosis comprises 11 behavioral and physical signs and symptoms, for which two are required for a SUD diagnosis. The severity of an individual's SUD is qualified as mild, moderate, or severe, when scoring met between two to eleven diagnostic criteria (American Psychiatric Association, 2013). A major complexity in GUD patients is the GHB withdrawal syndrome, due to high risk for agitated delirium and epileptic seizures (Wood, Brailsford, & Dargan, 2011). Furthermore, prospective studies show dramatically high relapse rates among patients with GUD after detoxification, of up to 65% within three months (Dijkstra et al., 2017).

Most studies on GHB use focus on specific GHB-using populations, like partygoers, patients presenting at emergency department with GHB intoxication, or GUD patients presenting at addiction care. As a result, literature is inconclusive concerning demographic characteristics and typical GHB-user patterns. From a public health perspective, an overview of different populations using GHB is urgently needed, especially given the potential risks associated with GHB use. Better understanding of the differences between user groups is necessary in order to design adequate prevention, treatment and harm reduction policies. The aim of this review was to obtain an overview of different profiles of GHB-using populations described in the available literature. We describe demographic characteristics and GHB use patterns (amount, frequency, function, and social context) in these studies, and explore differences in psychosocial aspects and psychiatric comorbidity between these populations.

Methods

Search strategies

We conducted a systematic review following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). Articles published from January 1997 up to October 2019 were considered for inclusion in the review. Databases Pubmed, PsycINFO, Embase, Cochrane, Web of Science, and CINAHL were searched using the following strategy: [*Sodium Oxybate [MeSH]* OR *GHB* OR *gamma-hydroxybutyrate* OR *gamma-hydroxybutyric acid* OR *4-hydroxybutanoic acid* OR *4 hydroxybutyrate sodium* OR *gamma-butyrolactone* OR *sodium gamma hydroxybutyrate* OR *sodium oxybutyrate* OR *somsanit* OR *xyrem* OR *sodium oxybate* OR *gamma-butyrolactone* OR *GBL* OR *1,4-butanediol* OR *1,4-BD*] AND [*behavior, addictive [MeSH]* OR *substance-related disorders [MeSH]* OR *addiction [MeSH]* OR *Drug dependence [MeSH]* OR *substance use disorder** OR *drug use disorder** OR *abuse** OR *dependence* OR *addicti** OR *use pattern**]. MESH headings might differ slightly for each database. References from different articles were also reviewed, including review articles that were removed from the search.

Study selection

Original observational studies focusing on GHB use, misuse, dependence or addiction that were published in the English or Dutch language were included. Qualitative, narrative, and controlled studies were excluded. We excluded controlled studies due to the possible influence of each study's inclusion and exclusion criteria on the generalisability of the population. Studies focusing on pharmaceutical GHB use (e.g. narcolepsy, alcohol addiction) and mechanistic studies (pharmacological and biological effects of GHB) were also excluded. Furthermore, we excluded studies in which GHB-use was a small minority of the studied population and/or without description of demographic characteristics. Finally, studies concerning involuntary ingestion (e.g. when taken as a rape-drug) were excluded.

Using the software Rayyan (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2016) two reviewers (EJ and HB) independently assessed the inclusion or exclusion based on titles and abstracts. Disagreements were resolved via discussion and consensus between the two reviewers.

Data analysis

Tables were used to summarize all studies, including the study aim, design, methods, population (including demographics), results and additional comments on the included studies. It was expected that study design, setting, population, and reported outcomes varied significantly, given the large variation in user groups of GHB. Therefore, we decided a priori not to perform meta-analyses.

Results

Study selection

Details of the search strategy and results are shown in Fig. 1. The literature search (March 2018) resulted in 2847 citations and 1417 unique references after de-duplicating from consulted databases. Update of the search (September 2019) resulted in 372 new unique references. After reviewing titles and abstracts, we kept 80 articles to read in full-text. Primary reasons for exclusion based on abstract alone were related to the population studied (e.g. focusing on pharmaceutical GHB use), the publication type (comments, review, single case studies, mechanistic studies), and non-English language (except Dutch). Based on consensus between the two reviewers, 60 of the 80 articles were included. Six articles describing two individual studies were excluded as they were controlled studies; for one controlled study the participants were already included in this review as they were also part of an observational study, the other controlled study was completely excluded. The other 14 articles were excluded due to lack of description of demographic characteristics of the sample. In the 60 included articles, 51 unique samples were described.

