"Every accomplishment starts with the decision to try.
The challenge is not to go where the path may lead, but to go
instead where there is no path and leave a trail."
Ralph Waldo Emerson

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THE DETOXIFICATION APPROACH FOR PATIENTS WITH GHB DEPENDENCE

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according to the decision of the Council of Deans

to be defended in public on Wednesday, February 3, 2016
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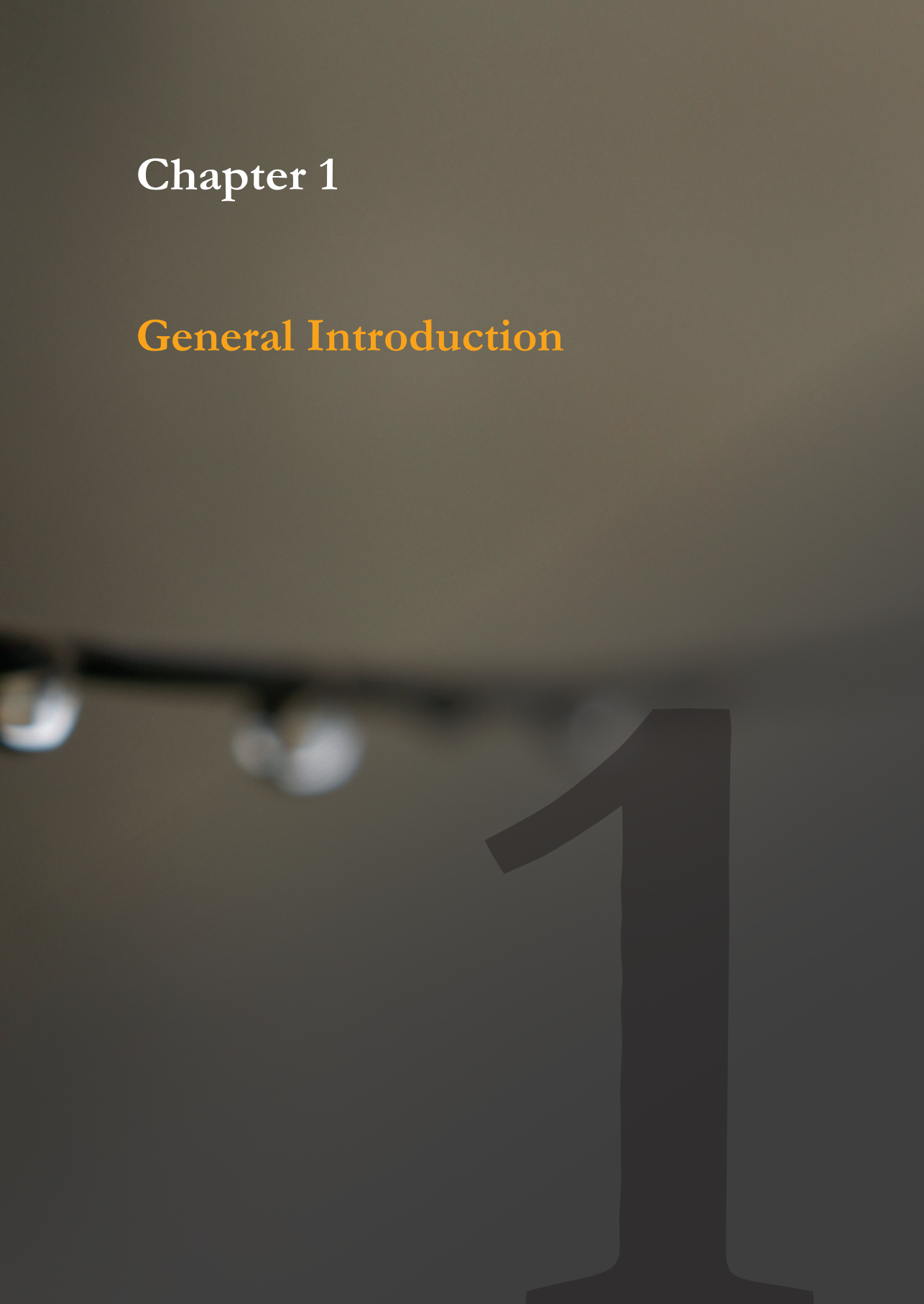
by

Rama Mohamed Kamal
Born on June 8, 1971
in Omdurman (Sudan)

TABLE OF CONTENTS

Chapter 1

General Introduction



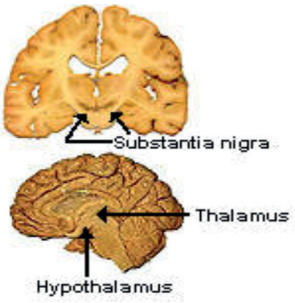
GENERAL INTRODUCTION

This dissertation is the result of frequent clinical encounters with the growing health issue of Gamma hydroxybutyric acid (GHB) dependence in the Netherlands. Over the last decade the popularity and prevalence of illicit recreational GHB use has increased in the Netherlands, leading, according to the Consumer & Safety Committee, to a six-fold increase in the number of incidents and emergency room admissions and aggressive interaction with the forces of law. In 2009, 1200 patients were treated for GHB overdose[1]. A sharp increase has been reported in the number of patients requesting treatment from addiction care facilities and psychiatric hospitals. Physicians have been confronted with cases of severe GHB withdrawal. The literature provides little information on the process of detoxification from GHB. The published case reports did not provide consensus on a structured, safe and effective GHB detoxification method to be followed, in which life-threatening complications can be avoided or minimized, within medium-care facilities. The best tradition of evidence-based medicine , if there is no evidence available, is that professionals should then be curious and undertake the task of starting their own research, looking for answers which help to improve the daily practice and quality of life of their patients. Therefore, this journey was started in 2009, based on available neuro-pharmacological insights, with the first description of a possible approach to treat these patients[2], and expanded, with the aim of developing an efficient and safe detoxification treatment for these patients, which was and still is a challenge.

This introductory chapter summarizes (pharmacological) characteristics of GHB, emphasizing the complexity of its effects. First, I will illustrate the function and importance of GHB as an endogenous substance. Then the prevalence of illicit (street) GHB use and the related health risks will be presented, followed by a discussion of GHB dependence and the magnitude of this problem in the Netherlands. Finally, the description of the GHB withdrawal syndrome and the known medical treatment approaches will be presented. This chapter ends with an overview of the aims and an outline of this thesis.

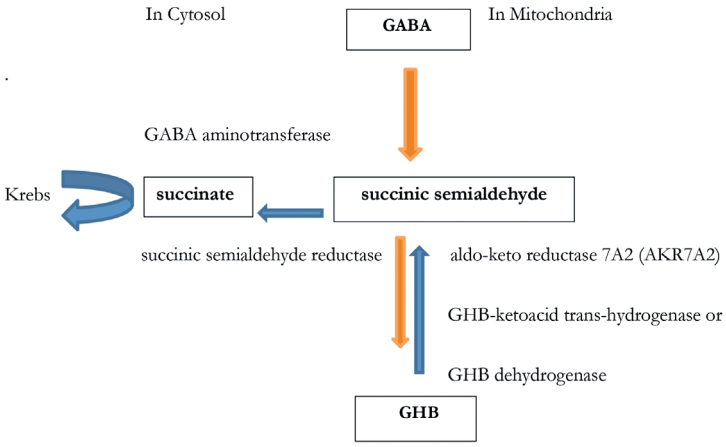
GHB as an endogenous compound

The complex effects of GHB as a psychoactive substance are partially caused by its endogenous existence. GHB occurs naturally in the human brain and body. It has a structure comparable to that of its precursor gamma aminobutyric acid (GABA). It has been shown that the fetal brain, in humans as well as in other species, contains high concentrations of GHB which drop rapidly after birth[3]. GHB is broadly distributed in the brain and reaches concentrations of 1-4 μM[4]. The highest levels of GHB exist within the substantia nigra, thalamus, and



hypothalamus, whereas the cerebellum and certain areas of the cerebral cortex contain the lowest concentrations[5, 6].

GHB is also found in many peripheral organs such as the kidney, heart, and skeletal muscles, in concentrations considerably higher than those in the whole brain[7, 8]. Yet, its function in the peripheral tissues is unknown. In the central nervous system, GHB is synthesized through transamination and reduction of GABA[9, 10]. GABA is converted by GABA aminotransferase into succinic semialdehyde. This is subsequently reduced within cytosol or mitrochondria by succinic semialdehyde reductase, a NADP+-dependent oxido-reductase, or by aldo-keto reductase 7A2 (AKR7A2), producing GHB in cellular perinuclear regions. AKR7A2 appears to be the main physiologically relevant enzyme that synthesises GHB[11].
The catabolism of GHB involves its oxidation to succinic semialdehyde, followed by its entry into the Krebs cycle as succinate. It appears that the site of GHB degradation varies during development. Two enzymes which appear to be important in this process have been identified in animal experiments: GHB dehydrogenase, responsible for the majority of GHB breakdown in the foetus and young animals, and GHB-ketoacid transhydrogenase, which is responsible for most of GHB metabolism in adult animals[5, 12].

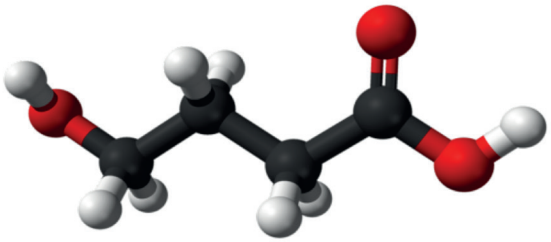


The existence of endogenous GHB and its connection with GABA and succinic acid as precursors is demonstrated by the clinical observation that a deficiency of succinyl semialdehyde dehydrogenase, the enzyme which normally removes succinyl semialdehyde, which is a precursor of GHB, leads to an abnormal accumulation of GHB[13]. This is a condition which is associated with severe but often unrecognized psychiatric disorders[14], and symptoms which resemble those reported in cases of illicit GHB intoxication. Administration of external GHB can affect the

negative feedback control between the precursors, more specifically GABA and GHB, resulting in a dis-balance leading to, for example, a decrease in GABA synthesis. However, it has been suggested that GABA is not the only source of endogenous GHB. Therefore, the probability of the presence of other precursors has to be considered. It has been suggested/shown that endogenous 1,4-butanediol (a component of lipid-diols) may serve as such an alternative precursor for GHB[15]. Despite the fact that the complete and exact function of endogenous GHB is still unclear, endogenous GHB influences several physiological functions due to its putative function as a neuromodulator and neurotransmitter. This has led to several medical indications for the administration of exogenous GHB, as outlined below. Nevertheless, the effect of and interaction between the endogenous GHB and exogenous GHB is not fully described and was a relevant reason for starting an expanded review to be able to understand this relationship which will be outlined further in this thesis.

Medical use of GHB

GHB was synthesized for the first time in 1964 by Laborit and colleagues as an analogue of gamma-aminobutyric acid (GABA)[16]. It differs from this primary inhibitory neurotransmitter by the substitution of a hydroxyl group with an amino group, creating $C4H8O3$[12]. GHB is a 4-carbon fatty acid chain with a carboxyl group at one end, and hydroxy- functionality at the gamma position.



The first described in vivo effects of GHB were hypothermia, hypnosis, anaesthesia, and anticonvulsant effects, without apparent respiratory depression or toxicity. In 1977, GHB started its actual therapeutic career as a hypnotic in sleep disorders[17] e.g. 'essential hypersomnia'[18]. Studies were conducted to test its effect in the treatment of schizophrenia, but these were unsuccessful[19, 20]. GHB usage was revived in the last two decades as a medication for the treatment of several disorders, under the name Sodium oxybate[21]. Sodium oxybate is approved for the treatment of narcolepsy with cataplexy in adult patients in Europe, USA, and Canada (Xyrem®). In the case of this condition, GHB is given orally at bedtime to improve nocturnal sleep quality, thus reducing cataplexy episodes during the day[22]. Sodium oxybate is approved in Germany as an

anaesthetic (Samsonite®)[23]. It is used in Austria and Italy for the treatment of opioid withdrawal (Alcover®), although the evidence supporting this indication is very limited[24, 25]. Sodium oxybate (pharmaceutical GHB) has been reported to be safe and effective in the treatment of alcohol withdrawal syndrome and in the prevention of relapses in alcohol dependence (Alcover®)[26-28]. The exact mechanism of GHB's therapeutic role in alcohol withdrawal and relapse prevention is not entirely known.

Several studies support the fact that GHB has a low potential to induce physical dependence and withdrawal symptoms during therapeutic usage, when dosage is kept within therapeutic margins of 4.5 to 9 grams per day[29-31]. However, neuropsychiatric symptoms have been reported upon abrupt cessation of Sodium oxybate, including case reports on depressive symptoms, including suicidal ideation[32], anxiety, visual hallucinations, and religious delusions[33]. Moreover, abuse of GHB has become an increasing health burden, as outlined below.

Illicit GHB

Pure GHB is found as sold white powder, but more often it is available as a salty-tasting solution. Users take tablespoonful's, capfuls or just a sip from a bottle[20;27;28]. Because of the salty taste, users often mix GHB with soft drinks or just dilute GHB with water, in order to neutralize its salty flavor[20;27]. Most users are ignorant of the exact doses of GHB they use. Where they do know the amount per dose, it is mostly counted in millilitres and not in grams. GHB is a drug which can be easily produced and is cheap and very accessible to the abusers.

GHB and its precursor GBL were initially introduced, used and abused by bodybuilders, because these compounds were reported to stimulate the production of growth hormone[34, 35]. Later on, GHB became popular as a recreational club drug in Europe and it is generally commercialized in vials containing 5 ml. This popularity is related to its rapid psychoactive effects, including euphoria, reduced anxiety, drowsiness, an increase in muscle relaxation, enhanced sensuality, emotional warmth and sexually stimulating effects[36, 37].

