WHEN THE PARTY IS OVER

ADDRESSING CLINICAL CHALLENGES IN PATIENTS WITH GHB USE DISORDERS

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in patients with GHB use disorders

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General introduction

General introduction

Gamma-HydroxyButyric acid (GHB) has first been described in 1961 (Laborit, 1964). However, it took until the early nineties before use became more wide spread amongst the general public (The Centers for Disease Control, 1991). Its addictive potential went unnoticed until the mid-nineties, when the first dependent users were reported (Galloway, Frederick, & Staggers, 1994; Galloway et al., 1997). From 2000 onwards a limited number of case-studies from different countries can be found and only in 2013 the first study with more than 10 GHB dependent patients was published (de Weert-van Oene, Schellekens, Dijkstra, Kamal, & de Jong, 2013). To date, there are still fewer than 100 publications on GHB dependence or GHB use disorder (GUD) to be found on Pubmed. These numbers show how limited the research on GUD is. Available studies focus mostly on GHB intoxication and coma's (Busardo & Jones, 2015; Grund, de Bruin, & van Gaalen, 2018; Mason & Kerns, 2002) and withdrawal management (De Jong, Kamal, Dijkstra, & De Haan, 2011; Dijkstra et al., 2017; Kamal, van Iwaarden, Dijkstra, & de Jong, 2014; McDaniel & Miotto, 2001; Karen Miotto & Roth, 2001; Tarabar & Nelson, 2004). However, studies are only observational and often cross-sectional. Moreover, there's limited information available about subgroups of GHB users, treatment needs, the clinical relevance of GHB induced coma's, best detoxification method and effective relapse management.

This introductory chapter summarizes the characteristics of GHB and patients with GUD. First the neuropharmacology of GHB will be discussed. Then the prevalence of non-medical GHB use and related acute health risks are described. This is followed by a discussion of the GUD syndrome and currently available treatment strategies. Finally, the chapter ends with an overview of the aims and outline of this thesis.

Neuropharmacology of GHB

GHB is a short-chain fatty acid that is an endogenous precursor and metabolite of the most important inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Fig. 1) (Laborit, 1964; Tarabar & Nelson, 2004). GHB itself acts both as neurotransmitter and as neuromodulator after passing the blood-brain barrier. GHB has a rapid onset of action after ingestion (Tmax=25 to 40 minutes) and a short half-life (T½=30-60min) (Brenneisen et al., 2004). The effect of GHB is bidirectional: at low doses, it stimulates the GHB receptor, increasing the flow of the activating neurotransmitter glutamate (Ferraro et al., 2001; O. C. Snead & Gibson, 2005). GHB receptors are primarily located within the prefrontal cortex and the hippocampus, and in a lesser extent within the striatum, thalamus and cerebellum (Kemmel et al. 2006; Snead 2000). At high doses, GHB is responsible for the increased release of GABA, mainly through the $GABA_B$ receptor (Andriamampandry et al., 2006; Bay, Eghorn, Klein, & Wellendorph, 2014; Lingenhoehl et al., 1999). This explains why users

of GHB experience both activating and sedating effects of GHB. Given that GHB has a particular fast metabolism and a small dose-response window (Busardo & Jones, 2015), there's a high risk of overdose. GHB induced overdose results in a transient coma, often lasting one to four hours (Korf, Nabben, Benschop, Ribbink, & Van Amsterdam, 2014). The exact mechanism of action and function of endogenous GHB are currently unknown, in large part due to the limited number of studies.

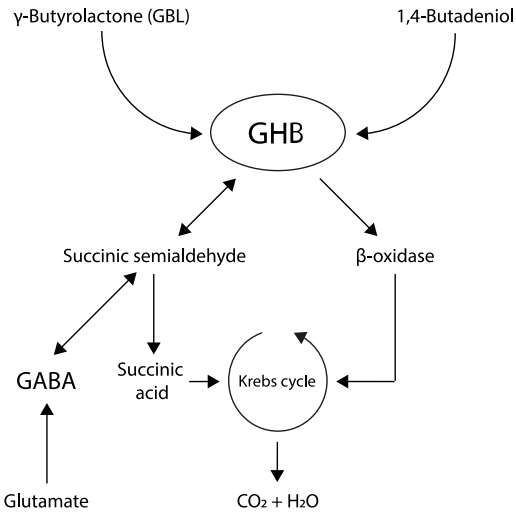

Figure 1 Schematic view of metabolic inter-relationships between GHB and its precursors GBL (γ-Butyrolactone) and BD (1,4-Butanediol) and the biosynthesis and degradation of the GABA.

Recreational GHB use

GHB has been reported to be mainly used and misused in Australia, the US and Europe (Louisa Degenhardt, Darke, & Dillon, 2003; European Monitoring Centre for Drugs and Drug Addiction, 2016; Phan, Arunogiri, & Lubman, 2020; O. C. Snead & Gibson, 2005). Overall, the prevalence of GHB use seems limited, however GHB is often not systematically studied in national drug monitors. Estimates of last-year GHB use among the general population varied from 0.1 to 1.7% (Kamal et al., 2017). The use of GHB seems to be considerably higher in specific subpopulations, such as gay and bisexual men (Bourne A, Reid D, Hickson F, Torres Rueda S, 2014; Ramchand, Fisher, Griffin, Becker, & Iguchi, 2013; Theodore, Durán, & Antoni, 2014). GHB has shown to have prosocial (Bosch et al., 2015) and erotogenic properties (Bosch et al., 2017). This explains why the common motives for using GHB are associated with relaxing, social disinhibition and increased sexual drive

(Dijkstra et al., 2017; Sumnall, Woolfall, Edwards, Cole, & Beynon, 2008). Other drivers of GHB use are the global availability via the internet, web marketing, easy at home to manufacture and low costs(J. G. C. van Amsterdam, van Laar, Brunt, & van den Brink, 2012).

While the prevalence of GHB use is low, GHB is the fourth most common substance in emergency presentations in Europe (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2018). In Europe up to 20% of all hospital admissions for drug use is GHB related (Addiction, 2019; Dines et al., 2015), in the Netherlands this is even one fifth. These numbers could suggest that GHB is used more often than reported in surveys, but could also be GHB specific, and related to the frequent overdosing of GHB due to narrow therapeutic window (Busardo & Jones, 2015).

GHB use disorder

In this thesis the term GUD is frequently used to address the substance use pattern commonly called addiction. Though GUD is not explicitly mentioned as a disorder in DSM-5 (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force, 2013), it could be placed under the "Sedatives" category within the chapter "Substance Use Disorders". Patients with GUD do adhere to key symptoms of substance use disorders, such as taking larger doses or longer periods of GHB than meant to, not managing to stop using GHB, spending a lot of time using GHB, experiencing craving towards GHB, not managing social/work obligations due to GHB use, continued GHB use even when it causes relationship problems, giving up important social activities due to GHB use, using GHB in situations that put one in danger, continuing GHB use even when one knows that it will worsen their physical or psychological condition, developing tolerance and experiencing withdrawal when GHB use is discontinued (Beurmanjer et al, 2016; Dijkstra et al., 2017; Galloway et al., 1997; Gonzalez & Nutt, 2005; K. Miotto et al., 2001; J. G. C. van Amsterdam et al., 2012).

Tolerance to GHB can develop within weeks of the first use, with rapid dose escalation and shorter time intervals between dosages. Several other factors contribute to the highly addictive properties of GHB. From a pharmacology perspective, GHB takes effect within a very short period of time after ingestion, but the high is relatively short due to short half-life. This reinforces taking multiple doses on single events, increasing the chance of developing tolerance. Furthermore, the user doesn't experience downsides after use, such as a hangover. GHB-induced coma's are not experienced as negative (de Weert-van Oene et al., 2013), likely due to amnesia and the stimulating effects of GHB at low doses just before waking up after a GHB-induced coma. This limits negative associations with GHB use, users will not remember passing out and/or feel fine after waking up adding to the idea of the innocence of GHB-induced coma's. Recent studies suggest however that GHB-induced comas are associated with (verbal) memory impairments in patients

with GUD (Raposo Pereira, McMaster, Polderman, de Vries, et al., 2018a; Raposo Pereira, McMaster, Polderman, DAT de Vries, et al., 2018). Moreover, in this cross-sectional study GHB-induced comas were also associated with alterations in long-term memory networks and lower hippocampus/lingual gyrus activity while performing memory tasks (Raposo Pereira, McMaster, Polderman, de Vries, et al., 2018a). These cogntive problems could also influence the development of GUD, as deminished cognitive function has also been connected to increased use in other substance use disorders.

While most recreational users take exact doses measured in millilitres, dependent users often just take a sip of a bottle when they feel they need the next dose. By the time that users present themselves at addiction care facilities there is usually a complete loss on control over GHB use, using every 1-3 hours and around 85 ml GHB per day. Poly substance use is common, mainly co-use of amphetamines and sedatives such as benzodiazepines (Dijkstra et al., 2017; Kamal, Dijkstra, Loonen, & De Jong, 2016). Co morbid psychiatric disorder such as anxiety, mood and personality disorders are also frequently reported (Dijkstra et al., 2017).

In the literature the best described part of GUD is the GHB withdrawal syndrome. This syndrome often has a fulminant course with rapid onset and swift progression of severe withdrawal symptoms. GHB withdrawal symptoms include: tremor nausea, vomiting, tachycardia, insomnia, diaphoresis, anxiety and nystagmus. When the withdrawal is not properly addressed adverse events such as hypertensive crisis, severe agitation, delirium and epileptic seizures can occur (Galloway et al., 1994; Gonzalez & Nutt, 2005; McDonough, Kennedy, Glasper, & Bearn, 2004; O. C. Snead & Gibson, 2005; M. Van Noorden, Kamal, Dijkstra, Brunt, & De Jong, 2016).

Little is known about the prevalence of GUD due to the absence of surveillance and systematic reporting mechanisms, and there is a reasonable chance of underestimation due to frequent home use (Tibor M. Brunt, Koeter, Hertoghs, van Noorden, & van den Brink, 2013). In their sample of regular GHB users, Miotto et al. (K. Miotto et al., 2001) reported that 21% were physically dependent (DSM-IV-TR) on GHB. Degenhardt et al. (Louisa Degenhardt, Darke, & Dillon, 2003) reported 4% dependence on GHB among a sample of recreational GHB users. However, the majority of participants in the Degenhardt et al. study had only recently started using GHB and used GHB less frequently than the participants in the Miotto et al. study. Due to the absence of longitudinal studies, little can be said about the transition from recreational use to addiction.

In recent years the number of studies on patients with GUD applying for detoxification has slowly increased. In the Netherlands it is estimated that the number of patients with GUD seeking help has increased from 4 per 100,000 inhabitants in 2007 to 48 per 100,000 inhabitants in 2014. The number of patients admitted to Dutch addiction treatment centres for GHB detoxification increased from 63 patients in 2008 to 1200 patients in 2015, about 1.2% of the total population in addiction treatment (M. S. van Noorden, Mol, Wisselink, Kuijpers, & Dijkstra, 2017).

Treatment for GHB use disorder

The risks associated with GHB withdrawal pose a challenge from a clinical point of view. In clinical practice two pharmacological treatment regimens are commonly used to counteract withdrawal symptoms during GHB detoxification: tapering with benzodiazepines (BZD) (McDonough, Kennedy, Glasper, & Bearn, 2004) and tapering with pharmaceutical GHB (Dijkstra et al., 2017). While both detoxification methods are currently in use, studies comparing both methods had not been conducted at the start of this thesis.

During BZD tapering diazepam or lorazepam are usually administered to supress withdrawal symptoms. BZD have an allosteric effect on GABA-A-receptors, resulting in increased sensitivity for GABA (Lorenz-Guertin, Bambino, Das, Weintraub, & Jacob, 2019). Benefits of BZD's are the wide availability, low costs and patients can directly quit their GHB use. However, a large number of (case-)studies have been published suggesting BZD resistance in patients with GUD(M. S. van Noorden, Kamal, Dijkstra, Mauritz, & de Jong, 2015), resulting in having to use extremely high doses of BZD's in order to treat withdrawal (Craig, Gomez, McManus, & Bania, 2000; Neu, 2018). In spite of these high doses, delirium was common (Delic, 2019; Harris, Harburg, & Isoardi, 2020; Neu, 2018) and often additional medication such as phenobarbital (Sivilotti, Burns, Aaron, & Greenberg, 2001) and propofol (Dyer, Roth, & Hyma, 2001) was needed to treat the fulminant course of GHB withdrawal.

Pharmaceutical GHB is the preferred detoxification method in the Netherlands. This is prescribed off-label to patients during GHB detoxification (Kamal et al., 2014). The inpatient detoxification starts with a titration phase where the right dose of pharmaceutical GHB is found on which patients are stable and experience neither withdrawal nor sedation. After one or two days the detoxification phase starts, where patients receive GHB every two to three hours. During this phase the dose of pharmaceutical GHB is tapered off gradually each day. GHB tapering has shown to be associated with a high success rate and limited adverse events in several large non-randomized trials (Beurmanjer H, Verbrugge CAG, Schrijen S & DeJong CAJ, 2016; Dijkstra et al., 2017).

After detoxification patients with GUD either continue with inpatient treatment or receive outpatient care. The treatment of GUD relies mostly on generic substance use disorder treatments, based on the principles of cognitive behavioural therapy. It is also common that patients receive help with debts, daytime activities and (finding new) housing or are placed in an assisted living facility (Beurmanjer H, Verbrugge CAG, Schrijen S & DeJong CAJ, 2016; Joosten, Van Wamel, Beurmanjer, & Dijkstra, 2020). One of the main problems in the treatment of patients with GUD is the fast relapse and high drop-out rates in patients with GUD (M. S. van Noorden et al., 2017). This results in many patients leaving care before treatment has properly started. Subsequently, it may add to demoralisation of both patients and treatment staff, when patients frequently relapse into GHB use. It is important to get more insight in treatment needs and factors contributing to these high relapse rates.

Recently there's also been an interest in prescribing the GABA-B agonist baclofen to patients with GUD after detoxification to prevent relapse (Kamal, Schellekens, De Jong, & Dijkstra, 2015). Baclofen and GHB show many similarities in working mechanism, mainly activating GABA-B receptors, with the added benefit that baclofen ($T_{½}$ = 2–6 h) has a longer half-life than GHB ($T_{½}$ = 30–60 min). There's some evidence that baclofen could help in limiting craving and anxiety, and subsequently increase abstinence rates in patients with alcohol use disorder (G. Addolorato et al., 2002; Giovanni Addolorato et al., 2007), and also in patients with GUD (Kamal, Loonen, Dijkstra, & De Jong, 2015). However, at the start of thesis, this had not been studied in larger populations of patients with GUD.

Aims and outline of this thesis

The main purpose of this thesis is two-fold, 1) to further our understanding of the GHB using population and treatment needs of patients with GUD, and 2) to evaluate the two existing pharmaceutical GHB interventions: GHB detoxification and baclofen relapse management. The specific research questions are:

Part 1: Understanding the GHB using population

1. Which different profiles of GHB-using populations, including GUD, are described in the literature? (chapter 2)
2. How do patients with GUD perceive their GHB use and what do they need from treatment? (chapter 3)
3. To what extent do patients with GUD show cognitive impairment, and is there a relationship with GHB-induced coma's and relapse? (chapter 4)

Part 2: Evaluating existing GHB specific interventions

4. How does detoxification with pharmaceutical GHB compare with detoxification with benzodiazepines in patients with GUD in terms of withdrawal severity, craving levels and occurrence of adverse events? (chapter 5)
5. What is the effect of prescribing baclofen to patients with GUD after detoxification on relapse rates? (chapter 6)

Part 1: Understanding the GHB using population

Chapter 2 aims to create an overview of the different subpopulations of GHB users and their characteristics regarding demographics, substance use and psychosocial aspects. For this purpose, a systematic review was conducted, which describes the results of 51 studies on different GHB user groups.

Chapter 3 focusses on the problem that patients with GUD often leave treatment prematurely and show high relapse rates. This qualitative cross-sectional observational

study consisted of semi-structured interview, which explored illness perception and treatment needs in 20 treatment-seeking patients with GUD. The analysis was based on the principles of Grounded Theory by two interviewers and an independent researcher.

In Chapter 4 the relationship between cognitive performance, coma's, GUD and relapse rates will be discussed. In this prospective cohort study a consecutive series of patients with GUD (n=137) admitted for detoxification were recruited at six addiction care facilities in the Netherlands. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairments before and after detoxification. Follow-up duration for the assessment of relapse in GHB use was three months.

Part 2: Pharmacological treatment interventions for patients with GHB use disorder.
Chapter 5 compares two detoxification methods for patients with GUD. In this multicentre non-randomised comparison of two treatments-as-usual, patients with GUD received benzodiazepine tapering or pharmaceutical GHB tapering (matched sample). Withdrawal was assessed using the Subjective and Objective Withdrawal Scales, craving was assessed with a Visual Analogue Scale, and adverse events were systematically recorded.

Chapter 6 focusses on the potential effectiveness of baclofen to prevent relapse in GHB use, after detoxification. This out-patient, multicentre, open-label, non-randomized, controlled trial in patients with GUD (n = 107) Treatment as usual (TAU) was compared with TAU plus baclofen 45-60 mg/day for 3 months. Outcome measures were rates of lapse (any use) and relapse (using GHB on average once a week or more), based on self-report. Side effects were monitored with a baclofen side-effects questionnaire.

Chapter 7 Summarizes the key findings of this thesis, its scientific and clinical relevance, the limitations of the present studies, and the recommendations for future research.

PART 1

Understanding the GHB using population

2

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

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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 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 hydroxy-butyrate sodium OR gammabutyrolactone 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

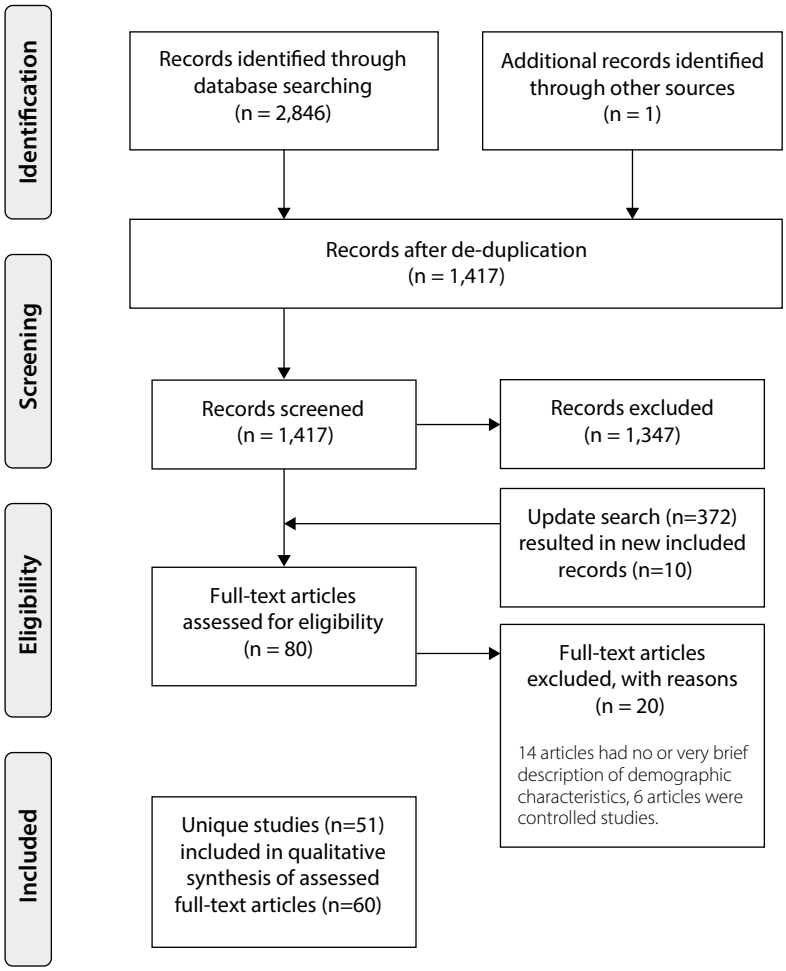

Figure 1 Flowchart of the search strategy and results

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 (supplement I). 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.

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). KapitanyFoveny, 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 forsexual 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 ($P<.05$).

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 GHBrelated 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 sufficient 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.

3

A qualitative approach in understanding illness perception and treatment needs in patients with GHB use disorder

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Abstract

Background: The party drug Gamma hydroxybutyrate (GHB) is highly addictive. GHB use disorder (GUD) has poor treatment outcome, with relapse rates over 60% within three months after detoxification. In order to get a better understanding of the limited treatment success, we explored GUD patients' illness perceptions and treatment needs.

Methods: In a qualitative cross-sectional observational study, using a semi-structured interview based on the works of Kleinmann, illness perceptions were explored among treatment seeking GUD patients (n=20). The analysis was based on the principles of Grounded Theory by the two interviewers and an independent researcher.

Results: GUD patients had mainly positive views towards GHB. GHB was perceived as strongly rewarding and perceived as the solution to psychosocial problems, rather than the cause. After repeated re-admissions GUD patients perceived themselves as addicted to GHB and GHB use as more problematic. They reported a need for personalized treatment goals, which were mainly aimed towards dealing with psychiatric symptoms and social reintegration.

Conclusion: GUD shares many characteristics with other substance use disorders, in line with gradual development from positive reinforcement in early stage GUD to negative reinforcement in later stages of more compulsive GHB use. Future studies should investigate whether personalization of treatment goals, like social reintegration, lead to better treatment outcomes.

Introduction

The party drug GHB (gamma hydroxybutyrate) is an endogenous neurotransmitter (Snead 3rd & Gibson, 2005), known for its prosocial (Bosch et al., 2015), relaxing and erotogenic properties(Bosch et al., 2017), but can also be addictive (T M Brunt, van Amsterdam, & van den Brink, 2014; L Degenhardt, 2003; Kamal et al., 2017; M. Van Noorden et al., 2016). GHB is also registered and widely prescribed for the treatment of narcolepsy (Busardò, Kyriakou, Napoletano, Marinelli, & Zaami, 2015). Main motives for using GHB recreationally include social disinhibition, increased sexual drive, forgetting problems, helping to fall asleep and replacement for alcohol without hangover (Dijkstra et al., 2017; Sumnall et al., 2008). While prevalence of GHB use in most European countries is lower dan 1% of the general population, it is the fourth most common substance in emergency room presentations in Europe(European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2018). Overdosing of GHB is common due to its narrow boundaries between plasma levels required for the desired effect and plasma levels associated with overdose (Degenhardt, 2003). Overdose commonly results in temporary coma or in more extreme cases in respiratory depression (van Amsterdam, Brunt, Pennings, & van den Brink, 2015). GHB users themselves counterintuitively seem not to consider these coma's harmful (de Weert-van Oene et al., 2013). Several studies show that recurrent use of GHB can lead to a substance use disorder (SUD), in about 4% to 21% of cases (Carter, Pardi, Gorsline, & Griffiths, 2009; Louisa Degenhardt, Darke, & Dillon, 2002; Karen Miotto & Roth, 2001). Dependent users take GHB up to 12 times a day or more (Galloway et al., 1997; Gonzalez & Nutt, 2005). Severe withdrawal symptoms occur when they stop using GHB, including severe autonomic dysregulation, anxiety, delirium and seizures (Craig et al., 2000; McDaniel & Miotto, 2001; McDonough et al., 2004; M. S. van Noorden, van Dongen, Zitman, & Vergouwen, 2009). It is therefore recommended for dependent GHB users to stop using GHB with medical support. Most common detoxification methods are tapering off with high doses of benzodiazepines or with pharmaceutical GHB in a clinical setting (Dijkstra et al., 2017; Kamal et al., 2017). Over 60% of patients with a GHB use disorder (GUD) relapse within three months after detoxification (Dijkstra et al., 2017). GHB dependent patients consume relatively more (mental) health care than any other group of patients with (SUD) and are frequently hospitalized at emergency rooms for comas and withdrawal (Mol, Wisselink, Kuijpers, & Dijkstra, 2014; M. S. van Noorden et al., 2017). Given the many negative consequences of GHB use, and limited treatment success of GUD on the one hand, versus the positive perceptions about GHB among GUD patients on the other we aim to explore how GUD patients see their own condition/situation of GHB use and what they think should be done to help them. We applied a qualitative approach to illness perceptions, using the most widely studied theoretical model of illness perceptions: the Self-Regulation Model (SRM) (Leventhal, Meyer, & Nerenz, 1980; Howard Leventhal, Phillips, & Burns, 2016). This model proposes that patients form common-sense beliefs concerning their illness, in

order to understand and cope with health threats. Illness perceptions can be measured using questionnaires(Moss-Morris et al., 2002), assessing patients' drawings (Klis et al., 2008), and interviews (Groleau, Young, & Kirmayer, 2006).

A meta-analysis of 45 studies on mainly somatic diseases (Hagger & Orbell, 2003) shows that illness perceptions are linked to patients' coping strategies, treatment seeking behaviour, adherence, and outcome (Hagger & Orbell, 2003; Jones, Smith, & Llewellyn, 2016). For instance, the more patients view their illness as controllable the more likely they are to use problem focused coping strategies (Hagger & Orbell, 2003). Patients who perceive their condition as highly symptomatic, chronic and serious, are more likely to use avoidant coping strategies in dealing with their condition. Importantly, in patients with SUD, perceived controllability is a predictor of recovery (Chan & Mak, 2016). No studies have been conducted in individuals with GUD. The current study aims to provide insight in 1) how dependent users perceive their GHB use and 2) what they need from treatment.

Methods

Design

The proposed study is a qualitative cross-sectional observational study. A qualitative approach was used because personal interviews give a more in depth and detailed account of individuals´ perceptions than questionnaires. In accordance with the SRM we explored believes of participants concerning their GHB use and dependence, and how they coped with this during the interview (H Leventhal et al., 1980; Howard Leventhal et al., 2016). To do this we used the approach of the Explanatory Models of Arthur Kleinmann (Kleinman, 1978; KLEINMAN, 1978; Kleinman & Benson, 2006). An explanatory model consists of all opinions about the cause of a disease, the beginning of symptoms, the pathophysiology, the course, and treatment of the disease. The interview had three main topics: the development of GUD, the perception of GHB use and the treatment needs of the participants. A translated topic list can be found in appendix I. The study protocol was approved by the intern institute's scientific committee. Participants participated in the study voluntarily and they were guaranteed anonymity.

Participants

Interviews were held between November 2015 and June 2016, with a total of 20 participants, each of which was interviewed once. Recruitment took place through three addiction care facilities in the Netherlands: Novadic-Kentron, Jellinek and IrisZorg, using snowball sampling. The inclusion criteria were: between 18 and 40 years old, having had treatment for GUD (according to DSM-IV criteria) in the past two years, and willing to provide informed consent. Exclusion criteria: currently in withdrawal, current acute severe psychiatric disorders such as major depression, bipolar disorders, psychotic disorders and/

or suicidal tendencies. Comorbidity was assessed by treating counsellors when participants were asked to participate in the study and by the interviewers on inclusion, based on clinical judgement. All counsellors were experienced with screening for psychopathology in patients with GUD. No participants were excluded from the study. To determine if participants were still abstinent in the period before and during the interviews self-report was used, though GHB can be reliably detected in urine within a window of about 12 hours (Abanades et al., 2007; Brenneisen et al., 2004). Participants were rewarded with a €20,- gift voucher after the interview.

Analysis

All interviews were recorded and transcribed. The analysis was performed based on the principles of Grounded Theory (Glaser & Strauss, 1967; Strauss & Corbin, 1994) by the two interviewers (HB & EA) and one independent researcher (LO) specialized in qualitative analysis. During this process a theory is build based on systematically gathered and analysed reports of the participants, without trying to test pre-existing theories. This allows the data to better resemble the reality of the participants and offer a better insight in and understanding of their perceptions. The analysis started with identifying recurring concepts using "open coding" after the first five interviews. In this analytic process the concepts are identified and their properties and dimensions are discovered in the interview data. Each of three analysts did this separately, after which the concepts were compared. Based on these results, questions were added to the topic list of the next fifteen interviews. The concepts found with open coding were then related to categories and subcategories and used to identify similarities and dissimilarities between the participant's stories. Then the interviews were analysed using "selective coding", focusing on the identified concepts and categories relevant for answering the main research questions on illness perception and treatment needs. The results formed a conceptual framework for formulating answers on the research questions. The team met on a regular basis to discuss both the cluster analysis and proposed thematic categories.

Results

Description of participants

Participants were between 25 and 35 years (μ=31 years) old, 60% were male (n=12). They had a GHB use history of two to ten years and had been admitted for GHB treatment with an average of four times (range 2-30). The treatment consisted of detoxification in a clinic followed by either inpatient or outpatient programs, based on cognitive behavioural therapy for GUD. All participants had also received prior treatment for other comorbid psychiatric disorders, mainly anxiety, (unipolar) mood and personality disorders. Out of twenty participants, eighteen reported to be abstinent for GHB at the time of the interview,

two participants were using GHB again. Their stories did not differ from the other 18 abstinent participants. Saturation started to occur after 12 interviews.

Development of GHB use disorder

Most participants reported regular substance use, mainly cannabis and stimulants such as amphetamine and ecstasy, before they first tried GHB. Substance use started between the age of twelve and twenty-five years old. Most participants were introduced to GHB through friends at parties and after parties. After using GHB they experienced that they were able to party longer and harder, that they felt more self-assured, had more intense sex and no hangover the next day. Using GHB was, at first, something one did occasionally in the weekend.