In line with our expectation, included studies differed in the primary GHB use population of interest and comprised different settings. Most studies included GHB users presenting at emergency departments ($n = 22$): in Europe ($n = 13$), United States ($n = 5$) and Australia ($n = 4$). Several studies recruited people using GHB from the general population ($n = 11$) or at addiction care ($n = 8$). A couple of studies investigated GHB-related mortality ($n = 6$), gay and bisexual men ($n = 2$), people living with HIV (PLWH) ($n = 1$), and people driving under the influence of GHB ($n = 1$). Detailed information about the study populations is presented as supplementary material. First, we summarize the results regarding demographic characteristics, GHB use patterns, and psychosocial aspects across settings. Secondly, we synthesize the information from the individual studies to identify the primary groups of people using GHB.

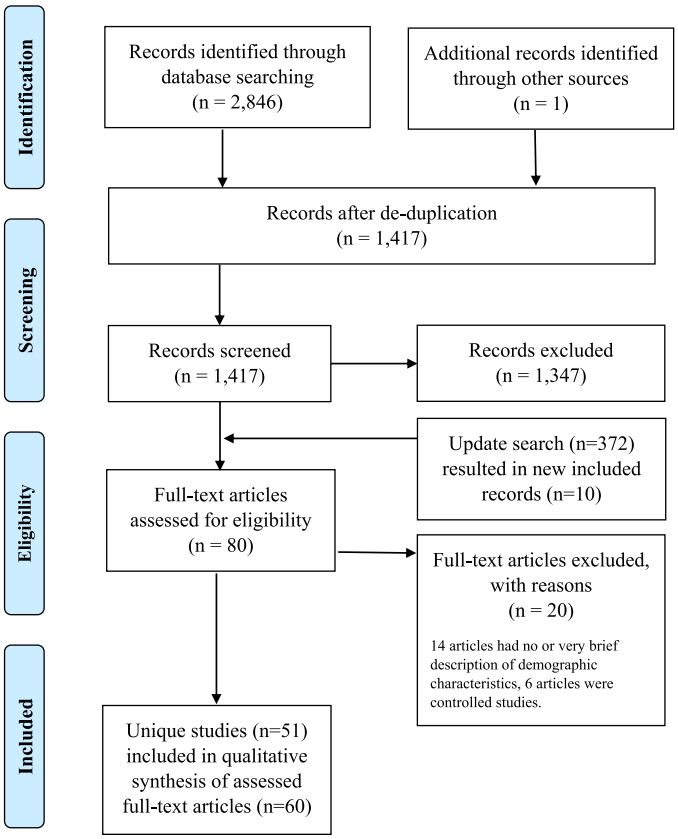

Fig. 1. Flowchart of the search strategy and results.

Demographic characteristics, GHB use and psychosocial aspects across settings

People reporting at emergency departments with GHB overdose

Studies (n = 22) on people using GHB who present at Emergency Departments show that these people are typically young males (male sex: mean 60%, range 54–93%; average age: 25 years, range 21–32 years). From 1999 to 2003, an increase of GHB-related incidents with women was reported (from 38% to 60%) by Anderson et al. (2006). Kapitany-Foveny, Zacher, Posta, and Demetrovics (2017) found that men were more severely intoxicated than women. None of the studies reported education level or current employment status.

Only Liechti, Kunz, Greminger, Speich and Kupferschmidt (2006) and Miro, Nogue, Espinosa, To-Figueras, and Sanchez (2002) reported the GHB dose used (average: 6 ml, range 1–12 ml). Prevalence of GUD was identified in four studies, varying between 5% to 59% (Anderson et al., 2009; Boyd, Kuisma, & Randell, 2012; Liakoni, Walther, Nickel, & Liechti, 2016; Liechti et al., 2006). Presence of psychiatric problems was mentioned in three studies, varying between 6 and 27% (Chin, Sporer, Cullison, Dyer, & Wu, 1998; Horyniak et al., 2013; Liechti et al., 2006).