General epidemiology of recreational use and abuse

Since the mid-1990s, recreational use of illicit GHB has been reported throughout Europe. In the Netherlands, GHB was legally available in smart shops until 1996. In 2002 it was placed in Schedule II (soft drugs) of the Opium Law and in 2012 the Dutch government transferred GHB to Schedule I (hard drugs) of this law, which made possession and production of GHB illegal38. Little is known about the prevalence of recreational GHB use. Low prevalence was estimated in recent years among the general population in some European countries, e.g. 0.1% recent use in

the United Kingdom in 2010 (British Crime Survey, 2011). National estimates of the prevalence where GHB use exists in Europe, in both adult and school populations, remain low(1-1.4%)[44,74]. For example, GHB use was reported as 2% among regular clubbers in the UK in 2011[44], and 1 % of Norwegian youth aged 15-20 years[75].

In the Netherlands in 2009, 1.3% of the Dutch general population (15-65 years) reported a lifetime prevalence of GHB use. Around 0.4% (44,000 people) reported having used GHB in the last year, while it was used by 0.2% (22,000) during the last month[39, 40]. Other research has estimated that nearly 150,000 people have experience with GHB and that there are over 20,000 current GHB users within the general population[47].

GHB is particularly popular among young people attending entertainment events. In 2011, data in the Netherlands revealed that 7% of these young visitors had at some time used GHB recreationally and 1% had used GHB recently[41]. GHB recreational use appears to have shifted from young adults to other age groups with a mean of 28 years during recent years[42, 43], where 'home usage' has been identified in 'house party' settings[44] and in swingers and gay scenes.

In the Netherlands, GHB and its precursor gamma butryrolactone (GBL) have been on the increase as drugs of abuse during the years since 2007. In 2011 the National Drug Incidents Monitor registered a total of 3,652 reported drug-related incidents and stated that 30% of these incidents were caused by GHB[4]. GHB is often used in combination with alcohol or other drugs such as amphetamine, cocaine, cannabis, and ecstasy[45]. In the 2010 study by Brunt and colleagues, 69% of GHB-dependent inpatients had combined GHB with alcohol, 53% with cannabis, 29% with ecstasy, 33% with amphetamines, and 28% with cocaine[42]. Comparable numbers were mentioned in an earlier survey[46].

Risks of GHB abuse, the Dutch problem

GHB abuse involves several risks and adverse consequences. GHB disinhibition may result in uncomfortable situations, in which the user can be emotional, lose self-control and show unpredictable behaviour such as aggressiveness, engaging in risky behaviours such as reckless driving and exceeding their own sexual limits, as well as those of others, causing possible sexual crime. In the media, GHB tends to be referred to as a rape drug. Nevertheless the prevalence of GHB in cases of confirmed drug-facilitated sexual assault is relatively low[38, 48]. All of the above is overshadowed by the occurrence of serious medical complications such as intoxication, coma, and death. Emergency department (ED) treatment of GHB-inflicted disorders increased, as mentioned earlier, from 300 in 2005 to 1200 (23 case/w) ED treatments in 2009[49]. The risk of acute illicit GHB overdose/intoxication is clear. There is a small margin between the dosage inducing the desired effects and a loss of consciousness. Another reason is the absence of a standard concentration of GHB. Variation from 400 mg/ml to almost 850 mg/ml have been measured. The average concentration of illicit street GHB in the Netherlands is 650 mg/ml. Regardless of the growing recognition of GHB-related health problems, it is unfortunate that the 'black out' (i.e. coma) state – which is often experienced by abusers – is still seen by them as

a relatively harmless side effect of GHB. Clinically, recognizable GHB intoxication symptoms are ataxia, confusion, seizures, vomiting, constricted pupils, bradycardia, and hypothermia[50]. In addition, involuntary movements, agitation, aggression, hallucinogenic effects and profound delirium are considered dangerous symptoms of acute GHB intoxication[51]. Finally, CNS depression eventually leads to coma and respiratory depression.

Table 1: GHB acute intoxication symptoms

GHB dose (mg/kg)	Cardiovascular/ pulmonary	Central nervous system	Gastrointestinal
50-70	Bradycardia, Cheyne-Stokes breathing	Constricted pupils, ataxia, involuntary movements, coma	Nausea, vomiting
>70	Cardio-respiratory collapse, respiratory acidosis	Hallucinations, delirium, hypothermia	Abdominal cramps

Worldwide, approximately 400 deaths associated with GHB or its precursors have been reported[52-55]. It is unclear how many deaths may be linked to GHB in the Netherlands. In 2011, six cases were registered in the Causes of Death statistics by the national authorities (CBS). It is unknown, however, whether GHB was the actual cause or a contributory factor in these deaths. In 2011, the Netherlands Forensic Institute (NFI) also registered a total of five cases in which GHB was the primary cause of death and three others in which GHB use played an indirect role in their death[47, 39]. Thus, exact statistics on the total number of casualties/deaths related to GHB misuse up until 2014 are not available due to of the lack of relevant research data.

GHB dependence

Substance use disorder (SUD) is defined as continuous uncontrolled use of a psycho-active substance regardless of the resulting repeated negative social consequences, such as reduction or lack of involvement in social and occupational obligations, with interpersonal conflicts and legal problems. In the case of substance dependence, the emphasis is usually on the physiological concerns such as tolerance and withdrawal symptoms. SUD is divided into substance abuse and substance dependence and has been established in DSM-IV as compulsive behaviour in seeking and taking substances [56]. In the case of substance dependence, the emphasis is on the occurrence of tolerance and withdrawal symptoms. The recently introduced DSM-5 criteria recognize that mental and behavioural aspects are more specific to SUDs than the physical domains of tolerance and withdrawal, which are not unique to dependence. GHB-dependent patients show all the stated characteristics of substance dependence, also those recently introduced into the DSM-5 criteria, especially the intensive and serious psychiatric and psychological symptoms of acute

GHB withdrawal and craving. Nevertheless, GHB dependence is not mentioned separately, in either in DSM-IV or DSM-5.

Daily administration of GHB, 3-6 times day and night, can lead to tolerance and apparent withdrawal symptoms and causes abusers to become dependent within weeks[57].

Little is known about the exact prevalence of chronic GHB dependence in the USA and Europe due to the absence of surveillance and systematic reporting mechanisms[76]. Nevertheless, the request for help for GHB in the Dutch population increased from 4 in 2007 to 48 per 1 million inhabitants in 2012. The demand for treatment of GHB addiction in the Netherlands in 2012 stood at an average of 5 per 100,000 of the population. The number of patients seeking treatment in the addiction care sector increased significantly in these years from 0.1% to 1.2% of the total patient population in addiction care, from 60 patients in 2007 to 769 in 2012. Nearly one third of these (32%) were admitted for inpatient treatment[45]. As yet, no statistics have been published about the prevalence in 2013 or 2014. One of the possible explanations for this increase in problematic GHB use might be its accessibility and the relative ease in manufacturing it from readily available precursors, such as the unscheduled cleaning product GBL[58]. Chemistry kits, reagents, and recipes for converting GHB prodrugs into GHB can be easily purchased over the internet. However, the availability is thought to have diminished slightly since the national restrictions on the production, sale, and use of GHB became effective. Nevertheless, it created an increase in the abuse of the GHB precursor GBL – a clinical observation,- but unfortunately- no solid data are available on the prevalence of the use of GBL amongst the Dutch population. However, GBL can result in more severe withdrawal symptoms, as pure GBL is, per unit of volume, about threefold stronger, and more potent than GHB-preparations currently used in the Netherlands. Another reason for GHB popularity is the low/limited possibility of its detection in body fluids due to the short time frame of its presence in urine and blood. GHB is eliminated rapidly from the body. This means that GHB can only be detected in blood plasma up to 4 to 5 hours after ingestion and in urine up to 8 to 10 hours after ingestion[59]. This makes it difficult to test for GHB, which is why GHB is not included in routine drug screening tests. This can make it a popular substance amongst people who are regularly tested for drugs (army personnel, airline pilots, etc.), and thus could also signify a threat to the safety of non-users. More importantly, there is minimal potential for social control as GHB produces no typical odour by abuse and users can easily participate in public events and consume the colourless water-like liquid without raising any suspicion of drug misuse. Together with the low price, these are all factors that can lower the threshold to experimentation, use, abuse, and finally dependence on GHB.

The GHB withdrawal syndrome

The withdrawal syndrome occurs in drug-dependent individuals on cessation or reduction of use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period and/or in high doses. The withdrawal syndrome shows, according to the WHO definition, a group of symptoms of variable clustering and degree of severity with a time-limited onset and course

related to the type of substance and dose being used. The syndrome may be accompanied by signs of physiological disturbance translated as physical dependence. A withdrawal syndrome is one of the indicators of substance dependence.

Evidence of the development of GHB tolerance and GHB withdrawal syndrome presenting physical dependence which can occur within weeks of frequent daily use, has been stated in numerous case reports of chronic heavy GHB users[57, 60-67]. The severity of the withdrawal reactions is usually stated by dependent patients as one of the main reasons for taking GHB around the clock at intervals of 2 to 4 hours. The GHB withdrawal syndrome may consist of several symptoms including insomnia, muscular cramping, tremor, diaphoresis, restlessness, anxiety, autonomic instability, hallucinations and delirium[68].

Table 2: Clinically observed withdrawal symptoms of GHB (Snead 2005,Gonzalez 2005,Wojtowicz 2008)

Mild (prevalence)	Moderate (prevalence)	Severe (prevalence)
Tremor (67%)	Restlessness	Hallucinations (63%)
Insomnia (58%)	Mild anxiety or agitation	Tachycardia (63%)
Diaphoresis (35%)	Muscular cramping	Severe anxiety (46%)
Nausea and vomiting (35%)		Hypertension (44%)
		Psychomotoric restlessness or agitation (40%)
		Delirium (12%)
		Rhabdomyolysis (7%)
		Seizures (7%)
		Autonomic instability

Complications can be serious to life-threatening if left untreated, including rhabdomyolysis, liver, and renal failure[69], and require admission to a high to intensive medical supportive care setting. GHB exerts its effects by affecting the regulation of neurotransmitters or simulating their actions at their receptors (e.g. GABA-B, subtypes of GABA-A), and subsequently within the nerve cell itself, often in highly specific ways. The neurobiological explanation of GHB dependence and withdrawal is discussed in detail in chapter two of this thesis.

Treatment of signs and symptoms of withdrawal: detoxification

The process of providing special help and medication-based treatment to reduce or. relieve withdrawal symptoms is known as detoxification. Psychoactive substance detoxification is and should be an early step in a long-term treatment. The rapid increase in the number of GHB abusers experiencing complicated withdrawal points to the need for expert medical knowledge to provide detoxification. However, although GHB dependence and withdrawal has been described in the literature for more than a decade, knowledge is only available from case reports. In these

case reports GHB was replaced with another sedative substance. The most frequently applied approach has been the administration of high doses of the GABAA agonists benzodiazepines (mainly diazepam and lorazepam). The mechanism of action of benzodiazepines is not precisely known, but is probably stimulation of inhibitory GABA-ergic (inter)neurons decreasing the stimulation of the central nervous system caused by the GHB withdrawal[57]. Several cases showed resistance to this medical support, were extremely tolerant to the sedative effects of benzodiazepines, and needed very high dosages [e.g. 300 mg diazepam, 22 mg Lorazepam/ day][67]. Orally or even parenterally administered benzodiazepines did not reduce the likelihood of developing delirium. Close medical supervision and constant monitoring of oxygen saturation is required and, in some cases, mechanical ventilation is obligatory. Within Novadic-Kentron addiction care, our experience with GHB detoxification by means of benzodiazepines was not successful, as described in the case report included in **chapter 5a** of this thesis.

Apart from benzodiazepines, numerous other drugs have been tried to provide detoxification.

- In cases of benzodiazepine resistance, barbiturates [pentobarbital and phenobarbital] or propofol are administered[70]. They were suggested due to their effect via GABA-A receptors and the fact that they also have anti-glutamatergic effects[71]. Sometimes complete general anaesthesia is induced. Both treatments require the equipment and monitoring facilities of an intensive care setting.
- Anticonvulsants, e.g. gabapentin, are usually added to benzodiazepines in the case of sleeping problems. This is attributed to their regulatory effect on the excitatory neurotransmitter glutamate.[72] However, there is still no scientific evidence which supports this practice.[72]
- High-dosage antipsychotic drugs, which have shown a limited effect on the withdrawal symptoms. Furthermore, they may increase the risk of a dystonic reaction and the development of a malignant neuroleptic syndrome[73]. This is in addition to a reduction of the seizure threshold which can increase the risk of developing convulsions.
- Baclofen, a GABA-B receptor agonist, was discussed in one case report as a treatment at a low dose as part of a benzodiazepine regime.[29]

Physicians in addiction care facilities were confronted with the new trend of GHB abuse, which is accompanied by a high risk of rather severe and uncontrollable withdrawal symptoms, especially in the case of sudden cessation of GHB. Recent research has focused mainly on the description of the withdrawal syndrome and the related complications, with administration of very high doses of benzodiazepines, mostly provided in IC units. There were no treatment guidelines/protocols available which were established as a suitable approach for safe and effective detoxification of GHB dependence in medium-care facilities. These physicians were initially left empty-handed, and due to the high doses of benzodiazepines required, the risk of complications and the lack of protocols, addiction care centres were reluctant to admit GHB-dependent patients for detoxification or crisis management. This was, in fact, the starting point for the development of a

new GHB detoxification method by the Novadic-Kentron Institute for Addiction Care by means of pharmaceutical GHB: DeTiTap®, which stands for Detoxification with Titration and Tapering. Within the Novadic-Kentron Institute for Addiction Care, a start was made by developing a concept protocol for this detoxification method which might be an alternative to the use of high doses of benzodiazepines. The DeTiTap method was first described in several case reports by Kamal and colleagues[2]. These reports showed several tapering approaches: 1) administration of a standard GHB dose and increasing the interval between the doses daily or, 2) usage of a standard dose interval and decreasing the GHB dose per administration. This was followed by an explorative pilot study conducted with 23 patients to select the better of these two approaches of titration and tapering/detoxification with respect to the subjective withdrawal severity reported and the safety of treatment.. This will be discussed in **chapter 5a**. Replicating these findings and testing the method/protocol in a larger population and evaluating its efficiency constituted the aim of a new research project. Because the Novadic-Kentron Institute for Addiction Care is affiliated with the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA), a multi-centre project was proposed.