"I only used (GHB) in the weekend, but when I felt bad during the weekdays I sometimes took some GHB and I felt fine again. This use increased over time and GHB became part of my routine."

During this early phase GHB was often combined with amphetamines, as this allowed participants to party longer. When participants started using GHB during weekdays the frequency of use increased rapidly. Physical dependence commonly developed over a time period of at least two years, with some exceptions of weeks. The combination with amphetamines became less common when participants became dependent on GHB, instead benzodiazepines were more frequently used to cope with withdrawal.

Reasons to start using during weekdays were feeling hangover from parties in the weekend, skipping a night of sleep, and boredom. Initially, GHB use during weekdays resulted in better functioning at work or study because participants felt more confident, less stressed and experienced more pleasure in their daily activities. Participants who had depressed moods or were socially anxious felt that GHB made them feel and function better. This was confirmed by their social networks. Under the influence of GHB people were more active and satisfied with their lives. Participants reported only positive effects of GHB use during this period and experienced no down sides at all. They described it as "wonder drug", "solution for everything" and "perfect antidepressant". Under the influence of experienced positive effects, frequency of use increased. The occasional passing out due to overdosing was not perceived as problematic.

"GHB changed my personality, it's like liquid competences, it made me a 2.0 person instantly. You almost had to do nothing and you got so much in return for using GHB."

After using GHB daily for a while participants started to feel anxious and experienced tremors/trembling when they weren't using GHB. First, participants did not associate these complaints with GHB use and they solved these by taking more GHB. This process repeated itself to a point where withdrawal symptoms were so severe that participants started

becoming aware that they needed to take GHB in order to prevent withdrawal. At this point school, work and relationships started to suffer and it became harder to maintain functioning in everyday situations. When participants were no longer able to maintain their daily activities, the frequency of GHB use increased further. Participants now felt stressed, gloomy and bored each time the effects of GHB faded out. This led to the point where using GHB was just to prevent withdrawal. GHB was then used in a frequency between once every fifteen minutes to two hours, and participants were intoxicated 24 hours a day. Severe sleeping problems occurred, which were dealt with by using more GHB and overdosing to pass out in order to get some sleep. Participants additionally used benzodiazepines to sleep or prevent withdrawal. These GHB-induced comas would eventually happen on a daily basis.

"You need more and more GHB and it basically controls you day and night, because you need to have it. At one point you start using almost anything [e.g. benzodiazepines] in order to sleep for a few hours."

Perceptions of GHB

Participants generally reported a transition in their perceptions of GHB with increasing use. Initially, they had a rather positive attitude towards GHB. They mentioned that using GHB mainly had advantages for them and quitting GHB mainly disadvantages. Mainly when not using GHB, during periods of abstinence, and after detoxication, participants felt empty and lonely.

Participants compared GHB with alcohol, which they perceived much more harmful for them. They reasoned that after drinking alcohol they felt hungover, and after GHB they felt fine the next day. GHB use didn't cause any harm to them in the short term. According to the participants, their GUD didn't leave any damage, either physical or psychological. Passing out was mainly a problem for the bystanders and family members, not for participants themselves. When they woke up they felt fine. Participants described passing out as something positive, because they didn't feel anything when they passed out and they could sleep for a while. Even waking up in a hospital was something they got used to and was not considered a relevant issue.

"Oh yes, I passed out all the time and ended up in hospital. It was kind of normal for me. At afterparties it was very common that people passed out. We called it GHB sleep. I don't think it's bad, it's something you accept."

During the interview participants mentioned that finally their GHB use became problematic and they called themselves dependent. All of them mentioned that it took them multiple treatment admissions to reach this conclusion. Participants reported their main burden to be physical dependence. The schedule of taking GHB every two hours to prevent withdrawal was perceived as inconvenient. Participants dealt with withdrawal by taking

more GHB. Withdrawal symptoms started with heavy sweating, followed by shaking, palpitations, anxiety and visual hallucinations. When they became hardly able to keep up with withdrawal further on in their GHB dependence they wanted to stop being dependent on GHB. This was the moment to develop more negative perceptions about GHB and the main motivation for detoxification.

"Without GHB I felt like I was dying. My hart pounded so hard in my chest. Everything around me was frightening and intimidating, everything was too much to cope."

During withdrawal participants experienced high levels of anxiety, panic attacks and hallucinations. They referred to this as psychological dependence, meaning a combination of complaints such as anxiety, depressive moods and feeling suicidal. All these problems and negative feelings disappeared instantly when GHB was used again. Depressed mood and anxiety were the main reasons to start using GHB again. During the long period of GHB use a wide range of problems developed, such as loneliness, high debts, loss of work, and sometimes homelessness. Realising these problems when being sober increased stress and the need to use GHB again.

Participants reported severe sleeping problems after detoxification. They considered this one of their main problems and were aware that these were the result of their GHB use. During the night they woke up every few hours to take GHB in order to prevent withdrawal and induce sleep. After detoxification sleeping problems often continued for several months.

Treatment needs

Participants found it hard to pin point what they needed from treatment. Participants initially tried to quit GHB on their own at home, but few managed to significantly reduce their GHB intake. During home detoxification without medical support the development of delirium and psychotic symptoms was common. The reason why participants first tried to detoxify themselves, instead of seeking professional care, was that they didn't perceive themselves as "addicted", requiring professional treatment.

When participants were "admitted in crisis", after for example being found in a delirious state, they didn't remember the actual admission itself. As their mental state improved during detoxification, they realized that they were admitted and often left the clinic because of lack of motivation for treatment. After failed attempts to quit on their own, participants had themselves admitted in addiction care. Family, particularly parents, played an important role in seeking help. Especially during the first few treatment episodes, participants reported that they didn't want to let their family down and agreed to go through detoxification for the sake of their family. Prior to detoxification most participants had limited or no expectations about the treatment programs they would enrol after detoxification.

"I had myself admitted to comfort my mother. I thought I will fool the counsellors for a few weeks and then go back to GHB again."

The initial treatment goal of participants was detoxification, so they were no longer physically dependent on GHB. Abstinence was not their goal due to the perceived positive effects of GHB. The suggestion from therapists that it might be better not to use GHB overwhelmed them and caused fear and irritation. Participants wanted to use GHB without being physically dependent on it. Some said they just played being motivated for abstinence in order not to upset their family. After several relapses they started to realize that control over their GHB use was hard to maintain and motivation for abstinence started to emerge.

"Well, I feel split about quitting GHB. On the one hand I feel so in love with it, it solves all my problems! But on the other side I know that it won't bring me anything in the long run. However, I've never came across something that would make me say that I don't want to use GHB anymore. Even a friend who overdosed on GHB didn't make me want to quit fully."

Participants' treatment needs were mainly aimed towards their psychological and emotional problems. After detoxification they felt overwhelmed with psychological complaints. Learning how to deal with setbacks, stress, anxiety, depression and boredom without GHB were often mentioned as main treatment needs. Participants felt that the treatment after detoxification focused too much on GUD, while this was not perceived as their main problem after detoxication.

"As soon as you quit with GHB everything gets far worse. I never felt as bad as after detoxification. Stress and anxiety, it all comes back 10 times stronger as it has ever been. The only solution to this is the evil [GHB] itself, you want to start using again so everything goes away again. This makes it so hard to really make the choice to quit."

Participants mentioned that treatment should also focus on social problems. During treatment they end the contact with their "user-friends", however these were usually the only social contacts they had left besides family. Participants wanted help with making new, non GHB-using friends. Without GHB, meeting new people was difficult to them, because they felt insecure to act amongst people when abstinent. This made them socially anxious, which negatively influenced initiating social contacts in order to develop friendships. For some it was almost impossible not to continue meeting other dependent users, because family members or partners were GHB dependent as well. Some wanted to find a new place to live, in order to get away from their old lives and have a fresh start. Others became homeless and needed help in finding proper housing in order to benefit from treatment. Having high debts made this difficult. The latter was also mentioned as

something participants would like to have help with in order to get their lives back on track. Another problem that participants faced was how to fill the days with activities now that they were abstinent/sober, especially when school was dropped and/or jobs were lost when they were dependent on GHB. Therefore, they expressed the need for help in finding new employment or education. Without proper meaningful daytime activities boredom became a big problem, which tended to lead back to using GHB in order to fill their empty lives. Social problems caused a lot of stress in participants after detoxification. This combination of problems led to the loss of overview making it hard to adhere to, and profit from treatment.

Discussion

The goal of this study was to get a better understanding of the illness perceptions of people with GHB use disorder, and to identify their treatment needs. Participants in the current study mainly had positive associations with GHB, despite many negative consequences. Participants considered psychological and social problems (e.g. depression and anxiety) their main burden. GHB was mainly seen as a solution to these problems. Concerning treatment needs, participants stated that counsellors should focus on psychological problems instead of talking mainly about GUD and abstinence. Participants wanted to learn to deal with their emotions and anxieties and needed help in getting their lives back on track, by getting daytime activities, normal friends and housing.

Interpreting the data in the context of the SRM (H Leventhal et al., 1980; Howard Leventhal et al., 2016) of illness perceptions it becomes clear why many GHB dependent patients get stuck in a loop of relapses. While GHB use was seen as a health threat by clinicians, participants perceived GHB as a solution for other problems that they experienced as health threats. Thus, negative reinforcement was a main driver of continued use of GHB, as also seen in patients with other SUDs. (Kwako & Koob, 2017)

From the interview data, we identified three phases in the course of development, which showed similarities to described phases in other SUDs (Volkow, Koob, & McLellan, 2016). Based on the reports of the participants, the first phase can be characterized as positive reinforcement phase. During this phase participants experienced strong rewarding effects of GHB, bigger life satisfaction, no downsides and a gradual increase of GHB use. By combining GHB with stimulants, such as amphetamines, participants tried to extend their parties. Second is the dose escalation phase, in which GHB is used every day of the week and multiple times a day. While some of the first signs of GUD started to emerge, users didn't connect these to their GHB use. Taking more GHB instantly solved problems of withdrawal. They had to adapt their daily activities to their increased use, because it became harder to function without GHB. This developed into the third phase, which can be categorized as the negative reinforcement phase. GHB had to be used day

and night every few hours in order to supress withdrawal symptoms and negative affect. Participants often turned to combination use with benzodiazepines in reaction to withdrawal symptoms. The initial positive associations with GHB use remained present in this phase. Although users did become aware that something is wrong, consecutive GHB use made them forget this. This lead to a situation where they were either awake and intoxicated, or sleeping due to a GHB induced coma by intentional overdosing. During this phase GHB use was perceived as both the source and the solution to their problems. The described changes in affect and subsequent changes in behaviour could be caused by changes in the neurocircuitry, which are also described in the development of other substance use disorders (Koob, 2006; Koob & Simon, 2009; Koob & Volkow, 2016).

In our study participants showed a mainly positive view towards the use of GHB, "it made them a better person". One explanation for the positive view towards GHB was explained by the absence of negative feedback loops. The substance has strong rewarding effects and participants feel no negative effects such as a hangover after alcohol or stimulants use (Snead 3rd & Gibson, 2005). This and the almost instant intoxicating effects of the substance could explain why the participants remain to have positive associations with GHB. Another explanation is that some studies suggest that GHB has antidepressant properties (Bosch & Seifritz, 2016; Ha et al., 2009)

The realisation that GHB has downsides usually came during the negative reinforcement phase, when participants enrolled into treatment. After detoxification they realized that the years of active GUD led to limited education, unemployment, social isolation, and or loss of a sense of purpose. This and the remaining positive association towards GHB can lead to a vicious cycle when there is no reasonable alternative for the substance use (McKay, 2017). For GUD patients their experienced psychological problems (mainly anxiety and depression) increased after detoxification, this is then followed by renewed GHB use, relapse and another detoxification, at which point the burden of psychological problems increased again. This process is seen often in patients with SUD, for instance in alcohol (Schellekens, de Jong, Buitelaar, & Verkes, 2015). Patients with alcohol use disorder who suffered from co morbid anxiety disorders were more prone to show early relapse after detoxification.

The expressed treatment needs by participants were mainly aimed towards dealing with depression and anxiety, and not towards GHB or abstinence. Participants in the current study mentioned that their "real" problems started only after detoxification. According to the participants, treatment for GUD should focus on psychological problems, helping patients get proper housing, a supportive social network and meaningful daytime activities and/or work. Abstinence was initially not rewarding to the participants, but made them feel worse. This is not uncommon in substance dependent patients, as after long term substance use they sometimes have few positive reinforcements left in their life, outside the drug itself (McKay, 2017; McLellan, Lewis, O'Brien, & Kleber, 2000).

Besides psychological problems, treatment for GUD should, according to the participants, be focused on helping patients get proper housing, a supportive social

network and meaningful daytime activities and/or work. Previous studies also showed that a lack of these basic needs predicts relapse in both alcohol and drug dependent patients (McLellan et al., 2000). A review of treatment effects in patient with SUD and co morbid disorders showed that motivational interviewing is effective in establishing a therapeutic alliance, personal goals and subsequent treatment retention. Highly structured therapy programs with intensive outpatient treatments, case management and contingency management are most effective for complex groups of patients (Kelly, Daley, & Douaihy, 2012). Given the complexity which is seen often in patients with GUD a similar approach in treating both GUD and co-morbid problems could be considered. It is important that the treatment goals are personal and not necessarily directly aimed towards abstinence. Besides psychosocial treatment, pharmacotherapy might also support patients during the process of recovery. Recently studies (Harmen Beurmanjer, Kamal, de Jong, Dijkstra, & Schellekens, 2018; Kamal, Loonen, et al., 2015) prescribing baclofen to GHB dependent patients after detoxification showed promising results in lowering relapse and increasing treatment adherence.

The current qualitative study was the first in which illness perception in GHB dependent users was studied. All participants had prior treatment for GUD, and 90% was abstinent at the time of the interview. This suggests selection bias towards a sample of participants motivated for and able to reach abstinence. Participants had a GHB use history of two to ten years and had been admitted for GHB treatment with an average of four times. All participants had also received treatment for other disorders, mainly anxiety, (unipolar) mood and personality disorders This corresponds to GHB dependent patients in treatment, as relapse rates, treatment consumption and treatment re-enrolment are high. (Dijkstra et al., 2017; M. S. van Noorden et al., 2017) This makes the group likely a good representation of the treatment seeking patients with GUD. However the results cannot be extrapolated to the entire GUD population, as non-treatment seeking GUD users were not included in the study. A recall bias should also be taken into account as participants had to remember what they thought and felt during a period of almost permanent intoxication. In future studies a longitudinal approach, where participants are interviewed during use, treatment and after treatment could solve this issue.

Most participants used multiple substances, making it hard to classify certain effects as GHB specific. Differences were clarified as much as possible during the interview, in order to pinpoint which effects were GHB specific. Future studies should explore differences in illness perceptions and treatment needs between patients with different SUD's.

Conclusion

Participants in the current study had mainly positive views towards GHB, while at the same time being aware of their GUD. On the one hand they mainly perceive GHB as a solution to their psychosocial problems, rather than the cause. On the other hand they see themselves as dependent on GHB, with many negative consequences. The substance is considered strongly rewarding, without short-term downsides, possibly due to the absence of a negative feedback loop. Problems start mainly after detoxification, when they are confronted with anxiety and dysphoria. The positive associations with GHB use stay even during severe GUD. This is likely to contribute to the high relapse and drop-out rates observed in this population. Participants reported a need for personalized treatment goals, which were mainly aimed towards dealing with psychiatric symptoms and social reintegration. Treatment programs might initially explore patients' perceptions towards GHB and their treatment needs on psychosocial areas. Given the wide range and severity of problems that come with GUD, intensive treatment programs with attention for personal treatment goals could be considered. Future research should focus on studying the effectiveness of this approach.

4

Cognitive impairments in patients with GHB use disorder predict relapse in GHB use

Submitted as

Beurmanjer H. Bruijnen C.J.W.H., Greeven P.G.J., De Jong C.A.J., Schellekens A.F.A, Dijkstra B.A.G. Cognitive impairments in patients with GHB use disorder predict relapse in GHB use. (submitted)

Abstract

Background: The recreational use of Gamma-hydroxybutyrate(GHB) is associated with frequent overdoses, coma and the risk of developing GHB use disorder(GUD). Several studies suggest negative effects of GHB use or related comas on cognition. Since relapse rates are high in GUD, and cognitive impairment has been associated with relapse in other substance use disorders, we aim to investigate the 1) prevalence of cognitive impairment before and after detoxification, 2) relationship between GHB use, comas and cognitive impairment, and 3) association between cognitive impairment and relapse after detoxification in GUD patients.

Methods: In this prospective cohort study a consecutive series of patients with GUD (n=137) admitted for detoxification were recruited at six addiction care facilities in the Netherlands. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairments before and after detoxification. Follow-up duration for the assessment of relapse in GHB use was three months.

Results: A substantial number of patients with GUD screened positive for cognitive impairment before (56.3%) and after (30.6%) detoxification. Most patients showed impairment on the memory domain (58.8%). Cognitive impairment was not related to the severity of GUD or number of GHB-induced comas. Regression analysis showed that only the memory score predicted relapse.

Discussion: Cognitive impairment seems highly prevalent among patients with GUD, possibly related to the risk of relapse. The absence of a relationship between the severity of GUD, level of GHB use, the number of GHB-induced comas and cognitive impairment suggest that other factors may also contribute to the observed cognitive impairment.

Background

Gamma-hydroxybutyrate (GHB) is a GHB and GABA-B receptor agonist and an increasingly popular party drug, mainly due to its euphoric, sociability and sexually stimulating effects (Addiction, 2019; Bosch et al., 2015, 2017; Sumnall et al., 2008). However, GHB use is also associated with frequent overdoses, comas (Beurmanjer et al., 2019), hospital admissions (Dijkstra et al., 2017), and a risk of physical dependence (Kamal et al., 2017). In line with DSM-5 criteria for substance use disorder (SUD) (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force, 2013), physical GHB dependence is commonly part of GHB use disorder (GUD), with a pattern of continued use despite negative consequences, craving for GHB and loss of control over GHB intake (Beurmanjer et al., 2019).

Patients with GUD generally show high drop-out and relapse rates, up to 50-60% within three months after detoxification (Beurmanjer, Kamal, de Jong, Dijkstra, & Schellekens, 2018; M. S. van Noorden et al., 2017). The reenrolment rate of patients with GUD is twice as high as seen in patients with alcohol or cannabis use disorder(M. S. van Noorden et al., 2017). It is unknown why relapse rates are higher among patients with GUD compared to other SUD. It has been suggested that the prosocial effects of GHB with few noticeable downsides could play a part in the high relapse rates (Beurmanjer et al., 2019; Bosch et al., 2015). Other suggested explanations are the high levels of anxiety in patients with GUD (Beurmanjer et al., 2019), similar to for example patients with alcohol use disorder (Schellekens et al., 2015).

Another aspect that might be particularly relevant in the context of relapse in patients with GUD is cognitive impairment. In general, cognitive impairment has been associated with relapse in several SUDs, e.g. alcohol (Czapla et al., 2016), cocaine (Turner, LaRowe, Horner, Herron, & Malcolm, 2009) and opioids (Ma, Mei, Wang, Liu, & Zhou, 2019). While research on cognitive impairment in GUD is limited, several studies suggest negative effects of GHB on cognition. For instance, a double blind, placebo controlled study with healthy volunteers showed that GHB intoxication temporarily impaired working- and episodic memory, in a dose dependent manner (Carter, Griffiths, & Mintzer, 2009). Recent studies also suggest that GHB-induced comas are associated with (verbal) memory impairments in patients with GUD (F., 2017; Raposo Pereira, McMaster, Polderman, de Vries, et al.; Raposo Pereira, McMaster, Polderman, DAT de Vries, et al., 2018). Moreover, in this cross-sectional study GHB-induced comas were also associated with alterations in long-term memory networks and lower hippocampus/lingual gyrus activity while performing memory tasks (Raposo Pereira, McMaster, Polderman, de Vries, et al., 2018).

GHB-induced comas are common in patients with GUD, with 84% having experienced GHB-induced comas at least once, and often even on a daily basis (Beurmanjer et al., 2019; Dijkstra et al., 2017). Therefore, cognitive impairment might result from repeated comas due to excessive GHB use, and can potentially be an important factor in the high relapse

rates observed in patients with GUD. To our knowledge no studies on the relationship between cognitive impairment and relapse in patients with GUD have been published to date. This prospective cohort study aimed to investigate in patients with GUD 1) the association between cognitive impairment, the number of GHB-induced comas and severity of GHB use; and 2) the association between cognitive impairment and relapse in GHB use after detoxification.

Methods

Design

This study is a prospective, observational, multicentre cohort study, of patients with GUD. Due to the observational design, the study was exempted from medical ethical review by the Medical Ethical Committee of the Medical Spectrum Twente. Part of the data of the monitor has already been published as an open label trial with baclofen(9).

Participants

A consecutive series of patients with GUD (according to DSM-IV criteria of substance dependence) who were admitted for detoxification at one of six participating addiction care facilities in the Netherlands (IrisZorg, Mondriaan, Novadic-Kentron, Tactus Verslavingszorg, Victas and Verslavingzorg Noord-Nederland) were recruited (n=137). Inclusion criteria were 18-65 years old, a need for inpatient GHB detoxification, and comprehension of the Dutch language. Exclusion criteria were the presence of acute psychiatric problems interfering with study participation, such as mania or acute psychosis. A physician screened patients on these criteria before detoxification. All patients signed informed consent, before they were included in the study.

Measurements

Demographic data

Demographic data (sex, date of birth, ethnicity, housing situation, source of income and level of education) were collected through self-report.

Measurements of Addictions for Triage and Evaluation (MATE)

The MATE is a structured clinical interview that measures the history, frequency and consequences of drug use, including medical, social and psychological problems(Schippers, Broekman, Buchholz, Koeter, & Van Den Brink, 2010), based on the Composite International Diagnostic Interview (CIDI) (Andrews & Peters, 1998). For this study 'Module 1: Drug Use' was used to assess GHB and other substance use patterns. During this structured interview patients were asked about their drug use over the past 30 days (number of days and amount used) and lifetime (total years of use of at least 3 days per

week). The MATE has a good inter-rater reliability, ranging between 0.75 and .92 and is part of standard clinical assessment in Dutch addiction care (Schippers et al., 2010).

GHB questionnaire

In addition to the questions on GHB use in the MATE, the GHB questionnaire was included to obtain more detailed information on GHB use patterns(Dijkstra et al., 2017). The original questionnaire has 28 questions regarding motivation for GHB use, first introduction to GHB, location of use, frequency of use, dose, duration of use, comas, hospital admissions and experienced withdrawal symptoms. For this study we included only the five questions on the frequency of GHB use, the dose of GHB used (in millilitres), the duration of GHB use (in months), the duration of daily GHB use (in months) and how often participants experienced a coma due to GHB use in their lifetime.

The Montreal Cognitive assessment (MoCA)

The MoCA (Bruijnen, Jansen, et al., 2019; Nasreddine Z, 2005) was used to screen for cognitive impairment. It consists of 12 items measuring: executive functioning; visuospatial abilities; attention, concentration and working memory (referred to as 'attention' from now on); language; abstract reasoning; memory; and orientation. For this study the Dutch MoCA versions 7.1 and 7.2 were used to minimize learning effects, with version 7.1 administered at T1 and 7.2 at T2. The administration of the MoCA takes approximately 15 minutes. A higher score represents better cognitive performance. An adjustment for level of education is applied. Participants with a low level of education receive two extra points, and participants with an average level of education receive one extra point to their total score, while maintaining a maximum score of 30 points(Bruijnen, Jansen, et al., 2019). In line with previous studies, a cut-off score of 25 or lower was used as an indicator of cognitive impairment (Nasreddine Z, 2005). The MoCA is widely used in clinical practice for the screening on cognitive impairment in various populations and has a moderate to excellent inter-rater reliability (k=0.46 – k=0.94) (Cumming, Lowe, Linden, & Bernhardt, 2018).

Treatment outcome

Three months after detoxification all patients were contacted either in person (when the patient was still in treatment) or by phone when patients where no longer in treatment. During this interview patients were asked about their GHB use in the past three months and whether they had relapsed in GHB use. Patients were considered non-relapse if they had used GHB less than 5 times in the past three months. Abstinence was not confirmed using systematic urine or blood tests, due to the narrow timeframe in which GHB can be detected as a result of its short half-life (Abanades et al., 2007).

When patients could not be reached, a predetermined close contact of the patient was approached about treatment outcome. In cases where nobody was available, patient

records were examined for treatment outcome. The last clinical observation was carried forward in this case.

Procedure

Patients were informed about the study before admission to the clinic (before detoxification). After informed consent forms were signed, the demographic data, the MATE and the MoCA 7.1 were collected by a trained nurse or psychologist prior to detoxification (T1). After detoxification, on average 20.1 days later, the MoCA 7.2 was administered (T2). Three months after detoxification patients were contacted to assess relapse into GHB use (T3). Data collection occurred between January 2014 and May 2015.

Analysis

The patient characteristics for age, sex, substance use, MoCA scores (domain, total and cut-off) were summarized using descriptive statistics for both T1 and T2. Differences between the MoCA scores T1 and T2 were analysed using repeated measures ANOVAs for all domain scores and the total score, and Chi^2 test for categorical variables. Only patients with data available for both time-points were included in these analyses.

For each patient a total GHB exposure score was calculated by taking 'the average daily dose of GHB' times 'the number of days GHB was used in the past thirty days' times 'the months of daily GHB use'. To study the relationship between MoCA scores (total scores), the number of comas and GHB use (dose per day, months of use, months of daily use, and GHB exposure score) Pearson and Spearman correlations were used where appropriate.

The difference on MoCA scores (total score and domain scores) between relapsed and abstinent patients at the three-month follow-up was analysed using MANOVA. In order to assess the predictive value of the MoCA, a backward logistic regression was performed with relapse as the dependent variable and MoCA scores as the independent variables. P-values <0.05 (two-sided) were considered statistically significant. Data were analysed with SPSS Statistics 26.

Results

Patient characteristics

Data of 103 patients were analysed in this study, including 80 MoCA measurements at T1 and 62 at T2. In total 39 patients had completed MoCA measurements at both T1 and T2. These 39 patients did not differ from patients with a MoCA on either T1 or T2 for sex, age, GHB dose, length of daily GHB use, number of comas and MoCA scores. Their mean age was 28.5 years (SD: 6.47) and 68% were men. The mean duration of daily GHB use was 3 1.3 months (SD: 32.61), with a mean of 89.9 ml GHB per day (SD: 52.60). GHB-induced comas

were common, with 41.4% reporting five or less GHB comas, 18.4% between six and nineteen times, 19.5% between twenty and fifty times, and 20.7% reported to have experienced more than fifty comas in their lifetime. Co-morbid substance use in the past 30 days was the highest for nicotine (83,7%), followed by stimulants (50%), alcohol (43,5%), cannabis (33,7%) and cocaine (33,7%).

Scores on MoCA

Patients scored on average 24.2 points on the MoCA (SD: 3.01) at T1 and 25.8 points (SD: 2.78) at T2, with a trend towards significance (Wilks' Lambda=.903, F(1,38)=4.076, p=.051) for patients with both a MoCA on T1 and T2, see Table 1 . Fewer patients scored below the cut-off score on T2 than on T1 (χ^2 (1) = 5.214 p= .022). In total 27 patients improved their scores between T1 and T2, five had the same score and seven had a lower score. On domain level, patients performed lowest on Memory and highest on Orientation on both T1 and T2. No significant differences were observed on domain level between T1 and T2.

Table 1 MoCA-scores on T1 and T2

	T1 (n=39)		T2 (n=39)	
	Mean (sd)	**%**	**Mean (sd)**	**%**
Executive Functioning & Visuospatial Abilities (0-6)	4.36 (1.20)	72.7%	4.74 (1.17)	79.0%
Attention (0-6)	5.00 (1.07)	83.3%	5.13 (1.08)	85.5%
Language (0-5)	4.40 (1.05)	88.0%	4.66 (0.63)	92.2%
Abstract Reasoning (0-2)	1.63 (0.62)	81.5%	1.81 (0.44)	90.5%
Memory (0-5)	2.94 (1.58)	58.8%	3.52 (1.54)	70.4%
Orientation (0-6)	5.84 (0.48)	97.3%	5.79 (0.48)	96.5%
Total (0-30)	24.16 (3.01)	80.1%	25.65 (2.78)	85.5%
Below cut-off*	56.3%		30.6%	

*p<.005

% comprises the mean percentage of points obtained on the Montreal Cognitive Assessment.

Relationship between GHB coma, GHB use, and cognitive impairment

MoCA total scores did not correlate with number of comas, GHB dose, total length of GHB use, length of daily GHB use and GHB exposure score on both T1 and T2, see supplement II.

Relationship between relapse and cognitive impairment

Patients who remained abstinent at follow-up scored higher on Attention, Memory and Total score at T1 in comparison with patients who relapsed in GHB use between detoxification and follow up. More patients who remained abstinent scored above the cut

off-score of 25 on the MoCA at T1, compared to patients who relapsed. No relationship was found between treatment outcome and MoCA scores on T2. The results are shown in Table 2.