Fifteen studies reported on prevalence of co-ingestion of other substances (median 60%, range 12–93%). The most reported substances were alcohol (median 39%, 17 studies), cocaine (12%, 12 studies), cannabis (10%, 10 studies), amphetamines (median 20%; 9 studies), 3,4-methyleendioxymethamfetamine (MDMA) (median 18%; 7 studies), opioids (median 8%; five studies), sedatives (10%; five studies), and methamphetamines (two studies: 9% and 24%). Ketamine use was reported in six studies, but only by 2,5% (median) of the individuals. More than one substance next to GHB was reported by two studies by 12,5% of individuals (Chin et al., 1998; Krul & Girbes, 2011).

Most common mentioned reason for GHB-use was recreation (range 90–99%). Some studies reported accidental ingestion (4%), unintentional GHB use (29%), sexual assault (2,8%), poisoning (4%), or suicide attempt (1–3%). Toxicity differ between studies. Severe intoxication was reported in three studies (range 10–72% of individuals), profound unconsciousness in 44% of the participants (Dietze, Cvetkovski, Barratt, & Clemens, 2008; Dutch & Austin, 2012; Van Sassenbroeck et al., 2007). Most of them happens at weekend (46% - 90%) or during the night (40% - 67%) (Liechti & Kupferschmidt, 2004; Miro et al., 2017; Miro, Nogue, Espinosa, To-Figueras, & Sanchez, 2002)

People using GHB recruited from the general population

People using GHB recruited from the general population were predominantly young males (median 74%, range 47–90%), with a mean age of 27 years (range 24–32 years). Studies reporting education level and/ or employment status (9 out of 11) showed that most respondents completed at least secondary education (median 67%) and were employed or student (median 64%, range 17% to 90%). People started using GHB around the age of 24 years (range 22 to 27 years). The median frequency per occasion was six doses with an interval of 1.5 h between doses. Duration of GHB use was only mentioned in two studies (1 versus 4 years). Most respondents reported prior GHB use over the past year (median 82%, 4 studies), and several during the past month (median 37%, 3 studies). Weekly use varied between 3,5% and 45% of the participants (median 40%, 3 studies). On average 17% (range 4–41%, 6 studies) reported daily GHB use / dependence. Two studies reported current psychiatric problems (9%), past psychiatric treatment (28%), and or mental history (59%) (Miotto et al., 2001; Stein et al., 2011, 2012).

The majority (n = 10) of studies reported co-ingestion of other substances, mostly alcohol (median 40%), MDMA (median 36%), amphetamines (median 30%, 3 studies) and cannabis (median 24%, 3 studies). Other reported substances were ketamine (median 7%, 2 studies) and cocaine (median 43%, 1 study). People using GHB at home more frequently mixed GHB with other substances than those using GHB in nightlife settings (52% versus 26%) (Sumnall, Woolfall, Edwards, Cole, & Beynon, 2008).

The studies describe different populations using GHB, ranging from those using GHB infrequently at parties to those using frequently alone at home. Most commonly mentioned motives for GHB use were recreational (18–65%, 2 studies), being more self-confident (13–78%, 3 studies), happiness, euphoria, having lots of energy, getting high (46–79%, 4 studies), to enhance dancing (19%–64%, 3 studies), and to improve sex (16–71%, 7 studies). Other reported motives included forgetting daily worries, letting go, dampening of emotions, depression or anxiety (41%, 72%), improving sleep (76%), small private party (30–35%), being alone (17%, 20%), to treat withdrawal symptoms (17%), to explore altered states of consciousness (13%), or body building (2–6%). Most participants in the study of Stein et al. (2011) started using GHB for positive reasons, which later turned into dealing with negative feelings (depression, anxiety).

GHB-induced comas were frequently reported in three studies (at least one occasion: 25%–69%). Overdose was mostly unintentional (Grund, de Bruin, & van Gaalen, 2018). Participants who experienced GHB overdose more often used GHB alone, had used GHB more frequently and for a longer period of time than those without overdose (Degenhardt et al., 2002; Degenhardt, Darke, & Dillon, 2003; Grund et al., 2018). Other factors related to coma were using > 4 ml GHB, using GHB to feel more confident and having a lower level of education (Grund et al., 2018).