The National GHB monitor 1.0

Because of the growing problem of GHB-dependent patients, NISPA started a project named GHB Monitor 1.0, commissioned by the National program "Scoring Results" and supported financially by the Dutch Ministry of Health, Welfare and Sports (VWS). The GHB monitor is a multi-centre research project involving six Dutch addiction treatment facilities. A clinical cohort was studied in the period from 2010 to 2012. The DeTiTap® detoxification method® by means of pharmaceutical GHB was carried out and monitored closely during this project.

The goals of the project were:

a) To evaluate the efficiency and safety of the DeTiTap detoxification process, documenting the factors that influence the effects of this new method.
b) To compare the DeTiTap with GHB detoxification by means of benzodiazepines, in terms of indication, efficiency and safety.
c) To gain insight into the population of GHB-dependent patients.
d) To establish and develop a practice-based guideline/protocol for GHB detoxification.
e) To provide a platform to share GHB detoxification experiences within the Dutch addiction care system.

The project proposal was approved by the Medical Ethical Committee of the Medical Spectrum Twente (MST METC), because of the observational nature of the project, working with a standard protocol which did not constitute any additional burden for the patients concerned. The present thesis is mostly focused on the objectives presented in points a, c, and d specifically.

Aims and outlines of this thesis

The main purpose of this thesis is to evaluate the detoxification treatment by means of titration and tapering of pharmaceutical GHB, to examine the factors influencing the withdrawal symptoms and the medication choice during detoxification, and to provide a practice-based GHB detoxification guideline for GHB-dependent patients in the Netherlands with a well evaluated and widely supported practice-based set of recommendations. The specific research questions are:

1. Which neurobiological pathways of exogenous GHB explain its addictive character and the complex GHB withdrawal syndrome? (**Chapter 2**)
2. Which psychiatric comorbidity is diagnosed in the GHB-dependent patients and which influence could it have on the pattern of GHB misuse and the quality of life of these patients? (**Chapter 3**)
3. Does concomitant substance use influence the withdrawal syndrome presentation and the choice of medical treatment during detoxification? (**Chapter 4**)
4. How can we perform GHB detoxification by means of pharmaceutical GHB and is it an effective and safe method for the treatment of GHB withdrawal symptoms within the setting of medium-care addiction care facilities? (**Chapter 5a, 5b**)
5. In the case of benzodiazepine-resistant acute withdrawal state in general hospital settings, is detoxification by means of pharmaceutical GHB a suitable treatment to avoid severe complications? (**Chapter 6**)
6. Can GHB detoxification be provided in an outpatient setting? (**Chapter 7**)
7. Could Baclofen play a role in relapse management by means of decreasing craving? (**Chapter 8a,8b, 8c**)

Chapter 2 explores the aetiology of and neurobiological pathways leading to GHB dependence and explains the reported withdrawal symptoms.

Identifying the psychiatric comorbidity is the first step towards improving medical choices in treating patients during the detoxification phase, based on a well-founded explanation of the observed and expected withdrawal symptoms. This effect can dictate the type and setting and may influence the state and presentation of withdrawal during the detoxification process. **Chapter 3** assesses the prevalence of the psychiatric comorbidity and the level and type of psychological distress before and after the detoxification phase and their impact on the pattern of GHB misuse and quality of life of these patients.

Chapter 4 presents and assesses the add-on effect of the concomitant abuse of sedatives (alcohol and/or benzodiazepines) and stimulants (cocaine and/or amphetamines) on the withdrawal symptoms.

In **Chapter 5a**, the detoxification by means of titration and tapering of pharmaceutical GHB is explained in a pilot study, including results of the first 23 patients treated with this method worldwide. **Chapter 5b** provides an evaluation of GHB detoxification by means of titration

and tapering of pharmaceutical GHB in a naturalistic study of 274 patients during an inpatient treatment period within the addiction care facilities. In this chapter, the safety and efficacy of this treatment approach is assessed as well as the accuracy of the practice- based protocol upon which the treatment is based.

In **Chapter 6**, a practice-based protocol for GHB detoxification in general hospitals is presented by describing the treatment of three cases of GHB-dependent patients admitted to a general hospital with severe GHB-withdrawal syndromes. In all cases, the efficiency of treatment with pharmaceutical GHB is reported, after failure to stabilize the patient with high-dose benzodiazepine treatment.

In **Chapter 7**, the decision rules to determine the GHB detoxification setting for prepared and scheduled treatment within addiction care facilities are dealt with by means of a vignette study. This has also resulted in an outcome practice- based protocol, which is added to the thesis.

Chapter 8a presents the first results of a study on the effect of baclofen (GABA-B agonist) on relapse rates by means of a case series report and the possible complication in **chapter 8c**.

Chapter 8b proposes a protocol for an open label study, assessing the effectiveness of baclofen in reducing craving for GHB and relapse rates in GHB-dependent patients after detoxification.

Finally, **chapter 9** summarizes the key findings of this thesis, its scientific and clinical relevance, the limitations of the present studies, and the recommendations for future research.

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Chapter 2

The Neurobiological Mechanisms of Gamma - Hydroxybutyrate (GHB) Dependence and Withdrawal and their Clinical Relevance

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ABSTRACT

Objective: GHB has gained popularity as a drug of abuse. In the Netherlands the number of patients in treatment for GHB-dependence has increased sharply. Clinical presentation of GHB-withdrawal can be life-threatening. We aim, through this overview to explore the neurobiological pathways causing GHB-dependency and withdrawal and its implications on treatment choices.

Methods: In this work we review the literature discussing the findings from animal models to clinical studies focused on the neurobiological pathways of endogenous but mainly exogenous GHB.

Results: Chronic abuse of GHB exerts multifarious neurotransmitter and neuromodulator effects on GABA, glutamate, dopamine, serotonin, norepinephrine and cholinergic systems. Moreover, important effects on neurosteroidogenesis and oxytocin release are wielded. GHB acts mainly via a bi-directional effect on GABA-BR (subunit B1and B2) depending on the involved subunit of GIRK channel involved, and an indirect effect of the cortical and limbic inputs outside the NAc. GHB also activates a specific GHBR, and β1 subunits of α4 GABA-AR. Reversing this complex-interaction of neurobiological mechanisms by abrupt cessation of GHB-use, results in a withdrawal syndrome with diversity of symptoms, of different intensity depending on the pattern of GHB-abuse.

Conclusion: The GHB withdrawal symptoms cannot be related to a single mechanism or neurological pathway, which implies that different medication combinations are needed for treatment. A single drug class, such as benzodiazepines, gabapentin, or antipsychotics, is unlikely to be sufficient to avoid life-threatening complications. Detoxification by means of titration and tapering of pharmaceutical GHB can be considered as a promising treatment that could make poly-pharmacy redundant.

Keywords: Gamma- hydroxybutyrate, GHB, Neurobiology, Dependence, Withdrawal, Detoxification, Review

1. INTRODUCTION

Gamma-hydroxybutyric acid (GHB) is a short-chain fatty acid that occurs naturally in the human brain acting as a neurotransmitter and neuromodulator[1]. GHB was developed in the 1960s as an anesthetic agent[2], but its use in anesthesia remained limited due to inadequate analgesia, the emergence of delirium, and proconvulsive effect`[3]. As a therapeutic drug (Xyrem®; sodium oxybate), GHB is currently used worldwide in the treatment of narcolepsy with attacks of cataplexy[4]. It is also approved in Austria and Italy to treat alcohol dependence and withdrawal (Alcover®)[5], and it is used off-label for opiate withdrawal. .Over the last decades, GHB has gained popularity as a recreational drug and drug of abuse in Europe and the Netherlands[6, 7]. Yet GHB use seems to be on the low side. National estimates of the prevalence of GHB-use in both adult and school populations where GHB use exists in Europe, remain low (1-1.4%)[8, 9]. GHB use was reported as, 2% among UK regular clubbers in 20119, 1.3% in the general population in the Netherlands (15-65 years) 10, 11 and 1 % of the Norwegian youth aged 15-20 years[12]. Little is known about the exact prevalence of chronic GHB dependence in USA and Europe due to the absence of surveillance and systematic reporting mechanisms[13]. Nevertheless, the number of GHB users seeking help has increased in recent years[9]. In the Netherlands the number of patients admitted to addiction treatment centres for GHB-detoxification has quadrupled in the past years from 63 patients in 2008 to799 patients in 2012[14]. Add to that the fact that GHB related drug incidents increased substantially, e.g. 20% of the reported 3652 drug incidents in the Netherlands in 20117 and 7 % of the subsequent acute poisoning admissions in Norway.[12]

The abuse potential of GHB is most likely the result of its anxiolytic, hypnotic and euphoric effects[15]. After the ban on the commercial trade of GHB, and subsequent classification as a schedule 1 drug, abuse extended to gamma butyrolactone (GBL) and 1, 4-butanediol (1, 4-BD)[15,16]. GBL and 1, 4-BD are precursors of GHB, available as common industrial chemicals, and when ingested are rapidly metabolized into GHB, exerting the same clinical effects[17]. GHB-dependent users who dose multiple times daily, are repeatedly presented to emergency departments with acute intoxications, GHB-withdrawal syndromes and GHB-related traumas[18]. Severe manifestations of GHB-intoxication include central nervous system depression, hypoventilation, bradycardia, myoclonus, and seizures. Agitation or delayed delirium may occur, as well as complications such as metabolic acidosis and Wernicke's encephalopathy which may be lethal[19-21]. The clinical presentation of GHB-withdrawal ranges from mild tremors, tachycardia, hypertension, anxiety, agitation, seizures, and insomnia to profound disorientation, increasing paranoia with auditory and visual hallucinations, delirium, agitation and rhabdomyolysis[22]. The pharmacological and neurobiological mechanism of action of GHB which is responsible for its therapeutic and abuse related effects is not entirely clear. However, over the last few years an increasing number of animal studies and some human studies have focused on examining the mechanism of action of GHB. Several recent reviews have thoroughly addressed the neurobiology of GHB-intoxication, e.g. van Amsterdam and colleagues[23]. Therefore, the aim of this review will

be to provide a neurobiological explanation of the complexity of GHB dependence and the GHB-withdrawal syndrome and its clinical implications. In order to understand this complexity, firstly the effects of exogenous GHB (ExGHB) are reviewed by exploring the resemblances between the endogenous GHB (EnGHB) and ExGHB neurobiological mechanism of action, and secondly the neurobiological pathways of GHB dependence and withdrawal.

2. ENDOGENOUS AND EXOGENOUS GHB

ExGHB was synthesized by Laborit in 1960 as a potential GABA-agonist and analogue that induces sedation. Bessman and Fishbein later discovered that GHB is an endogenous compound existing in the brain of humans[24]. EnGHB concentrations in the human brain reach about[11–25] μM in the striatum[25], whereas the cerebellum and certain areas of the cerebral cortex contain the lowest concentrations[26]. ExGHB add to these concentrations where GHB-levels above the vitreous cut-off endogenous urine concentrations of 6-10 mg/L are considered to be exogenous [27, 28]. ExGHB seems to pursue almost the same neurobiological pathway as EnGHB as regards metabolism, neuronal uptake, release and degradation process in the brain, and it could be expected to provide equivalent physiological effects.

2.1 Source and Metabolism

EnGHB has several precursors; GABA through transamination and reduction in the neuronal compartment by GABA-transaminase and succinic semialdehyde reductase (SSR)[29, 30]. GBL as detected in the rat brain 1 and 1,4 BD, which exists among lipid-diols in the human brain[31]. ExGHB share the same precursors (figure 1)[26]. When ingested in humans, ExGHB is absorbed rapidly and has a peak plasma concentration within 30 to 90 minutes after ingestion[32]. The overload of the EnGHB system in the brain by administration of ExGHB which can easily cross the placenta and the blood-brain barrier (BBB) 17 and penetrates into brain cells, will probably increase GHB concentration in the vesicles, depending on the threshold level of GHB in the neuronal cytosol[33]. ExGHB as well as EnGHB co-localizes with GABA in its nerve terminals[26,33]. It is released into the extracellular space by Ca^{2+} dependently neuronal depolarization from GHB-ergic terminals[21, 34]. The elimination or degradation process seems to be similar for both EnGHB and ExGHB (figure 1), and is strictly controlled by the negative feedback influence of the reaction products.[17, 35] In addition, ExGHB has nonlinear dose dependent renal clearance, which increases at higher GHB plasma concentrations[36], most likely due to the saturable reabsorption in the kidney.[37-39] This may explain in part the renal failure process presentation during GHB intoxication which might be fatal.