Table 2 Treatment outcome and MoCA scores

	T1			T2		
	Abstinent (n=28) Mean score (sd)	**Relapse (n=52) Mean score (sd)**	**p-value**	**Abstinent (n=29) Mean score (sd)**	**Relapse (n=33) Mean score (sd)**	**p-value**
Executive Function & Visuospatial Abilities	4.42(1.14)	4.33(1.24)	0.721	4.80(1.08)	4.69(1.26)	0.750
Attention	5.32(0.86)	4.83(1.13)	0.047*	5.27(1.07)	5.00(1.09)	0.319
Language	4.46(1.04)	4.37(1.07)	0.691	4.72(0.59)	4.61(0.66)	0.463
Abstract Reasoning	1.57(0.69)	1.65(0.59)	0.576	1.72(0.53)	1.89(0.33)	0.167
Memory	3.61(1.42)	2.58(1.55)	0.005*	3.83(1.47)	3.24(1.58)	0.138
Orientation	5.82(0.39)	5.85(0.45)	0.810	5.83 (0.47)	5.76(0.50)	0.574
Total*	25.21(2.91)	23.60(2.94)	0.021*	26.17 (2.24)	25.21(2.91)	0.163
Below cut-off	56.6%	76.9%	0.030*	27.6%	42.4%	0.171

*P<.05

Given that only the MoCA scores on T1 were related to treatment outcome, only these scores were used in the backward logistic regression analyses to explore the predictive value of the MoCA for relapse. The logistic regression model was statistically significant, $\chi^2(1) = 8.617$, $p < .003$, with only memory as a significant predictor in the final model. The model explained between 10.2% and 14.1% (Nagelkerke R^2) of the variance in relapse and correctly classified 68.8% of the cases. Each point scored on the subscale T1 Memory increases the odds of abstinence with 1.64.

Discussion

This study investigated cognitive impairment in patients with GUD, and its relationship with 1) GHB use patterns and 2) relapse in GHB use after detoxification. Using the MoCA, a substantial number of patients with GUD screened positive for cognitive impairment before detoxification (56.3%). Cognitive functioning improved after detoxification with still about one third screening positive for impairment (30.6%). The cognitive domain showing the strongest impairment was memory. No correlation was found between

cognitive impairment and the number of comas, GHB use patterns, or severity of GUD. Cognitive impairment before detoxification, particularly on the subscale memory, was associated with relapse.

In the current sample, more than half of the patients had an indication for cognitive impairment during admittance, with a total average score on the MoCA of about 24. A recent study observed similar to slightly better MoCA scores in patients admitted with alcohol, cannabis, stimulant and opioids use disorders (scores: 25, 26, 26, and 25 respectively) (Bruijnen, Dijkstra, et al., 2019). Though no direct comparison between these samples can be made, this does raise the question whether the observed cognitive impairments in patients with GUD are specific for excessive GHB use or related to (indirect) negative effects of substances of abuse on cognitive performance in general. Furthermore, it is important to note that most patients with primary GUD have poly substance use problems, often stimulants (Beurmanjer et al., 2019; Dijkstra et al., 2017), making it difficult to differentiate between effects of GHB and other substances.

Patients showed a trend towards improvement in total scores and a significant decrease in scoring below cut-off score between T1 and T2, indicating that cognitive functioning partially recovered during detoxification. This is in line with studies in SUD patients using other sedatives, including alcohol (Wobrock et al., 2009) and benzodiazepines (Ros-Cucurull et al., 2018), who also show improvement of cognitive functioning during abstinence. It is important to note that patients in the current study were only abstinent of GHB for several days when T2 was administered. Therefore, further improvement with prolonged abstinence cannot be ruled out and is to be expected. Literature on alcohol has for instance shown that cognitive function can improve up to after six weeks to over a year of abstinence (Walvoort, Wester, Doorakkers, Kessels, & Egger, 2016). Future studies should further investigate recovery of cognitive impairment in patients with GUD with long-term abstinence.

Patients with GUD scored particularly low on the subdomain Memory, also when compared to studies in patients with other SUDs (Bruijnen, Dijkstra, et al., 2019). Since GHB receptors are predominantly expressed in the hippocampus, this observation might reflect the direct effects of GHB in the brain (Carter, Griffiths, et al., 2009; Castelli et al., 2000; Xie & Smart, 1992). GHB-induced comas have also been suggested to affect hippocampal activity, both in humans (Raposo Pereira, McMaster, Polderman, de Vries, et al., 2018) and animals (Johansson, Grönbladh, & Hallberg, 2014), which could also contribute to the observed memory problems. Since memory is a broad concept (Chaudhuri & Fiete, 2016), with various sub domains (e.g. working memory, long-term memory, declarative memory, etc), future studies should explore which specific memory domains are most affected in patients with GUD.

Despite several studies suggest that cognitive impairment in patients with GUD might be caused by GHB-induced comas (Raposo Pereira, McMaster, Polderman, de Vries, et al., 2018; Raposo Pereira, McMaster, Polderman, DAT de Vries, et al., 2018) the current

study did not observe a relationship between the number of self-reported GHB-induced comas and cognitive impairment. Several methodological limitations hamper strong conclusions concerning the (causal) relationship between GHB-induced coma and cognitive impairment. First, studies, including ours, commonly rely on self-reported comas. A detailed and reliable account of the total number of GHB-induced comas is hard to obtain due to its frequency (usually on a daily basis (Beurmanjer et al., 2019), amnesia (as this might be an aspect of GHB-induced coma itself) (Sumnall et al., 2008), and the observed memory impairment in patients with GUD. Second, as seen in other samples, patients with GUD often also use other substances. These might also contribute to cognitive impairment in these patients. Finally, it may also be that it is not the number of GHB-induced comas or substance use levels that contribute to cognitive impairment. Similar to patients with other SUDs our data did not find a relationship between MoCA scores and years of regular use, (GHB) dose, severity of dependence and coma's (Bruijnen, Dijkstra, et al., 2019). This suggests that other factors might be involved, for instance lack of sleep, malnutrition or other psychiatric or somatic comorbidities. Future studies should explore mechanisms contributing to cognitive impairment in patients with GUD and other SUDs.

The current study shows that MoCA scores, in particular performance on the memory domain, were associated with the risk of relapse. This is in line with studies in other SUD, such as alcohol (Czapla et al., 2016), cocaine (Turner et al., 2009) and opioids (Ma et al., 2019), where cognitive impairment is associated with the risk of relapse and poor treatment retention. Cognitive functions are crucial to direct behaviour and obtain control over impulses and emotions (Loughead et al., 2015), including substance use. Cognitive impairment in patients with SUD (including GUD) might thus interfere with taking control of substance use, to change behaviour, and reach treatment goals (Loughead et al., 2015; Volkow & Morales, 2015). SUD patients with cognitive impairment might require treatment adaptations focussing on cognitive enhancement (Rensen, Egger, Westhoff, Walvoort, & Kessels, 2019; Verdejo-Garcia, 2016). Indeed, several studies have shown that such personalized treatments approaches can be efficacious in patients with SUD and cognitive impairment(34). To what extent this might also benefit patients with GUD remains to be studied.

The results of this study should be viewed in the light of several limitations. First, the MoCA is not a diagnostic tool for cognitive impairment. While the MoCA has been shown to be a valid screening instrument in patients with SUD (Bruijnen, Dijkstra, et al., 2019; Bruijnen, Jansen, et al., 2019), no extensive neuropsychological assessments were used in the current study. Therefore, future studies should confirm the current findings, using more detailed neuropsychological assessments across different cognitive domains. Another limitation is that most patients with primary GUD have poly substance use, often stimulants (Beurmanjer et al., 2019; Dijkstra et al., 2017; Kamal et al., 2016). It is therefore impossible to disentangle GHB effects on cognitive impairment from the effects of other

substances. In addition, the observed persistent cognitive impairments could have been present before the use of GHB (or other substances) started.

In conclusion, in the current study about half of patients with GUD had an indication for cognitive impairment before detoxification, decreasing to about one third after detoxification. Cognitive impairment before detoxification, particularly memory problems, were associated with a higher relapse risk after detoxification. Current findings warrant clinical attention for cognitive impairment in patients with GUD, for instance by screening for cognitive impairment using the MoCA, and full neuropsychological assessment during a sufficient period of abstinence after detoxification when appropriate. Future studies should confirm these findings and explore whether GUD patients with cognitive impairment require specific treatment adaptations.

PART 2

Pharmacological treatment interventions for patients with GHB use disorder

5

Tapering with pharmaceutical GHB or benzodiazepines for detoxification in GHB-dependent patients: a matched-subjects observational study of treatment-as-usual in Belgium and the Netherlands

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Abstract

Background: The Gamma-HydroxyButyric (GHB) acid withdrawal syndrome often has a fulminant course, with a rapid onset and swift progression of severe complications. In clinical practice two pharmacological regimens are commonly used to counteract withdrawal symptoms during GHB detoxification: tapering with benzodiazepines (BZD) or tapering with pharmaceutical GHB. In Belgium standard treatment is tapering with BZD, while in the Netherlands pharmaceutical GHB is the preferred treatment method. Though BZD are cheaper and readily available, case studies suggest GHB tapering results in less severe withdrawal and less complications.

Aims: This study aimed to compare two treatments-as-usual in tapering methods on withdrawal, craving and adverse events during detoxification in GHB-dependent patients.

Method: In this multicentre non-randomized indirect comparison of two treatments as usual, patients with GHB dependence received BZD tapering (Belgian sample: n=42) or GHB tapering (Dutch sample: n=42, matched historical sample). Withdrawal was assessed using the Subjective and Objective Withdrawal Scales, craving was assessed with a Visual Analogue Scale, adverse events were systematically recorded. Differences in withdrawal and craving were analysed using linear mixed model analysis, with ''days in admission'' and ''detoxification method'' as fixed factors. Differences in adverse events were analysed using Chi-square analysis.

Results: Withdrawal decreased over time in both groups. Withdrawal severity was higher in patients receiving BZD tapering (subjective mean=36.50, SD=21.08; objective mean= 8.05, SD=4.68) than in patients receiving pharmaceutical GHB tapering (subjective mean=15.90; SD=13.83; objective mean=3.72; SD=2.56). No differences in craving were found. Adverse events were more common in the BZD than GHB group, especially delirium (20 vs 2.5%, respectively).

Conclusions: These results support earlier work that BZD tapering might not always sufficiently dampen withdrawal in GHB-dependent patients. However, it needs to be taken into account that both treatments were assessed in separate countries. Based on the current findings tapering with pharmaceutical GHB could be considered for patients with GHB dependence during detoxification, as it has potentially less severe withdrawal and less complications than benzodiazepine tapering.

Introduction

Gamma-HydroxyButyric (GHB) acid is a short-chain fatty acid, biosynthetically derived from the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Wong, Chan, Gibson, & Snead, 2004), it binds to GHB and GABA-B receptors (Laborit, 1964). GHB is mainly used in Australia, the US and Europe (Louisa Degenhardt et al., 2003; Dines et al., 2015; Nicholson & Balster, 2001), for its euphoric and sedating effects (Beurmanjer et al., 2019; Busardo & Jones, 2015; Kamal et al., 2017). GHB has a very narrow bandwidth between the plasma level for desired clinical effects and overdose, often resulting in temporary coma (Brenneisen et al., 2004; Corkery et al., 2015). GHB overdose can however be fatal, especially when combined with other substances (Corkery et al., 2015). Regular GHB use can lead to GHB use disorder (GUD) (M. Van Noorden et al., 2016). While prevalence of GHB use is still limited in Europe, between 0.1%-1.5% of the adult population, it has been rising in the past decade(Kamal et al., 2017). Little is known about the number of people with GUD, but it is estimated that up to 21% of GHB users develops GUD(K. Miotto et al., 2001). GUD is characterized by frequent GHB administration (every 1-3 hours) to prevent withdrawal (Beurmanjer et al., 2019; Kamal et al., 2017). The GHB withdrawal syndrome often has a fulminant course, with a rapid onset and swift progression of severe withdrawal symptoms (Dijkstra et al., 2017; Kamal et al., 2017). Withdrawal symptoms include: tremor, nausea, vomiting, tachycardia, insomnia, diaphoresis, anxiety and nystagmus. Adverse events during withdrawal include hypertensive crisis, severe agitation, delirium, and epileptic seizures (Kamal et al., 2017).

The severity and complexity of GHB withdrawal poses a clinical challenge during detoxification. In clinical practice two pharmacological treatment regimens are commonly used to counteract withdrawal symptoms during GHB detoxification: tapering with benzodiazepines (BZD) and tapering with pharmaceutical GHB. BZD have an allosteric effect on GABA-A-receptors, resulting in increased sensitivity for GABA (Lorenz-Guertin et al., 2019). Benefits of BZD compared to pharmaceutical GHB are the wide availability in medical settings, low costs and that tapering with BZD allows patients to directly quit using GHB. However, several case studies describe BZD resistance (M. S. van Noorden et al., 2015), where despite extremely high doses of BZD, in one case up to 700mg of diazepam per day, delirium still develops (Craig et al., 2000; Neu, 2018). Others describe the necessity of additional sedating medication, such as phenobarbital (Sivilotti et al., 2001) and propofol (Dyer et al., 2001), in order to treat delirium. Pharmaceutical GHB has the same pharmacological properties as "street-GHB". GHB-assisted tapering requires up to 12 doses (every 2 hours) a day (Dijkstra et al., 2017). GHB tapering has been shown to be associated with a high success rate of 85% and limited adverse events in several large non-randomized trials (n=450). Reported adverse events during detoxification were mainly hypertension (7%) and delirium (2%) (Beurmanjer H, Verbrugge CAG, Schrijen S & DeJong CAJ, 2016; Dijkstra et al., 2017). It is suggested that tapering with pharmaceutical GHB might be preferable

over BZD treatment, due to its pharmacological similarity with street GHB. BZD mainly act at GABA-A receptors, whereas GHB mainly acts at GHB and GABA-B receptors. BZDs might therefore be less effective in supressing GHB withdrawal because they target different receptors to GHB. A disadvantage of GHB tapering is its shorter half-life, requiring GHB administration throughout the night which interferes with sleep. Continued GHB use could also be seen as reinforcing compulsive substance use, potentially maintaining symptoms, such as craving (Kwako & Koob, 2017).

While both methods are currently in use, studies comparing both methods are not available. This study aimed to indirectly compare these two tapering methods for the detoxification of GHB in patients with GUD. In Belgium physicians are not allowed to prescribed pharmaceutical GHB for GHB withdrawal and BZD tapering is the standard of care. In the Netherlands, tapering with pharmaceutical GHB detoxification is the preferred option, based on the existing literature and national guidelines. Therefore, the current study made a matched comparison between the two treatments-as-usual in each country. Based on current literature and the pharmacological profile of GHB, it is expected that the pharmaceutical GHB tapering has 1) a less severe withdrawal syndrome, 2) fewer adverse events, and 3) higher craving levels during the detoxification process in patients with GUD, compared to the tapering with BZD.

Methods

Study Design

The study was a multicentre non-randomized indirect comparison of two treatments of usual, comparing the effectiveness between BZD tapering in Belgium and GHB tapering in the Netherlands in patients with GUD. Ethical approval for the Belgian part was obtained from the Institutional Review Board ZNA/OCMW Antwerpen (E.C. Approval N° 4664). For the Dutch part, the Medical Ethical Research Committee Twente and Central Committee on Research Involving Human Subjects (CCMO) approved the pharmaceutical GHB protocol and considered that the study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). The data from this study was published in 2017 (Dijkstra et al., 2017) and a sample from this dataset is used in the current study. Off-label use of pharmaceutical GHB for GHB detoxification was approved by the Dutch Health care Inspection and is now considered the standard detoxification treatment for patients with GUD in the Netherlands. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the above mentioned boards and committees.

Participants

Participants were patients with GUD who received an indication for inpatient detoxification. Patients were Included if they had 1) a diagnosis of GHB dependence according to the DSM-IV-TR, and 2) where aged >18 at time of admission to the hospital. Patients were excluded if they were not able to complete the study questionnaires, e.g. due to insufficient knowledge of the Dutch language or in the case of severe, acute psychiatric co morbidity that required immediate medical attention, interfering with study participation (e.g. Delirium, mania, psychosis or suicidal tendencies). Participants for BZD treatment were those admitted at the psychiatric ward of the Sint-Erasmus Hospital (part of Ziekenhuis Netwerk Antwerpen (ZNA) in Belgium (n=42) between October 2015 and May 2018, where BZD tapering is treatment-as-usual. Participants for pharmaceutical GHB tapering were selected from a historical sample (n=229) previously recruited, between March 2011 and December 2012, from six addiction treatment centres in The Netherlands (IrisZorg, Novadic-Kentron, Tactus, Victas, Mondriaan GGZ and Verslavingszorg Noord Nederland) (Dijkstra et al., 2017). Based on this sample a matched group (n=42) was selected. For matching a 3-step approach was used. First, based on the Belgium sample the range for age, months of daily GHB use and the daily dose of GHB before admission was determined. Second, all patients within the historical comparison group of pharmaceutical GHB tapering who scored outside these ranges on one or more variables were excluded. Next, we drew a random sample of 42 patients from this comparison sample. Written informed consent was obtained from all patients prior to data collection in both samples

Measurements

Socio demographics and substance use

Demographics and other clinical data were obtained from chart reviews (admission data, discharge data and the discharge summary). Substance use and classification of substance dependence was assessed using the Measurement of Addicts for Triage and Evaluation (MATE) section one (Schippers et al., 2010). The MATE section one defines participants' current substance use (last thirty days) and lifetime substance use. For GHB use, the GHB questionnaire was used (Dijkstra et al., 2017). This GHB questionnaire assesses the pattern of GHB use, including the total years of use, daily dose in ml, ml per dose and time interval between doses.

Withdrawal symptoms

Withdrawal severity was assessed using the Subjective and Objective Withdrawal Scale (SWS/OWS) (Handelsman et al., 1987). The SWS, a 5-point Likert scale (0-4) with a maximum score of 132, is filled out by patients and consists of 33 items related to withdrawal. It includes both mental and physical withdrawal items like "I feel anxious," "I see things that aren't there," "I'm trembling" and "I'm tired". The OWS is filled out by the nursing staff and is based on clinical observations. The scale consists of 33 items scored dichotomously (Yes or No).

Craving

The Visual Analogue Scale (VAS) was used to asses craving on 0-10 scale. Patients ticked the number that applied to their current experienced level of craving. The VAS is widely used in health research, and is commonly used in studies to assess severity of craving in patients with substance use disorders(Dijkstra et al., 2017; Schmitz et al., 2017).

Adverse events

After detoxification, patients and staff were asked to fill out a discharge questionnaire (Dijkstra et al., 2017) to identify adverse events. In addition, discharge summaries were reviewed for any adverse events or other issues that emerged during detoxification. Adverse events were interpreted as untoward medical occurrences in a participant, such as delirium, other events resulting in severe discomfort for the patients, life-threatening situations, or admittance to intensive care unit.

Detoxification treatment

Detoxification with BZD

Diazepam (or lorazepam when serious liver disease was present) was titrated based on vital parameters. Vitals were measured once per 30 minutes. When blood pressure rose above 140/90 mmHg and/or heart rate rose above 100 beats per minute (bpm) diazepam 10mg (or lorazepam 2.5mg) was administered. In the event of a more than 20 mmHg rise in pressure (systolic or diastolic blood), and/or 20 bpm increase in heart rate the diazepam dose was increased with 20mg (or lorazepam 5mg). The dose of diazepam (or lorazepam) was adjusted every thirty minutes, if needed, until blood pressure and heart rate dropped below 140/90 mmHg and 100 bpm, respectively. The total detoxification and tapering schedule took on average seven days.

Detoxification with pharmaceutical GHB

Detoxification started with a titration phase, where patients were treated with pharmaceutical GHB on 70% of their street GHB dose. Next, the GHB dose was titrated up in case of withdrawal and titrated down in case of sedation, until the right pharmaceutical GHB dose was found on which patients were stable and experienced neither withdrawal, nor sedation. This usually took between one and two days, after which the tapering phase started. During the tapering phase the GHB dose was lowered by 300mg GHB per given dose per day. The interval between doses was usually two hours, or up to three hours depending on withdrawal severity. For a more detailed description of the protocol see(Dijkstra et al., 2017). The total detoxification and tapering schedule took on average 11 days.

Treating delirium

In the case of delirium an atypical antipsychotic (quetiapine, olanzapine) or haloperidol was prescribed in the Netherlands (Dijkstra et al., 2017). In Belgium, also clotiapine was prescribed in addition to the aforementioned medications.

Procedure

After signing the informed consent, the MATE and GHB questionnaires were filled out. During detoxification withdrawal symptoms and craving were monitored three times a day. After the detoxification process, and before discharge of the hospital the discharge questionnaire was filled out.

Analysis

Group differences in baseline characteristics were compared using one-way-ANOVA's for continuous variables and Chi-square for non-continuous variables. A linear mixed model (LMM) analysis was used with withdrawal (SWS, OWS) and craving (VAS craving)-scores as dependent variables and "days in admission" (within-subjects variable) and "detoxification method of use" (between-subjects variable) as fixed factors. For all three questionnaires average scores per patient per day were calculated, in order to avoid daytime variation. Since BZD tapering lasted seven days on average we only analysed differences in withdrawal severity and craving between the two conditions over the first seven days of detoxification. Adverse events and dropout rates were compared between groups by a chi-square tests. P-values <0.05 (two-sided) were considered statistically significant. Data were analysed with SPSS Statistics 24.

Results

Patient characteristics

A total of 84 patients (≈70% males) were analysed in this study: 42 received BZD and 42 received pharmaceutical GHB during their detoxification. The groups did not differ on demographic and GHB use characteristics. While all patients used multiple substances in the thirty days before admission, no differences between the groups were found (see Table 1). Nicotine, stimulants and alcohol were most commonly used besides GHB by participants in both groups in the past thirty days. An overview of BZD and GHB doses prescribed during detoxification for both groups is shown in table 2

Table 1 Patient characteristics of BZD and pharmaceutical GHB detoxification groups

	BZD (n=42)	Pharmaceutical GHB (n=42)	p
Male: n (%)	29 (69.0%)	31 (73.8%)	p=.801
Age: years (sd)	30.5 (5.5)	28.7 (5.6)	p=.130
Months of daily GHB use (sd)	44.8 (46.4)	51.1 (33.4)	p=.493
Daily ml GHB (sd)	76.7 (61.9)	75.7 (52.4)	p=.953
Co-morbid substance use (In past thirty days)			
-nicotine	92.3%	94.2%	p=.702
-stimulants	76.0%	59.1%	p=.090
-alcohol	55.6%	60.4%	p=.637

Table 2 Tapering doses of pharmaceutical GHB in grams in the Netherlands, and diazepam in milligrams in Belgium.

Day	Average GHB dose in grams (SD)	Average diazepam dose mg dose (SD)
1	28.24 (10.51)	60.32 (38.61)
2	25.01 (10.07)	100.34 (64.15)
3	22.13 (9.83)	74.16 (45.77)
4	19.60 (9.24)	63.55 (27.95)
5	18.08 (8.68)	51.86 (25.44)
6	16.12 (8.38)	44.74 (38.10)
7	14.02 (6.47)	33.74 (29.76)
8	11.56 (5.94)	
9	8.46 (5.66)	
10	6.28 (6.93)	
11	4.80 (3.25)	

Subjective withdrawal symptoms

LMM analysis showed that patients reported a decrease in withdrawal symptoms (SWS) over time during the detoxification (main effect of time: $F(6,11)=6.481$, $p<.003$). Patients in the pharmaceutical GHB group had lower SOS scores (mean=15.90; SD=13.83) than those in the BZD group (mean=36.50; SD=21.08), indicating less severe withdrawal in the GHB group (main effect of group: $F(1,1688)=42.336$, $p<.001$), see Figure 1. No interaction effect between group and time was found. Since BZD tapering lasted seven days on average the comparison of subjective withdrawal shown in only over the first seven days of detoxification. The results did not differ when the full eleven days pharmaceutical GHB tapering were included in the analysis.

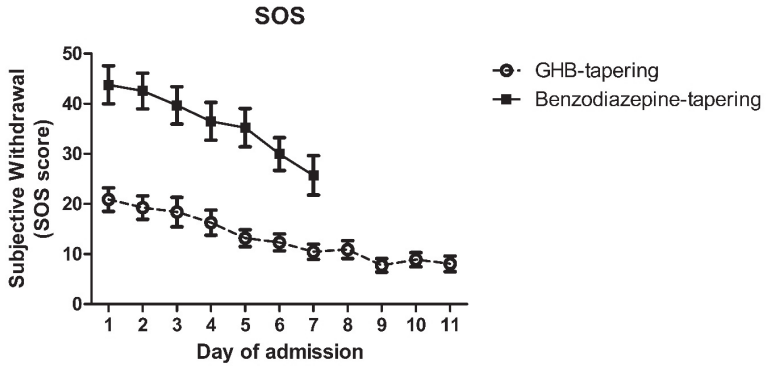

Figure 1 Experienced subjective withdrawal (SWS) during detoxification in patients receiving BZD tapering or pharmaceutical GHB tapering.

Objective withdrawal symptoms

LMM showed that withdrawal symptoms (OWS) scored by the staff decreased over time during detoxification in both groups (main effect of time: $F(6,50)=6.7$, $p<.001$). Patients in the pharmaceutical GHB group showed lower severity of withdrawal symptoms (mean=3.72; SD=2.56) compared to the BZD group (mean=8.05; SD=4.68), indicating less severe withdrawal in the GHB group (main effect of group: $F(1,102)=39.2$, $p<.001$), see Figure 2. There was an interaction effect between time and group ($F(6,50)=3.0$, $p<.05$), indicating that the observed withdrawal symptoms pattern differs between the two treatments over time. This interaction effect is mainly driven by an increase in withdrawal severity on day 3 of admission in the BZD group, see figure 2. Since BZD tapering lasted

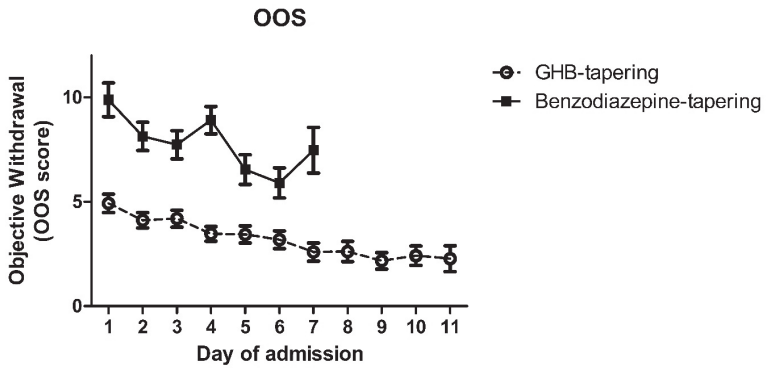

Figure 2 Observed objective withdrawal (OWS) during detoxification in patients receiving BZD tapering or pharmaceutical GHB tapering.

seven days on average the comparison of objective withdrawal shown in only over the first seven days of detoxification. The results did not differ when the full eleven days pharmaceutical GHB tapering were included in the analysis

Craving

LMM showed that craving diminished over time during detoxification in both groups (main effect of time: $F(1,6)=6.88$, $p<.001$), see Figure 3. No differences in craving scores were found between BZD and GHB tapering. Since BZD tapering lasted seven days on average the comparison of craving shown in only over the first seven days of detoxification. The results did not differ when the full eleven days pharmaceutical GHB tapering were included in the analysis

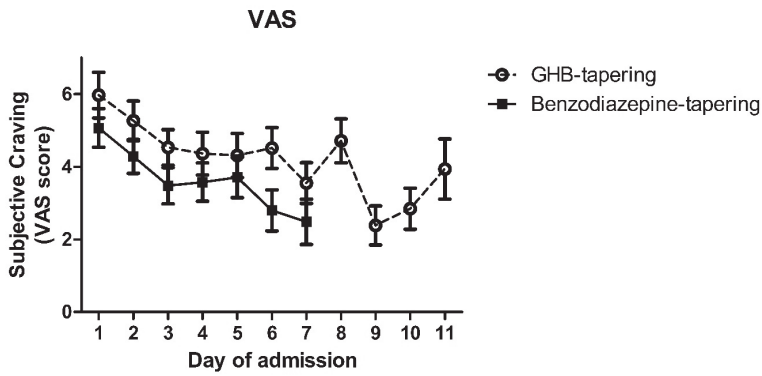

Figure 3 Experienced craving (VAS) during detoxification in patients receiving BZD tapering or pharmaceutical GHB tapering.

Adverse events

Adverse events were more common in the BZD group, with 29% (n=12) of BZD patients developing an adverse event during detoxification, compared to 5% (n=2) of the patients in the pharmaceutical GHB group ($\chi^2(1)=8.5714$, $p=003$). The majority of adverse events was related to delirium. Delirium was more common in the BZD group (21%, n=9), compared to the pharmaceutical GHB group (2%, n=1) ($\chi^2(1)=7.2649$, $p=.007$). Two patients receiving BZD tapering were transferred to the intensive care unit of the hospital, after developing delirium. Both patients developed severe agitation during their delirium. Other reported adverse events were latent suicidal thoughts, severe nightmares and memory problems in the BZD group.

Discussion

This study compared BZD and GHB tapering in GUD patients. In line with the hypotheses GHB tapering was associated with a milder withdrawal syndrome and fewer adverse events (including delirium) during detoxification, compared to BZD treatment. Contrary to our hypothesis, no differences in craving scores between the two groups were found. These findings suggest that tapering with pharmaceutical GHB might be more comfortable and safer than detoxification with BZD in patients with GUD. The difference in reported adverse events, in particular delirium, is highly relevant from a clinical perspective. In the GHB group one in forty patients developed delirium, in comparison to one in five in the BZD group.