Patients in addiction care using GHB

People using GHB presenting at addiction care were also mostly young males (50–89%, average age 27–34 years). van Noorden, Mol, Wisselink, Kuijpers, and Dijkstra (2017) found that GUD patients were significantly younger than other substance use disorder patients (median age 25 versus 35 years). The five studies reporting employment status

showed unemployment in 48–70% of patients. Four studies reported on level of education, though information was inconsistent and difficult to compare. Psychiatric problems (30–92%) and GUD (77–100%) were reported in five and three studies, respectively. Higher GHB use was significantly associated with treatment drop-out (Cappetta & Murnion, 2019) and re-admission (Dijkstra et al., 2017).

Most patients reported concurrent polysubstance use (68%–71%), mostly with alcohol (median 29%), cannabis (33%, 3 studies), cocaine (23%, 3 studies), benzodiazepines (22%, 2 studies), and MDMA (13%, 3 studies). Two studies mentioned the use of ketamine and mephedrone (respectively 3 and 37%; 7 and 48%). Amphetamine (25%), methamphetamine (25%), and opioids (8%) were mentioned once. Last month percentages were substantially higher.

Patients initially used GHB for recreational purposes (56%), like euphoria (54%) and improved sex (18%, 19%). Other reasons were friends use it (40%), sedation (27%), psychological reasons (22%), unsatisfied with other drugs (19%), no hangovers (16%), and cheap (11%) (Brunt, Koeter, Hertoghs, van Noorden, & van den Brink, 2013; Durgahee, Allen, & Williams, 2014). The most common reason why patients entered GHB treatment were because of sleep problems (31%), followed by social problem (23%), psychological problems (20%), physical problems (19%) and passing out (8%) (Brunt et al., 2013). A similar transition in motivation was reported by Dijkstra, de Weert-van Oene, Verbrugge and de Jong (2013), where patients initially used GHB for mainly positive reasons (euphoria, no hangover, enjoying sex more, etc.) followed by mainly negative reasons for using GHB during admittance for detoxification (eg. helping to forget problems, to help fall asleep, to prevent withdrawal, etc.).

GHB-related mortality

GHB-related mortality was found predominantly in males (69–100%) with an average age of 29 years (range 25–34 years). Most people accidentally deceased after intoxication (86%), mostly at home or a friend's place (49–67%), or in hospital (20–33%). Chemsex was mentioned in 25% of the cases (Hockenhull et al., 2017). Corkery, Loi, Claridge, Goodair, & Schifano (2018)) reported that 5% of the deceased people were unemployed.

Most cases had co-ingestion with other psycho-active substances, predominantly alcohol (median 30%, five studies), MDMA (median 7%, two studies), amphetamine (median 32%), and cocaine (median 32%). Opioids (30%), ecstacy (29%), benzodiazepines (24%), ketamine (24%), mephedrone (24%), and cannabis (9%) were mentioned by one study. Two studies reported high comorbid substance use, but did not differentiate between different substances (Jones, Holmgren, Kugelberg, & Busardo, 2018; Zvosec, Smith, Porrata, Strobl, & Dyer, 2011). Reasons for GHB use was only reported in one study with 21 participants (Corkery, Loi, Claridge, Goodair, & Schifano, 2018).

Gay and bisexual men

Two studies (Halkitis & Palamar, 2006; Hammoud et al., 2018) examined GHB use in gay and bisexual men and compared this group with a group gay and bisexual men without GHB use. The average age was 32 to 38 years. Most of them were employed (77–85%) and well-educated (57–66% college/university level). Of the total studied population 20% to 29% reported GHB use, on average 6 days in the past four months. Reported locations of GHB use were dance clubs (63%), parties (37%), sex parties (37%), friend's place (36%), sex clubs or bathhouses (31%), bars (29%), and at home alone (14%). Participants who used GHB were more likely to use other substances, mainly methamphetamine (56%), MDMA (47%), and ketamine (41%). Most mentioned reasons for GHB use were sexual reasons (30%), availability of GHB (25%), or to lose inhibitions (24%). Findings indicate that GHB is a key drug in chemsex among gay and bisexual men (Hammoud et al., 2018), but not all gay and bisexual men use GHB for sexual reasons (Halkitis & Palamar, 2006). Gay and bisexual men using GHB recreational seemed to have lower overdose rates (15%) compared to other groups using recreational GHB (Hammoud et al., 2018). As overdoses were more common among gay and bisexual men who used GHB at least monthly or more compared to less GHB use (Hammoud et al., 2018), the on average low frequency of GHB use among gay and bisexual men could be an explanation for the relatively low overdose rates. Factors associated with GHB use in the past 6 months were: being HIV-positive, having more gay friends who use drugs, a greater number of sexual partners, group sex, and unsafe sex with casual partners (Hammoud et al., 2018).