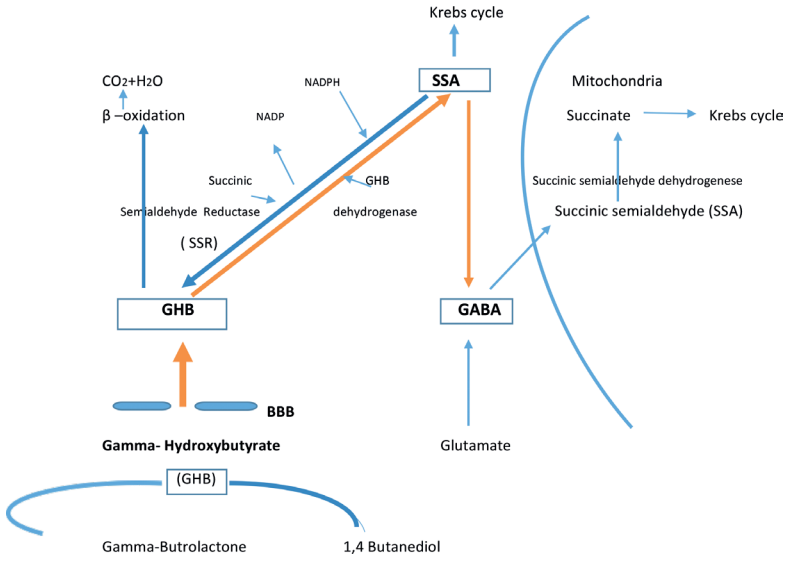

Figure 1: (Exogenous & Endogenous) GHB metabolism

Gamma-aminobutyric acid (GABA) is converted to succinic semialdehyde by GABA transaminase (in mitochondria), followed by reduction of succinic semialdehyde to GHB by cytosolic succinic semialdehyde reductase. Succinic semialdehyde dehydrogenase, converts succinic semialdehyde to succinate leading to energy production via the Krebs cycle.

Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD) are converted to GHB and cross the blood brain. GHB oxidation takes place forming succinic semialdehyde by NADP+ linked succinic semialdehyde reductase. The succinic semialdehyde undergoes further metabolism to either GABA or succinate. The GHB dehydrogenase is capable of metabolizing GHB to succinic semialdehyde. Another metabolism pathway of GHB is through a β -oxidation process.

2.2 Physiological Effect

After crossing the BBB, ExGHB in low doses could initiate the same physiological functions of EnGHB. This clarifies some of the interesting therapeutic perspectives of ExGHB and may partially explain its unfortunate abuse liability. GHB levels are believed to rise in the case of hypoxia and/or ischemia and excessive metabolic demand to protect central and peripheral tissues (e.g. myocardium).[1] Results of animal studies demonstrate the direct protective action of GHB treatment against oxidative stress-induced cell death ,apoptosis and nerve cells death mechanisms which suggests that GHB may also control neuro-protection also against transient global lesions.[40-42] This effect is achieved through reducing cell energy requirements and cerebral energy metabolism via the increase in brain concentrations of glycogen and glucose and a decrease in concentrations of pyruvate, lactate and alpha ketoglutarate[1] which lowers oxygen demand and consumption by the brain and other tissues. Low levels of GHB also function as a

feedback inhibitor of lipid peroxidation[43, 44]. This could explain the limited impact experienced by abusers following GHB induced coma/ blackouts which leads to the inaccurate assumption of the drug's safety, increasing GHB attraction and ultimate abuse. On the other hand and despite the suggested neuro-protective role, animal studies of repeated or prolonged exposure to GHB in rats showed noticeable neurological cell loss in the CA1 hippocampus and the prefrontal cortex[45]. Functional tests in rodents confirmed the presence of impairments in working and spatial memory[45-47], which can be lasting[48]. However, human studies systematically investigating the long lasting effects of GHB use on cognitive functions are lacking.

Another physiological function of GHB which has been beneficial in therapeutic aspects is its impact on the sleep pattern in humans and rodents. This effect could be one of the potential risks for abuse and dependence liability of GHB when used as self-medication, especially in patients suffering from sleep disturbances. Just as EnGHB plays an important role in sleep physiology[49], ExGHB also counteracts sleep latency and promotes deep slow wave non-REM sleep[44, 50] e.g. in depressed patients[51]. Human consolidation of sleep[52] with dose as low as 0.32–0.56 g/70 kg plasma concentration[53] should be considered. This effect is produced via stimulation of the GHB specific receptors (GHBR), for which GHB has a high affinity[54]. GHBR has an ontogenetic molecular identity profile distinct from GABA-B receptors (GABA-BR), and different subtypes[55]. In the median raphe nucleus and the dentate gyrus of the hippocampus one of the regions with the highest expression of GHB high-affinity binding sites, as well as in several brain regions involved in sleep physiology, GHB but not baclofen as pure GABA-B agonist induced c-Fos expression[56, 57]. GHB in nano- to micromolar concentrations[58] exerts effects via GHBR high-affinity site and is suggested to be counteracted by the GHBR antagonist NCS-382[56]. Some studies stated in contrast, that pre-treatment with NCS-382 potentiated, rather than antagonized, a GHB-induced sedative hypnotic effect[59] which was offset by others who questioned the antagonistic properties of NCS-382 on GHBR since it failed to block the effect of GHB on hypomotility and sedation/ hypnosis[60-62]. The involvement of GHBR was confirmed when the specific GHBR agonist c-hydroxyvaleric acid was proved to mimic the sedative effects of GHB without binding to the GABA-BR[58, 63]. Higher supra-physiological concentrations (such as ExGHB) down-regulate the GHBR and eliminate the tonic inhibitory control of GHBR on the GABA pre-synaptic element. As a result, both GABA-release and GABAergic tone increase, inducing sleep[64]. Nevertheless, the exact involvement of GHBR is still unclear. The effects of GHB on sleep have also been suggested to be mediated by β1 subunit containing α4-GABA-A receptor-(GABA-AR)[65, 66] which are highly sensitive to low concentrations of GHB (levels of 1.0 μM GHB or below in neuronal level), when the concentration increases an additional δ-subunits GABA-AR would putatively become involved[66, 67]. In summary, GHB ingested in low doses could initiate some physiological effects mediated mainly by GHBR, the β1 subunits of α4 GABA-AR. These effects which have positive therapeutic functions may unfortunately provide a potential risk for abuse. Studies presenting the exact GHB concentration needed to produce all of these effects in humans are lacking.

Table 1: Receptors mediating GHB effect [54, 65, 66, 67, 82, 136, 167]

	GHB-R	GABA-BR	GABA-AR
Description	G-protein-coupled high and low-affinity GHB-binding component	Coupled to second messenger systems and Ca 2+ and K + channels via G-proteins.	Heterooligomeric R ligand-gated C1- channels ,α, β1and γ subunits also ρ subunits of GABA-AR. Homooligomeric R with intrinsic C1 channels.
High Density	Hippocampus (median raphe nucleus & dentate gyrus), grey matter cerebral cortex, NAc	Cerebellum , Thalamus followed by Hippocampus	Hippocampus and cortex, cerebellar, retina and Xenopus oocytes
Effect GHB	High affinity full agonist	Low affinity full agonist	Full agonist and with some subtypes Partial Agonist
(Behaviour) effect	Physiological : sleep and memory	Addiction	Sleep , decrease anxiety
Other Agonists	NCS- 356	baclofen and CGP27492	Benzodiazepines, TACA
Antagonist	NCS-382	CGP35348, Phaclofen	Bicuculline, CGP36742

3. CHARACTERISTICS OF BEHAVIOURAL EFFECTS OF EXOGENOUS GHB

A special characteristic of GHB is the nonlinear oral absorption with limited capacity at higher doses[52, 68]. This leads to an increased interval of time to achieve Tmax and a decrease in the normalized Cmax. For example, the average time to achieve peak-concentration increased from 25 minutes at a dose of 12.5 mg/kg, to 45 minutes at a dose of 50 mg/kg[17, 35]. The mean peak plasma concentration decreases with the presence of food in the stomach. GHB can be behaviourally active at doses as low as 0.32 g/70kg within 10 to 20 minutes after ingestion, with a short duration of action[53]. Higher doses [e.g. 0.56g/70kg] produces a longer duration of action[32, 53], thus, often an abrupt and dose-dependent effect. Furthermore, GHB effects are biphasic, with initial stimulant-like effects followed by a mixture of sedation and stimulant-like effect as blood concentrations rise[69]. All of the above can explain the abuse pattern and the repeated GHB administration in doses between supra-physiological and pharmacological levels per ingestion, at a maximum interval of 4 hours to achieve the targeted reward effect every time.

4. NEUROBIOLOGICAL PATHWAY OF GHB DEPENDENCE

4.1 Dose, Intensity of abuse and physical dependence

When GHB is administered in therapeutic doses such as 3–9 g/night or day for the treatment of narcolepsy or alcohol dependence, the development of tolerance to the effect of GHB is unlikely to occur[70, 71]. In these studies, signs of physical dependence or symptoms of withdrawal after discontinuation were not reported[15, 72-74]. On the other hand, studies in baboons showed that lower doses such as 56 mg/kg can induce possible drug abuse effects[70, 75]. Repeated administration of GHB at least 3-6 times per day can lead to tolerance, dependence on the behavioural and neurochemical effects with apparent withdrawal symptoms[26, 76]. In humans, physical dependence has been described within days to weeks of frequent and heavy use[76-78]. The average self-administered dose reported in dependent patients ranges from 32- 67.2 g/day[79] to a maximum of 144 g/day[77], at intervals of 45 min to 2.5 hours. The severity of physical dependence on GHB is also a function of the dose and duration of abuse[80]. Thus, not unexpectedly, high doses and/or longer periods of dosing may be critical for physical dependence on GHB[70, 79].

4.2 GHB dependence liability

GHB use is considered to have a high dependence potential. It may be related to the reward mechanisms involved and the self-medication use patterns.

4.2.1 Reward mechanism of GHB

GHB shares the neuronal circuits that are believed to mediate the rewarding and drug-seeking behaviour aspects of most abused drugs including mesolimbic dopaminergic and glutamatergic neurons in the ventral tegmental area (VTA) and the nucleus accumbens (NAc).[81-84] Besides mediating rewarding effects, the activation of the mesolimbic dopamine system is also thought to be centrally involved in the induction of repetitive drug use[85]. GHB seems to have distinguishable pathways in these neurological processes which contribute to its dependence liability. GHB has a bidirectional effect on the GABA-BR influencing the GABA neurons and dopamine neurons in opposite ways. GHB can indirectly reduce the excitability of the NAc. GHB has a recognised impact upon glutamate transmission levels and a neuromodulator effect on serotonin.

a) GHB bidirectional effect on GABA-BR and GABAergic neurons facilitate dopamine release

The properties of dependence /tolerance and behavioural effects of GHB seem to be consistent with the involvement of the GABAergic receptors, mostly the GABA-BR [61, 86, 87]. GHB activates the GABA-BR directly or indirectly through the metabolic conversion of GHB to GABA and GHB-mediated feedback control of GABA release[21, 67]. Subtypes of the GABA-BR (subunit GABA-B1 and B2) are important in mediating the effects of GHB [21, 88-92]. GHB is distinguished by its discriminative stimulus properties on GABA-BR, despite the low-affinity partial agonist

character[85, 87]. GHB has a bi-directional effect on the GABA-BR[85] leading to opposite effects: an increasing (stimulating) effect on one side, and decreasing (inhibitory) on the other side. This effect depends on the localization of the GABA-BR and type of the G-protein-dependent ion inwardly rectifying potassium (GIRK) channel subunits, which mediate the inhibitory effects of G-coupled receptors, like GABA-BR[93]. The GIRK channels are responsible for maintaining the resting membrane potential and excitability of the neuron. Once the GABA-BRs are activated, they allow for the dissociation of the G protein into its individual α-subunit and βγ-complex so it can in turn activate the K+ channels. The G proteins couple the inward rectifying K+ channels to the GABA-BR, mediating a significant part of the GHB inhibition effect[94]. It has been shown that there is differential coupling efficacy (EC50) of GIRK channels in the VTA neurons that is to say, cell-specific expression of GIRK in VTA neurons can differ, with respect to 1, 2c and 3 GIRK subunits. Mostly GIRK1/2 heteromultimeric channels are expressed at the surface in GABA neurons and GIRK2c/3 is expressed in dopamine neurons [85, 95, 96]. This difference in the coupling between GABA-BR and GIRKs subunits provides a mechanism for generating that bi-directional modulation effect of GHB on the neurons mesolimbic dopamine system. Due to the increased efficiency or full activation of the GIRK channel subunits (1/2) coupling to the GABA-BR in the presynaptic GABAergic neurons, these neurons are more sensitive to GHB, and can be targeted even at low doses of GHB as agonist[55, 85]. Despite that, these GABAergic neurons normally exert an inhibitory effect on the dopaminergic neuronal activity. GHB activation of GIRK channels on GABA interneurons suppresses their spontaneous activity and leads to disinhibition of the dopamine neurons, increasing their firing rate and enhancing VTA dopamine output.[97] In other words, GHB activation of the pre-synaptic GABA-BR inhibits GABA release and this, in turn, disinhibits dopaminergic neuronal activity. GHB also lowers the tone in the GABAergic neurons, decreasing the firing rate of the postsynaptic neurons[81]. This can lead indirectly to disinhibition of dopamine neurons. GHB also promotes the release of dopamine post-synaptically [26, 53] as putative GHB-producing neurons are surrounded by dopaminergic terminals, suggesting a direct interaction between GHB and dopamine.[98]

In mice, repeated exposure to GHB increased the GABA-BR GIRK channel coupling efficiency in the dopamine neurons through down-regulation of RGS-2, a member of the regulator of G protein signalling (RGS) protein family[93], another mechanism that might be associated with tolerance.