BZD might not sufficiently counteract GHB withdrawal symptoms in all patients (Craig et al., 2000; Neu, Sofin, & Danker-Hopfe, 2018; Strand, Petersen, Nielsen, & Boegevig, 2017; M. S. van Noorden et al., 2015). The current findings are in line with several case studies on detoxification of GUD patients, where delirium was common in BZD tapering, despite very high BZD doses (Craig et al., 2000; Kamal et al., 2017; Rosenberg, Deerfield, & Baruch, 2003). This difference might be explained by the different working mechanism of BZD´s and GHB. Where BZD's primarily affect GABA-A receptors (Lorenz-Guertin et al., 2019), GHB binds to GABA-B and GHB receptors(Laborit, 1964). Withdrawal symptoms of GHB, probably mediated through GABA-B and GHB receptors, might thus not be sufficiently suppressed through BZD acting through GABA-A. Furthermore, BZD use has been associated with the development delirium in some cases (Zaal et al., 2015). This might have further contributed to the increased risk of delirium in the BZD group.

In the present study withdrawal symptoms were more severe in patients treated with BZD from the start of detoxification, compared to patients treated with pharmaceutical GHB. This might be related to differences in the titration procedure between the two conditions. Where initiation of BZD administration was based on increased blood pressure and/or heart rate (symptom triggered), pharmaceutical GHB administration was initiated two hours after the last ingestion of street GHB, and then continued every two hours in a fixed schedule. Furthermore, patients might develop withdrawal symptoms before their blood pressure and/or heartrate increase. Therefore, patients treated with pharmaceutical GHB might have experienced fewer withdrawal symptoms from the start of detoxification than patients treated with BZD. Therefore, differences in titration procedure between the conditions might also have contributed to the differences in withdrawal severity that we observed.

Another important difference between BZD and GHB detoxification is the duration of the detoxification. Tapering with BZD's took on average seven days and tapering with GHB eleven. GHB detoxification thus seems more gradual, and might therefore be associated with fewer withdrawal symptoms and adverse events, including delirium, as compared to BZD tapering. The observed increased withdrawal severity and risk for delirium in the BZD

group might thus also be related to more rapid detoxification with BZD tapering, compared to GHB tapering. Since the vast majority of patients receiving BZD tapering did not experience any adverse events and had on average a shorter detoxification period, it could be argued that pharmaceutical GHB tapering could also be done in seven days. However, this will likely increase withdrawal severity and possibly also the risk of adverse events like delirium.

Some additional considerations regarding both treatment options as assessed in this study. First, tapering with GHB requires frequent administration of doses during the entire day and often also during the night. This is a demanding procedure for both the patient and staff. However, prevention of delirium and other adverse events of GHB withdrawal clearly outweighs the burden for patients and staff. Second, the length of admission in the GHB tapering group was shorter than reported in other publications on the Dutch GHB sample (Beurmanjer H, Verbrugge CAG, Schrijen S & DeJong CAJ, 2016; Dijkstra et al., 2017). The discrepancy in length of stay between this study and past GHB studies with the Dutch sample is likely accounted by the matching process, as the Belgium sample used, on average, a lower GHB dose than commonly reported in the Netherlands (Dijkstra et al., 2017). Patients using higher doses of street GHB are more likely to experience severe withdrawal and adverse events like delirium during detoxification and BZDs are less effective in preventing delirium in this population. Given that our study participants use lower-than-average doses of street GHB prior to detoxification, the current findings may be an underestimation of the beneficial effects of pharmaceutical GHB compared to BZD in more severe GUD populations.

Lastly, substitution of ´street´ GHB with pharmaceutical GHB means that patients have to continue to use a substance that they are trying to quit. It can be speculated that this continued use could reinforce GHB use and sustain the compulsive pattern of use (Kwako & Koob, 2017). However, no differences in craving levels were found between the two groups, indicating that patients in the GHB group did not experience a stronger need to use than patients in the BZD group. It would be interesting to study if type of detoxification influences relapse rates after detoxification in future longitudinal studies.

While future studies would ideally use randomized controlled designs to replicate our findings, this might not be feasible in this patient population for several reasons. First, patients with GUD often come into treatment in acute situations requiring immediate care due to a fast-developing severe withdrawal syndrome. This complicates informed consent and randomization procedures. Second, the results from the current study in combination with existing literature point towards potentially high risks of complications during BZD tapering in patients with GUD. This further complicates randomization to BZD versus GHB tapering from ethical point of view, as BZD tapering might be inferior to pharmaceutical GHB tapering. The current comparative study was mainly possible due to juridical restrictions of pharmaceutical GHB use in Belgium, offering the possibility of an observational non-randomized trial.

Future research on GHB detoxification should also focus on optimisation of the duration of detoxification and study whether some patients could profit more from one method or the other. For instance, it is likely that in patients with relatively low levels of GHB use, BZD tapering might be sufficient to counteract GHB withdrawal, whereas in patients using high levels of GHB pharmaceutical GHB might be the preferred option. Cost-effectivity should also be taken into account, as pharmaceutical GHB is more expensive than BZD's.

Future studies should also focus on the GABA-B agonist baclofen as an alternative for BZD and/or GHB tapering in GUD (Beurmanjer, Kamal, de Jong, Dijkstra, & Schellekens, 2018; Lingford-Hughes et al., 2016). Since baclofen has a longer half-life than GHB and targets GABA-B receptors, it might effectively suppress GHB withdrawal. Moreover, baclofen tapering might allow patients to quit using GHB, preventing withdrawal, with only three to four daily dosages (Beurmanjer et al., 2018; Kamal, Loonen, Dijkstra, & De Jong, 2015). Furthermore, baclofen has been suggested to be effective in reducing relapse after detoxification(Beurmanjer et al., 2018; Kamal et al., 2015). Given its similarities to GHB, baclofen might also be a candidate for GHB substitution therapy.

The current findings should be viewed in the light of some limitations of this study. Given the explorative, non-randomized, design of the study and the fact that each treatment was assessed in a different country and a different institution, there is a risk for selection bias and procedural confounding respectively. However, the two groups were matched and did not differ on key variables, such as level of GHB use, duration of GHB use, co morbid substance use, age, and gender. Both populations were Dutch speaking, and The Netherlands and (Flemish) Belgium are culturally bound together. This minimizes the risk of an effect of language and cultural differences between groups. It is also important to note that both groups received a similar treatment by experienced medical staff. No additional (psychotherapy) treatment was offered at both institutes during detoxification, ruling out the influence of one treatment being more extensive than the other. Yet, any confounding effect of selection bias or treatment institute cannot be fully ruled out. Another possible limitation is that delirium assessments were based on clinical observations, as reported in the discharge summaries written by the treating psychiatrist and in the treatment outcome forms. The use of a structured scale, such as the Delirium Observation Screening Scale (DOS), might have been more reliable (Schuurmans, Shortridge-Baggett, & Duursma, 2003).

Conclusion

In patients with GUD, detoxification with pharmaceutical GHB showed less severe withdrawal symptoms and less adverse events, specifically delirium, than detoxification with BZD's. This supports earlier work that BZD's might not always sufficiently dampen withdrawal in GUD. Based on the current findings tapering with pharmaceutical GHB could be considered for patients with GHB dependence during detoxification, as it has potentially less severe withdrawal and less complications than benzodiazepine tapering.

6

Baclofen to prevent relapse in gamma-hydroxybutyrate (GHB)-dependent patients: a multicentre, open-label, non-randomized, controlled trial

Published as

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Abstract

Background: Gamma-hydroxybutyrate (GHB) dependence is associated with a severe, potentially lethal, withdrawal syndrome and relapse rates as high as 60% within three months of detoxification. Baclofen has been shown to decrease self-administration of GHB in mice and reduce relapse in a case series of GHB-dependent patients. Controlled studies on the effectiveness of baclofen to prevent relapse in GHB-dependent patients are lacking.

Aim: To assess effectiveness of baclofen in preventing relapse in GHB-dependent patients.

Methods: An out-patient multicentre, open-label, non-randomized, controlled trial in GHB-dependent patients (n=107) in the Netherlands. Treatment as usual (TAU: n=70) was compared with TAU plus baclofen 45-60mg for three months (n=37). Outcome measures were rates of lapse (any use) and relapse (using GHB on average once a week or more during), based on self-report. Side effects were monitored with a baclofen side effects questionnaire. Treatment groups were compared using chi-square analyses, with both per protocol (PP) and intention to treat (ITT) analyses.

Results: GHB-dependent patients treated with baclofen after detoxification showed no reduced lapse rates, but reduced relapse and dropout rates, compared to patients receiving TAU only (24% versus 50%). While both ITT and PP analyses revealed similar results, the effectiveness of baclofen prescribed per protocol was slightly higher than in ITT analysis.

Conclusions: This study showed potential effectiveness of baclofen in preventing relapse in patients with GHB dependence after detoxification. Though promising, future studies with longer follow-up and a randomized double-blind design should confirm these findings before recommendations for clinical practice can be made.

Introduction

In Europe misuse of gamma-hydroxybutyrate (GHB) has increased over the past decade, particularly in The Netherlands, Norway, Spain and the United Kingdom (European Monitoring Centre for Drugs and Drug Addiction, 2016). GHB originally emerged in the nineties as an innocent party-drug, but later proved to be highly addictive. Precise prevalence rates are unknown due to a lack of systematic surveillance on GHB use (T. Brunt & Schrooten, 2014). Physical dependence on GHB can develop within weeks, when used daily (McDaniel & Miotto, 2001). GHB dependence is associated with a severe, potentially lethal, withdrawal syndrome and high relapse rates of 60% within three months of detoxification(4). However, studies on relapse prevention in GHB dependence are lacking.

GHB is a short-chain fatty acid, which is biosynthetically derived from the inhibitory neurotransmitter GABA (Tarabar & Nelson, 2004). It occurs naturally in the brain, predominantly in the hypothalamus and basal ganglia (Bessmann & Fishbein, 1963; O. C. 3rd Snead & Morley, 1981). GHB binds to GABA-A-receptor, GABA-B-receptor and GHB-receptor (Laborit, 1964). It has a rapid onset of action after ingestion, reaching maximum concentration (Tmax) in a short period. GHB's clinical effects include sedation, euphoria, and in higher doses hypoventilation and coma, see (Kamal et al., 2017) for further details.

Baclofen might be an adequate substitute for GHB. It is a high-affinity GABA-B receptor agonist, similar to GHB (Crunelli, Emri, & Leresche, 2006; Cruz et al., 2004), but with a longer half-life (T½=2-6hours). This has the theoretical advantage of more stable drug-plasma levels, and subsequent GABA-B activation, with less frequent dosing (i.e. three times daily, instead of twelve)(Dijkstra et al., 2017). Indeed, one animal study in mice showed that baclofen reduced GHB self-administration (Fattore, Cossu, Martellotta, Deiana, & Fratta, 2001). To date, only one case series on baclofen treatment (30-60mg per day) in GHB dependence has been reported, showing three-month abstinence in nine out of eleven cases(Kamal, Loonen, et al., 2015). Baclofen has also been shown to increase abstinence rates and reduce craving and anxiety in alcohol-dependent patients (G. Addolorato et al., 2002; Giovanni Addolorato et al., 2007; Agabio, Preti, & Gessa, 2013; Cryan & Kaupmann, 2005; Terrier et al., 2011). However, several studies failed to replicate these effects (Beraha et al., 2016; Muller et al., 2015).

These findings warrant further studies on the potential efficacy of baclofen in the treatment of GHB use disorders. To our knowledge, no clinical studies on the effects of baclofen in GHB use disorders have been published. Here, we investigated the effectiveness of baclofen in recently detoxified GHB-dependent patients to prevent relapse in an open-label, non-randomized, controlled clinical trial. Specifically, we tested the hypotheses that patients receiving baclofen on top of treatment as usual (TAU) after GHB detoxification have decreased relapse rates compared to patients receiving TAU.

Methods

Study design

The effectiveness of baclofen was assessed in a multicentre, open-label, non-randomized, controlled clinical trial (see protocol publication, Kamal et al, 2015). After detoxification from GHB, patients received TAU or TAU combined with baclofen, based on patient preference. Participants provided written informed consent. The study was approved by the Medical Ethics Committee, Twente Medical School (METC/14015.am) study number NL40321.044.13. The study was registered in the Netherlands Trial Register with number NTR4528.

Participants

GHB-dependent patients (according to DSM-IV criteria of substance dependence) were recruited at six addiction care facilities (IrisZorg, Mondriaan, Novadic-Kentron, Tactus, Victas and VNN) in The Netherlands, when admitted for detoxification. Inclusion criteria: completed GHB detoxification, wish for abstinence, continuing out-patient treatment after detoxification, age between 18-40 years, and comprehension of Dutch. Exclusion criteria: physical contra-indications for baclofen (e.g. liver problems, renal impairment, hypertension, diabetes, seizure disorder, pregnancy), severe psychiatric conditions (e.g. bipolar disorder, major depression, psychotic disorders, suicidal ideations), use of anxiolytics, stimulants or hypnotics after detoxification, or previous misuse of baclofen. Of 137 GHB-dependent patients admitted for detoxification, 107 were eligible for participation. Thirty-seven patients received baclofen on top of TAU; 70 received TAU only. During admission, a physician informed patients about the baclofen study. A flowchart is shown in figure 1.

Sample size calculation

Sample size calculation was based on the effectiveness of baclofen in alcohol use disorders. Though the literature on baclofen's efficacy in alcohol use disorders is contradictory, several studies do suggest a beneficial response of baclofen versus placebo (abstinence rates 70% versus 20-30%)(Giovanni Addolorato et al., 2002, 2007). Anticipating a smaller effectiveness in GHB dependence (three month abstinence rates 60% versus 40%) based on our previous studies(Dijkstra et al., 2017), approximately 30 patients per group are needed in order to detect any significant effects of baclofen, with α=.05 and β=.80 (Kamal, Schellekens, et al., 2015)

Treatment intervention

Baclofen

Participants initially received 15mg per day, divided over three doses, which was gradually increased over a period of 10 days to 45mg daily. When patients reported no or limited effects of baclofen on anxiety and craving after two weeks without side effects, the dose

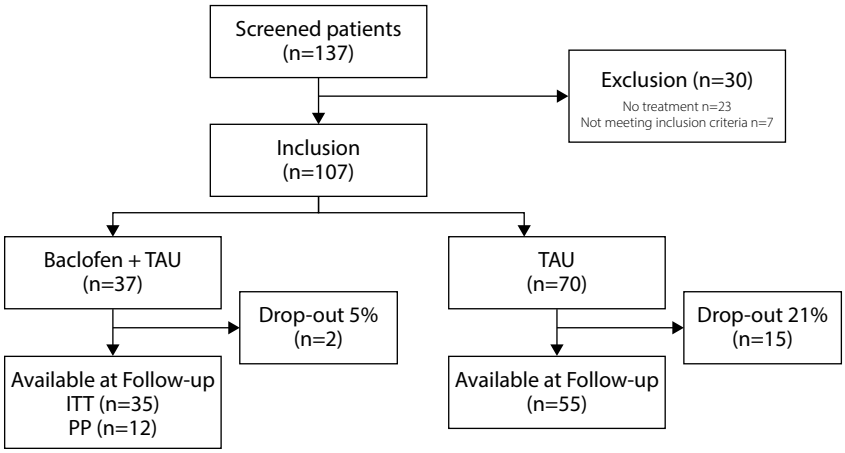

Figure 1 Flowchart participants included in the study.

was increased to a maximum of 60mg daily. This dose was maintained for 10 weeks. In case of relapse or adverse events, immediate cessation of treatment was considered to avoid intoxication hazards. Compliance was assessed during weekly meetings between the prescribing physician and the patient

Treatment as usual (TAU)

All participants received TAU as provided by their addiction treatment centre, including cognitive behavioural therapy with additional treatment for social, psychiatric, and medical problems if necessary.

Outcome measures

Lapse and Relapse

Lapse and relapse were measured by self-report on a questionnaire at three-months follow-up. Lapse was defined as any use of GHB and relapse as weekly use of GHB during the past 3 months. Patients who were no longer in care at follow-up were contacted through telephone and e-mail. Those unavailable for follow-up were considered relapsed.

Side effects

Safety of baclofen was monitored using a baclofen side effects questionnaire, both self-monitored and observed by treating physicians. This questionnaire was based on the side effects of baclofen reported in the literature(Kamal, Loonen, et al., 2015), containing 21 items with a five-point Likert scale (range: 0=never to 4=always). Examples are vomiting, nausea and diarrhoea. See supplementary table 1 for the complete list.

Analysis

Demographics were calculated using descriptive statistics and compared between groups using univariate analysis of variance (ANOVA) and chi-square analyses. Lapse, relapse and relapse including drop-out rates in each group were compared using chi-square analyses. In contrast to the original protocol publication(Kamal, Schellekens, et al., 2015), we only analysed primary outcomes using both intention to treat (ITT) and per protocol (PP) analyses, due to the limited influx of patients receiving baclofen after a prolonged inclusion period (n=37 instead of n=80). In the more conservative ITT analyses all participants receiving baclofen were compared to TAU. In the PP analyses only those participants receiving baclofen according to the protocol were compared to TAU.

Though a historical control group was available for comparison (Kamal, Loonen, et al., 2015), only the current control group was included in the analyses. First, the current control group is substantially larger that the intervention group, making addition of an extra control group redundant. Second, relapse rates in the current control group were substantially lower compared to our historical control group (50% versus 65% respectively). Finally, the current control group was more comparable to the baclofen group in terms of received TAU. Therefore, adding a historical control group to the analyses was considered of no added value.

All analyses were carried out in SPSS version 21, with alpha <.05 considered significant.

Results

Demographics

Patients in the baclofen group were more often male than in the TAU group, but gender was not related to treatment outcome. There were no other differences in demographics, GHB use or psychiatric comorbidity, see Table 1. Of the 37 patients receiving baclofen (included in ITT analysis), 13 received baclofen according to protocol (included in PP analysis).

Effectiveness

ITT analysis showed no difference in lapse rates (χ^2=0.20, p=.885) and relapse rates excluding drop-out (χ^2=3.29, p=.069) in the baclofen-treated group, compared to TAU, see Table 2a. In the baclofen group relapse rates including drop-out as relapse were lower compared to TAU (χ^2=6.59, p=.010). PP analysis showed no difference in lapse rates (x^2=1.99 p=.158), but lower relapse rates in the baclofen group when drop-out rates were not included (x^2=3.97, p=.046) and included as relapse (x^2=5.31, p=.021), compared to TAU, see Table 2b.

Table 1 Demographics and GHB use per sub group.

	Treatment as usual (N=70)	Baclofen + Treatment as usual (N=37)	Test statistic	p
Male %	54%	74%	χ^2=4.68	.030
Age. mean (SD)	28.9 (7.8)	29.5 (7.0)	F(1.98)=.014	.905
Employment %	31%	32%	χ^2=0.01	.916
GHB use. mean (SD)				
- Months using GHB	58.3 (42.2)	63.5 (43.0)	F(1.85)=.285	.595
- Months using daily GHB	27.4 (28.2)	41.2 (43.0)	F(1.79)=2.958	.089
- GHB gram daily	55.6 (53.8)	46.1 (40.9)	F(1.93)=0.797	.374
- Interval between doses (hours)	1.8 (0.73)	1.84 (0.64)	F(1.85)=0.114	.736

Side effects

Patients reported overall limited side effects, with the most frequently reported being: feeling tired (28%), sleepiness (14%) and feeling depressed (14%). No serious adverse events were reported.

Table 2a Comparison of (re)lapse in GHB use in the three months after detoxification between patients prescribed baclofen (ITT) and patients who received treatment as usual.

	Treatment as usual	Baclofen + Treatment as usual	Test statistic	p-value
Patient completed follow-up	N=55	N=35		
Lapse (any use)	47% (n=26)	46% (n=16)	χ^2=0.20	.885
Relapse	38% (n=21)	20% (n=7)	χ^2=3.29	.069
Patients including drop-out	N=70	N=37		
Relapse†	50% (n=35)	24% (n=9)	χ^2=6.59	.010

† Drop-out is considered relapse in GHB dependent patients, therefore only relapse is mentioned.

Table 2b Comparison of (re)lapse in GHB use in the three months after detoxification between patients prescribed baclofen according to the study protocol (PP) and patients who receive treatment as usual.

	Treatment as usual	Baclofen + Treatment as usual	Test statistic	p-value
Patient completed follow-up	n=55	n=12		
Lapse (any use)	47% (n=26)	25% (n=3)	χ^2=1.99	.158
Relapse	38% (n=21)	8% (n=1)	χ^2=3.97	.046
Patients including drop-out	n=70	n=13		
Relapse†	50% (n=35)	15% (n=2)	χ^2=5.31	.021

† Drop-out is considered relapse in GHB dependent patients, therefore only relapse is mentioned.

Discussion

This is the first case-control study evaluating the effectiveness of baclofen to prevent relapse in GHB-dependent patients. Patients receiving baclofen per protocol after detoxification showed reduced relapse rates, compared to patients receiving TAU, supported by a similar trend towards beneficial effects of baclofen in the ITT analysis. Mild tiredness, sleepiness and depressed feelings were reported in the baclofen group as most relevant side effects of baclofen.

These results are comparable with an earlier case series (n=11) on baclofen treatment in GHB-dependent patients, showing 81% abstinence rates during three months follow-up, without significant side effects (Kamal, Loonen, et al., 2015). Similarly, Fattore et al. (2001) showed prevention of self-administration of GHB in mice when treated with baclofen (0.625 and 1.25 mg/kg). Importantly, a lower dosage of baclofen (0.312 mg/kg) did not prevent GHB self-administration. There is currently no consensus on the most appropriate dose of baclofen in addiction treatment. In line with the previous case series, we prescribed a relatively low dosage of baclofen (45-60mg daily) in comparison with studies on alcohol dependence (up to 300mg daily(Rolland et al., 2015). As higher doses of baclofen might be more effective, future studies on baclofen effectiveness in GHB dependence should also study higher doses of baclofen. However, caution is warranted as data about safety of high dose baclofen are limited.

GHB, baclofen and alcohol share a similar pharmacological profile. Studies on alcohol dependence have shown that GHB is effective in reducing alcohol craving and intake (Giovanni Addolorato, Leggio, Ferrulli, Caputo, & Gasbarrini, 2009). So it's conceivable that baclofen should be effective in reducing GHB dependence in view of its efficacy to reduce alcohol dependence (Mirijello et al., 2015). In light of the longer half-life of baclofen compared to GHB, it can also be speculated that baclofen might be considered a substitute for GHB(Rolland et al., 2014). The currently poor prognosis in GHB dependence and severity of complications might justify a substitution therapy approach (Dijkstra et al., 2017). Recently, baclofen raised attention for its potential effectiveness for the detoxification of GHB (Lingford-Hughes et al., 2016). One could also suggest using baclofen to ameliorate GHB withdrawal during detoxification, without tapering off completely, in order to prevent relapse. This would likely increase treatment adherence in some patents, preventing them from dropping out of treatment and relapse in GHB use.

Given the explorative, non-randomized, open-label design of our study, the results need to be interpreted with caution and further studies are needed in order to confirm our findings. Several limitations should be considered when interpreting the results. First, sample size was limited and lower than anticipated. Moreover, patients who chose baclofen treatment might have been more motivated for full abstinence, adding to the chance of good outcome at follow-up. Yet, we did observe similar findings to previous animal work and a case series of GHB-dependent patients (Fattore et al., 2001; Kamal, Loonen, et al., 2015). The observed effectiveness of baclofen, despite a limited sample size, does suggest treatment potential of baclofen in patients with GHB use disorders.

Second, TAU was not specified in the current study. Any variation in TAU between groups might confound the results. While we have no such indication when it comes to psychosocial treatment, it is however possible that some patients in the TAU group were prescribed benzodiazepines on top of their psychosocial treatment. Therefor a potential confounding effect cannot be fully ruled out. Third, abstinence was not confirmed using systematic urine or blood tests, due to the narrow timeframe in which GHB can be detected as a result of its short half-life (Schep, Knudsen, Slaughter, Vale, & Mégarbane, 2012). We relied on self-report measures, with potential recall bias, particularly given the open-label design of the study. Compliance with the baclofen treatment also was assessed by self-report, during weekly meetings between the prescribing physician and the patient. Pill count was not used. This is a potential confound of the data, since compliance is considered highly relevant for the effectiveness of baclofen. Finally, follow-up duration was three months after detoxification, which makes drawing conclusions about long-term effects impossible. Fourth, side effects where not measured in the TAU group, therefor reported side effects cannot be solely attributed to baclofen. Many of the reported side effects are common in GHB-dependent patients in general after detoxification (Dijkstra et al., 2017). Future studies should address long-term efficacy of baclofen in GHB dependence, using placebo-controlled, randomized designs in substantially large samples.

Conclusion

This study showed that baclofen could be a potential candidate for preventing relapse in GHB-dependent patients after detoxification, particularly when administered strictly according to the protocol. Though promising, future studies with longer follow-up and a randomized double-blind design should be conducted to confirm these findings, before recommendations for clinical practice can be made.

7

Summary and Discussion

Summary

The aims of this thesis were to 1) further our understanding of the GHB using population and treatment needs of patients with GUD, 2) test pharmacological treatment interventions in patients with GUD. In this chapter, I will present and discuss the main findings and their implications, starting with a summary of the included chapters, followed by the overall conclusions, clinical implications, general issues and suggestions for further research.

Part 1: Understanding the GHB using population

Chapter 2 SUB-GROUPS OF PEOPLE WHO USE GHB

To get a better overview of people who use GHB we conducted a systematic review of the literature on (sub-)populations of GHB users. The identified GHB-using populations can be roughly categorized by increasing severity level of GHB use as recreational use of GHB without adversities; recreational use of GHB with adversities, and people with GUD. Differences between these populations were mainly related to frequency of GHB use, reasons for GHB use, as well as level of education, work status, and psychiatric comorbidity. The more severe the adversities, the more likely users display higher levels of GHB dose, frequency of use, GHB-induced coma's, negative reasons for use, co-substance use and psychiatric co-morbidity. Patients with GUD have more often a lower level of education and are more often unemployed, compared to recreational users. Due to the lack of longitudinal studies the trajectory from recreational GHB use, to problematic GHB use and the development of GUD remains unclear.

Chapter 3 ILLNESS PERCEPTIONS AND TREATMENT NEEDS IN PATIENTS WITH GUD

In order to get a better understanding of patients with GUD we held in depth interviews about illness perceptions and treatment needs. These interviews showed that patients with GUD had mainly positive views toward GHB. They described GHB as a fast-working substance, that makes a person feel confident, with no downsides. There's no hangover and the temporary GHB-induced coma's feel harmless, or are not noticed at all. When GHB use becomes more frequent patients keep experiencing mainly strong rewards, despite the start of withdrawal symptoms. Withdrawal symptoms are however not recognized as such and usually lead to more GHB use, starting a downward spiral. As a result, GHB is viewed as the solution to all personal problems, rather than the cause. This positive attitude remains strong in patients, even when GUD becomes more severe. The main expressed treatment needs were related to mood and anxiety symptoms and not towards GHB or abstinence. Other areas that patients requested help with were get proper housing, a supportive social network, and meaningful daytime activities and/or work.

Chapter 4 COGNITIVE IMPAIRMENT IN PATIENTS WITH GUD

While research on cognitive impairment in patients with GUD is limited, several studies show that GHB use and in particular GHB induced coma's are associated with memory problems. Our study used the Montreal cognitive assessment (MoCA) to screen for cognitive impairments in patients with GUD before and after detoxification. The study showed a substantial number of patients with GUD screened positive for cognitive impairment before detoxification. Cognitive functioning improved after detoxification with still about one third screening positive for impairment. The cognitive domain showing the strongest impairment was memory. Cognitive impairment before detoxification, particularly on the subscale memory, was associated with relapse.

Part 2: Pharmacological treatment interventions for patients with GHB use disorder

Chapter 5 GHB DETOXIFICATION

Two pharmacological treatment regimens are commonly used to counteract withdrawal symptoms during GHB detoxification: tapering with benzodiazepines (BZDs) and tapering with pharmaceutical GHB. Our study aimed to compare both tapering methods and determine whether one should be preferred over the other. The results showed that GHB tapering was associated with a milder withdrawal syndrome and fewer adverse events (including delirium) during detoxification, compared with BZD treatment.

Chapter 6 RELAPSE MANAGEMENT FOR PATIENTS WITH GUD

There is no GUD specific relapse management available in current practice. Several studies however have suggested that the GABA-B agonist baclofen could help supress craving and anxiety in patients with GUD(Kamal, Schellekens, et al., 2015; Lingford-Hughes et al., 2016). In our open label study, we prescribed baclofen up to 60 mg to patients with GUD after detoxification. The results showed that patients receiving baclofen per protocol after detoxification had reduced relapse rates compared with patients receiving treatment as usual, supported by a similar trend towards beneficial effects of baclofen in the intention to treat analysis. Limited side effects were reported.

Discussion

Part 1: Understanding the GHB using population

GUD: similarities and differences with other SUDs

GHB is a relatively new substance and its addictive properties were first described twenty years ago (Galloway et al., 1997; K. Miotto et al., 2001). While it is broadly acknowledged that GHB use can lead to a substance use disorder (Craig et al., 2000; K. Miotto et al., 2001; O. C. Snead & Gibson, 2005), it is not mentioned in the DSM-5 (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force, 2013). Prevalence seems limited (Addiction, 2019), but the problems associated with GUD are substantial (Dijkstra et al., 2017; M. S. van Noorden et al., 2009). Furthermore, there are reports of increasing prevalence of GHB use (Addiction, 2019; Arunogiri et al., 2020), which could result in increased prevalence of GUD. The relative novelty combined with a very limited number of studies into GUD could explain why it is often seen as a special group of patients. GUD is often perceived as one of the most severe and dangerous to treat substance use disorders by clinicians (Krul & Girbes, 2011; M. S. van Noorden et al., 2009). The literature in combination with the research from this thesis shows however that GUD is in many ways a regular substance use disorder. Below I will outline where GUD is much alike other substance use disorders and what seems rather specific for GUD.