People driving under the influence of GHB

Individuals arrested for driving under the influence of GHB (Jones, Holmgren & Kugelberg, 2007, 2008) were mainly male (95%), with an average age of 26 years. Sixty-one percent of cases had used other drugs besides GHB. The mean concentration GHB tends to increase with the age of offenders ($P<0.05$).

People living with HIV (PLWH) using GHB

In one study, 50% of outpatients with an HIV infection (Camacho, Matthews, & Dimsdale, 2004) used GHB. They experienced increased energy (21%), euphoria (18%), and weight-loss (11%). The population was mainly male (89%), mostly between 26 and 39 years of age.

Synthesis of results

The identified GHB-using populations in the included studies can be categorized as recreational GHB use without adverse effect (e.g. (frequent) drug-induced comas); recreational GHB use with adverse effect (e.g. (repeated) comas), and people with GUD.

Across all people using GHB, the majority (55% to 90%) were males, in their late twenties and early thirties. Most people start using GHB recreationally for its euphoric effects. GHB is often used by experienced drug users (Grund et al., 2018), potentially explaining why GHB is often used in combination with other substances. GHB overdoses were related to both dose and frequency of regular GHB use (Cappetta & Murnion, 2019; Grund et al., 2018; Korf, Nabben, Benschop, Ribbink, & van Amsterdam, 2014; Miotto et al., 2001). The risk of a GHB overdose might also be related to the co-use of other (sedating) substances, like alcohol and benzodiazepines (Grund et al., 2018). The most reported substances used besides GHB across all groups were alcohol (21–58%), stimulants (15–77%), and cannabis (8–50%). There are indications that GHB is often combined with stimulants (mainly cocaine and amphetamines), in order to counteract sedative effects of GHB (Beurmanjer et al., 2019; Brunt, van Amsterdam, & van den Brink, 2014).

If people become dependent on GHB, the reason for their use shifts from using for euphoric effects to prevent withdrawal and to forget problems (Brunt et al., 2013; Dijkstra et al., 2017). Patients with GUD are more often unemployed than people using GHB recreationally. Frequent use of GHB and other substances is likely to interfere with employment. Vice-versa, a lack of job perspective could contribute to increased substance use and faster progression into GUD. The level of education among patients with GUD seems comparable to patients with alcohol use disorder, but lower compared to patients with cannabis, cocaine, amphetamine, and opioid use disorders (van Laar et al., 2019).

In parallel with the development of GUD over time, patients with GUD report increasing use of sedatives in order to prevent GHB withdrawal and counteract insomnia (Beurmanjer et al., 2019). A study among Dutch patients with GUD in addiction care reported sedative use in 42% of patients (de Weert-van Oene, Schellekens, Dijkstra, Kamal, & de Jong, 2013). Patients with GUD reported a history of psychiatric problems in 30% to 78% of cases (Choudhuri, Cross, Dargan, Wood, & Ranjith, 2013; Durgahee et al., 2014; Kamal, Dijkstra, de Weert-van Oene, van Duren, & de Jong, 2017).