In summary, GHB leads to the suppression of the spontaneous activity of the GABA neuron through decreased transmitter release (presynaptic inhibition) and concomitant hyperpolarization (postsynaptic inhibition), besides an opposite direct effect on the dopamine neurons. These pathways cause disinhibition of the dopamine neurons, especially in the VTA, and provides an explanation for its strong abuse potential. Added to that, GHB in high doses is metabolized at first to succinic acid. A sufficient amount of succinic acid will be formed within the brain to inhibit the formation of GABA from glutamate, and results in lowered concentrations of GABA[34, 52]. Thus, the GABA system is down-regulated and its ability to inhibit neurotransmitter

release is reduced. The foregoing, especially the activation of the mesolimbic dopamine system, can explain the increased reward addictive process which accentuates craving and GHB-seeking behaviour.

b) GHB affects glutamate transmission and controls hippocampal and NAc glutamate levels

Glutamate plays a key role in modulating both the progress of the sensitization of addiction behaviours and their expression such as drug-seeking[83]. Exogenously applied GHB controls hippocampal glutamate levels in a concentration-dependent manner. It is reported that the systemic administration of low doses of GBL, as a precursor of GHB, augments long-term potentiation (LTP)/ depolarisation, causing transient plasticity in the CA1 intra-hippocampal region and mediated by GHBR activation increases hippocampal glutamate transmission[102-104]. GHB in millimolar concentrations exerts the same effect[103, 105] mediated by the N-methyl-D-aspartate receptor (NMDAR) gated ion channel[106].There is an intrinsic connectivity between the hippocampus, known for its role in long-term memory, and the midbrain (VTA) dopamine regions and the NAc, known for their role in motivation and reward processing[107]. It is also speculated that the dopamine receptors (D1) mediated increase of NMDA current on the dopamine neurons, cause a rise in presynaptic glutamate release and elevate the activity of prefrontal glutamatergic input to the VTA[83]. A sequence of synaptic events which induces GHB addiction-related behavioural sensitization. Glutamatergic plasticity in the NAc is critical for the expression of these behaviours[108]. GHB could indirectly reduce glutamate transmission via a bi-directional effect on the presynaptic glutamatergic GABA-BR, where the heteroreceptors are more sensitive to GHB than the autoreceptors[109]. Therefore, repeated engagement of GHB drug-seeking might cause, as with other drugs, an enduring imbalance in glutamate homeostasis in the NAc, leading to a progressively greater reliance on the motor sub-circuit, and a reduced influence of the limbic sub-circuit[110]. In conclusion, the effect of GHB in glutamate release and transmission contributes to the GHB addiction behaviours sensitization and expression by enhancing the memory of reward and the accompanied excitation effect.

c) GHB has an indirect effect on the NAc neurons

GHB shares with other drugs of abuse the ability to reduce the excitability of the NAc neurons, which contribute to its abuse potential[55, 81]. Conversely, GHB differs as it has no direct GABA-BR mediated effect on the medium spiny neurons of the NAc, as stated by Molnár and his colleagues[62]. Thus the reduced activity of NAc observed after systemic GHB administration[81] is related to an indirect effect of the cortical and limbic inputs outside the NAc. There, GHB activates, post- and presynaptic GABABRs hence hyperpolarizing cells and decreasing their glutamate-mediated synaptic responses[99], then merging into NAc and increasing the release of dopamine into the reward mediating area NAc[85]. This is in addition to a GHB main cellular effect in the NAc, executed via a repetitive transient elevation of astrocytic $Ca^{2}+$ independent neuronal

signalling.[62, 100] This in turn leads to neuronal hyperpolarization and suppresses baseline excitatory synaptic activity[101], a reaction which is proved to be mediated by a putative novel GHB agonist-specific and succinate sensitive but NCS-382 insensitive receptor in the astrocytic target[100]. This ability of GHB achieved at a lower dose than the concentration necessary to activate GABA-BRs[55, 62] is a powerful means for rapid modulation of network activity which can explain the rapid process and intense reward dependence effect of GHB. The main reward pathway of GHB, as we mentioned earlier, is through its effect on GABA and Glutamate, however, GHB is suggested to have a neuromodulator effect on serotonin adding to the experienced reward effect and dependence liability potential.

d) GHB's effect on serotonin amplify reward

Animal studies imply that GHB in pharmacological and recreational doses induced an increase in serotonin turnover associated with a rapid intracellular metabolism, which may explain the absence of an increase in serotonin.[97, 111, 112] A decrease in the extracellular concentration of serotonin was observed[111], probably due to intraneuronal deamination of newly synthesized serotonin which remains in the cytoplasmic pool. GHB effects mediated by GHBR increase tryptophan and its uptake in brain tissue by facilitating the dissociation of tryptophan from its albumin binding sites.[1, 111, 113] On the other hand, a GABA-BR dual control of dorsal raphe serotonergic neurons activity has been suggested, which appears to be similar to that exerted on dopaminergic neuronal activity.[44, 114] An interrelationship between both serotonergic and dopaminergic systems, where dopamine release has been shown to be increased by serotonin, is suggested and confirmed by the described projections from the substantia nigra and the VTA to the dorsal raphe nucleus, and in the striatum[111, 115].This can produce a direct inhibitory effect on GABAergic terminals or interneurons and an indirect excitatory state[116], contributing to the rewarding euphoric effect of GHB.

4.2.2 Neurobiology of self-medicating with GHB use

GHB also has a neuromodulator effect on several other neurotransmitters and neuro-hormones which may explain its self-medicating use and may add to its high dependence liability.

a) GHB's effect on adrenergic activity and growth hormone

Sustained daily administration of GHB for 2 and 10-day periods in rats decreased both the spontaneous firing rate and the evoked burst firing of the locus coeruleus (LC) adrenergic neurons[44, 117]. This attenuation of adrenergic neuron firing rate may be important to the anxiolytic and sedative effects associated with GHB. The exact mechanism by which GHB elicits its effects on these neurons is not clear. However, the ability of GHB to activate GABA-AR and GABA-BR, which has been identified on adrenergic neurons[114], may partially explain this effect. GABA tonically inhibits cortical cholinergic neuronal activity[118]. GHB in repeated recreational doses mediated by GABA-BR inhibits GABA, and could subsequently increase cholinergic activity.

GHB seems to increase the acetylcholine content in several rat brain regions, including the hippocampus, and reduce extracellular levels of acetylcholine [119]. This suggests that GHB reduces cholinergic neurotransmission effective in stress conditions and contributes to its anxiolytic effect, and hence to its abuse potential.

The effect of GHB on the cholinergic system can result subsequently in a change of growth hormone (GH) levels. GHB-induced GH secretion in humans[120] is due to stimulation of not only the cerebral GABA-BR[119], but also the specific pituitary GHBR[121]. The GH stimulating effect of GHB seems to correlate with its capacity to induce Slow Wave Sleep [122, 123]. This can contribute to its appeal for abuse amongst youth.[124]

b) GHB neuromodulates neurosteroids and oxytocin

The decrease in neurosteroids and α4β1δ up-regulation has been associated with increased anxiety[66, 125]. Experiments in rats have suggested that GHB positively modulates GABA-AR and NMDAR, leading to an increase in the synthesis of neuroactive steroids, such as the centrally synthesized progesterone analogues allopregnanolon and allotetrahydrodeoxy - corticosterone[126,127]. This modulation can also explain the anxiolytic effect of GHB. GHB has been shown to reduce hypothalamus–pituitary–adrenal (HPA) axis hyperactivity in humans, which may lead to a decrease in stress hormones (e.g. corticotropin-releasing hormone (CRH)) and an increase in oxytocin. The effect of oxytocin is also facilitated by interactions with the mesolimbic dopamine system[122]. Stimulation of oxytocin neurons might be one of the mechanisms by which the GHB modulates the dopaminergic tone. Both neurosteroids and oxytocin are discussed as playing a critical role in the regulation of social and sexual behaviour, anxiety, stress, aggression and the modulation of depression[128].

c) GHB's effect on the opioid system

Despite the fact that the exact interactions between GHB and the opioid system are poorly understood, and no direct stimulation of mu, delta and kappa receptors could be shown, the GHB dopamine release in the striatum is possibly accompanied by the release of endogenous opioids. This indicates a certain opioid-ergic analgesic and sedative effect of GHB which can be antagonized by naloxone.[23, 129, 130]

All preceding deliberated self-medication, anxiolytic, antidepressant and sedative effects of GHB, while forming a part of its therapeutic potential, do however contribute to and play an important role in its potential addiction liability risk.

5. GHB ABUSE VERSUS MEDICAL USE

Despite the fact that the neurobiological mechanisms presented also apply to medically used GHB, studies have shown that patients using GHB medically have very low abuse liability[15]. This

could be explained in some cases such as for example in narcolepsy patients by the exhibited deficiency in the hypocretin/orexin system in the form of a decrease in mutations of the hypocretin/orexin gene, peptide and neurons. The hypocretin/orexin system plays a role in the activation of the mesolimbic dopamine system. This deficiency lead to reduction of pleasure associated with reward processing, effects of addictive drugs, and risk-taking behaviour [131-133]. This might provide an explanation for the limited abuse potential in these patients. In general it seems that GHB dependence associated with withdrawal symptoms is exhibited in animal models and human cases [131] when high doses with a minimum of 11-18 g/d [77, 134] are used in an around the clock frequency pattern [135], which is not the case in the one to two dose daily regime applied in most therapeutic interventions.

6. NEUROBIOLOGICAL EFFECTS OF CHRONIC GHB ABUSE

The action of GHB during chronic abuse in the mesolimbic system is suggested to be mediated mainly through GABA-BR[81, 82]. Nevertheless, the involvement of GHBR in other brain regions (such as the hippocampus) cannot be excluded[103]. Chronic GHB exposure desensitizes GHB and GABAB receptors, thus reducing their ability to inhibit neurotransmitter release[136]. Chronic GHB abuse can affect the most important neuroregulators. It down-regulates the GABA system. Chronic GHB abuse firstly increases glutamate level, and subsequently decreases the maximal density of NMDA binding sites, and down-regulates NMDAR (e.g. in the frontal cortex)[47,110]. By repeated exposure to higher doses of GHB, the dopamine neurons would be directly hyperpolarized, resulting in a decrease in VTA dopamine release[55, 85], accompanied with up-regulation of D1 and D2. Chronic treatment of rats with GHB showed an increase of mRNA expression of dopamine D1 and D2 receptors in brain regions that are rich in GHB receptors [137], and development of tolerance to the effect of GHB on brain dopamine levels. Thus, the mesolimbic dopamine system becomes "hypofunctional" in the GHB dependent brain. Increased serotonin turnover in chronic GHB abuse can lead to more inhibition in dopamine concentration in the brain[97] as well as reduced noradrenergic and cholinergic activity[117].

In addition to these main effects mentioned of chronic GHB misuse. GHB displays partial agonism at α4β1δ-receptors compared with GABA, but does not replace the GABA effect, and in the case of chronic GHB abuse α4β1δ GABA-AR can be up-regulated due to decreased GABA effect[66]. The neurosteroids effect can increase as the α4β1δ-subtype has been identified as an important target for endogenous neurosteroids. Finally, the possible involvement of the extra-synaptic subtypes of GABA-AR may explain the sedative effect during chronic GHB abuse, despite the low GABA concentration. Chronic abuse is also associated with sustained opioid release.

7. POSSIBLE NEUROBIOLOGICAL MECHANISM OF WITHDRAWAL

The discontinuation of GHB intake in chronic dependent abusers reverses the neurobiological effect of GHB and produces a variety of (adverse) withdrawal symptoms Due to the previously mentioned effects of GHB on GABA and glutamate which reflects on the different neurotransmitter systems, the state observed during withdrawal is likely to be the result of a complex interaction. The withdrawal syndrome consists of several symptoms which may persist for several days. In the initial period of abstinence, features include physical symptoms and signs such as tremors, miosis, sweating, tachycardia, palpitations, dyspnoea, nausea, vomiting, diarrhea and abdominal pain and a prevailing anxiety-related behaviour [76, 77, 138]. These are related to stimulation of the sympathetic system, due to an increase in noradrenaline and acetylcholine as the result of an impairment of the feedback inhibition on GABA. In a study on rats, a significant 33% increase in spontaneous noradrenergic neuronal activity and a robust 79% increase in burst firing were found to be due to GHB withdrawal [117]. The loss of GHB ability to attenuate the LC activity increases noradrenaline [117] and may be important in causing anxiety during withdrawal . In addition, α4β1δGABA-AR up-regulation has been associated with increased anxiety and hyperalgesia because of disinhibition of GABAergic neurons output [66]. Part of the occurrence of arousal symptoms such as anxiety during GHB withdrawal can also be explained by the decrease in neurosteroids concentration, which is a positive allosteric modulator of the GABA-AR and NMDARs [55, 127, 128, 139].

It has been suggested that, after chronic abuse of drugs, dopamine release is compromised. Studies have pointed to the relevance of dopamine in withdrawal. It has been documented that, during withdrawal, striatal dopamine response or receptor availability was significantly low in cocaine abusers[140], and striatal D2 receptor was down regulated in alcohol and heroine abusers [141,142]. This neurological state seems to be different in the case of GHB, and the low dopamine level is reversed rapidly to a high level after cessation of GHB. The increase may persist and explain the latent psychosis /delirium within 2-4 weeks after withdrawal/ abstinence[22, 143].