Staging

In Chapter 3 we described a model for the development of GUD when people start using GHB on a regular basis, consisting of three stages, based on in depth interviews. These stages are rather similar to the stages of development as described for other substance use disorders (Volkow et al., 2016). We have labelled these as positive reinforcement phase, dose escalation phase and the negative reinforcement phase. First, the substance is used for fun or other positive reinforcement. After a while, when tolerance develops, the substance needs to be used in other to feel and function normally. In the final stage the main motivation to use substances is to prevent withdrawal, and negative affect, often called negative reinforcement (Volkow et al., 2016). Figure 1 shows the schematic development of substance use disorders based on Koob, 2013 (Koob, 2013), which we here translate to GUD.

Anxiety

Many substances can dampen feelings of anxiety, like alcohol, cannabis and benzodiazepines (Vorspan, Mehtelli, Dupuy, Bloch, & Lépine, 2015). However, feelings of anxiety generally return after the acute effects of substance wear off. Repeated intake of these substances can paradoxically lead to increased feelings of anxiety, which can drive further substance use, starting a downward spiral (Becker, 2017; Koob, 2013). GHB seems no

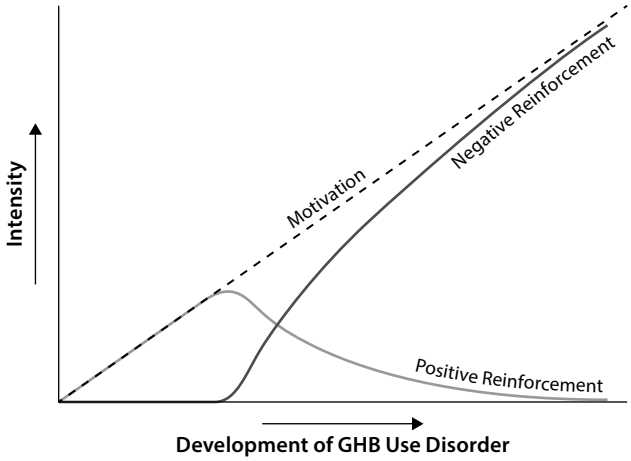

Figure 1 The development of GUD and motivation for GHB use, based on the model of Koob (Koob, 2013)

exception to this (Beurmanjer et al., 2019). The very short half-life of GHB might even speed up this process (Schep, Knudsen, Slaughter, Vale, & Mégarbane, 2012).

It could be argued that people with high levels of anxiety who use GHB are more likely to use GHB more frequently because of its anxiolytic effects. This might make them more vulnerable to develop GUD and as a result they are overrepresented in the GUD patient population. However, as mentioned before frequent GHB use itself might also increase feelings of anxiety as part of withdrawal (Beurmanjer et al., 2019). While intoxicated, or passed out, this numbs their emotional states. However, during detoxification feelings of anxiety commonly return with increased intensity (Dijkstra et al., 2017).

Feelings of anxiety can maintain for a prolonged period of time after detoxification, which might contribute to the risk of relapse, as also shown in other substances of abuse with temporarily dampening effects on anxiety, like alcohol (Schellekens et al., 2015). While a causal relationship has not yet been established, the interaction between feelings of anxiety and GHB use is frequently observed and has been suggested as an important explanation for the high relapse rates associated with GUD by patients themselves in chapter 3.

Cognitive impairments

An important predictive factor of relapse in patients with SUD are cognitive impairments (Czapla et al., 2016; Turner et al., 2009). Our study in chapter 4 showed that the majority of patients with GUD had an indication for cognitive impairment at the start of detoxification. This could be attributed to the active GHB use at the time of measuring and the known

effects of GHB on memory (Carter, Griffiths, et al., 2009). This is supported by the fact that many patients' scores improved after detoxification. However, a stable environment, with healthy food and improved sleep, could of course also have attributed to cognitive improvements (Garcia & Salloum, 2015; Sinha & Jastreboff, 2013).

Still, about a third of patients with GUD had an indication for cognitive impairments after detoxification (see chapter 4). This is a relatively high number compared to other SUDs, especially when taking the young age and short length of GUD into account (Bruijnen, Dijkstra, et al., 2019). Similar to patients with other SUDs our data did not find a relationship between MoCA scores and years of regular use, (GHB) dose, severity of dependence and coma's (Bruijnen, Dijkstra, et al., 2019). This suggests that other factors might be involved, for instance lack of sleep, malnutrition or other psychiatric/somatic comorbidities.

Illness perception of GUD

Though the developmental trajectory of GUD seems to follow the classic development of SUDs and its symptoms are similar to other SUD's, patients with GUD show higher relapse rates than most other groups. Roughly half of the patients relapse within three months after detoxification (Beurmanjer et al., 2018). In chapter 3, patients reported that the way they viewed GHB might have contributed to this. GHB was considered the ultimate drug by most participants. According to them, a small dose of GHB will boost self-esteem, makes stress disappear and all problems to be solved for a moment. On top of this, these upsides don't have a hangover, and no one seems to notice GHB use. As long as people keep using GHB, they perceive to function normally without downsides of drug use. The absence of this negative feedback loop might contribute to the relatively rapid development of severe SUD at a relatively young age in our study population.

Patients with GUD, like other substance use disorders, reported the illusion of control: "I can always quit tomorrow". While this limited insight in their illness is similar to other SUD's, the absence of a negative feedback loop is prescribed by users as something unique (Beurmanjer et al., 2019). This could explain why even abstinent patients with GUD keep describing GHB as "the perfect drug" and remain to have very strong positive associations with it. These positive associations could contribute to fast relapse in daily GHB use.

Role of stigma in GUD

Stigma is common towards patients with SUD's by both the public and healthcare services (Van Boekel, Brouwers, Van Weeghel, & Garretsen, 2013). However, GHB seems to come with more stigmatisation than other substances (Palamar & Halkitis, 2006). During my research I've come across many clinicians who described patients with GUD as "difficult" and sometimes even as the "most difficult group" of patients with SUDs. A mixed-method study from 2011 (Koekkoek, Hutschemaekers, van Meijel, & Schene, 2011) showed that the

'difficult' patient-label is associated with professional pessimism, passive treatment and possible discharge or referral out of care. Typically, patients with multiple problems, like patients with GUD, lack one clear diagnosis or are eligible for many diagnoses. The 'difficult' patient-label may be easily given in such cases, obscuring a more useful or valid diagnosis, and possibly harming the patient (Koekkoek et al., 2011).

In contrast, it was reported that a clear psychiatric diagnosis 'protects' patients from professional pessimism, especially one with a perceived neurobiological basis. The status of 'difficult' patient is easily reinforced by subsequent patient and professional behaviour, turning initial help-seeking behaviour into 'difficult' or ineffective chronic illness behaviour, and ineffective professional behaviour (Koekkoek et al., 2011). The relative novelty of GHB and the lack of studies into treatment modalities for this population could make them extra vulnerable to be misunderstood and labelled as difficult. This underlines the need for continued research and dissemination of the results among (mental)healthcare professionals. This will likely help preventing patients being labelled as difficult and the stigma that comes with it. In order to achieve this, guidelines have been developed, seminars and webinars have been organised over the past years, including post academic training programs for psychologists, psychiatrists, and addiction physicians. More importantly, recently the first comprehensive GUD treatment guideline (Joosten et al., 2020) was developed and distributed open access among mental healthcare workers. This guideline includes the results from this thesis and an extensive overview of all available relevant information regarding the treatment of patients with GUD that is currently known.

Considerations for Policy interventions to prevent GHB use-related harm

Based on the studies in this thesis, several recommendations can be made to prevent GHB use-related harm. While many people who use GHB view the substance as innocent, it is evident from the literature that this is not the case. Prevention policies should be put in place to draw attention for potential risks of GHB use. For instance, GHB-induced coma's might feel innocent, but there is sufficient evidence to suggest these can lead to cognitive problems and accidents.

Furthermore, we've seen that GUD can evolve fast and that initial signs of GUD can easily be overlooked by the patient until it is too late. Phan and colleagues (Phan et al., 2020) have done several suggestions regarding prevention and harm-minimalization strategies aimed at GHB users in Australia. For instance, making several short screenings lists for healthcare professionals, as well as compact harm-minimalization advice aimed at people who are using GHB. The latter is drawn up following the acronym STAYING SAFE (see table 1) and could function as simple and basic information that prevention workers can give to GHB users. Future studies should however determine if providing this information actually prevent adverse events in people using GHB.

Table 1 STAING SAFE overview

STAYING SAFE	
S	Seek medical attention immediately if you have taken too much GHB. Do not use other drugs in the hope of reversing the effects.
T	Two or more substances used at the same time increase the risk of overdose significantly (especially sedatives; eg alcohol, ketamine).
A	Always measure GHB doses accurately (eg with a syringe or pipette). Wait until the effects are felt and do not re-dose for at least two hours.
Y	You should always avoid using GHB on your own and always use in a safe place and with someone who has not taken it, as it is common to become unconscious.
I	If you have used and are going to sleep, sleep on your side in case you are sick. Place sleeping or unconscious friends in the recovery position.
N	Never keep GHB in drink bottles, where it might be drunk by others not aware of the content. Add food colouring to avoid accidental drinking.
G	GHB is addictive and dependence can happen quickly. Avoid frequent use, especially daily use.
S	Severe and potentially serious GHB withdrawal symptoms occur if you are dependent and you miss a dose or reduce amounts taken abruptly.
A	Acute withdrawal symptoms and have no GHB? Seek medical help immediately in an emergency department.
F	Find medical support for planned GHB detoxification. Do not attempt to stop abruptly on your own. If you want to reduce your dose, do so in very small doses until you find medical support.
E	Employ methods to stabilise your use; consumption diaries can be helpful.

Originally from Phan and colleagues(Phan et al., 2020)

Once people start developing GUD it is important that they receive care to prevent them slipping away from society and fall between the cracks of the healthcare system. The Trimbos Institute has recently written a comprehensive guideline(Nijkamp, 2019) for municipalities for tracking people with GUD and getting them in care, partly based on studies from this thesis. Phan and colleagues (Phan et al., 2020) also provide a comprehensive overview of materials to be used in the at risk group for GUD. These include an English screening list for GUD and a brief intervention aimed at people who use GHB and are at risk for GUD or display other problems due to their GHB use. For an overview in Dutch, screenings tools and treatment options, the recently published GHB treatment guide can be viewed (https://nispa.nl/projecten/behandeling/handreiking-ghb-behandeling).

Part 2: Pharmacological treatment interventions for patients with GHB use disorder

Considerations concerning detoxification in patients with GUD

In the literature there's an ongoing discussion regarding the difficulties that come with treating GHB withdrawal. In this thesis we presented the first comparison between two detoxification methods, showing that tapering with pharmaceutical GHB can be considered the preferred option for detoxification when compared to benzodiazepines. This is in line with the limited number of studies in the literature on this topic (Dijkstra et al., 2017; McDonough et al., 2004; Neu, 2018) and could be explained by the effects of GHB on the GHB receptor and GABA-B receptor, compared to the BZD's only working on the GABA-A receptor (O. C. Snead & Gibson, 2005). While tapering with pharmaceutical GHB can be considered a safe and effective detoxification method, healthy sleep patterns in patients are continuously disturbed due to the short half-life of GHB. It therefore remains important to further optimize GHB detoxification methods. In the next paragraphs I will propose some directions for future studies on improving the treatment for patients with GUD, particularly on the use of baclofen.

Considerations concerning pharmacological relapse prevention in patients with GUD

A potential substitute for pharmaceutical GHB with a longer half-life could be the GABA-B agonist baclofen. Given the similar pharmacological profiles of GHB and baclofen, future studies should reveal whether baclofen could actually function as a substitute to GHB. Baclofen was found to have positive results as part of GHB relapse management, further study is however needed to confirm these results in an experimental setting.

Given the pharmacological similarities between GHB and baclofen, future studies should also focus on the broader potential of baclofen in the treatment patients with GUD. Recently several case-studies have been published that used baclofen in the detoxification of GHB (Coenen, Dijkstra, Batalla, & Schellekens, 2019; Habibian, Ahamad, McLean, & Socias, 2019). While these initial results are positive, there's no evidence yet that it can be considered a reliable alternative to pharmaceutical GHB tapering. However, if baclofen is able to function as substitute for GHB during detoxification, in a similar way as benzodiazepines are to alcohol, this might be relevant in the detoxification of patients with GUD. First, the frequency of drug administration during detoxification could be drastically decreased in comparison with pharmaceutical GHB. This would allow patients to instantaneously quit GHB, sleep more and decrease the number of staff that is required to constantly monitor them. Second, its potential as relapse management would allow a smooth transition from detoxification to relapse management, where patients continue to use a low dose of baclofen in order to increase treatment retention and abstinence from GHB. Following the principles of contingency management, baclofen could be handed out once a week during psychotherapeutic outpatient treatment. This would

allow patients to slowly taper off, as well as allowing them to learn new skills aimed at preventing a relapse in GHB use, before baclofen is fully tapered off. The potential effects of baclofen could also be used to develop new harm reduction strategies for those patients who repeatedly relapse, in a similar fashion as with methadone programs developed for opioid use disorder patients. Given the prolonged half-life, baclofen could be used to stabilize and structure patients and their environments before starting a new treatment cycle aimed at full recovery.

However, further studies are needed to explore these potential benefits of baclofen in the treatment of patients with GUD. These studies should focus on establishing effectiveness, finding the optimal therapeutic dose, and monitoring for potential risks and side effects in patients with GUD.

Considerations for psychosocial interventions in patients with GUD

Besides pharmacological interventions, patients with GUD also require non-pharmacological interventions, though these were not studied as part of this thesis. As concluded in part 1 of this discussion, GUD should be considered a regular SUD. Therefore, existing evidence-based treatment programs for SUD should be considered for GUD patients as well. However, there are a few issues that should be taken into consideration. First, we showed frequent cognitive impairment, especially when patients are still using GHB (chapter 4). These cognitive impairments will likely result in patients having trouble overseeing their situation, planning accordingly for their recovery, and memorizing what is discussed in psychotherapy sessions. This suggests that patients with GUD might benefit from adjusted treatment approaches, taking these cognitive impairments into account, for instance by providing support in planning, cognitive training, and more frequent therapy sessions with sufficient repetition (Rensen et al., 2019; Verdejo-Garcia, Garcia-Fernandez, & Dom, 2019).

Second, we observed little ambivalence towards GHB in GUD patients (chapter 4). This will require a strong focus on motivational interviewing to create engagement in patients (Diclemente, Corno, Graydon, Wiprovnick, & Knoblach, 2017). This should be supported by psycho-education, perhaps in collaboration with former patients that are now part of peer support groups.

Third, the increased feelings of anxiety as observed in chapter 3 might need special (non-pharmacological) attention. Preparing patients what they are going to experience in combination with learning behavioural strategies how to deal with feelings of anxiety could make it easier for them to endure the first phase of abstinence. To further help the recovery process, I recommend to include (healthy) significant others and/or family/ friends that can provide support to the patient during treatment, especially outside the therapeutic program. A healthy support network that is aware of the vulnerabilities of the patient might be able to provide support during difficult situations.

Considerations for treatment planning and organisation of care for patients with GUD

The negative effects of acute GHB intoxication, withdrawal symptoms and risk for adverse events combined with limited illness insight, high anxiety levels, and cognitive impairment place clinicians for a dilemma; where and how to start with the treatment of GUD? On the one hand, we want patients quitting GHB as fast as possible in order to start both the physical and mental recovery, as well as lifting the negative effects of GHB intoxication on cognition. On the other hand, if we start detoxification with limited preparation, there's a good chance that many patients are not fully aware what's happening and will likely quit treatment during or soon after detoxification, given that they might feel overwhelmed being sober again with the return of stress, anxiety and the full realisation what has happened. Subsequent drop-out from treatment often leads to a fast relapse (25% within the first week)(Dijkstra et al., 2017), which results in a negative treatment experience and requires patients to start the same cycle over and over again.

Looking at the severity of the problems in many domains in patients with GUD as observed in chapter 1-3, it is clear that many patients need extensive treatment and support in order to recover. Given the high drop-out rates, the main focus for improving treatment outcome in patients with GUD should be preventing drop-out, and increasing the period of sobriety. When the latter proves too difficult in the short run a different treatment approach should be undertaken, aimed at reducing harm and improving autonomy in the patient, as suggested by Koekkoek and colleagues(Koekkoek et al., 2011).

In order to improve treatment delivery by health professionals, it is important that they have a good understanding of GUD and its accompanying behaviour. This will allow them to anticipate on the needs of patients during treatment. It is recommended that staff working with patients with GUD receives training and education regarding GUD. As a first step to achieve this, a guideline for the treatment of patients GUD (Joosten et al., 2020) was composed, based on the results of several recent studies, including this thesis.

Methodological considerations

The current thesis should be viewed in the light of several strengths and weaknesses. A major strength is the use of multiple methods to study the topic. We applied literature review, qualitative and quantitative designs, as well as cohort studies and clinical trials. We present the first model for the development of GUD and measured cognitive impairments in patients with GUD seeking treatment. Furthermore, we published the first comparative study into GHB detoxification comparing pharmaceutical GHB and benzodiazepines, and tested baclofen to prevent relapse for the first time.

However, several limitations should also be considered during the interpretation of the current results. From the current literature (chapter 2) it becomes clear that there is

little systematic research into the population GHB users and that available studies often have a limited number of participants. This makes it hard to describe sub-populations in detail. Differences in definitions of key demographic data, substance use and psychiatric symptoms further complicates comparing study populations. More importantly, the lack of longitudinal studies made it impossible say anything about the transition or recreational use to GUD.

In chapter 3 we applied qualitative methods to get some insight in this transition by interviewing patients about the their GUD. While this method gives a lot of information, there is a risk of recall bias, especially due to the distorting effects of GHB on memory. However, while this limitation can of course influence the accounts of patients, it remains their view of the situation. Therefore, the results remain clinically relevant, despite any potentially distorting effects of GHB use or GUD.

The presumed memory problems were confirmed in chapter 4, where many GUD-patients scored low in the MoCA. However, the design of the study, the prevalent polysubstance use and prolonged sleep difficulties make it impossible to disentangle causal GHB effects on cognitive impairment from the effects of other factors. In addition, the cognitive impairments could have been present before the substance use started. Nonetheless, whether causality cannot be established, the results still warrant clinical attention for cognitive impairment in the treatment of patients with GUD.

In part 2 of this thesis two treatments (chapters 5 & 6) were evaluated, while we used control groups in both our treatment evaluation studies, no randomized controlled trial (RCT) designs were used. The detoxification comparison (chapter 5) was based on a matched control group design, which cannot control for all factors that might influence the outcome of the study. Furthermore, the two sites differed in treatment initiation. During the start of BZD treatment, administration started based on changes in vital parameters. Pharma GHB treatment followed more subjective parameters to start administrating pharmaceutical GHB. This difference may have influenced the reported withdrawal. For the comparison of detoxification methods, an RCT would of course be ideally. However, given the fulminant course of GHB withdrawal, risks for serious adverse events and in the literature described problems with BZD detoxification this seems not possible in humans for both practical and ethical reasons.

While the results in the baclofen study in chapter 6 were promising, the open label design should be taken into account. This leaves the risk of mainly including highly motivated patients who are well aware of the risk of relapse and comparing them to patients with an overall higher chance of relapse.

Finally, it should be considered that treatment outcome mainly relied on self-report in our studies, lacking objective validity. This is largely due to the unreliability of blood and urine toxicological tests when it comes to testing for GHB use. Furthermore, the results in this thesis are mainly based on observational and cross-sectional studies coming from the Netherlands. This makes it hard to point out casual relationships and determine all factors

of influence in the results in general. Furthermore, future studies should test whether our findings also generalize to other countries.

Conclusion

This thesis shows that GUD is a complex syndrome that largely adheres to general SUD characteristics. Patients with GUD often display severe substance use problems, with comorbid substance use, high anxiety levels, cognitive impairment and problems across all areas of life, despite a relatively young age. The frequent presence of high anxiety, cognitive impairment and limited illness insight might contribute to high levels of drop-out and relapse. Detoxification with pharmaceutical GHB seems the safest method currently available to taper patients with GUD. Baclofen requires further study, but seems a promising part of relapse management for patients with GUD and should be studied further in this regard.

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Nederlandse samenvatting en discussie

Nederlandse Samenvatting en discussie

De doelstellingen van dit proefschrift waren om 1) ons begrip van de GHB gebruikende populatie te vergroten en de behandelingsbehoeften van patiënten met een stoornis in het gebruik van GHB (GUD) in kaart te brengen, 2) het testen van farmacologische behandelingsinterventies bij patiënten met GUD. In dit hoofdstuk zal ik de belangrijkste bevindingen en hun implicaties bespreken, te beginnen met een samenvatting van de opgenomen hoofdstukken, gevolgd door de algemene conclusies, klinische implicaties, beperkingen en suggesties voor verder onderzoek.

Deel 1: Inzicht in de GHB gebruikende populatie

Hoofdstuk 2 SUBGROEPEN VAN MENSEN DIE GHB GEBRUIKEN

Om een beter overzicht te krijgen in kenmerken van mensen die GHB gebruiken, hebben we een systematische review van de literatuur over (sub)populaties van GHB-gebruikers uitgevoerd. De geïdentificeerde GHB-gebruikende populaties kunnen grofweg worden ingedeeld naar toenemende ernst van GHB-gebruik als recreatief gebruik van GHB zonder complicaties; recreatief gebruik van GHB met complicaties en mensen met GUD. Verschillen tussen deze populaties waren voornamelijk gerelateerd aan de frequentie van GHB-gebruik, redenen voor GHB-gebruik, evenals opleidingsniveau, werkstatus en psychiatrische co morbiditeit. Hoe ernstiger de complicaties, hoe groter de kans dat gebruikers hogere niveaus van GHB-dosis, gebruiksfrequentie, GHB-geïnduceerde coma's, negatieve redenen voor gebruik, co-middelengebruik en psychiatrische co morbiditeit vertonen. Patiënten met GUD hebben vaker een lagere opleiding genoten en zijn vaker werkloos dan recreatieve gebruikers. Door het ontbreken van longitudinale studies blijft het traject van recreatief GHB-gebruik naar problematisch GHB-gebruik en de ontwikkeling van GUD onduidelijk.

Hoofdstuk 3 ZIEKTEPERCEPTIES EN BEHANDELINGSBEHOEFTEN BIJ PATIËNTEN MET GUD

Om een beter begrip te krijgen van patiënten met GUD hebben we diepte-interviews gehouden over ziektepercepties en behandelbehoeften. Uit deze interviews bleek dat patiënten met GUD overwegend positief stonden tegenover GHB. Ze beschreven GHB als een snelwerkende stof, die een persoon een zelfverzekerd gevoel geeft, zonder nadelen. Er is geen kater en de tijdelijke GHB-geïnduceerde coma voelt onschadelijk aan, of wordt helemaal niet opgemerkt. Wanneer GHB-gebruik frequenter wordt, blijven patiënten vooral sterke beloning ervaren, ondanks het begin van ontwenningsverschijnselen. Ontwenningsverschijnselen worden vaak niet als zodanig herkend en leiden doorgaans tot meer GHB-gebruik, waardoor een neerwaartse spiraal begint. Hierdoor wordt GHB gezien als de oplossing voor persoonlijke problemen, niet als de oorzaak. Deze positieve houding

blijft sterk aanwezig bij patiënten, zelfs wanneer GUD ernstiger wordt. De belangrijkste uitgesproken behandelbehoeften waren gerelateerd aan stemmings- en angstsymptomen en niet aan GHB of onthouding. Andere gebieden waar patiënten hulp bij vroegen was goede huisvesting, een ondersteunend sociaal netwerk en zinvolle dagbesteding en / of werk.

Hoofdstuk 4 COGNITIEVE BEPERKINGEN BIJ PATIËNTEN MET GUD

Hoewel onderzoek naar cognitieve stoornissen bij patiënten met GUD beperkt is, tonen verschillende onderzoeken aan dat GHB-gebruik en in het bijzonder herhaalde GHB-geïnduceerde coma's verband houden met geheugenproblemen. Onze studie gebruikte de Montreal Cognitive Assessment (MoCA) om te screenen op cognitieve stoornissen bij patiënten met GUD voor en na detoxificatie. De studie toonde aan dat een aanzienlijk aantal patiënten met GUD positief werd gescreend op cognitieve stoornissen vóór detoxificatie. Het cognitief functioneren verbeterde na detoxificatie, maar nog steeds scoorde een derde positief voor cognitieve stoornissen. Het cognitieve domein dat de sterkste beperking vertoonde, was het geheugen. Cognitieve stoornissen vóór detoxificatie, vooral op de sub-schaal geheugen, waren geassocieerd met terugval.

Deel 2: Farmacologische behandelingsinterventies voor patiënten met GUD

Hoofdstuk 5 GHB-DETOXIFICATIE

Twee farmacologische behandelingsregimes worden vaak gebruikt om ontwenningsverschijnselen tijdens GHB detoxificatie tegen te gaan: afbouwen met benzodiazepinen (BZD's) en afbouwen met farmaceutische GHB. Onze studie was bedoeld om beide tapering-methoden te vergelijken en te bepalen of de ene de voorkeur verdient boven de andere. De resultaten toonden aan dat het afbouwen van GHB geassocieerd was met een milder ontwenningssyndroom en minder bijwerkingen (waaronder delier) tijdens detoxificatie, vergeleken met behandeling met BZD.

Hoofdstuk 6 TERUGVALMANEGEMENT VOOR PATIËNTEN MET GUD

Er is in de huidige praktijk geen GUD-specifiek terugvalmangement beschikbaar. Verschillende onderzoeken hebben echter gesuggereerd dat de GABA-B-agonist baclofen kan helpen bij het verminderen van zucht en angst bij patiënten met GUD. In onze open-label studie hebben we baclofen tot 60 mg voorgeschreven aan patiënten met GUD na detoxificatie. De resultaten toonden aan dat patiënten die baclofen volgens protocol kregen na detoxificatie, een lager terugvalpercentage hadden in vergelijking met patiënten die enkel een reguliere behandeling kregen. Er zijn beperkt bijwerkingen gemeld.

Discussie

Deel 1: Inzicht in de GHB gebruikende populatie

GUD: overeenkomsten en verschillen met andere stoornissen in middelengebruik

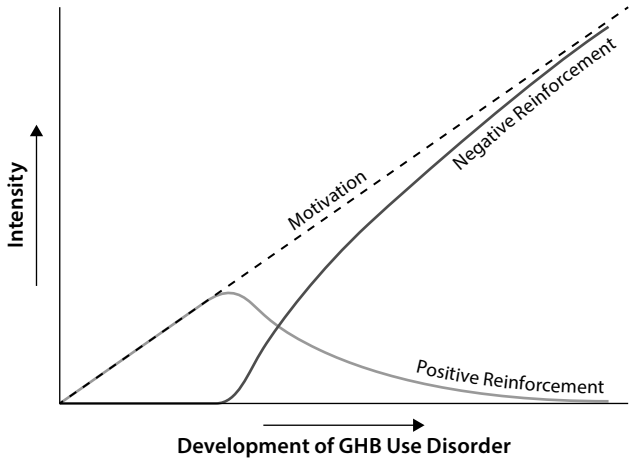
GHB is een relatief nieuwe stof en de verslavende eigenschappen ervan werden twintig jaar geleden voor het eerst beschreven (Galloway et al., 1997; Miotto et al., 2001). Hoewel algemeen wordt erkend dat GHB gebruik kan leiden tot een stoornis (Craig, Gomez, McManus, & Bania, 2000; Miotto et al., 2001; Snead & Gibson, 2005), wordt het niet genoemd in de DSM-5 (American Psychiatric Association. & American Psychiatric Association. DSM-5 Task Force, 2013). De prevalentie lijkt beperkt (Addiction, 2019), maar de problemen die samenhangen met GUD zijn substantieel (Dijkstra et al., 2017; M.S. van Noorden et al., 2009). Bovendien zijn er meldingen van een toenemende prevalentie van GHB-gebruik (Addiction, 2019; Arunogiri et al., 2020), wat zou kunnen resulteren in een verhoogde prevalentie van GUD. De relatieve nieuwheid in combinatie met een zeer beperkt aantal onderzoeken naar GUD zou kunnen verklaren waarom het vaak als een bijzondere groep patiënten wordt gezien. GUD wordt door clinici vaak gezien als een van de meest ernstige en gevaarlijke van alle stoornissen in het gebruik van middelen (Krul & Girbes, 2011; van Noorden et al., 2009). De literatuur in combinatie met het onderzoek uit dit proefschrift laat echter zien dat GUD in veel opzichten een reguliere middelenstoornis is. Hieronder zal ik aangeven waar GUD lijkt op andere stoornissen in het gebruik van middelen en wat specifiek lijkt voor GUD.