Information about sexual minorities was found in six studies in which people were recruited from the general population (Anderson, Kim-Katz, Dyer, & Blanc, 2010; Brown University Digest of Addiction Theory and

Application, 2007; Degenhardt & Dunn, 2008; Degenhardt et al., 2002, 2003; Kim et al., 2008; Kim, Anderson, Dyer, Barker, & Blanc, 2007; Sumnall et al., 2008), three studies about patients in addiction care (Bell & Collins, 2011; Cappetta & Murion, 2019; Durgahee et al., 2014), one study about GHB related deaths (Corkery, Loi, Claridge, Goodair, & Schifano, 2018), and two studies in a sample of gay and bisexual men (Halkitis & Palamar, 2006; Hammoud et al., 2018). Most studies including sexual minority groups only describe sexual orientation without further analyses of motives for GHB use. Yet, several studies do show that among sexual minorities people mainly use GHB for its sexually stimulating effects.

Discussion

This review aimed to create an overview of different GHB-using populations as described in the literature, in order to inform adequate policy responses. Overall, the included studies show young males to be overrepresented among people using GHB, and a high level of co-use of substances across different populations of people using GHB. The identified GHB-using populations can be roughly categorized by increasing severity level of GHB use as recreational use of GHB without adverse effects; recreational use of GHB with adverse effects, and people with GUD. Sexual minorities, mainly gay and bisexual men, using GHB might represent a specific subpopulation with a distinct GHB use pattern.

A previous study distinguish three groups with increasing severity of GHB use: people with modest GHB experience (up to 50 times), considerable GHB experience (50 to 200 times) and abundant GHB experience (more than 200 times) (Grund, van Gaalen, & de Bruin, 2015). Where the first group tends to avoid passing out due to GHB overdose, the latter sees GHB-induced comas to be an unavoidable part of their GHB use. Despite the severity people using GHB generally experience a low level of concern with respect to those comas (Beurmanjer et al., 2019). The current synthesis of studies shows a classification based on the negative consequences instead of the amount of GHB. The negative consequences do have a relation with amount of use, but also with co-substance use and the reason to use GHB. The percentage of GHB-related accidents, leading to potentially life-threatening situations and hospitalization (European Monitoring Centre for Drugs & Drug Addiction, 2017), is high compared to other drugs and this should be the focus of policy interventions.

First, policy interventions should aim at preventing the transition from recreational substance use to GHB as most are experienced recreational substance users prior to starting GHB use. The Ecstasy and Related Drugs Reporting System (EDRS) is a good example that successfully tracked the increase of GHB use in Australia and could be of use to identify transitions to GHB use (Dunn, Topp, & Degenhardt, 2009). When people use GHB regularly, intervention programs should aim at reducing the level of GHB use and preventing GHB use-related harm (Phan, Arunogiri, & Lubman, 2020). As health issues and safety reasons are the main reasons for quitting GHB, besides legal issues (Anderson et al., 2010), prevention programs should focus on education about these risks. Furthermore, people using GHB often perceive overdose situations and comas as harmless (Beurmanjer et al., 2019; Palamar & Halkitis, 2006). Education about the potential lethal and long-term cognitive consequences of GHB use might contribute to reducing GHB use and GHB-related harm.

Second, specific targeted intervention strategies might be required for prevention of transition to GUD. Specifically, people using GHB for non-recreational reasons (e.g. to cope with psychosocial problems) and/or those who are unemployed might be at risk. However, it is a major challenge to reach out to these at-risk populations, since GHB use is often difficult to detect and hidden, because most people use at home and there is a strong stigma towards GHB (Grund et al., 2015; Palamar & Halkitis, 2006).

Another specific target population consists of gays and bisexual men using GHB in the context of chemsex: men having sex with men (MSM). Though they less frequently experience GHB-related comas, they more often have other health consequences related to GHB use, like sexually transmitted deceases (Evers et al., 2020; McCall, Adams, & Willis, 2015). Additional targeted prevention strategies might therefore best focus on the health issues specific for this population (Sewell et al., 2019).

In line with the above, a personalized approach to prevent GHB-related harm has been proposed (Grund et al., 2015). Individually tailored advice should preferably be based on a thorough assessment of GHB use and its context (Phan et al., 2020). In the Netherlands, several interventions have been suggested over the past years, such as a GHB-helpline and a 'G-app' with information on monitoring and dosage, dosage syringes and timers, and an awareness campaign on risks of overdosing (Grund et al., 2015). This meets the need for non- didactic educational materials (Palamar & Halkitis, 2006). For patients with GUD referral to specialized care facilities is warranted, aiming to supervise detoxification attempts and prevent relapse. In case of opioid dependence substitution treatment is very common and thoroughly studied, however for patients with GUD no substitution treatment is yet available (Beurmanjer, Kamal, de Jong, Dijkstra, & Schellekens, 2018).