In more severe cases of withdrawal, patients experience symptoms such as hypertension, insomnia, agitation, paranoia, disorientation, confusion, aggression, and auditory and visual hallucinations[76].These symptoms are probably mainly due to a sudden increase of dopamine concentrations in the frontal cortex and thalamus associated with the presence of D1 and D2 up-regulation status. An effect which can be hypothesized to be related to the increased activity of the hippocampal neurons and the inhibited effect of pre-lateral frontal cortex projection through D2 receptors[144] and the reduced GABAergic transmission[88]. Due to these mechanisms in addition to the associated manipulation of serotonin levels[115], patients may also suffer from depression, and in severe cases, they develop delirium and/or psychosis. One of the withdrawal complications of GHB described is an excited delirium syndrome. The clinical findings often include: tachypne,

sweating, severe agitation, elevated temperature, delirium, non-compliance and poor awareness to instructions, lack of fatiguing with unusual strength and pain tolerance [145, 146]. This state can be explained by both the persistent dopamine increase with serotonin dysregulation, and it does not react upon administration of antipsychotics.

Impairment of the sleep-mediating effects of GHB via the β1-containing GABA-AR[66] lead to insomnia. The thermic effects of GHB withdrawal are dose-dependent and can occur due to a decrease in metabolic heat production and/or an increase in cutaneous circulation[1, 91]. The recognizable symptoms here are hyper- or hypothermia, tremors and reflex sweating. Likewise, due to modulation of serotonin, uncontrolled muscle contraction caused by hyperkinesia and clonus takes place. In some studies, seizures were also observed[22, 76]. A serotonin syndrome like state is generated. The low pain threshold observed e.g. muscle pain and skin sensitivity are possibly due to a decrease in the enhancement of endogenous opioids release. Furthermore, a reverse of the inhibition of cholinergic neuronal activity is followed by a significant increase in acetylcholine and noradrenaline levels[119]. These can slow down depolarization and increase neuronal excitability, resulting in irregularities in the heart rate and blood pressure, precipitating anxiety and insomnia, an increase in locomotor activity and the production of lactate and other toxins from skeletal muscle[117]. Besides the previously mentioned serotonin effect, the latter may cause rhabdomyolysis and finally lead to renal malfunction.

In summary, the withdrawal complications could be related to the increase in: sympathetic activity, dopamine, serotonin, decrease in opioids and the prolonged down-regulation of the GABA system. Thus, during GHB-withdrawal, GABA alone as the most inhibitory neuroregulator of the brain is no longer capable of opening the ion channels. On the other hand, glutamate as the dominant excitatory factor undergoes dysregulation in addition to increases in both dopamine and serotonin levels in the brain. This is associated with up-regulation of D1, D2, NMDR and GABA-A receptors. All of these preceding results in cellular hyper-excitability that is easily stimulated by excitatory postsynaptic potentials which are thought to be responsible for the previously mentioned complex withdrawal state.

Table 2: Possible neurological explanations for the GHB withdrawal symptoms and signs

Withdrawal Symptom	Possible main Neurotransmitter effect
Auditory /visual hallucinations Paranoia	+ Dopamine
Tremors	+ Acetylcholine, Serotonin
Tachycardia / Palpitation	+ Acetylcholine, +Noradrenaline
Hypertension	+ Noradrenalin
Sweating/ Hyperthermia	+ Dopamine, +Noradrenaline , - Serotonin
Anxiety	- GABA, + Glutamate, - Neurosteroids, fluctuation Serotonin
Agitation/ Aggression	+ Serotonin, + Glutamate
Pain	- Opioid
Insomnia,/Sleeping disorder	- GABA , +Dopamine
Disorientation/ Delirium	+ Dopamine, + Noradrenaline ,- GABA
Depressive reaction	- Serotonin, -Neurosteroids , GABA
Hypo / Hyperthermia	+ Dopamine
Muscle contractions/ Convulsion	+ Acetylcholine, - GABA ,

+ Increase, - decrease/inhibition

8. CLINICAL IMPLICATION ON WITHDRAWAL TREATMENT AND RELAPSE

The complexity of the neurobiological pathways, the involvement of several receptors and neurotransmitters, are repeatedly translated in severe withdrawal presentations and inconsistent treatment approaches. Abrupt cessation of long-term, high dose GHB abuse can rapidly lead to a severe uncontrolled situation e.g. psychosis and aggression. Prolonged withdrawal state has been reported, lasting up to 3 weeks in several cases[77, 138, 147, 148] and in some patients for 4 weeks to months[134], a state which is characterized by disorientation, depression, anxiety, panic attacks and insomnia[77, 134]. The intensity of the withdrawal symptoms can urge abusers to maintain their illicit GHB levels by re-dosing frequently and around the clock[21], sometimes risking the danger of overdoses and intoxication. Severe withdrawal symptoms such as aggression and agitation have, in some cases, been effectively treated with benzodiazepines as GABA-A agonist[135, 143, 149]. In numerous others, nonetheless, resistance to benzodiazepines was reported and the delirium / psychosis and agitation state persisted, despite the particularly high dosages of benzodiazepines e.g. daily doses of diazepam 230 mg 79 or lorazepam 22.5 mg IV [138]. Treatment alternatives as antipsychotic agents were considered and caused neuroleptic malignant like syndrome state[150]. Barbiturates were suggested[151], due to their ability to open directly both GABA-AR and, for a longer duration, the voltage-gated chloride channels[149]. Pentobarbital and phenobarbital also have anti-glutamatergic effect via the amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/

kainate receptors[152], and might lead to decreasing the high glutamatergic state during withdrawal. Baclofen as GABA-B agonist can also have a role in the treatment. The difference in abuse liability of GHB and baclofen may be explained by the differential coupling of GABA-BR to GIRK channels[26, 85, 55] . In contrast to GHB, baclofen, due to its high affinity for the GABA-BR, would at typical therapeutic levels inhibit both GABAergic and dopaminergic neurons and decrease dopamine release[85]. However, clinicians should consider the danger of a rapid dose which could induce psychosis and aggravate the withdrawal symptoms, as has happened as in some cases[153]. Benzodiazepine-resistant cases were successfully and safely treated with pharmaceutical GHB titration and tapering[154].

However, GHB dependent patients report high relapse rates shortly after GHB detoxification treatment[155], which could be related to an increased impulsivity reaction. Despite the fact that it is clear that impulsivity is probably multifarious where different aspects may contribute to different clinical syndromes, it is proposed that the balance between serotonin and dopamine transmission is critical in the aetiology of impulse Control[156, 157]. Abnormal increase in dopamine transmission at D2 and D3 receptors e.g. treatment-induced impulsivity in Parkinson's disease patients[158, 159] and serotonin dis-balance or decrease can increase impulsivity (impulsive choice) in humans. This is a state present during the GHB withdrawal phase and may persist for weeks. The impulsive behaviour in this case is characterised by impatience to delayed rewards (i.e. increased delay discounting) and an increased likelihood of premature responding[160, 161]. At the same time, other neurotransmitters are thought to play a role here[161] such as e.g. manipulations of the noradrenergic system[162] and the decreased GABA levels in dorsolateral prefrontal cortex [163], also presented during withdrawal. Thus, it could be expected that within a period of several weeks after detoxification, GHB dependent patients might show an impaired capacity to inhibit their premature responses, risky decision-making and disregard the relative value of delayed rewards, which may play a prominent role in the reported relapse behaviour.

9. DISCUSSION AND CONCLUSIONS

GHB has become a popular drug in Europe over the last decades[7]. This popularity has resulted in an increase in GHB-intoxications, and more recently, dependence. GHB-dependent patients repeatedly suffer from a complicated withdrawal syndrome which can be life-threatening[18,22] and challenging to treat. Therefore, in this review we aimed to follow the neurobiological pathway responsible for GHB dependence and provide an explanation for the complexity of the withdrawal syndrome. The past few years have seen important developments in our understanding of GHB neurobiology and some of the key cellular mechanisms of its actions have been revealed. The endogenous GHB signalling system in the brain can be easily, and similarly stimulated by peripheral administration of GHB, which follows almost identical metabolism routes and neurobiological pathways accountable for some of its therapeutic effects. The mechanism of action of ingested

GHB is distinctive from many other drugs with dependence properties, since it is distinguished by its bidirectional discriminative stimulus properties on GABA-BR. This can induce mainly GABAergic inhibition and dopamine disinhibition. GHB does not have a lack a direct effect on the GABAergic neurons and glutamatergic pathways in the NAc, but it reduces the activity of NAc through an indirect pathway producing cortical and limbic inputs outside the NAc. GHB is suggested to cause an elevation of the astrocytic Ca+2 dependent neuronal signals within the NAc which explains the rapid rewarding effect of GHB[62]. Several factors contribute to the potential GHB dependence liability, for instance the self-medication role in sleep regulation, the high rewarding euphoric state, the anxiolytic and depression modulating effect. All of the above confirms that GHB can be highly addictive with an intensive pattern of abuse and has an obvious impact on the psychological state of the patients. Chronic GHB abuse as presented in animal (rat) studies may lead to GABA system down-regulation[52], and to up-regulation of dopamine receptors D1 and D2[137], and is also associated with up-regulated NMDARs[103]. Chronic GHB abuse modulates serotonin and noradrenaline levels[44, 111, 114]. The aforementioned may predict the status of brain excitability during GHB withdrawal, manifested due to disinhibition of glutamate and an increase in dopamine release which seems to differ in rate and speed from other drugs of abuse. The increased central dopamine levels during the GHB withdrawal phase can persist for 1–2 weeks because of slow elimination of the active metabolite carbon disulfide, leading to delayed psychosis with hallucinations and possible prolonged delirium[164]. In conclusion, cessation of GHB abuse may result in a rapid withdrawal syndrome based on a complex interaction of different neurobiological mechanisms reached through stimulation of GABA-B, high affinity GHB and GABA-A receptors. It reveals a level of complexity in regulation and functional alterations well beyond the GABA system, involving several key brain neuromodulators and neurotransmitters to include glutamate, dopamine, serotonin, noradrenaline modifications, also others such as neurosteroids and oxytocin. All the withdrawal symptoms cannot be related to a single dominant mechanism or neurological pathway which implies the need for different medication combinations to proceed with treatment. Detoxification aid with a single drug class, such as, for example, benzodiazepines, gabapentin, or antipsychotics will not be sufficient to avoid complications and has been shown to provoke treatment resistance[165, 166]. Physicians should be aware of this complexity, which can be a legitimate explanation for the use of pharmaceutical GHB, in a titration and tapering approach, as a promising detoxification treatment method which could make poly-pharmacy redundant, especially in the case of dependence on high doses of GHB. In the first weeks after cessation of abuse, therapists should also consider a potential increase in impulsive behaviour of GHB dependent patients, related to a possible persistent high level of dopamine and serotonin dis-balance. This behaviour might lead to a rapid relapse in GHB use. Therefore, patients should receive intensive counseling immediately, preferably during detoxification, and should be provided with psycho-education to decrease relapse rates.

It is important, in light of the often unpredictable and severe effects of GHB, to translate the urgency of new insights into treatment tactics and prevention of complications.

Several limitations of this review are noted. There is limited published research available to reveal the exact neurobiological targets of GHB in humans. Therefore, neurobiological profiles of the dependence and abuse liability were mostly illustrated from studies in animals. Studies often focused on GABAergic agonists ligands in general and not specifically on GHB. It was difficult to determine whether an exact relationship exists between dependence, withdrawal features and the amount of GHB ingested. Future human studies will be of great help in resolving these important issues.

Disclosure statement

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Chapter 3

Psychiatric Comorbidity Prevelence and Effect on the Pattern of Gamma-Hydroxybutyrate (GHB) Misuse and Quality of Life of GHB Dependent Patients

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ABSTRACT

Objective: Understanding the psychiatric state and psychological distress level of patients with GHB dependence is important to develop effective detoxification and relapse management methods. Our aim is to assess the prevalence of the psychiatric comorbidity and psychological distress level and its association with their pattern of misuse and quality of life.

Methods: Ninety-eight patients were tested with MINI plus, BSI, DASS and EuroQol-5D as a part of the Dutch GHB detoxification monitor in seven addiction treatment centers.

Results: A high rate of psychiatric comorbidity (78.6%) was detected, mostly current anxiety (38%), lifetime mood (31%), and psychotic disorders (21%). The level of psychological distress was significantly higher than the standard reference group, especially in patients with current psychiatric comorbidity (BSI Global Severity Index mean 1.61 versus 1.09, $p \leq .01$). Increased GHB misuse was associated with the presence of lifetime psychosis (higher dose and shorter interval), current mood disorders (rpb = .23, p=0.025) and psychological distress psychoticism. Current anxiety, mood disorders and high psychological stress influenced quality of life in a negative way.

Conclusion: GHB dependence is characterised with serious psychiatric comorbidity and psychological distress associated with increased GHB use and a lower quality of life. This should be considered during detoxification to avoid extreme withdrawal symptoms. Initial integral mental health treatment is necessary for these patients to support treatment compliance, avoid relapse and to improve their quality of life.

Keywords: GHB dependence, Gamma-hydroxybutyrate, anxiety, psychiatric co-morbidity, psychological distress, quality of life.

1. INTRODUCTION

The high prevalence of co-morbidity between substance use disorders and other psychiatric disorders is well established[1-4]. One of the most appealing explanations suggested, is that drugs with their explicit psychotropic effects are used to cope with emotional distress[5, 6] especially psychiatric disorders. Primary specific psychiatric disorders are proved to be associated with an increased risk of later substance use, abuse and/or dependence as shown in studies concerning e.g. nicotine, alcohol, and illicit drugs[7, 8], and emphasised in hospitalized inpatients[9]. The psychiatric disorders may modify the course of substance use disorders, as they are associated with neurobiological alterations in the brain stress circuits[10, 11]. Under conditions of increased cognitive or emotional demand during distress/stress states, corticolimbic dopaminergic, glutamatergic and GABA-ergic activity modulate the prefrontal cortical function[10, 12]. This may alter the sensitivity of the mesolimbic dopaminergic system to stress, which can potentiate reward pathways, increase susceptibility to substances self-administration, induce reinstatement of drug-seeking behaviour, and promote relapse in substance use [6, 13, 14]. Likewise, patients with co-occurring disorders show more emergency room visits and psychiatric hospitalization, greater family instability, social exclusion and suicidal risk[15]. Furthermore, the drug-specific treatment of substance use disorders is negatively influenced by comorbid psychiatric disorders, with decreased treatment compliance, abstinence and increased relapse rates[16-18].