Stagering

In hoofdstuk 3 hebben we een model beschreven voor de ontwikkeling van GUD wanneer mensen regelmatig GHB gaan gebruiken, bestaande uit drie fasen, gebaseerd op diepte-interviews. Deze stadia lijken veel op de ontwikkelingsstadia zoals beschreven voor andere stoornissen in het gebruik van middelen (Volkow, Koob, & McLellan, 2016). We hebben deze bestempeld als positieve bekrachtigingsfase, dosis-escalatiefase en de negatieve bekrachtigingsfase. In het begin wordt GHB gebruikt voor ontspanning of een andere positieve bekrachtiging. Na een periode van regelmatig gebruik, wanneer tolerantie zich ontwikkelt, wordt GHB steeds vaker gebruikt om zich normaal te voelen en te functioneren. In de laatste fase is de belangrijkste motivatie om GHB te gebruiken het voorkomen van onthouding en negatief affect, vaak negatieve bekrachtiging genoemd (Volkow et al., 2016). Figuur 1 toont de schematische ontwikkeling van stoornissen in middelengebruik op basis van Koob, 2013 (Koob, 2013), die we hier vertalen naar GUD.

Angst

Veel middelen kunnen angstgevoelens tijdelijk verminderen, zoals alcohol, cannabis en benzodiazepines (Vorspan, Mehtelli, Dupuy, Bloch & Lépine, 2015). Gevoelens van angst



Figuur 1 De ontwikkeling van GUD en motivatie voor GHB-gebruik, gebaseerd op het model van Koob (Koob, 2013).

keren echter over het algemeen terug nadat de acute effecten van middelen zijn uitgewerkt. Herhaalde inname van deze stoffen kan paradoxaal genoeg leiden tot verhoogde gevoelens van angst, wat verder middelengebruik kan stimuleren en een neerwaartse spiraal kan beginnen (Becker, 2017; Koob, 2013). GHB lijkt hierop geen uitzondering (Beurmanjer et al., 2019). De zeer korte halfwaardetijd van GHB zou dit proces zelfs kunnen versnellen (Schep, Knudsen, Slaughter, Vale, & Mégarbane, 2012).

Men zou kunnen stellen dat mensen met een hoge mate van angst die GHB gebruiken, vaker GHB gebruiken vanwege de anxiolytische effecten. Dit kan hen kwetsbaarder maken voor het ontwikkelen van GUD en als gevolg daarvan zijn ze oververtegenwoordigd in de GUD-patiëntenpopulatie. Echter, zoals eerder vermeld, kan frequent gebruik van GHB zelf ook angstgevoelens verhogen als onderdeel van onthouding (Beurmanjer et al., 2019). Terwijl ze onder invloed zijn of out, verdooft dit hun emotionele toestand. Tijdens detoxificatie komen gevoelens van angst echter vaak met verhoogde intensiteit terug (Dijkstra et al., 2017).

Gevoelens van angst kunnen na detoxificatie langdurig aanhouden, wat kan bijdragen aan het risico op terugval, zoals ook blijkt uit onderzoek bij andere middelen met tijdelijk dempende effecten op angst, zoals alcohol (Schellekens, de Jong, Buitelaar & Verkes , 2015). Hoewel een oorzakelijk verband nog niet is vastgesteld, wordt de interactie tussen gevoelens van angst en GHB-gebruik vaak waargenomen en wordt dit voorgesteld als een belangrijke verklaring voor de hoge terugvalpercentages geassocieerd met GUD door patiënten zelf in hoofdstuk 3.

Cognitieve stoornissen

Een belangrijke voorspellende factor voor terugval bij patiënten met een stoornis in middelengebruik (SUD) zijn cognitieve stoornissen (Czapla et al., 2016; Turner, LaRowe, Horner, Herron, & Malcolm, 2009). Onze studie in hoofdstuk 4 liet zien dat de meerderheid van de patiënten met GUD een indicatie had voor cognitieve stoornissen bij het begin van detoxificatie. Dit kan worden toegeschreven aan het actieve gebruik van GHB op het moment van meten en de bekende effecten van GHB op het geheugen (Carter, Griffiths, & Mintzer, 2009). Dit wordt ondersteund door het feit dat de scores van veel patiënten verbeterden na ontgifting. Een stabiele omgeving, met gezonde voeding en verbeterde slaap, zou natuurlijk ook kunnen hebben bijgedragen aan cognitieve verbeteringen (Garcia & Salloum, 2015; Sinha & Jastreboff, 2013).

Toch had ongeveer een derde van de patiënten met GUD een indicatie voor cognitieve stoornissen na detoxificatie (zie hoofdstuk 4). Dit is een relatief hoog aantal vergeleken met andere SUD's, zeker wanneer rekening wordt gehouden met de jonge leeftijd en korte duur van GUD (Bruijnen et al., 2019). Net als bij patiënten met andere SUD's vonden wij geen verband tussen MoCA-scores en jaren van regelmatig gebruik, (GHB-) dosis, ernst van afhankelijkheid en coma (Bruijnen et al., 2019). Dit suggereert dat andere factoren een rol kunnen spelen, bijvoorbeeld slaapgebrek, ondervoeding of andere psychiatrische / somatische co morbiditeit.

Ziekteperceptie van GUD

Hoewel het ontwikkelingstraject van GUD de klassieke ontwikkeling van SUD's lijkt te volgen en de symptomen vergelijkbaar zijn met die van andere SUD's, vertonen patiënten met GUD hogere terugvalpercentages dan de meeste andere groepen. Ongeveer de helft van de patiënten hervalt binnen drie maanden na detoxificatie (Beurmanjer et al., 2018). In hoofdstuk 3 rapporteerden patiënten dat de manier waarop zij naar GHB keken hieraan kan hebben bijgedragen. GHB werd door de meeste deelnemers als het ultieme medicijn beschouwd. Een kleine dosis GHB verhoogt volgens hen het gevoel van eigenwaarde, kan stress doen verdwijnen en alle zorgen even wegnemen. Bovendien komen deze voordelen zonder kater achteraf en lijkt niemand het gebruik van GHB op te merken. Zolang mensen GHB blijven gebruiken, ervaren ze dat ze normaal functioneren zonder de nadelen die ze wel bij andere drugs ervaren. Het ontbreken van deze negatieve feedback lus zou kunnen bijdragen aan de relatief snelle ontwikkeling van ernstige SUD op relatief jonge leeftijd in onze studiepopulatie.

Patiënten met GUD rapporteerden, net als bij andere stoornissen in het gebruik van middelen, de illusie van controle: "Ik kan morgen altijd stoppen". Hoewel dit beperkte inzicht in hun ziekte vergelijkbaar is met die van andere SUD's, wordt de afwezigheid van een negatieve feedback lus door gebruikers beschreven als iets unieks (Beurmanjer et al., 2019). Dit zou kunnen verklaren waarom zelfs abstinente patiënten met GUD GHB blijven omschrijven als "het perfecte medicijn" en er nog steeds zeer sterke positieve associaties

mee hebben. Deze positieve associaties zouden kunnen bijdragen aan een snelle terugval in het dagelijkse GHB-gebruik.

De rol van stigma in GUD

Stigma ten aanzien van patiënten met SUD's komt veel voor, zowel binnen onze maatschappij als de gezondheidszorg (Van Boekel, Brouwers, Van Weeghel, & Garretsen, 2013). GHB lijkt echter met meer stigmatisering te komen dan andere middelen (Palamar & Halkitis, 2006). Tijdens mijn onderzoek ben ik veel clinici tegengekomen die patiënten met GUD omschrijven als 'moeilijk' en soms zelfs als de 'moeilijkste groep' van patiënten met SUD's. Een mixed-method study uit 2011 (Koekkoek, Hutschemaekers, van Meijel, & Schene, 2011) toonde aan dat het 'moeilijke' patiënt- label in verband wordt gebracht met professioneel pessimisme, passieve behandeling, doorverwijzing of beëindiging van zorg. Patiënten met meerdere problemen, zoals patiënten met GUD, missen doorgaans één duidelijke diagnose of komen in aanmerking voor veel diagnoses. Het 'moeilijke' patiëntlabel kan in dergelijke gevallen gemakkelijk worden gegeven, waardoor een meer bruikbare of geldige diagnose wordt verhuld, hetgeen mogelijk schadelijk is voor de patiënt (Koekkoek et al., 2011). Daarentegen werd gevonden dat een duidelijke psychiatrische diagnose patiënten 'beschermt' tegen professioneel pessimisme, vooral een diagnose met een vermeende neurobiologische basis. De status van 'moeilijke' patiënt wordt gemakkelijk versterkt door patiënt- en professioneel gedrag, waarbij aanvankelijk hulpzoekend gedrag wordt gekwalificeerd als 'moeilijk' of ineffectief chronisch ziektegedrag en ineffectief professioneel gedrag (Koekkoek et al., 2011). De relatieve nieuwheid van GHB en het gebrek aan studies naar behandelingen voor deze populatie kunnen hen extra kwetsbaar maken om verkeerd begrepen en als moeilijk bestempeld te worden. Dit onderstreept de noodzaak van onderzoek en bovenal de verspreiding van de resultaten onder (geestelijke) gezondheidswerkers. Dit zal waarschijnlijk helpen voorkomen dat patiënten als moeilijk worden bestempeld en het stigma dat daarmee gepaard gaat. Om dit te bereiken zijn de afgelopen jaren richtlijnen ontwikkeld, seminars en webinars georganiseerd, waaronder postacademische opleidingen voor psychologen, psychiaters en verslavingsartsen. Belangrijker is dat onlangs de eerste uitgebreide GUD-behandelrichtlijn (Joosten, Van Wamel, Beurmanjer, & Dijkstra, 2020) werd ontwikkeld en vrij werd verspreid onder hulpverleners in de geestelijke gezondheidszorg. Deze richtlijn bevat de resultaten van dit proefschrift en een uitgebreid overzicht van alle beschikbare relevante informatie over de behandeling van patiënten met GUD die op dit moment bekend is.

Overwegingen voor beleid te voorkoming van schade door het gebruik van GHB

Op basis van de onderzoeken in dit proefschrift kunnen verschillende aanbevelingen worden gedaan om schade door het gebruik van GHB te voorkomen. Hoewel veel mensen die GHB gebruiken het middel als onschuldig beschouwen, blijkt uit de literatuur dat dit niet het geval is. Preventiebeleid dient er op gericht te zijn om de mogelijke risico's van GHB-gebruik onder de aandacht te brengen. GHB-geïnduceerde coma's kunnen bijvoorbeeld onschuldig aanvoelen, maar er is voldoende bewijs om aan te nemen dat deze kunnen leiden tot cognitieve problemen en ongelukken.

Bovendien hebben we gezien dat GUD zich snel kan ontwikkelen en dat de eerste tekenen van GUD gemakkelijk over het hoofd kunnen worden gezien door de patiënt totdat het te laat is. Phan en collega's (Phan, Arunogiri, & Lubman, 2020) hebben verschillende suggesties gedaan met betrekking tot strategieën voor preventie en schadebeperking, gericht op GHB-gebruikers in Australië. Bijvoorbeeld het maken van meerdere korte voorlichtingsfilmpjes voor zorgprofessionals en compact schadebeperkingsadvies gericht op mensen die GHB gebruiken. Deze laatste is opgesteld me de afkorting STAYING SAFE (zie tabel 1) en zou kunnen dienen als basisinformatie die preventiewerkers aan GHB-gebruikers kunnen geven. Toekomstig onderzoek moet echter uitwijzen of het verstrekken van deze informatie daadwerkelijk helpt het verkleinen van risico's bij mensen die GHB gebruiken.

Als mensen eenmaal GUD gaan ontwikkelen, is het belangrijk dat ze zorg krijgen om te voorkomen dat ze uit de samenleving wegglijden en tussen de kieren van de gezondheidszorg vallen. Het Trimbos-instituut heeft onlangs een uitgebreide richtlijn geschreven (Nijkamp, 2019) voor gemeenten om mensen met GUD op te sporen en in zorg te krijgen, mede op basis van onderzoeken uit dit proefschrift. Phan en collega's (Phan et al., 2020) geven ook een uitgebreid overzicht van materialen die kunnen worden gebruikt in de risicogroep voor GUD. Deze omvatten een Engelse screeninglijst voor GUD en een korte interventie gericht op mensen die GHB gebruiken en risico lopen op GUD of andere problemen vertonen door hun GHB-gebruik. Voor een overzicht in het Nederlands, screeningtools en behandelmogelijkheden is de recent verschenen GHB behandelhandreiking te raadplegen (https://nispa.nl/projecten/behandeling/handreiking-ghb-behandeling).

Deel 2: Farmacologische behandelingsinterventies voor patiënten met GUD

Overwegingen met betrekking tot detoxificatie bij patiënten met GUD

In de literatuur is er een voortdurende discussie over de moeilijkheden die gepaard gaan met het behandelen van GHB-ontwenning. In dit proefschrift presenteerden we de eerste vergelijking tussen twee detoxificatiemethoden, waaruit blijkt dat het afbouwen met

Table 1 STAING SAFE overview

STAYING SAFE	
S	Seek medical attention immediately if you have taken too much GHB. Do not use other drugs in the hope of reversing the effects.
T	Two or more substances used at the same time increase the risk of overdose significantly (especially sedatives; eg alcohol, ketamine).
A	Always measure GHB doses accurately (eg with a syringe or pipette). Wait until the effects are felt and do not re-dose for at least two hours.
Y	You should always avoid using GHB on your own and always use in a safe place and with someone who has not taken it, as it is common to become unconscious.
I	If you have used and are going to sleep, sleep on your side in case you are sick. Place sleeping or unconscious friends in the recovery position.
N	Never keep GHB in drink bottles, where it might be drunk by others not aware of the content. Add food colouring to avoid accidental drinking.
G	GHB is addictive and dependence can happen quickly. Avoid frequent use, especially daily use.
S	Severe and potentially serious GHB withdrawal symptoms occur if you are dependent and you miss a dose or reduce amounts taken abruptly.
A	Acute withdrawal symptoms and have no GHB? Seek medical help immediately in an emergency department.
F	Find medical support for planned GHB detoxification. Do not attempt to stop abruptly on your own. If you want to reduce your dose, do so in very small doses until you find medical support.
E	Employ methods to stabilise your use; consumption diaries can be helpful.

Originally from Phan and colleagues(Phan et al., 2020)

farmaceutisch GHB als de voorkeursoptie voor detoxificatie kan worden beschouwd in vergelijking met benzodiazepinen. Dit komt overeen met het beperkte aantal studies in de literatuur over dit onderwerp (Dijkstra et al., 2017; McDonough et al., 2004; Neu, 2018) en zou verklaard kunnen worden door de effecten van GHB op de GHB-receptor en GABA-B-receptor, vergeleken met de BZD's die alleen werken op de GABA-A-receptor (Snead & Gibson, 2005). Terwijl het afbouwen met farmaceutisch GHB als veilig en effectief kan worden beschouwd, blijven gezonde slaappatronen bij patiënten verstoord vanwege de korte halfwaardetijd van GHB. Het blijft daarom belangrijk om de detoxificatiemethoden van GHB verder te optimaliseren. In de volgende paragrafen zal ik enkele voorstellen doen voor toekomstige studies om de behandeling van patiënten met GUD te verbeteren, met name wat betreft het gebruik van baclofen.

Overwegingen met betrekking tot farmacologische terugvalpreventie bij patiënten met GUD

Een mogelijke vervanger voor farmaceutisch GHB met een langere halfwaardetijd zou de GABA-B-agonist baclofen kunnen zijn. Gezien de vergelijkbare farmacologische profielen van GHB en baclofen, zouden toekomstige studies moeten uitwijzen of baclofen daadwerkelijk zou kunnen functioneren als vervanging voor GHB. Baclofen bleek positieve resultaten te hebben als onderdeel van het terugvalmanagement van GHB, verder onderzoek is echter nodig om deze resultaten in een experimentele setting te bevestigen.

Gezien de farmacologische overeenkomsten tussen GHB en baclofen, zouden toekomstige studies zich ook moeten richten op het bredere potentieel van baclofen bij de behandeling van patiënten met GUD. Onlangs zijn er verschillende case-studies gepubliceerd die baclofen gebruikten bij de ontgifting van GHB (Coenen, Dijkstra, Batalla, & Schellekens, 2019; Habibian, Ahamad, McLean, & Socias, 2019). Hoewel deze eerste resultaten positief zijn, is er nog geen bewijs dat het kan worden beschouwd als een betrouwbaar alternatief voor farmaceutische GHB-tapering. Als baclofen echter kan fungeren als substituut voor GHB tijdens detoxificatie, op dezelfde manier als benzodiazepines voor alcohol, kan dit relevant zijn bij de detoxificatie van patiënten met GUD. Ten eerste zou de frequentie van medicijntoediening tijdens detoxificatie drastisch kunnen worden verlaagd in vergelijking met farmaceutische GHB. Hierdoor kunnen patiënten onmiddellijk stoppen met GHB, meer slapen en de personele inzet verminderen die nodig is om hen constant te monitoren. Ten tweede zou het potentieel van baclofen als terugvalmanagement een soepele overgang mogelijk maken van detoxificatie naar terugvalmanagement, waarbij patiënten een lage dosis baclofen blijven gebruiken om abstinentie van GHB te behouden en behandeluitval te voorkomen. Volgens de principes van contingentie management kan baclofen eenmaal per week worden meegegeven tijdens ambulante behandelingen. Hierdoor kunnen patiënten langzaam afbouwen en kunnen ze nieuwe vaardigheden leren om een terugval in het gebruik van GHB te voorkomen, voordat baclofen volledig wordt afgebouwd. De mogelijke effecten van baclofen kunnen ook worden gebruikt om nieuwe strategieën voor harm reduction te ontwikkelen voor patiënten die herhaaldelijk terugvallen, op een vergelijkbare manier als bij methadonprogramma's die zijn ontwikkeld voor patiënten met stoornissen in het gebruik van opiaten. Gezien de verlengde halfwaardetijd zou baclofen kunnen worden gebruikt om patiënten en hun omgeving te stabiliseren en te structureren voordat een nieuwe behandelingscyclus wordt gestart die gericht is op volledig herstel.

Er zijn echter verdere studies nodig om deze mogelijke voordelen van baclofen bij de behandeling van patiënten met GUD te onderzoeken. Deze onderzoeken moeten zich richten op het vaststellen van de effectiviteit, het vinden van de optimale therapeutische dosis en het controleren op mogelijke risico's en bijwerkingen bij patiënten met GUD.

Overwegingen voor psychosociale interventies bij patiënten met GUD

Naast farmacologische interventies hebben patiënten met GUD bovenal niet-farmacologische interventies nodig, hoewel deze niet zijn onderzocht als onderdeel van dit proefschrift. Zoals geconcludeerd in deel 1 van deze discussie, moet GUD worden beschouwd als een gewone SUD. Daarom moeten bestaande evidence-based behandelprogramma's voor SUD ook voor GUD-patiënten worden overwogen. Er is echter een aantal zaken waarmee rekening gehouden moet worden. Ten eerste hebben we laten zien dat het cognitief functioneren bij veel patiënten met GUD is aangedaan, vooral wanneer patiënten nog steeds GHB gebruiken (hoofdstuk 4). Deze cognitieve stoornissen zullen er waarschijnlijk toe leiden dat patiënten moeite hebben om hun situatie te overzien, hun herstel dienovereenkomstig te plannen en te onthouden wat in behandeling wordt besproken. Dit suggereert dat patiënten met GUD baat zouden kunnen hebben bij aangepaste behandelmethoden, rekening houdend met deze cognitieve problemen, bijvoorbeeld door ondersteuning te bieden bij planning, cognitieve training en frequentere therapiesessies met voldoende herhaling (Rensen, Egger, Westhoff, Walvoort & Kessels , 2019; Verdejo-Garcia, Garcia-Fernandez en Dom, 2019).

Ten tweede hebben we bij GUD-patiënten weinig ambivalentie waargenomen ten opzichte van GHB (hoofdstuk 4). Dit vereist een sterke focus op motiverende gespreksvoering om betrokkenheid van patiënten ten aanzien van hun behandeling te creëren (Diclemente, Corno, Graydon, Wiprovnick, & Knoblach, 2017). Dit zou ondersteund moeten worden door psycho-educatie, misschien in samenwerking met voormalige patiënten die nu deel uitmaken van peer support groepen.

Ten derde, de toegenomen angstgevoelens, zoals waargenomen in hoofdstuk 3, hebben mogelijk speciale (niet-farmacologische) aandacht nodig. Patiënten voorbereiden op wat ze gaan ervaren in combinatie met het aanleren van gedragsstrategieën om met angstgevoelens om te gaan, zou het voor hen gemakkelijker kunnen maken om de eerste fase van onthouding te doorstaan. Om het herstelproces verder te helpen, is het aan te bevelen om (gezonde) belangrijke naasten te betrekken die ondersteuning kunnen bieden aan de patiënt tijdens de behandeling, vooral buiten het therapeutisch programma. Een gezond ondersteuningsnetwerk dat zich bewust is van de kwetsbaarheden van de patiënt zou in moeilijke situaties ondersteuning kunnen bieden.

Overwegingen bij het plannen van de behandeling en de organisatie van de zorg voor patiënten met GUD

De negatieve effecten van acute GHB-intoxicatie, ontwenningsverschijnselen en risico op bijwerkingen in combinatie met beperkt inzicht in ziekte, hoge angstniveaus en cognitieve stoornissen plaatsen clinici voor een dilemma; waar en hoe te beginnen met de behandeling van GUD? Enerzijds willen we dat patiënten zo snel mogelijk stoppen met GHB om zowel lichamelijk als geestelijk te herstellen en de negatieve effecten van GHB-intoxicatie op cognitie op te heffen. Aan de andere kant, als we beginnen met detoxificatie

met beperkte voorbereiding, is de kans groot dat veel patiënten niet volledig weten wat er gebeurt en waarschijnlijk de behandeling zullen stoppen tijdens of kort na de detoxificatie, aangezien ze zich overweldigd kunnen voelen om weer nuchter te zijn met de terugkeer van stress, angst en het volledige besef wat er is gebeurd. Daaropvolgende uitval van de behandeling leidt vaak tot een snelle terugval (25% binnen de eerste week) (Dijkstra et al., 2017), wat resulteert in een negatieve behandelervaring en vereist dat patiënten dezelfde cyclus steeds opnieuw beginnen.

Kijkend naar de ernst van de problemen in veel domeinen bij patiënten met GUD, zoals waargenomen in hoofdstuk 1-3, is het duidelijk dat veel patiënten uitgebreide behandeling en ondersteuning nodig hebben om te herstellen. Gezien de hoge uitval-percentages, zou het voorkomen van uitval en het verlengen van de periode van nuchterheid de belangrijkste focus voor het verbeteren van het behandelresultaat bij patiënten met GUD moeten zijn. Wanneer dat laatste op korte termijn te moeilijk blijkt, moet een andere behandelaanpak worden gevolgd, gericht op het verminderen van schade en het verbeteren van de autonomie van de patiënt, zoals gesuggereerd door Koekkoek en collega's (Koekkoek et al., 2011).

Om goede ondersteuning te bieden in behandeling, is het belangrijk dat behandelaren een goed begrip hebben van GUD en het bijbehorende gedrag. Hierdoor kunnen ze anticiperen op de behoeften van patiënten tijdens de behandeling. Het wordt aanbevolen dat personeel dat met patiënten met GUD werkt, training en opleiding krijgt over GUD. Als eerste stap om dit te bereiken is een richtlijn voor de behandeling van patiënten GUD (Joosten et al., 2020) opgesteld, gebaseerd op de resultaten van verschillende recente onderzoeken, waaronder dit proefschrift.

Methodologische overwegingen

Het huidige proefschrift moet worden gezien in het licht van verschillende sterke en zwakke punten. Een kracht is het gebruik van meerdere methoden om het onderwerp te bestuderen. We pasten literatuuronderzoek, kwalitatieve en kwantitatieve designs toe, evenals cohortstudies en klinische trials. We presenteren het eerste model voor de ontwikkeling van GUD en meten cognitieve stoornissen bij patiënten met GUD die behandeling zoeken. Verder publiceerden we de eerste vergelijkende studie naar GHB detoxificatie door farmaceutische GHB en benzodiazepines te vergelijken, en bekeken we de mogelijkheden van het voorschrijven van baclofen als onderdeel van terugvalmanagement.

Bij de interpretatie van de huidige resultaten moet echter ook rekening worden gehouden met verschillende beperkingen. Uit de huidige literatuur (hoofdstuk 2) blijkt dat er weinig systematisch onderzoek is naar de populatie GHB-gebruikers en dat beschikbare onderzoeken vaak een beperkt aantal deelnemers hebben. Dit maakt het

moeilijk om subpopulaties in detail te beschrijven. Verschillen in definities van belangrijke demografische gegevens, middelengebruik en psychiatrische symptomen bemoeilijken het vergelijken van onderzoekspopulaties verder. Belangrijker nog, het ontbreken van longitudinale studies maakte het onmogelijk om iets te zeggen over de overgang of recreatief gebruik naar GUD.

In hoofdstuk 3 hebben we kwalitatieve methoden toegepast om enig inzicht te krijgen in deze transitie door patiënten te interviewen over hun GUD. Hoewel deze methode veel informatie geeft, bestaat er een risico op recall-bias, vooral vanwege de verstorende effecten van GHB op het geheugen. Hoewel deze beperking natuurlijk de herinneringen van patiënten kan beïnvloeden, blijft het hun kijk op de situatie. Daarom blijven de resultaten klinisch relevant, ondanks mogelijke verstorende effecten van GHB-gebruik of GUD.

De veronderstelde geheugenproblemen werden bevestigd in hoofdstuk 4, waar veel GUD-patiënten laag scoorden in de MoCA. De opzet van de studie, het veel voorkomende polymiddelengebruik en langdurige slaapproblemen maken het echter onmogelijk om causale GHB-effecten op cognitieve stoornissen los te koppelen van de effecten van andere factoren. Bovendien zouden de cognitieve stoornissen aanwezig kunnen zijn voordat het middelengebruik begon. Hoewel causaliteit niet kan worden vastgesteld, rechtvaardigen de resultaten klinische aandacht voor cognitieve stoornissen bij de behandeling van patiënten met GUD.

In deel 2 van dit proefschrift werden twee behandelingen (hoofdstukken 5 en 6) geëvalueerd, hoewel we hierbij controlegroepen gebruikten, waren dit geen gerandomiseerde gecontroleerde trials (RCT). De detoxificatievergelijking (hoofdstuk 5) was gebaseerd op een gematchte controlegroep design, dit kan niet voor alle factoren controleren die de uitkomst van het onderzoek zouden kunnen beïnvloeden. Bovendien verschilden de twee locaties in de start van medicatietoediening. Tijdens de start van de BZD-behandeling werd de toediening gestart op basis van veranderingen in vitale parameters. Farmaceutische GHB-behandeling volgde meer subjectieve parameters om te beginnen met het toedienen van farmaceutische GHB. Dit verschil kan de gemelde onthouding hebben beïnvloed. Voor de vergelijking van detoxificatiemethodes zou een RCT natuurlijk ideaal zijn. Echter, gezien het snelle beloop van het GHB onthoudingssyndroom, risico's op ernstige bijwerkingen en in de literatuur beschreven problemen met BZD-detoxificatie dit lijkt een RCT niet mogelijk bij mensen om zowel praktische als ethische redenen.

Hoewel de resultaten van de baclofenstudie in hoofdstuk 6 veelbelovend waren, moet rekening worden gehouden met het open label design. Dit laat het risico bestaan om voornamelijk zeer gemotiveerde patiënten op te nemen die zich terdege bewust zijn van het risico op terugval, en deze te vergelijken met patiënten met een algemeen grotere kans op terugval.

Ten slotte moet worden opgemerkt dat de uitkomst van de behandeling voornamelijk berustte op zelfrapportage in onze studies, waarbij objectieve validiteit ontbrak. Dit komt grotendeels door de onbetrouwbaarheid van toxicologische tests uit bloed en urine als het gaat om het testen op GHB-gebruik. Bovendien zijn de resultaten in dit proefschrift voornamelijk gebaseerd op observationele en cross-sectionele studies afkomstig uit Nederland. Dit maakt het lastiger om causale verbanden aan te tonen en alle factoren van invloed op de resultaten in het algemeen te bepalen. Toekomstige studies moeten testen of onze bevindingen ook te generaliseren naar andere landen.

Conclusie

Dit proefschrift laat zien dat GUD een complex syndroom is dat grotendeels voldoet aan algemene SUD-kenmerken. Patiënten met GUD vertonen vaak ernstige stoornissen in middelengebruik, polydrugsgebruik, hoge angstniveaus, cognitieve problemen en problemen op vele levensgebieden, ondanks een relatief jonge leeftijd. De frequente aanwezigheid van angstgevoelens, cognitieve problemen en beperkt inzicht in ziekte kan mogelijk bijdragen aan de hoge mate van uitval en terugval binnen deze groep. Detoxificatie met farmaceutische GHB lijkt de veiligste methode die momenteel beschikbaar is om patiënten met GUD af te bouwen. Baclofen vereist verder onderzoek, maar lijkt een veelbelovend onderdeel van terugvalmanagement voor patiënten met GUD en verdiend verdere studie in de toekomst.

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En tot slot, diegene die mij altijd vergezelde en steunde op deze promotiereis en vele andere reizen… Sarah, Sarah, Sarah.

Publications and grants

Publications and grants

Peer reviewed publications:

Wolf C. J. H., Beurmanjer H., Dijkstra B. A.G., Geerlings A., Spoelder M., Homberg J. R., Schellekens A. F.A. (2021) Characterization of the GHB withdrawal syndrome. *Journal of Clinical Medicine*.

Dijkstra B. A. G., Beurmanjer H., Goudriaan A. E., Schellekens A. F. A., Joosten E. A. G. (2021) Unity in diversity: A systematic review on the GHB using population. *International Journal of Drug Policy*.