The findings of this study have to be seen in light of some limitations, resulting in knowledge gaps and related recommendations for future studies. First, about half of the studies included less than a hundred subjects (45%), and the range between studies is large: between 7 (Boyce et al., 2000) and 1331 subjects (Anderson et al., 2006). We did not correct for these differences and this could have biased our results. A meta-analysis can be performed on predefined variables to solve this problem, however reported variables differ in definitions, completeness and accuracy, influencing valid comparisons between studies. For example, definitions for GHB dosage (variation in concentration), psychiatric problems (disorder or symptoms) and GHB dependence (frequency or severity of use) differ between studies. Another example is the description of comorbid substance use. Most, but not all, studies reported only the most commonly co-used drugs (Boyd et al., 2012; Dietze et al., 2008; Galicia et al., 2019; Galicia, Nogue, & Miro, 2011; Horyniak et al., 2013; Kapitany-Foveny et al., 2017; Liechti et al., 2006; Madah-Amiri, Myrmel, & Brattebo, 2017; Munir et al., 2008), or chose to report categories only. These differences affect the calculated numbers in this review and limit the possibility to integrate data and execute meta-analysis (Jager, Putnick, & Bornstein, 2017).

Second, included studies mainly consisted of retrospective database/cohort studies, followed by surveys and case series. Many studies focused on a particular setting, e.g. at Emergency Departments (43%), and to a lesser extent at addiction care (15%). Only 20% of the studies recruited participants from the general population, mostly using convenience sampling. These different recruitment methods help provide an overview of different GHB user groups, but may not necessarily reflect the experience of all GHB users. It therefore remains to be elucidated whether the identified GHB-using populations in the current literature are indeed specific sub-populations of people using GHB. As all studies are cross sectional, it remains unclear to what extent people using GHB shift from one group to the other over time, and who might be more resilient or vulnerable for a transition from recreational GHB use to GUD.

Third, our aim was to provide an overview of available studies on people using GHB. Studies from 10 years ago (45%) could be less relevant for today's policy. However, except from a shift in focus to GUD after 2010, we did not find substantial differences in the GHB literature over time. Our selection criteria of English articles resulted in a possible overrepresentation of studies carried out in the US (23%), Australia (18%), and parts of Western Europe (51% in particular the UK and the Netherlands). We did not specify ethnicity within studies, as most participants were white/European and none of the included studies made comparisons between different ethnicity. Both reduces the generalizability due to a risk of bias towards specific countries and sub-populations (e.g. Spanish-language countries). Various studies about MSM using GHB were not included in this review, as those studies did not report suf-

ficient sociodemographic data, or GHB use was not distinguished from other drugs.

For future research longitudinal studies should provide better insight in patterns and changes over time in GHB use, co-substance use, experienced comas, reasons to use, place of use, dependence diagnoses, psychiatric co-morbidity and social situation. Furthermore, population-based probability sampling strategies are advised, selecting predefined target groups (e.g. people with certain frequency of GHB use, sexual minorities, ethnic groups, specific age groups, or those with low/high social economic status), to allow for clear generalizability to both the target population and its sociodemographic subpopulations. Population-based probability sampling is still prohibitively costly and labor-intensive, but less compare to probability sampling without stratification and or clustering (Bornstein, Jager, & Putnick, 2013). When researchers are limited to convenience samples, homogeneous convenience samples are advised, e.g. with respect to one or more sociodemographic groups, as an alternative to conventional convenience samples (Jager et al., 2017). This limits 'noise' related to variation in subsamples (Bornstein et al., 2013). As a meta-analysis on existing data was not feasible due to different definitions and lack of sociodemographic information, we recommend the development of an international 'standard' protocol proposing standardized definitions related to GHB use, which will allow comparing data in the future. Furthermore, we would like to encourage researchers to make results from non-English speaking countries available.

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Declarations of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2021.103230.

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Further reading

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