Substance and psychiatric disorders influence the quality of life of these patients. Substance abuse causes gradual worsening in health related quality of life, more than in the general population[19,20]. Patients with comorbidity with Axis I or Axis II disorders have a worse quality of life (QoL) than people who use drugs without co-occurring disorders[21, 22]. Health related QoL is one of the parameters that reflect the impact of drug use on physical, emotional andsocial functioning, wellbeing, and treatment, on drug-dependent patients in their daily lives[23]. This information can be used by clinicians to make and adjust treatment decisions[24].

All foregoing is to be expected in case of Gamma-hydroxybutyrate (GHB) dependence but no studies on co-morbidity have been done and no information is yet available. In Europe GHB has gained popularity as a drug of abuse[25]. In the Netherlands, the prevalence of primary GHB dependence and the number of patients in addiction treatment has quadrupled in the recent years[26]. GHB, a precursor and metabolite of gamma aminobutyric acid (GABA) acts as neuromodulator and neurotransmitter in the human brain[27]. As GABA-B receptor agonist GHB modulates both reward and stress/anxiety systems, which explains its dependence liability, anxiolytic[28] and antidepressant effects[29]. Patients with GHB dependence have repeatedly reported using this substance in order to suppress their feelings of insufficiency, depression and anxiety[30]. It can be postulated that GHB dependence is associated with high psychiatric co-morbidity, but no empirical data is available.

Abrupt discontinuation of GHB by the patients with dependence can produce severe withdrawal symptoms such as anxiety, delirium with auditory and visual hallucinations, seizures, life threatening rhabdomyolyse, coma and death[31, 32]. Therefore, management of GHB dependence in the Netherlands has received considerable attention and has led to the establishment of detoxification methods[33-35]. To develop treatment and relapse management methods, it seems important to take into account the psychiatric state and psychological distress level of the patients with GHB dependence.

This study aims firstly to determine the prevalence of psychiatric comorbidity (PCO) in GHB dependent patients. Secondly, we want to evaluate the psychological distress (PD) levels in this patient population and the differences in the level of psychological distress experienced between the group with and without psychiatric comorbidity. Finally we aim to explore the association of the comorbid psychopathology and psychological distress with GHB pattern of use and quality of life in these patients.

2. METHODS

2.1 Design

The study has a naturalistic design. Data were obtained during the Dutch GHB detoxification monitoring project in seven addiction treatment centers in the Netherlands from March 2011 to September 2012. The Medical Research Ethical Committee (METC Twente) had no objections with regard tothe study.

2.2 Participants

Participants who filled out and completed all the relevant instruments for this study (MINI plus, BSI, DASS and EuroQol) formed the study population. They were a subpopulation of the inpatient GHB detoxification monitoring project in which a total number of 229 patients enrolled and followed a detoxification treatment by means of titration and tapering of pharmaceutical GHB[33, 34]. Patients were between 18 and 60 years old and were dependent on GHB according to the DSM-IV-TR general criteria for psychoactive substance dependence. Only pregnant women were excluded.

2.3 Measures

The Dutch version of the Mini International Neuropsychiatric Interview-plus (MINI-plus) was used by a trained psychiatric nurse to evaluate the PCO. It is a systemic structured interview to assess the main Axis I psychiatric disorders based upon the DSM –IV and ICD-10 criteria. It is used to determine and distinguish current and lifetime psychiatric disorders[36]. The MINI shows good psychometric properties and is reliable for the detection and classification of the PCO[37].

The Depression Anxiety Stress Scale (DASS), a 21-item self-report instrument[38], was used to

measure depression, anxiety, and stress. Participants were asked to use a 4-point severity scale to rate the extent towhich they have experienced each state over the past week. Scores for depression, anxiety and stress are calculated by summing the scores for the relevant items[38, 39].

Levels of psychopathology were measured using the Brief Symptom Inventory (BSI), a shortened form of the Symptoms Checklist 90 Revised. The BSI is a 53-item self-report symptom scale[40] measuring nine dimensions: somatisation, obsessive-cognitive problems, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. The score per dimension ranges from 0 to 4 [41].

The patient's QoL was measured with the EuroQol-5D (EQ-5D), a self-report instrument which assesses 5 domains of general health and functioning: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[42] on a 3-point scale (1=no problems, 2=some problems and 3=extreme problems). The scores are then converted by applying predetermined weights based upon EQ-5D evaluation for the general population [the Dutch algorithm was used to calculate the index]. This EQ-5D index is a societal-based numerical quantification of the patients' health status in a scale score from -.594 to 1 (1 is perfect health, 0 or lower is as bad as being dead). Participants rated their overall QoL, by means of a visual analogue scale (EQ-5D VAS). The VAS is a 100-mm vertical line from worst (0) to optimal health (100)[43].

The GHB questionnaire is a self-report questionnaire about the pattern of GHB use consisting of the years of use, total daily dose in grams, grams per dose and interval between dosages.

2.4 Study Procedure

During the 18 months of the GHB monitor project, all patients with an indication for inpatient GHB detoxification treatment were included. At intake the Measurement of the Addictions for Triage and Evaluation (MATE)[44] was used to determine GHB dependence according to the DSM-IV. Patients were provided with written and oral information about the study by a research assistant. Two weeks before admission, details of the study were reviewed with them, and informed consent to the treatment and the study procedure was obtained. After that, patients filled in the DASS, BSI, the EQ-5D and the GHB questionnaire. Subsequent to the end of the detoxification period a trained research psychiatric nurse interviewed the participants and evaluated the PCO by means of the MINI-plus.

2.5 Statistical methods

Statistical analyses were performed using SPSS 19. Descriptive analysis was used to report on the demographic variables, the prevalence of PCO and the level of PD. Differences between characteristics of the study participants and the total number of participants in the Dutch GHB were analysed with t-test for continuous data and Chi-Square test for categorical dichotomous data. The difference in the average level of PD experienced between the group with and without PCO was tested with the independent t-test and difference in the percentage of severe extreme scores was tested by Chi-squared test. Pearson's bivariate correlation (two-tailed) and Point-biserial

correlation were performed with PCO, BSI and DASS as independent variables to identify factors that influence the GHB pattern of misuse (dose and interval). Multiple linear regression analysis was undertaken to single the most influential factors of PCO and PD on the GHB pattern of misuse and Qol. All tests were two sided, a P-value ≤ 0.05 was considered significant.

3. RESULTS

3.1 Study population

Descriptive statistics about the characteristics of our study population (n=98) are provided in Table 1. The patients were predominantly young adults with limited education. At the time of the study 33% were employed. The average period of GHB use in this group was 4.4 years with a dose of 57.5 gram per day. There were no differences between the study population and the total GHB patient population in terms of age, gender, education, work situation and pattern of GHB use.

Table 1: Study population characteristics.

Characteristics	**Study population(N = 98)**
Male (%)	68.4%
Age in years, mean (SD)	28,02 (7.01)
Educational Level %	
Primary Education	13.8
Secondary Education	75.5
Higher Education	10.6
Work situation %	
Full time employment	22.3
Part time employment	11.2
Unemployment	29.8
Unfit for work	29.8
Student	6.4
	(mean, sd)
Years of GHB abuse	4.4(2.6)
GHB dose/day in gram	57 (37.6)
GHB administered dose in gram (	3.7(1.4)
Interval between doses in hours	1.8(0.7)

EQ-5D index	0.63(0.29)
EQ-5D VAS	51.6(23.6)

Table 2 : Prevalence of Psychiatric Co-morbidity GHB dependent inpatients (n=98) as measured with the MINI plus

Psychiatric diagnosis	**Present N (%)**
Any diagnosis except drug abuse	77 (78.6)
Current	
Any psychiatric disorder	63(64.3)
Mood disorders	13(13.3)
Anxiety	37(37.8)
Psychotic disorders	13 (13.3)
Post-traumatic Stress Syndrome	12 (12.2)
ADHD	19(19.4)
Adjustment Disorder	8 (8.2)
1 Psychiatric disorder	34 (34.7)
2 Psychiatric disorder	22 (22.4)
3 or more Psychiatric disorder	7 (7.1)
Lifetime	
Any psychiatric disorder	52 (53,1)
Mood disorders	30 (30.6)
Anxiety(only panic disorder)	12 (12,2)
Psychotic disorders	21 (21.4)
Any current suicide risk	13 (13,3)
Antisocial personality disorder	18 (18,4)

3.2 Prevalence of psychiatric co-morbidity

According to the MINI-plus 78% of the patients reported a psychiatric disorder (current or life time) besides substance abuse. As indicated in table 2, current anxiety disorders were most often reported, followed by ADHD, mood disorders and psychotic disorders. Twenty-nine percent of the patients had two or more current co-morbid disorders in addition to their substance use disorder. Lifetime psychiatric disorders were reported by 45.9% of the patients, with the highest frequency occurring in mood disorders (30.6%), followed by psychotic disorders (22%).

3.3 Psychological distress (PD)

Table 3 shows the psychological distress as measured with the BSI and the DASS.

According to the BSI the highest score was for obsessive and cognitive problems, depression, anxiety, and paranoid ideas. A severity score between 6-7 on the BSI, which is considered high or extremely high, was frequently reported, especially on somatisation, anxiety, and depression

scales. The mean scores of the DASS indicate moderate distress level in all three scales, depression, anxiety, and stress.

Table 3: BSI and DASS in the whole group, correlation between psychological distress and the current psychiatric diagnose

	All (n=98)		APDC (n = 63)	APDC		NPDC (n=35)	NPDC					
	mean (Sd)	%[1]	mean (Sd)	SE	%[1]	mean (Sd)	SE	%[1]	t	X[2]	GHB Dose	Dose Interval
BSI											r	r
SOM	1.34(0.97)	84,4	1.52 (1.02)	0,12	88,6	1.04 (0,80)	0,14	77,2	2.87**	2,19	0.29**	(-)0.19
O-C	1.78(1.15)	69,8	1.96 (1.18)	0,15	73,7	1.47 (1.06)	0,18	62,8	2.11*	1,26	0,18	-0,09
I-S	1.29(1.18)	55,1	1.46 (1.23)	0,16	61,9	0.99 (1.03)	0,17	42,9	2.01*	3,3	0,11	-0,09
DEP	1.59(1.18)	72,7	1.81 (1.21)	0,15	81,9	1.20 (1.04)	0,19	55,9	2.42*	7.47**	0,18	-0,2
ANX	1.52(1.03)	82,3	1.74 (1.05)	0,14	85,3	0.88 (1.05)	0,15	77,2	2.60**	1,002	0.25*	(-)0.21*
HOS	1.19(1.18)	61,5	1.27 (1.15)	0,15	67,9	1.05 (1.23)	0,19	51,4	1,12	2,88	0.21*	0,17
PHOB	1.03(1.10)	54,7	1.27 (1.14)	0,15	66,7	0.61 (0.89)	0,15	34,3	3.27**	9.36**	0,201	(-)0.21*
PAR	1.35(1.18)	56,8	1.52 (1.23)	0,16	62,3	1.05 (1.03)	0,18	47,1	1,61	2,06	0,19	-0,202
PSY	1.22(1.03)	75	1.44 (1.06)	0,14	78,7	0.84 (0.87)	0,15	68,6	2.74**	1,21	0.25*	(-)0.25*
GSI	1.4(0.99)	74,5	1.61(1.02)	0,13	78,3	1.09(0.88)	0,15	67,7	2.52**	1,3	0.22*	(-)0.21*
DASS												
	mean (Sd)	**%[2]**	**mean (Sd)**	**SE**	**%[2]**		**SE**	**%[2]**				
Depression	15.8(11.5)	30,6	18.32 (11.55)	1,46	39,7	11.14 (9.91)	1,62	14,3	1.74***	6.83**	0,76	-0,16
Angst	14.8(10.3)	40,8	16.98 (10.48)	1,33	47,6	10.97 (8.72)	1,49	28,6	1.95**	3.38*	0,09	-0,17
Stress	17.4(10.4)	25,5	19.30 (9.47)	1,21	30,2	13.83 (11.82)	1,87	17,1	2.67**	2,01	0,101	-0,11

- SOM - Somatization, O-C - Obsessive and cognitive problems, I-S - Interpersonal Sensitivity, DEP - Depression, ANX - Anxiety, HOS - Hostility, PHOB - Phobic Anxiety, PAR - Paranoid Ideation, PSY - Psychoticism, GSI - Global Severity Index.
- APDC = Any Psychiatric Disorder Current, NPDC = No Psychiatric Disorder Current
- SE = standard Error
- %[1] = Percentage High or Extreme High score 6-7. %[2] = Percentage of Sever or Extremely Sever score
- Significance p≤.05*, p≤.01**„ p≤.001***

3.4 Co-occurrence of PCO and PD

Patients with any current psychiatric disorder had in general significantly higher scores on all subscales of the BSI (except hostility) and on the DASS scales (table 3). With regard to the severity, patients with current PCO reported significantly more frequent high/extreme high scores on the BSI for symptoms such as e.g. depression and phobic anxiety; also more frequent sever/extremely severe depression and anxiety distress levels from the DASS (Table 3).