Bruijnen, C. J. W. H., Dijkstra, B. A. G., Walvoort, S. J. W., Budy, M. J. J., Beurmanjer, H., De Jong, C. A. J., & Kessels, R. P. C. (2020). Psychometric properties of the Montreal Cognitive Assessment (MoCA) in healthy participants aged 18–70. *International Journal of Psychiatry in Clinical Practice*

Beurmanjer, H., Luykx, J. J., De Wilde, B., van Rompaey, K., Buwalda, V. J. A., De Jong, C. A. J., Dijkstra, B. A. G., Schellekens, A. F. A. (2020). Tapering with Pharmaceutical GHB or Benzodiazepines for Detoxification in GHB-Dependent Patients: A Matched-Subject Observational Study of Treatment-as-Usual in Belgium and The Netherlands. *CNS Drugs*

Beurmanjer, H., Asperslag, E. M., Oliemeulen, L., Goudriaan, A. E., De Jong, C. A. J., Schellekens, A. S. A., & Dijkstra, B. A. G. (2019). A Qualitative Approach in Understanding Illness Perception and Treatment Needs in Patients with Gamma Hydroxybutyrate Use Disorder. *European Addiction Research*.

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Submitted publications:

Beurmanjer H., Bruijnen C. J. W. H., Greeven P. G. J., De Jong C. A. J., Schellekens A. F. A, Dijkstra B. A. G. Cognitive impairments in patients with GHB use disorder predict relapse in GHB use. (submitted).

Wolf C. J. H., Venselaar H., Spoelder M., Beurmanjer H., Schellekens A. F.A. and Homberg J. R. Structural identification of the gamma-hydroxybutyric acid receptor through a bioinformatics approach. (submitted)

Other publications

Joosten, E.A.G.; Wamel, A.L. van; Beurmanjer, H.; Dijkstra, B.A.G. (2020) Handreiking voor GHB behandeling. NISPA, Nijmegen

Joosten, E.A.G.; Wamel, A.L. van; Beurmanjer, H.; Dijkstra, B.A.G. (2020) Handreiking voor GHB behandeling; *Achtergronddocument*. NISPA, Nijmegen

Joosten, E.A.G.; Wamel, A.L. van; Beurmanjer, H.; Dijkstra, B.A.G. (2020) Kenmerken GHB verslaving en kernelementen GHB behandeling voor behandelaren, *factsheet*. NISPA, Nijmegen

Joosten, E. A. G., Beurmanjer, H., Dijkstra, B. A. G., Schellekens A. F. A. (2020) GHB gebruik, afhankelijkheid en behandeling. AccreDidact nascholing, Houten
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Beurmanjer, H.; Verbrugge, C.A.G.; Schrijen, S.P.J.W.; Schellekens, A.F.A.; Jong, C.A.J. de; Dijkstra, B.A.G. (2016) Behandeling van GHB afhankelijkheid na detoxificatie: Eindrapportage NISPA GHB monitor 2.0. NISPA Nijmegen

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Beurmanjer, H., De Jong, M., Poelmans, I., De Weert-van Oene, G. (2012) *TENDENS*: Trends in wonen, werken en middelengebruik: de Gelderse sociale kwetsbaarheid- en middelenmonitor, Eindrapport editie 2011-2012. IrisZorg, Arnhem

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- ZonMW, Project 'GHB behandelhandreiking' (2018) € 200.000
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Curriculum Vitae

Curriculum Vitae

Harmen Beurmanjer was born on January 10 1986 in Wageningen, the Netherlands. He studied Psychology at the Radboud University Nijmegen. During his studies he worked as a data assistant for the addiction care centre IrisZorg, focusing on a project that studied treatment perspective for patients with chronic substance use disorders. This experience motivated him to choose the specialisation of Clinical Psychology. In 2010 Harmen graduated from the Radboud University Nijmegen with a master's degree in Clinical Psychology.

After his graduation he reapplied to work at IrisZorg, this time in the role of researcher and advisor. In his new position he focused on mapping substance use and the need for treatment in the province of Gelderland. During this time, he also joined the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA).

In 2013 Harmen was invited by the NISPA to join a grant application for a new project aimed at improving withdrawal management for patients with a GHB use disorder. The Ministry of Health, Welfare and Sport (VWS) awarded the grant in 2014 for the project 'GHB 2.0', Harmen was then appointed as project coordinator. In the same year he started a new job at the addiction care centre Novadic-Kentron, where he continued his research on GHB use disorders. In 2015 he was awarded a stipend to start working on his PhD. Since then, Harmen has also been a member of the internal GHB expert council and the scientific committee of Novadic-Kentron. In addition, he regularly acted as a spokesperson in the media on behalf of his institution. In the same period, he was appointed as senior lecturer 'Addiction' at both the Radboud Centre Social Sciences in Nijmegen and Rino Zuid in Eindhoven for the post-academic training programs for Mental Health (GZ) psychologists.

After finishing his PhD Harmen continues to work at the main clinical facility of Novadic-Kentron in Vught, where he will mainly focus on acquiring the quality mark of "TOPGGz" for his department. Besides GHB use disorders his research will expand to further development of treatment approaches for patients with chronic pain and substance use disorders. Harmen will continue to combine his research and clinical work with the teaching and training of various healthcare workers in the field of substance use disorders.

Supplements

Supplement I

Unity in diversity: A systematic review on the GHB using population
B.A.G. Dijkstra, H. Beurmanjer, A.E. Goudriaan, A.F.A. Schellekens, E.A.G. Joosten

Overview included studies

People reporting at emergency departments with GHB overdose

Reference	Aim	Study design	Methods
Anderson et al., 2009; Dyer et al., 2001	To investigate the correlation between area-level socioeconomic status (SES) and GHB use patterns.	Cohort study (retrospective case record) from January 1, 1999 to July 1, 2007.	N= 210 (Anderson et al., 2009). N= 8, case series (Dyer et al., 2001). GHB-related cases reported to California Poison Control System (CPCS), United States, 24h emergency telephone consultation service for public and health care professionals.
Anderson et al., 2006	To analyse changes in GHB case reporting.	Retrospective case report study from 1-1-1999 through 31-12-2003.	N=1,331, GHB-related cases reported to California Poison Control System (CPCS), United States, 24h emergency telephone consultation service.
Boyce et al., 2000	Presentation of GHB related intoxications at an emergency department.	Case report	N=7, Patients presented at an emergency department in the UK who consumed GHB either alone or in conjunction with other drugs and alcohol.
Boyd et al., 2012	To study the frequency of injecting drug use among GHB/GBL overdose patients and whether there are temporal differences in the occurrence of GHB/GBL overdoses of injecting drug and recreational drug users.	Retrospective database study from 1-1-2006 to 31-12-2007.	N=100 GHB/GBL overdoses / n=90 patients. Ambulance and hospital records of suspected GHB/GBL overdose patients treated by Helsinki Emergency medical service, Finland: group A (n=39) overdose occurred on a Friday or Saturday night between 11pm-6am, group B (n=61) overdoses occurring outside this time frame.

Population description and results

Demographics: 67.7% male; over 30 years (40.0%); Median annual household income (x10.000 dollars): 5.2; Median home value (x100.000 dollars): 3.4; mainly urban participants.
GHB use: Reported GHB dependence in 18% of cases. Likelihood of major GHB adverse health outcomes increased 40% for every 100,000 dollar increase in median home values. There was a similar association regarding household income and related to 3 out of 4 high-risk behaviours (GHB dependence, GHB congener use, and co-use of other substances).
Other substance use: Co-use with other substances (16%) and alcohol alone (20%) at any time. Reported polydrug-use in past in 33.3%: alcohol (20.5%), amphetamine (6.7%), benzodiazepine (4.3%), cocaine (2.9%), cannabis (1.9%), MDMA (1.4%), opiates (1.0%), ketamine (0.5%), thyroid (0.5%), and SSRI's (0.5%).

Demographics: 55 % male (percentage of women increased from 38% to 60% between 1999 and 2003); M=27, SD=9 years; No/moderate income (26%), moderate (59%).
GHB use: 76% decrease of reported GHB cases from 1999 (n=426) to 2003 (n=101). Moderate severity in 59% of the cases.
Other substance use: Polydrug use was common. Alcohol use (self-reported) in 59% and 21% by laboratory testing. Laboratory results (n=152): ecstasy (29%), amphetamines (24%), cocaine (12.5%), cannabis (12%), benzodiazepines (10%).

Demographics: 57% male (n=4), M=21.9 years.
GHB use: Only substance GHB in 1 case.
Other substance use: 6 cases with co-ingestion of other substances; most mentioned were alcohol (n=3) and heroin (n=3).

Demographics: 49% male (group A) and 57% (group B); Median 24 (range 22-27) years (group A) and median 25 (range 23-29) years (group B).
Other: Location: group A: private (10%), public indoors (41%), and outdoors (41%); group B: private (25%), public indoors (18%), and outdoors (53%).
Other substance use: history of injecting drug-use 33% (group A) and 59% (group B). Polydrug and alcohol use was 80% (group A) and 62% (group B).

People reporting at emergency departments with GHB overdose *(Continued)*

Reference	Aim	Study design	Methods
Chin et al., 1998	To define the clinical characteristics and course of GHB overdose.	Retrospective database study.	N=88, cases of GHB ingestion at an emergency department of San Francisco General Hospital, United States (2 cases visited emergency department twice).
Couper et al., 2004	To present drug test results (GHB and other drugs) and clinical symptoms of patients presenting to the emergency department.	Retrospective database study over a period of 12 months.	N (total)=146, N (GHB confirmed in blood)=54. Suspected GHB-overdose patients admitted to the emergency department in a major Seattle Hospital (United States).
Dietze et al., 2008	To study the nature and extent of ambulance attendances involving GHB and to compare these with heroin-related attendances.	Retrospective database study from March 2001 to October 2005.	N=618 GHB related ambulance attendances in Melbourne Australia (362 involving GHB only and 256 involving the current use of GHB and other drugs).
Dutch & Austin, 2012	To examine medical assistance at dance events of GHB intoxications regarding clinical presentation, required interventions and patterns.	Retrospective database study from January 2010 through May 2011.	N=61, GHB-intoxicated attendees of St. John Ambulance medical assistance teams at 14 of 24 dance music festival events in the state of Victoria (Australia).
Galicia et al., 2011	To describe the clinical and epidemiological profile of GHB intoxicated patients.	Retrospective database study from April 2000 – December 2007.	N=505, GHB intoxicated (overdose) patients seen at the emergency department of a tertiary university hospital in Barcelona (Spain). Patients were divided into 1) pure GHB and 2) GHB and other drugs.
Galacia et al., 2019	To examine clinical impact of co-ingestion of ethanol in patients presenting to the ED with acute toxicity related GHB/GBL use.	Retrospective database study (secondary analysis) between October 2013 – December 2016.	N=609, patients attended at the emergency department of 22 participating centres in the Euro-DEN network (14 countries).

Population description and results

Demographics: 69% male; M=28, SD=5.9, range 18-51 years.
Other: Documented history of psychiatric problems in 5 cases (6%).
Other substance use: suspected co-ingestion of GHB and alcohol was 39% and GHB with other substances 28%, most commonly amphetamine (17%), ecstasy (14%), and cocaine (5%). Multiple substances in 11 of the 88 cases (12.5%).

Demographics: 60% male (83% male among detected GHB and 47% male among not detected GHB); median 25 (range 14-59) years, GHB detected: median 23 (range 17-59) years, not detected GHB: median 23 (range 14-54) years.
GHB use: 37% of the cases GHB was detected. Blood GHB-concentrations: M=137, median=137, range 29 to 490 mg/L.
Other substance use: In 37% of the cases other substances were detected besides GHB (most commonly): ethanol (41%), MDMA (19%), cannabis (11%), methamphetamines (9%), cocaine (9%), and citalopram (7%). In 70 out of 92 patients (76%), other substances than GHB were detected (most commonly): ethanol (48%), cannabis (18%), MDMA (13%), methamphetamine (7%).

Demographics: 60-65% male (total population), 60% male (GHB-mixed), 65% male (GHB only); GHB-mixed: <20 years (27%), 20-24 years (40%), 25-29 years (20%), 30-34 years (9%), and 35+ years (4%). GHB only: <20 years (21%), 20-24 years (42%), 25-29 years (23%), 30-34 years (8%), and 35+ years (6%).
GHB ambulance attendances: GHB-related attendances increased by around 4% per month (higher rate than found for heroin overdose attendances). More GHB-related cases were female (35-40%) than heroin cases (26%).
GHB-mixed: attended private space (22%), police co-attendance (14%), transport to hospital (92%). GHB only: attended private space (15%), police co-attendance (19%), transport to hospital (90%).
GHB cases were more likely to be attended in public, presented in a less unconscious state, and higher rate of transport to hospital than patients who took heroin.

Demographics: 64% male; M=22, IQR=20-25 years.
GHB intoxications: In 89% GHB intoxicated patients presented in an altered conscious state and 44% profoundly unconscious. Approx. 23% occurred at the last 2 hours of the event.
Other substance use: co-ingestion with ecstasy (21%), alcohol (13%), speed (11%).

Demographics: 68% male (total population), 70% male (pure GHB group), 68% male (combined GHB group); M=24.7 years; <25 years: 57% (pure GHB group) and 58% (combined GHB group).
Other: 80% of the attendees between 0.00-08.00h and 82% during the weekend.
GHB use: Only GHB in 24% and GHB combined with other substances in 76% of the cases.
Other substance use: most common other drugs were ethanol (64%), MDMA (30%), and cocaine (29%).

Demographics: Total population: 81% male; M=32.0, DE=8.4 years. GHB/GBL alone: 83.6% male; M=33.1, DE:7.9 years. GHB/GBL + ethanol: 79.8% male; M=31.5, DE=8.5 years.
Other: arrived by ambulance: total population (81.1%), GHB/GBL alone (68.3%), GHB/GBL + ethanol (86.6%).

People reporting at emergency departments with GHB overdose *(Continued)*

Reference	Aim	Study design	Methods
Horyniak et al., 2013	To define patterns and characteristics of emergency department presentations related to ecstasy and related drugs use.	Retrospective database study from 1 January 2008 through 31 December 2010.	N (total)=1347; N (GHB)=480. Ecstasy and related drug presentations at the emergency department of two tertiary hospitals in Melbourne (Australia).
Kapitany-Foveny et al., 2017	To assess frequency of facilitated sexual assaults and acquisitory crimes at emergency department; to examine possible differences between intentional / unintentional GHB use and GHB / GHB + polysubstance.	Retrospective database study between 14-9-2009 and 13-6-2013.	N= 408 casus (352 patients). Patients assumed or proven GHB consumption at a clinical toxicology ward of Péterfy Sándor Street Hospital Clinic and Casualty Centre in Hungary.
Krul & Girbes, 2011	To determine the health disturbances and severity of incidents of GHB-related First Aid Attendees at rave parties.	A prospective observational study from 2000 to 2008.	N=771 visitors of the First Aid Station reporting GHB-related health problems at rave parties in the Netherlands.
Liakoni et al., 2016	To described the clinical features of GHB toxicity.	Retrospective database study from January 2002 – September 2015.	N=78 (60 different patients). GHB-related intoxications at the emergency department of the University Hospital of Basel (Switzerland).
Lietchi & Kupferschmidt, 2004	To define the clinical features of GHB toxicity and to provide epidemiological data.	Database study between 1995 and 2003.	N=141 cases of GHB and GBL intoxication reported by physicians to the Swiss Toxicological Information Centre.
Liechti et al., 2006	To describe the clinical features of GHB and GBL toxicity	Retrospective database study between January 2001 and December 2003.	N=65 (48 different patients). GHB and GBL intoxications at the emergency department of the University hospital of Zurich (Switzerland).

Population description and results

Demographics (GHB population): 64% male; median 23.9, range 21.0-27.8 years.
Other (total population): 60% of the presentations in the weekend and 41% between 0.00-06.00h (total population).
Other (GHB population): history of psychiatric illness (10%), history of substance use (25%).
GHB use: Most cases were GHB-related (36%) with a peak in 2009. Amphetamine related presentations were older and more likely to have a history of substance use and/ or psychiatric illness than GHB related presentations.
Other substance use: Co-use of alcohol (35%).

Demographics: 54% male; M=26.9, SD=10.2, range 14-75 years.
GHB use: only GHB-use in 27.7% of the cases. Mean concentration in serum samples was 1205.66±2120.78 ng/mL and 6910.76±10294.02 ng/mL in urine samples. Minor intoxication in 69.5% of the GHB-only cases and 85.7% of the GHB-combined group. Severe intoxication in 9.6% of all cases and more among men (9.3%) than women (4%).
Other substance use: Most common co-ingested substance was ethanol (13.7%).
Other: Cases of intentional (n=111) and unintentional (n=46) GHB intake. GHB facilitated sexual assault occurred in 11 cases (2.8%), while acquisitory crimes occurred in 38 cases (9.6%) from the total sample (n=480).

Demographics: 66.4% male; M=25.7, SD=6.1 years of age.
GHB use: 252 (32.7%) attendees used GHB only (one substance).
Other substance use: 48.1% combined GHB with ecstasy, alcohol, or cannabis.
190 (24.6%) combined GHB with ecstasy, 123 (15.6%) with alcohol, and 61 (7.9%) with cannabis. Other persons (145, 18.8%) combined GHB with other substances: amphetamine (2.3%), cocaine (0.8%), or more than one substance. In total, 97 (12.6%) used a combination of GHB, ecstasy, and alcohol.

Demographics: 71% male; M=29, SD=8 years.
GHB use: Median GHB concentration was 240 (range 8.3-373) mg/L. Severe intoxication in 72%. Context of use: recreational substance use (90%), accidental ingestion (4%), poisoning (4%), suicide attempt (3%).
Other substance use: Prior history of substance abuse in 64%: GHB (53%), cannabis (21%), opiates (17%), cocaine (18%), MDMA (17%). Co-ingestion with alcohol and other substances in 65% (self-report): alcohol (33%), cannabis (18%), cocaine (17%), sedatives (15%), opiates (10%), amphetamine (5%), MDMA (5%), ketamine (1%).
Other: 53% between 8pm-8am and 46% during the weekend.

Demographics: 73% male; M=24, SD=7 years.
GHB use: Toxicity rates according to the Poisoning Severity Score were severe in 45%, moderate in 38%, and minor in 16%. Seven reports of chronic GHB use (daily use for at least some weeks).
Other substance use: co-ingestion with alcohol (22%), other drugs (34%): amphetamine (21%), cannabis (16%), cocaine (8%), opiates (5%), sedative (1%), ketamine (1%).
Other: weekend (Fr 17:00 – Mo 8:00): 52%, Late night (22:00-9:00): 49%.

Demographics: 63% male; M=24, range 16-41 years;
Other: Prior psychiatric history in 27%.
GHB use: doses: M=6, range 1 to 12ml. Daily use among 3 out of 48 patients. Recreational abuse in 99% and suicide attempt in 1% of the cases.
Other substance use: Documented history of substance use in 60% including GHB/GBL in 46%. Co-ingestion with alcohol or illicit drugs was 65% (26% more than two additional substances), mostly MDMA (18%) and cocaine (15%).

People reporting at emergency departments with GHB overdose *(Continued)*

Reference	Aim	Study design	Methods
Madah-Amiri et al., 2017	To examine characteristics and temporal trends of GHB/GBL ambulance attended overdoses.	Retrospective database between 2009-2015.	N=1112 cases of GHB/GBL overdose patients attended by emergency and ambulance services in Bergen (Norway).
Miro et al., 2002	To determine the number and percentage of GHB overdoses and to describe the clinical features and course of overdose.	Retrospective database study between April 2000 – June 2001.	N=104 presentations of GHB overdose at the emergency department of the University Hospital of Barcelona (Spain).
Miro et al., 2017	To study the profile of European GHB and GBL intoxication and analyse differences in clinical features of GHB/GBL intoxication with and without co-abuse.	Prospectively collected data between October 2013 to September 2014.	N=710 GHB/GBL patients attended at the emergency department of 16 participating centres in the Euro-DEN network.
Munir et al., 2008	To describe epidemiology, symptomatology, resource use and complications in patients presenting at the ED following GHB ingestion.	Retrospective database study between 1-12-2002 to 31-5-2005.	N=170 in 146 different individuals with GHB-related emergency attendances at St Vincent's Hospital in Melbourne (Australia).
Sporer et al., 2003	To describe the clinical features of patients with laboratory-confirmed GHB intoxication.	Prospective case series from July 1998 through January 1999.	N=16, patients with a clinical suspected GHB overdose at the emergency department of San Francisco General Hospital (United States).
Van Sassenbroeck et al., 2007	To examine the time course of awakening from GHB intoxication, the relationship to GHB plasma concentrations and the presence of other drugs.	Case series (2001-2003).	N=15, unconscious (GCS≤8) participants who were treated at medical stations at six large rave parties in Belgium.

Population description and results

Demographics: 67.6% male, male GHB patients were significantly older than females ($p < 0.001$), no gender differences were found for GBL; median 26 (range 13-64) years.
GHB use: 79.4% GHB-only use. 8.9% with suspected GBL-only use.
Other substance use: 11.7% reported co-use of GHB/ GBL with another substance (benzodiazepines, alcohol, amphetamines, or alcohol).
Other: Highest numbers during the weekend and 40% between 22.00-04.00h. Peak in February and May and lowest numbers in June and December.

Demographics: 64% male; M=23, SD=5, range 17-39 years;
GHB use: 3.1% of all toxicological emergencies, 18% emergencies caused by illicit drug use (2nd in ranking illicit drugs requiring emergency care). Mean dose 5-12 ml.
Other substance use: co-ingestion with alcohol (73%) and other substances (86%): amphetamines (43%), cocaine (25%), ketamine (11%), and cannabis (8%). Co-ingestion of GHB with two or more substances in 53%.
Other: 90% of the presentations during the weekend and 67% between 22.00-09.00h.

Demographics: 83% male; median 31, range 25-35 years.
GHB use: 12.6% of all intoxications were GHB/GBL related. Intoxication of GHB alone in 28.3% of the cases.
Other substance use: co-ingestion of GHB/GBL with another substance in 71.7%: alcohol (50%), amphetamine (36%), cocaine (12%), benzodiazepine (10%), cannabis (8%), heroine (7%), ketamine (4%), methadone (0.7%), and LSD (0.4%).
Other: more presentations during the weekend than weekdays.

Demographics: 63% male; median 22, range 16-60 years.
GHB use: GHB-only in 36% of the cases. GHB was in 0.2% of all illicit drug related intoxications.
Other substance use: co-ingestion of GHB with other substances in 64%: ecstasy (37%), ethanol (22%), methamphetamine (24%), ketamine (5%), cannabis (3%), prescription medication (2%).
Other: Highest number of presentations on public holidays and during weekends between 04.00-08.00h.

Demographics: 69% (11/16) male; median 25, range 20-39 years.
GHB use: Serum levels: median 180, range 45 – 295 mg/L. Urine levels: median 1,263, range 432-2,407 mg/L. No correlation between serum and urine levels. GHB-only in 31% (5/16).
Other substance use: Co-ingestion of ethanol in 44% (7/16), amphetamine and ethanol in 6% (1/16); and opiates, benzodiazepines, amphetamines, cocaine, and ethanol in 6% (1/16).

Demographics: 93,3% male; median=21, range 17-26 years.
GHB use: GHB plasma concentration at arrival was median=212, range 112 to 430 µg/ml.
Other substance use: 14 had ingested one or more other drugs; ethanol (7/15), MDMA (6/15), amphetamine (3/15), cannabis (5/15), cocaine (3/15).

People using GHB recruited from the general population

Reference	Aim	Study design	Methods
Anderson et al., 2010	To investigate reasons that might explain why the trend of declining GHB use is not paralleled internationally.	Anonymous internet-based survey (13-item created GHB survey instrument) from 30-10-2007 through 15-3-2008.	N=155 (70 U.S. and 85 non-U.S. responders from 15 different countries), survey respondents (≥18 years) who reported any lifetime or current use of GHB. Recruited through social networking internet sites by posting recruitment notices.
The Brown University Digest of Addiction Theory and Application, 2007	To obtain information on consumption habits, experiences, and beliefs of recreational GBH users.	Focus groups (10) between March and December 2004.	N=51, recruited through flyers and a website advertisement. People aged 18 to 52 years who reported using GHB at least once in the previous 12 months. Participants generally lived in the San Francisco area (United States).
Degenhardt et al., 2002; Degenhardt et al., 2003	To examine characteristics of GHB users, GHB and other drug use patterns, and harms associated with GHB use; To examine correlates, context and risk perceptions regarding GHB overdose among recreational GHB users.	Cross-sectional survey (by structured interviews) between January – June 2001.	N=76, recruited through various methods (e.g. snowball, news). Participants who used GHB in the previous 6 months. Participants lived in Melbourne and Sydney, Australia.
Degenhardt et al., 2008	To study patterns and correlates of GHB and ketamine use amongst a representative population sample of Australians.	National Drug Strategy Household Survey conducted in 2004. Two methods were used: (1) drop and collect method (2) and computer assisted telephone interview.	N=115, respondents (Australian, 14 years and older) who ever and in the preceding 12-months used GHB or ketamine.

Population description and results

Demographics: Total population: M=31.5, SD=10.1, median=29, range 18-67 years; 74% male, 23% female, 3% transgender; high school graduate or less (19%), some college (34%), bachelor degree or above (48%); not working (19%), attending school (12%), currently working (70%). U.S. respondents were older ($p = 0.0003$) and more highly educated ($p < 0.001$) compared to the non-U.S. respondents.
Other: Total population: heterosexual (66%), gay/lesbian/bisexual (34%).
GHB use: U.S. respondents: frequency of use: 1-2 (10%), 3-5 (16%), 6-20 (1%), <20 (72%); reason of use: body building (6%), being alone (20%), sexual (16%), dance/ clubs/ raves (20%), small private party (30%); quit using GHB > 6 months: yes (76%), no (24%); reason quitting: health/ safety (46%), legal (54%). Non-U.S. respondents: frequency of use: 1-2 (8%), 3-5 (9%), 6-20 (13%), <20 (69%); reason of use: body building (2%), being alone (17%), sexual (18%), dance/ clubs/ raves (29%), small private party (35%); quit using GHB > 6 months: yes (45%), no (55%); reason quitting: health/ safety (68%), legal (32%).

Demographics: 60% male, M= 31 years, over 50% had completed college with 22% completing post-graduate or professional degrees, annual income >$60,000 (28%), 71% unmarried, significantly more female than male respondents were working (81% vs. 47%).
Other: 61% heterosexual
GHB use: first use M=27 (range 13-50) years; duration of M= 4 (range 1-11) years; 36% were light users (used GHB < 5 times in their lifetime), 41% were moderate users (6-50 times), and 24% were heavy users (> 50 times); 88% used GHB infrequently (< 1 day/week) mainly at parties and social gatherings.
Other substance use: Large amount of the participants reported co-ingestion with other substance(s) at least once. Most commonly reported co-ingestion was with amphetamine, alcohol (43%), ecstasy, and marijuana.

Demographics: 79% male; M=27, SD=6.7, range 17-50 years; 90% completed high school and 78% completed coursed following school; most participants were currently employed or were student (tertiary education);
Other: 50% homosexual, 11% bisexual; small part (3%) of the population had a history of treatment for a drug use.
GHB use: median length of use: 1 year; median occasions of use: 15; first use M=26, SD=6.7, range 16-49 years; median years of use: 1 (range 0-12); median times ever used GHB: 15 (range 1-2000); median days of GHB use past 6 months: 4 (range 0-180); GHB- dependent: 4%; 53% had experienced a GHB overdose. Participants who experienced GHB overdose had used it more times (life-time) and for a longer period of time.
Other substance use: past 6 months: ecstasy (91%), amphetamine (77%), cocaine (83%), MDA (67%), methamphetamine (68%).

Demographics: 90% male, M=26 years, 17% postsecondary education (non-GHB-users 21%), 12% >AU$ 60.000, 49% employed, 26% married.
GHB use: first use M=24 years. Of the participants who ever used GHB, 76% did not use GHB in the past 12 months and 8% had used in the past month. A small part of the total population (0.5%) ever used GHB and a smaller population recently used GHB (0.1%). Lifetime GHB-use was highest amongst 20-29 years old.
Other substance use: past year use of alcohol (99%), at least one occasion of >11 drinks in 1 day (49%), amphetamine (61%), cannabis (76%), heroin (9%), cocaine (32%), hallucinogens (24%), ecstasy (70%), ketamine (12%), inhalant use (13%). GHB users were more likely to report recent use of various other drugs than non-users.

People using GHB recruited from the general population *(Continued)*

Reference	Aim	Study design	Methods
Grund et al., 2018	To identify risk and protective factors associated with comatose intoxication after GHB ingestion. To inform the development of tailored drug policy responses.	A cross-sectional survey between May and October 2014.	N=146, GHB consumers from different GHB consumption contexts recruited in both the urban Randstad and in smaller towns in the Netherlands (126) and Flanders (20) using a variety of sampling methods (through networks, websites, facebook, (peer) prevention services, and online drug discussion forums). Semi-structured questionnaire was used (146) and 15 in-depth interviews.
Kapitany-Foveny et al., 2015	To explore GHB's sexual effects, patterns of choice of sexual partners, frequency of experienced blackouts, and endured sexual or acquisitory crimes as a result of GHB use.	Survey	N=60, recreational GHB users (participants who ever used GHB at least once in their lifetime) recruited through snowball sampling via university students (Budapest, Hungary). Treatment seeking patients were not considered.

Population description and results

Demographics: 72% male; M=28, range 15-53 years, <21: 10%, >38: 10%; ethnic Dutch (74%), western immigrants (15%), ethnic Belgian (11%); Randstad (36%), outside Randstad (64%); primary education (15%), pre-vocational secondary education (30%), secondary vocational education (31%), senior general education or higher (25%); not in employment or education (38%), in employment (37%), in education (8%), both (17%); lives alone (36%), with partner (23%), with partner/family/guardians (18%), with friends (11%), sheltered housing (7%), homeless (3%), other – e.g. clinic (2%).

GHB use: 98% GHB last year and 64% last month. First GHB use at 22 years on average. GHB use life-time <50 (26%), 51-200 (24%), and >200 (50%). Last year use 87 days on average. GHB use less than once a week (60%), at least once a week (34%), daily (6%). Dose: M=4.5ml, median=4ml. Respondents took several doses per episode range 1-40 doses with median 6 doses. Time between doses: median= 1.5h, range 0.5-8h.

Most mentioned effects GHB: 'feeling more self-confident, being more sociable'(52%), in particular when interacting with (potential) sex partners; 'happiness and euphoria, and having lots of energy' (51%); 'the relaxed, happy and warm high' (46%), 'forgetting daily worries, letting go, dampening of emotions' (41%) and 'an enhanced sexual response' (38%). Most important negative aspects: 'risk of passing out'(48%), in particular in public settings, GHB's bitter taste (47%), the 'risk of becoming addicted' (41%),'difficulties in dosing' (26%), 'nausea/ vomiting' (25%), 'short term memory loss' (25%), GHB's bad reputation (13%) and 'dizziness'(13%).

Location of use: home (88%), at parties (53%), in nightlife (55%), outdoors (28%) or at school or in the workplace (6%). Use usually alone (14%), sometimes alone (31%), never alone (56%).

More than 9 in 10 experienced (light) nod, 69% experienced coma, coma last year (48%), coma last month (14%). Respondents who experienced coma M=81 times (CI 31-130), median=6, >100 times (10%), Overdose was mostly unintentional. Higher life-time GHB use increases likelihood of coma. Respondents taking >4 ml experienced more often comas (66%) than who took less (35%).

Other substance use: all respondents had a vast experience with a range of substances in addition to GHB with alcohol (83%) and amphetamines (60%) most mentioned. Recent heroin (14%) and crack (12%) use was relatively low and mainly found among older respondents with lower education and less often employed. In particular amphetamines were common among respondents who used GHB in the last month.

A variety of combination drug use patterns might affect risk of overdose.

Other: Living in the Randstad reported less comas (lifetime – last year 42-33%) than outside the Randstad (87-64%) who used larger and more doses on average. 72% comas reported at home, parties (12%), going outdoors (14%). Using alone is strongly related to coma. Other related factors to coma: using GHB to 'feel more confident', less education.

Demographics: 66.7% male; M=25.6, SD=4.6 years; 58,3% graduated from high school, 20 % graduated from college/ university; 43,1% unemployed, 27,6% part-time, 29.3% fulltime; 71,7% single.

GHB use: 63.3% no GHB-use past month, 3.4% daily GHB-use, 30% no GHB-use past year, 16.7% used GHB monthly. Participants reported increased sexual arousal (25.9%); sexual intercourse with strangers or others, but not their partners (34.8%); victims of acquisitory crimes (8.6%); victims of a sexual assault (3.4%); and experienced blackouts (24.6%).

Other substance use: Substance use (at least once) in past month: 55% cannabis, 27.1% MDMA, and 23.7% cocaine. Alcohol was used in 96.7% at least once.

People using GHB recruited from the general population *(Continued)*

Reference	Aim	Study design	Methods
Kim et al., 2007; Kim et al., 2008	To assess the performance characteristics of the survey instrument, high risk behaviours in relation to GHB related hospital treatment, and association between socio-demographic characteristics and risk behaviours.	Survey by FORGE (Factors in Overdose Research into GHB Effects). A structured, telephone-administrated questionnaire.	N=146, 131 interviews (90%). Kim et al., 2008: N=125, United States. One group (N=14) identified through California Poison Control System (CPCS) surveillance (GHB-users needing medical attention in health care facility). Second group (N=132) was recruited via internet postings, flyers in public places, physician referrals, and by snowball sampling.
Korf et al., 2014	To identify factors which increase the risk of overdosing (OD) with GHB among recreational drug users.	Survey (by interviews) between February 2012 and June 2012.	N=45, participants (≥ 18 years) with a lifetime prevalence of GHB use at 25 or more occasions, and at 1 or more occasions in the past 12-months. Participants were recruited through ethnographic fieldwork in public (clubs, festivals) and private settings (e.g. afterparties), and through snowball referrals in the Netherlands.
Miotto et al., 2001	To examine patterns of GHB use, its effects, and withdrawal.	Survey (interview) in 2 parts: one part reviewed demographic and psychiatric treatment history. Second part addressed GHB-use.	N=42 (120 responders, 42 came in for interview), recruited by advertisements for regular GHB-users in two local English language newspapers in Los Angeles (United States).

Population description and results

Demographics: 70.2% male; 55.7% < 30 years of age; some college or less (58%); unemployed 33.6%. Annual income <$20.000: 37.4%.
Other: gay/bi/transgender 26.7%
GHB use: life-time GHB-use > 20 times (42.0%); GHB-use while alone (38.2%); driving under the influence of GHB (29.0%); use of a GHB precursor or analogue (27.5%); use of GHB to treat withdrawal symptoms (16.8%); reported GHB related hospital treatment (20%), having sex under influence of GHB (64.1%).
Co-ingestion of ethanol or ketamine, driving under the influence of GHB, use of GHB to treat withdrawal symptoms were associated with increased risk of hospital treatment.
Other substance use: co-ingestion with alcohol (58%), ecstasy (38.9%), and ketamine (2.9%). Use of heroin ever: 22.1%.

Demographics: 47% male; M=23.8, SD=2.9; range 18-32 years; M=23.8, SD=2.9 years of education; 93% was employed and 62% was student; 22% had a stable relationship.
GHB use: first use M=21.5, SD=2.9, range 16-28 years; median amount per occasion 3.7ml per dose, 5 doses, 20ml total amount; experienced at least 1 GHB overdose (30 participants - 66.7%); GHB dependent (24%); 60% had never used GHB outdoors, 51% never in a nightlife setting, and 49% never at home at the 10 most recent occasions. Most frequently mentioned setting were a private party or afterparty (less to OD repeat participants).
Other substance use: past 30 days: alcohol (100%), at least 1 occasion of ≥ 5 drinks (69%), amphetamines (87%), ecstasy (84%), cocaine (58%), cannabis (71%), ketamine (62%), mushrooms (2%) and LSD (4%).
Life-time use: amphetamines (100%), ecstasy (100%), cocaine (100%), cannabis (97.8%), ketamine (82%), mushrooms (47%), and LSD (68%).
Rather common was co-use (before or simultaneously) with (Median Likert score 0 – 6) ecstasy (5) and amphetamines (4), whereas co-use of alcohol (2), cocaine (1), cannabis (1) or ketamine (1) was not.

Demographics: 76.2% male, M=26.3, SD=9.8 years, 39% employed,
Other: 73.8% heterosexual, 9.5% with current psychiatric problems; 9.5% past outpatient psychiatric treatment, 19% past inpatient psychiatric treatment.
GHB use: every day (21%), 1 day a week (24%), 1 day a month (20%), <1 per month (17%), other (14%); times per day: 1 (29%), 2-3 (43%), >4 (29%); overdose (26%); treated at ED (9%); physical dependence of GHB (21%), these participants reported use of GHB alone; 7 out of 9 (78%) daily GHB-users had a history of drug problems.
Reason GHB use: increased feelings of euphoria, relaxations, and sexuality.
Other substance use: Usually co-use reported in 71%: ecstasy (53%), cannabis (50%), cocaine (43%), amphetamine (40%), and alcohol (37%).

People using GHB recruited from the general population *(Continued)*

Reference	Aim	Study design	Methods
Stein et al., 2011; Stein et al., 2012	To assess patterns, experiences, and functions of GHB use.	Pilot study – Web-based survey. In 2003, over a 5-month period.	N=61, recruited through internet. Individuals with knowledge of GHB/ analogs through personal use or exposure to others' use.
Sumnall et al., 2008	To examine the relationship between intentions for GHB use, acute subjective experiences and patterns of use.	Online survey questionnaire on GHB behaviours, GHB use function, and subjective GHB effects.	N=189. Individuals reporting at least one lifetime use of GHB (home and club use). Recruited by advertisements hosted on appropriate websites.

Population description and results
Demographics: 80.3% male; M=31.85, SD=9.80 years; ≤ high school (12%), some college (38%), college degree (39%), graduate degree (12%); married (15%), co-habitate (13%), divorced (15%), never married (57%); employment fulltime (57%), part-time (10%), never (15%), other (18%). **Other:** mental health history (59%). **GHB use:** Past year: 93.4%, median use level ≤3 times per month. Qualified GHB/ analogue use disorder: 41.0%. Previously treated for GHB abuse: 30%. Function beginning to use: get high (79%), be more sociable (78%), improve sleep (76%), assist with depression or anxiety (72%), improve sex (71%), feel more energized (67%), and enhance dancing (64%). **Other substance use:** Reported other drug use (N=54) at least once a month were alcohol (68%), nicotine (50%), Cannabis (36%), melatonin (28%), ginko biloba (26%), and sleep aids (26%). Co-use with GHB (N=52): nicotine (38%), speed or amphetamine (30), ecstasy (26%), cannabis (24%), ketamine (12%), gingseng (12%), and prescription antidepressants (12%).
Demographics: 74.1% male; M=29.1, SD=8.6 years. **Other:** 64.6% heterosexual, 14.3% bisexual, 21.1% homosexual. **GHB use:** Most common functions of GHB were recreation (65.3%) and to enhance sex (60.3%). Most primary use function were recreation (but not in night clubs) (18.3%), to enhance sex (18.3%), to be sociable (13.1%), and to explore altered states of consciousness (13.1%). **Other substance use:** Most reported other substances were alcohol (96.8%), ecstasy (92.1%), and cannabis (90.5%). Reported co-ingestion in 68% including ecstasy (32.4%), alcohol (17.3%), cannabis (15.6%), and amphetamine (10.4%). More home users (52%) mixed GHB with other substances than those reporting use primarily in nightlife settings (26%). Homosexual respondents reported higher scores for positive sexual effects than heterosexuals ($p < 0.05$). This corresponds with the greater proportion of homosexuals than heterosexuals using GHB to enhance sex ($p < 0.05$). There were no other significant differences with respect to participant sexuality.

Patients in addiction care using GHB			
Reference	**Aim**	**Study design**	**Methods**
Bell & Collins, 2011	To describe morbidity associated with GBL dependence and withdrawal.	Case series between 1 July 2009 and 31 January 2010.	N=19, patients dependent on GBL at a specialist out-patient clinic and affiliated inpatient detoxification unit (UK). Inclusion criteria: use > 4 ml GHB on a daily basis or >6 times daily every day or a history of severe withdrawal symptoms or currently dependent upon other drugs.
Brunt et al., 201		Survey between March and September 2010 by DUDIT questionnaire – (Drug Use Disorder Identification Test).	N=75, inpatients (≥18 years) with primary GHB problems recruited from 4 different addiction treatment centres in the Netherlands (response rate 90,4%).
Cappetta & Murnion, 2019	To describe the baseline characteristics, treatment and retention in patients electively admitted for GHB withdrawal management.	Retrospective database study between July 2010 – June 2016.	N=12. Patients who admitted to inpatient withdrawal management unit in Sydney (Australia) who used GHB two or more times per week within a minimum duration of 3 months were included.
Choudhuri et al., 2013	To describe the psychiatric symptoms, management and outcomes of GHB and GBL withdrawal.	Case series (retrospective database study) between May 2008 – Sept 2011.	N=31 (20 different patients, including 4 patients attending ≥ 2), patients with a history of GHB withdrawal at an inpatient detox in a general hospital in London (UK).

Population description and results

Demographics: 89% male; M=27.9, range 21-37 years; well-educated population (no further information).
Other: 84% were gay men. Five patients were HIV-positive.
GHB use: All patients used GBL around the clock daily (12-40ml). Most started GBL-use when attending nightclubs.
Function of use: to achieve a state of sociable confidence, to facilitate sexual activity, and to sleep.
Seven patients lost jobs due to GBL dependence and several others reported having concerns at work.
Other substance use: Three patients had a prior history of substance dependence and all three dropped out. Frequent use of party drugs (ketamine, ecstasy, and methamphetamine) was common.

Demographics: 73% male; M=26.8, SD=9.1 years; education: none (2.7%), lower secondary/ vocational (77.4%), higher secondary/ pre-university (13.4%), university and post-graduate (6.7%); living single (57.3%), with partner (30.7%), with parents (10.7%), with friends (1.3%); no work (48%), fulltime work (21.3%), part-time (22.7%), studying (8.0%).
GHB use: First time use: past year (74.7%), > 1 year ago (14.7%), > 3 years ago (10.7%).
DUDIT-score M=26.9, SD=7.3, 77% had DUDIT-score >25, indicating dependence.
Motives for use: cheap (10,8%), sedation (26,3%), euphoria (54,0%), unsatisfied other drugs (18,7%), no hangovers (16,0%), better sex (18,0%), friends use it (39,7%), no motives (17,0%).
Motives for seeking treatment: Sleep problems (30.7%), social problems (22.7%), psychological problems (20.0%), physical problems (18.6%), passing out (GHB coma) (8.0%).
Other substance use: Last month use of alcohol (52%), cannabis (45.3%), ecstasy (24.0%), amphetamine (30.7%), cocaine (25.3). Last month co-use GHB and alcohol (44.0%), cannabis (36.0%), ecstasy (14.6%), amphetamine (25.3%), cocaine (22.7%).

Demographics: 50% male; M=33.1, range 20-48 years; 42 % employed; household status: private rental (50%), no fixed address (25%), other (25%); single (58%), partnered (42%); legal issues: current (58%), never (25%), previous (17%).
Other: heterosexual (42%), homosexual (25%), unknown (33%); HIV co-infection: yes (25%), no (33%), unknown (50%); comorbid mental health (92%), intravenous drug use: current (33%), previous (17%), never (50%); previous withdrawal management (42%); history of overdose (50%); referral pathway: self (42%), hospital (25%), other (33%).
GHB use: Duration of use (months): M=60, median:27, range 3-216; amount used in 24h (ml): M=16, median=10, range 1.5-40; frequency of use: daily (75%), ≥ 2 times/week (25%).
Other substance use (concomitant): stimulants (100%), tobacco (100%), cannabis (33%), alcohol (25%), benzodiazepine (25%), heroin (8%).
Other: GHB use of greater than 90 ml in the previous 7 days was significantly associated with not completing treatment despite being administered diazepam and/or neuroleptic.

Demographics: 85% male; M=27.5, SD=4.3 years.
Other: Prior documented psychiatric disorder other than substance use in 30% (6/20).
GHB use: median 27 (18 – 37) ml per day.
Other substance use: co-ingestion with other substances in 71% (22/31): crystal meth (32.2%), cocaine (22.5%), alcohol (19.4%), MDMA (9.7%), Mephedrone (6.5), ketamine (3.2%), and cannabis (3.2%).

Patients in addiction care using GHB *(Continued)*

Reference	Aim	Study design	Methods
Dijkstra et al., 2017; Jong, de et al., 2012; Kamal et al., 2016; Kamal et al., 2017; Weert, de – Oene, van et al., 2013	To explore the feasibility, effectiveness and safety of GHB detoxification by titration and tapering. Furthermore, to describe the clinical features of patients.	Observational multicentre study between February 2011 - December 2012	N=229, 274 admissions (Dijkstra et al., 2017; Weert, de – Oene, van et al., 2013); N=23 (Jong, de et al., 2012); N=95 (Kamal et al, 2016); N=98 (Kamal et al, 2017). GHB dependent inpatients for detoxification in the Netherlands.
Durgahee et al., 2014	To describe the patient characteristics, pattern of use, related problems and comorbidity.	Retrospective database study between 2008-2013.	N=27, patients with primary GBL/GHB misuse representing to the Substance Misuse Service in Brighton and Hove (UK).
Maxwell & Spence et al., 2005	To examine characteristics of individuals admitted to treatment for primary, secondary, or tertiary problems with club drugs.	Retrospective database study (Texas Commission on Alcohol and Drug Abuse (TCADA) between 1988-2003 (GHB was added in 1997 to the system).	N (GHB)=45, individuals admitted to treatment for primary, secondary, or tertiary problems with club drugs in publicly funded treatment in Texas (United States).
Noorden, van et al., 2017	To assess treatment consumption and re-enrollment among patients with GHB dependence comparison with other addictions.	Cohort study (LADIS database) of first treatment between 2008-2011 and consecutive treatments until 2013.	N (total)=71,679; N (GHB)=596. In- and out-patients with alcohol, drug and/or behavioural addictions with first treatment episode in the Netherlands.

Population description and results

Demographics: 69% male; M=28.8, SD=7.2 years; primary (13.8%), secondary (75.5%), and tertiary (10.6%); education; full-time (22,3%), part-time (11,2%), unemployed (29,8%) unfit for work (29,8%), student (6,4%); single (34.9%), with partner and/or children (24.7%), with parents (26.5%), other (14.0%).
Other: 16% re-admissions; nearly a quarter of the admission was not regular: 13% crisis and 10% urgent.
GHB use: First use M=25.0, SD=7.4 years. Years of use M=4.2, SD=3.3. Use past 30 days M=29.7, SD=1.4. Relapse within 3 months after detoxification was 64.6%. Estimated GHB dose per intake M=3.88, SD=2.1 g. Estimated daily GHB dose M=56.0, SD=40.3 g.
Other substance use: Co-use past 30 days (mean, SD): alcohol (13.1±11.6); cannabis (17.0±12.1); opiates (13.7±11.6); cocaine (9.1±10.7); stimulants (14.8±12.2); sedatives (21.5±11.2); other (26.2±8.3). Use of other substances: alcohol (51%), sedatives (42%), cannabis (41%), amphetamines (41%) and/or cocaine (31%).
Other: In 79% psychiatric comorbidity was detected, including anxiety (current 38%, lifetime 40%), mood (13%, 31%), and psychotic disorders (13%, 21%).

Demographics: 89% male; M=34, SD=7.2, range 18-45 years; 56% fulltime/student, 37% unemployed, off sick (4%), retired (4%); 56% rented/ owned accommodation, 22% local authority housing, 19% with family/friends, 4% hostel accommodation.
Other: 78% gay, 19% heterosexual, 4% bisexual; 89% reported anxiety symptoms (above cut-off); history of treatment for anxiety (52%); diagnose HIV-positive (37%).
GHB use: M=53, SD=46.1, range 5-200, median=40 ml per day. GBL use of M=53 ml/day. First use M=29, SD=8.7, range 18-45 years. Duration of use before first admission M=15, SD=10.0, median=12 months (range 2 months to 3 years). Frequency of use: hourly (41%), 2 hourly (44%), 3 hourly (7%), < daily 2 times (7%); 81% was physically dependent. Recreative use was reported by 56% (clubs, party scene), 22% for psychological reasons, and 19% in a sexual context.
Other substance use: 89% concurrent use, most reported: mephedrone 48% (13), ketamine 37% (10), alcohol 33% (9), benzodiazepines 19% (5), cocaine 15% (4), MDMA 11% (3).

Demographics: 71.1% male, M=29.3 years, M=11.8 years of education, 30% had work, M=7.174 dollar income (patients >17 years), 4.4% married, 8.9% homeless.
Other: 31.1% received medication for psychiatric or addiction problems. DSM-diagnose: Bi-polar (5.3%), depressive disorder (13.2%), no DSM-IV diagnose axis I/II (71.1%).
GHB use: First use M=20.5 years. Days of use before admission M=17.4. Abstinent in last month of treatment: 37.2%.
Other substance use: primary substance was in 26% club drugs; cannabis (11%), alcohol (6%), methamphetamine (26%), cocaine (7%), crack cocaine (12%), heroine (4%).

Demographics: 67% male; median=25, range 21-30 years. Median age of the other patients was significantly higher with 35 years ($p<0.001$).
GHB use: Primary reason in 0.9% of all patients with first treatment episode.
Other substance use: 68%.
Other: Number of treatment contacts: M=50.4, SE=3.62, median=20, range 7-51. Treatment duration: M=325.2, SE=13.52, median=229, range 90-430 days. Re-admission in 42.8%. All significantly higher than patients in treatment for other substances.

Gay and bisexual men			
Reference	**Aim**	**Study design**	**Methods**
Halkitis & Palamar, 2006	To examined patterns, contexts, and motivations for GHB use in a cohort of active club drug using gay and bisexual men.	Longitudinal study - Project BUMPS (Boys Using Multiple Party Substances): only baseline was used for this study.	N (total)=450; N (GHB)=131. Clubs drug using (past year) gay or bisexual men (≥ 18 years) in New York City (United States).
Hammoud et al., 2018	To examine factors associated with GHB use, its relationship to sexual risk behaviour, and the contexts, consequences, and motivations for its use.	An online prospective observational study.	N=3190, baseline measure of gay and bisexual men (GBM) about their use of GHB. The Following Lives Undergoing Change (Flux) Study is carried out among Australian GBM.

Population description and results

Demographics: M=32 years (significant difference (p=0.04) with non-GHB-users, M=33 years).
Other: gay 93% (non-GHB users 86% gay, significant difference p=0.03); HIV-positive (31%).
GHB use: 29.1% reported GHB-use. Use in previous 4 months: M=6.19, SD=12.45, median 2, range 1-100 days. Location of use: dance clubs (63.3%), circuit parties (37.5%), sex parties (36.7%), friend's / lover's place (35.8%), sex clubs or bathhouses (30.5%), bars (29.1%), and at home alone (13.8%). Men who used GHB at sex clubs (p=0.02) and sex parties (P<0.001) were older than users who did not use it in this setting. However, age is related to HIV status (HIV-positive men were older), suggesting that GHB use at sexual settings is associated with older HIV-positive men.
Other substance use: GHB combined with methamphetamine (56.5%), MDMA (46.6%), ketamine (41.2%), alcohol (26.0%),Viagra (22.1%), cannabis (21.4%), amyl nitrate (18.3%), rohypnol (10.7%), barbiturates (10.7%), crack (6.9%), hallucinogens (4.6%), and heroin (1.5%).

Demographics: 100% male
GHB use more than 6 months ago: M=37.3, SD=10.0 years. Education: less than university level (42.2%), under graduate level (29.6%), post graduate level (27.9%), not stated (0.3%). No work: 14.8%. In relationship: 51.0%.
GHB use less than monthly past 6 months: M=38.0, SD=10.3 years. Education: less than university level (33.7%), under graduate level (34.9%), post graduate level (30.8%), not stated (0.6%). No work: 23.3%. In relationship: 49.4%.
GHB monthly or more past 6 months: M=36.4, SD=10.2 years. Education: less than university level (42.5%), under graduate level (32.2%), post graduate level (25.3%), not stated (0.0%). No work: 21.8%. In relationship: 46.0%.
Other:
GHB use more than 6 months ago: (95.1%), HIV-positive (14.8%).
GHB use less than monthly pas6t 6 months: (98.9%), HIV-positive (15.7%).
GHB monthly or more past 6 months: (98.9%), HIV-positive (16.1%).
GHB-use: no GHB-use (n=2566, 80.4%), history of GHB-use (19.6%): used GHB more than 6 months ago (n=365; 11.4%), use past 6 months less than monthly (n=172, 5.4%), use past 6 months monthly or more frequently use (n=87, 2.7%). Overdose was experienced by 14.7%, more common among men who used GHB at least monthly or more (once: 22.7% vs. 28.7%; more than once 13.4% vs. 21.8%).
Being HIV-positive, having more gay friends, greater social engagement with gay men who use drugs, a greater number of sexual partners, group sex, and condomless anal intercourse with casual partners were independently associated with GHB use in the past 6 months. Greater social engagement with gay men who use drugs and group sex were independently associated with at least monthly use. More frequent GHB use was independently associated with experiencing overdose among GHB users. Obtain from: dealer (43.6%), gay friends (29.3%), sex partner (10.8). Participants who used GHB in last 6 months, most mentioned reason of use: sexually aroused (30.5%), it was available (25.1%), it would help them lose their inhibitions (24.3%). GHB-users who used GHB more at least monthly mentioned for fun, to encounter the effects of other drugs, to feel connected to other men, to lose their inhibitions, to make it easier to be the receptive partner during anal intercourse more often than men who used less frequently GHB. More frequent users ascribed more positive outcomes to their drug use.

Gay and bisexual men *(Continued)*

Reference	Aim	Study design	Methods
Hammoud et al., 2018			

People driving under influence of GHB

Reference	Aim	Study design	Methods
Jones et al., 2007; Jones et al., 2008	To examine the occurrence and concentration of GHB in blood samples of arrested drivers in relation to their age and gender.	Retrospective forensic toxicology database study between 1998 and 2006/2007.	2007: N= 473; 2008: N= 548 cases of 364 individual arrested for driving under influence with GHB in blood samples in Sweden.

People living with HIV using GHB

Reference	Aim	Study design	Methods
Camacho et al., 2004	To examine the use of dietary compounds by HIV-positive and their knowledge, use, and effects produced by GHB containing dietary compounds.	Survey with a data collection over a period of three months.	N=100, HIV-positive outpatients from University of California in San Diego (United States).

Population description and results

Other substance use:
GHB use more than 6 months ago: amyl nitrite (60.5%), cannabis (51.2%), ecstasy (39.5%), meth/ amphetamine (9.9%), cocaine (31.8%), crystal methamphetamine (28.2%), ketamine (7.7%), LSD (6.6%), heroin (0.3%).
GHB use less than monthly pas6t 6 months: amyl nitrite (76.7%), cannabis (55.8%), ecstasy (66.3%), meth/ amphetamine (19.2%), cocaine (46.5%), crystal methamphetamine (70.3%), ketamine (21.5%), LSD (9.3%), heroin (1.2%).
GHB monthly or more past 6 months: amyl nitrite (87.4%), cannabis (50.6%), ecstasy (64.4%), meth/ amphetamine (21.8%), cocaine (56.3%), crystal methamphetamine (87.4%), ketamine (42.5%), LSD (10.3%), heroin (2.3%).
Other:
GHB use more than 6 months ago: depression: minimal (40.8%), mild (25.5%), moderate (12.6%), moderately severe (6.6%), severe (6.0%), did not answer (8.5%). Anxiety: minimal (52.3%), mild (24.4%), moderate (8.8%), severe (6.0%), did not answer (8.5%).
GHB use less than monthly pas6t 6 months: depression: minimal (45.3%), mild (30.2%), moderate (9.3%), moderately severe (6.4%), severe (2.9%), did not answer (5.8%). Anxiety: minimal (59.9%), mild (25.0%), moderate (5.8%), severe (2.9%), did not answer (6.4%).
GHB monthly or more past 6 months: depression: minimal (35.6%), mild (25.3%), moderate (12.6%), moderately severe (5.7%), severe (5.7%), did not answer (14.9%). Anxiety: minimal (43.7%), mild (24.1%), moderate (13.8%), severe (5.7%), did not answer (12.6%).

Population description and results

Demographics: 95% male; 97% (GHB alone) and 94% (GHB combined with other drugs). Age: men M=26, SD=5.5, range 15-50 years; women M=32, SD=8, range 19-47 years; GHB alone: men M=25.3, SD=4.9 years; women M=34.0, SD=6.2 years; GHB combined: men M=26.4, SD=5.5 years; women M=31.3, SD=8.0 years.
GHB use: M=89, median= 82, range=8-340 mg/L. GHB alone in 39%. GHB alone: M=91, median= 83, range 2.5-97.5 percentiles= 16-200 mg/L. GHB combined with other drugs: M=88, median= 81, range 2.5-97.5 percentiles= 10-227 mg/L.
Mean concentration GHB tends to increase with age of offenders ($P<0.05$).
Concentrations of GHB in blood and ages of offenders remained constant over the 10-year study period.

Population description and results

Demographics: Total population: 89% male; 26-39 (57%), 40-55 (39%) years old. GHB population (n=52): 92% male; 26-39 (77%), >40 (23%) years old; M=15.8 years of education. Non-GHB using population (n=48): 85% male; 18-25 (6%), 26-39 (38%), >40 (56%) years old; M=15.7 years of education.
Other: Total population: gay (56%), heterosexual (33%). GHB population: gay (77%), heterosexual (13%). Non-GHB using population: gay (33%), heterosexual (54%). Eleven participants did not report sexual orientation.
GHB use: 52% (ever), 43% (past 6 months); 37 respondents used 1-10 times and 3 respondents 16-20 times last 6 months. Most common effect was increased energy (21%), euphoria (18%), and weight lost (11%). Of the total responders, 24% knew about the addictive potential (27% among users). One participant reported severe adverse side effects.

Supplement II

Cognitive impairments in patients with GHB use disorder predict relapse in GHB use
Beurmanjer H. Bruijnen C.J.W.H., Greeven P.G.J., De Jong C.A.J., Schellekens A.F.A, Dijkstra B.A.G.

Table 1 Correlations between MoCA scores, GHB use, GHB exposure and number of GHB induced coma's

	MoCA scores T1	**MoCA scores T2**
Daily GHB dose	-.152	.111
Months of daily GHB use	-.180	.202
Months of general GHB use	-.143	.167
GHB exposure score	-.217	.217
Number of GHB induced coma's	.978	-.079
	MoCA cut off T1	MoCA cut off T2
Daily GHB dose	-.075	.109
Months of daily GHB use	.020	-.093
Months of general GHB use	.129	-.192
GHB exposure score	.137	.147
Number of GHB induced coma's	.979	-.079

*p <.05

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