3.5 Correlation of PCO and PD with the pattern of GHB misuse

The average daily GHB dose used by the patients with a PCO was 62.2 versus 48.4 gram, in 1.8 hour interval. Pearson's bivariate correlation (two-tailed) analysis including the different PCO disorders showed that the presence of current mood disorders (rpb = .23, p=0.025) was associated with misuse of a higher GHB dose per day (mean 73.6 g/d). For psychotic disorders life time was an association for higher GHB dose per day (rpb = .31, p=0.002) (80.7 g/d) and a shorter interval (r= -.21,p= 0.041). A multiple linear regression with GHB dose (a log10 variable) as criterion variable showed that lifetime psychosis and current mood disorders were significant associated with an increase in GHB dose, it explained 17% of the variation in the GHB dose level (R^2= 0.172). Patients with current mood disorder are using 22.8 gram more GHB (β= .228, SE= .067, p=.001) and patients with life time psychotic disorders 18.0 gram more GHB (β= .180, SE= .055, p=.002). The GHB dose level can be calculated by the following model equation: GHB dose level = 18.25+ (.218 x current mood disorders MINI) + (.243 x lifetime psychotic disorders MINI) The overall significance of this model was confirmed in an ANOVA (f 9.901 en df 2.95, p=.000).

Pearson's Bivariate correlation (two-tailed) analysis and linear regression including the different subscales assessing PD (BSI and DASS) showed negative correlation between the interval of GHB use and BSI psychoticism score. No further associations were detected.

3.6 Psychiatric comorbidity, Psychological distress and Quality of life

The mean of the EQ-5D index of all patients (n=98) was 0.63 (sd= 0.29). The multiple linear regression analysis using the PCO showed that current anxiety and mood disorders accounted significantly for 14% of the variance of the EQ-5D (R^2 = 0.14, Adjusted R^2 = 0.12). A comparable analysis using all subscales of the BSI revealed that only phobic anxiety accounted significantly for the variance of the EQ-5D (R^2 = 0.257, Adjusted R^2 = 0.25). In the case of the subscales of the DASS, only the Stress subscale accounted significantly to the variance of the EQ-5D (R^2 = 0.101, Adjusted R^2 = .091). Combining all significant variables in a final stepwise multiple regression analysis revealed a two-factor model predicting 29% of the variance in the QoL score (R^2 = 0.293, Adjusted R^2 = 0.278), resulting in the following equation: EQ-5D index = 0.796 + (-.455 x phobic anxiety $_{BSI}$) + (-.196 x stress $_{DASS}$). The overall significance of this model was confirmed in an ANOVA (F= 15.733, p<.001).

4. DISCUSSION

Our study showed that a considerable percentage of GHB dependent patients admitted for inpatient detoxification had a current (64.3%) or life time (45.9%) psychiatric disorder. This percentage is even higher than major mental disorders in alcohol dependent (44%) and illegal substances dependent patients (64.4%) entering treatment [1, 45]. Anxiety disorders were the most prevalent co-morbid current psychiatric disorders. Mood disorders were the most common co-occurring lifetime diagnoses. These results can possibly be explained by the reported anxiolytic and antidepressant effect of GHB [27], and reports of patients in which they state that by using GHB they can overcome these feelings [30, 46]. Our results confirm this partially, as we found the presence of PCO such as current depression as well as lifetime psychosis, is a significant indicator of intensive GHB misuse.

In line with the high prevalence of psychiatric disorders these patients experienced high psychological distress levels especially in the domains of somatisation, anxiety, and depression. A high level of obsessive-cognitive problems were also reported which might indicate; concentration problems, forgetfulness, hesitation in decision-making. Psychoticism symptoms were also eminent which may indicate possible experiences of hallucinations and delusions related to direct moments of GHB intoxication or withdrawal,. Patients with current co-morbid psychiatric disorders experienced more severe psychological distress than those without current comorbidity in almost all scales. To interpret these results properly, it should be remembered that psychological stress was evaluated before the detoxification process. In that period of evaluation patients were still using GHB and due to its short-term effects patients could be intoxicated or experiencing any withdrawal symptoms. Nevertheless these psychological distress reports give cause for alarm as they pointed out the complex pathology that patients are going through during their GHB dependence. It is also unknown to what extent the reported psychopathology and psychological distress are the result of chronic GHB dependence or an indication of underlying anxiety, depressive or psychotic symptoms that are relieved by GHB use in a flawed method of self-medication.

For the choice of medical treatment approach both addiction medicine and liaison psychiatry specialists should be prepared for the combination of current mood disorder, lifetime psychotic disorder or psychological psychoticism, with an increase in illicit GHB dose and shorter intervals. The mean subjective QoL index (0.63) in our patient population was lower than in patients with chronic psychiatric disorders such as schizophrenic and delusional disorders[47]. Despite the shorter period of GHB use (mean 4 years) in comparison with patients in methadone maintenance therapy (mean 15 years) the QoL index and VAS were lower in the GHB patients, (0.63, 51) versus the (0.66, 61) reported by Carpentier et al[48]. Current psychopathology such as anxiety disorders and psychological distress level proved to be an influential factor on QoL.

The present study had several limitations. We only studied patients who were admitted to an inpatient detoxification program, so generalization to GHB users overall cannot be made. We did not studythe effect of PCO, PD or QoL on treatment compliance and relapse after detoxification. Our sample size was too low to take into account the concomitant use of other substances, whereas poly-drug dependence is known to be associated with elevated prevalence of psychiatric co-morbidity[49, 50]. Finally the psychiatric co-morbidity and the psychological distress were measured at different times, as PD was measured in a period where signs and symptoms of intoxication or withdrawal could be intermingled, whereas patients were abstinent when the MINI interview was obtained. On the other hand and despite the different measurement moments strong positive correlation between the current and lifetime psychiatric diagnosis and the psychological distress was detected.

5. CONCLUSION

In conclusion we have found that many GHB dependent patients admitted for inpatient detoxification suffer from several psychiatric disorders and experience quite a lot of psychological distress. This state influences the pattern of GHB misuse which should be taken into consideration during detoxification from GHB to avoid extreme withdrawal symptoms and complications. Actual co-morbidity especially influences the quality of life of the patients. It is recommended that attention be paid to initial integral mental health treatment for patients with GHB dependence and psychiatric comorbidity to support treatment compliance, avoid relapse and to improve their quality of life.

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Chapter 4

The Effect of Co-occurring Substance Use on Gamma-Hydroxybutyric Acid (GHB) Withdrawal Syndrome

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ABSTRACT

Objectives: GHB withdrawal is a complex syndrome which can be potentially life-threatening. Additionally, GHB-dependent patients frequently report co-occurring substance use of other psychoactive drugs. We assessed the add-on effect of co-use on GHB withdrawal symptoms.

Methods: We conducted an open label, pretest-posttest design study with 95 patients selected from 229 inpatients admitted for detoxification, who were divided into GHB only (GO, n=40), GHB plus sedatives (GSE, n=38), and GHB plus stimulants (GST, n=17) groups. GHB withdrawal was evaluated by means of the Subjective Withdrawal Scale (SWS). Co-use add-on effects on the severity of withdrawal symptoms were evaluated, 2.5 hours after the last illicit GHB self-administration (T1) when withdrawal was expected and 2.5 hours later, after administration of a very low dose of pharmaceutical GHB (T2).

Results: The GO group reported high scores of psychomotor retardation symptoms at T1 and T2, in addition to noticeably high cravings, agitation and restlessness at T1 and anxiety at T2. There was no significant difference in withdrawal intensity in all symptom clusters between T1 and T2 for both GSE and GO groups. However, the GST group reported decrease in symptoms intensity except for psychomotor stress after five hours. At T1, GST and GSE groups reported more muscle twitches than GO as a significant add-on effect to the GHB withdrawal. At T2, the GST group experienced more agitation (p=.009), restlessness (p=.001), and rapid pulse (p=.034) than the GO group.

Conclusion: Co-use, especially of stimulants, caused an add-on effect on the GHB withdrawal symptoms within the first five hours.

Keywords: Gamma-hydroxybutyric acid, GHB, Detoxification, Withdrawal, Co-use, Dependence

1. INTRODUCTION

Gamma-hydroxybutyric acid (GHB) is a gamma-aminobutyric acid (GABA) metabolite, and precursor which can cross the blood-brain barrier[1]. GHB is used clinically in the treatment of narcolepsy with catalepsy and alcoholism[2]. It has become a popular recreational substance and is on the rise as a drug associated with use disorder in several countries, including the Netherlands[3]. Dependent GHB users dose at regular intervals (every 1–3 hours), taking similar doses around-the-clock[4]. Withdrawal from GHB can occur within 2-3 hours and is reported to be a complex syndrome characterized by autonomic instability and significant changes in mental state. Case reports indicate that dependent users can suffer from a rapidly deteriorating withdrawal syndrome which frequently results in delirium and can be potentially life-threatening[5,6].

In the Netherlands, 42% of GHB abusers have reported co-abuse of other psychoactive drugs such as amphetamine (11%), cocaine (11%), alcohol (7%), cannabis (7%), benzodiazepines (2%), and ecstasy (1%)[8]. Similarly, 65% of GHB users who presented to an emergency department in Switzerland with GHB-related medical problems, co-ingested alcohol or illicit drugs, mostly MDMA and cocaine[9].

During withdrawal from chronic drug abuse, the symptoms observed are related to drug-induced adaptive changes (plasticity or allostasis) within neurotransmitter, neuropeptide, and neuroendocrine systems; physiological mechanisms which are responsible for re-establishing bodily and neurological equilibrium[10,11]. GHB withdrawal state is associated with glutamate-dependent hyperactivity involving neurotransmitter systems such as dopamine and norepinephrine (NE)[12]; a distinct effect exerted via the GABA-B receptors, GHB receptors[1], and subtypes of GABA-A receptors[13]. Through alcohol and benzodiazepine withdrawal, down regulation of GABA-A receptors can lead to increased sensitivity of the glutamatergic NMDA and AMPA receptors in the frontal lobe, medial septal nuclei, and in certain hippocampal regions[14]. In this way, the central inhibition is decreased due to diminished GABA activity associated with increased excitation as a result of increased glutamate, dopamine, and NE activity[15,16]. Psychostimulants such as amphetamine and cocaine influence the processes of release, reuptake and metabolism of monoamine neurotransmitters. The chronic use of psychostimulants depletes monoamine neurotransmitter stores, such as serotonin and norepinephrine. This effect is suggested to be associated also with decrease in dopamine transporters[17,18,19]. A mechanism which may cause an increase in the extracellular levels of dopamine with chronic use withdrawal. It has been implied that psychostimulant use and withdrawal are associated with alterations to cognitive and emotive behaviours regulated by the dorsal and ventral hippocampus such as anxiety behaviour[20].

The similarities and differences in the aforementioned neuro-pharmacological effects would alter the presentation of the GHB withdrawal, which is of clinical relevance for the choice of appropriate medical interventions.

The aims of this study are to describe the first few hours of GHB withdrawal syndrome without medical intervention using other medication, to evaluate the add-on effects of psychoactive

substance co-use on this syndrome, and to assess the changes in withdrawal presentation over time, in association with co-use. We hypothesize that the simultaneous use of alcohol, benzodiazepines, cocaine, or amphetamine will increase the severity of GHB withdrawal, becoming even more severe if left untreated for several hours.

2. METHODS

2.1 Design

We conducted an open label, pretest-posttest design study, in a consecutive series of GHB-dependent patients admitted for controlled inpatient GHB detoxification as part of the Dutch National GHB Detoxification Monitor study (GHB Monitor). The GHB Monitor is a prospective study, and baseline data (psychiatric and somatic) were obtained before the start of the detoxification process. The GHB Monitor was conducted at seven addiction treatment facilities in the Netherlands, between March 2011 and September 2012, and included 229 patients. The GHB Monitor study protocol was approved by the Medical Ethical Board (Medisch Spectrum Twente), with the protocol in accordance with the Declaration of Helsinki.

2.2 Participants

Participants were either male or non-pregnant female patients aged between 18-60 years, who reported GHB as their main drug of misuse, and were dependent according to the DSM-IV-TR general criteria for psychoactive substance dependence. They agreed to be admitted for controlled inpatient GHB detoxification as part of the GHB Monitor study. From the aforementioned patients, those who had provided complete data about substance co-use were included, and as such the selection of the patients included in this study was done retrospectively.

The exact co-use pattern of each participant included in this study in the last 30 days before admission was assessed separately. Co-use of psychoactive substances was considered only when daily consumption during minimally seven consecutive days within the last 30 days before admission was reported. Patients who used GHB simultaneously with substances other than alcohol, benzodiazepines, cocaine or amphetamine (e.g. cannabis or both stimulants and sedatives concurrently) were excluded. Only current (in the last 30 days before admission) co-use was considered for this study, and past co-use of drugs or alcohol was not assessed.

Participants were divided into three groups according to the effects and the expected mechanisms of action of the daily abused drugs: 1) GHB dependent without current co-use (GO), 2) GHB dependent with current alcohol and/or sedative co-use (GSE), thus co-use of alcohol ≥ 5 standard glass or ≥10 gram pure alcohol equivalent per day for the last seven days prior to admission, or benzodiazepines equivalent to 10 mg/day diazepam or more for the last 15 days prior to admission, 3) GHB dependent with current stimulant co-use (GST), amphetamine and/or cocaine use ≥ 1g/d, daily for the last 15 days prior to admission.

2.3 Procedure

2.3.1 Detoxification treatment

A detoxification inpatient regime by means of titration and tapering of oral pharmaceutical GHB (industrial pharmacologically-prepared GHB) (150 mg/ml) was provided[21,22]. Via titration, the GHB dose needed to keep the withdrawal symptoms (WS) to a minimum was established. The first pharmaceutical GHB dose during the titration phase was administered within 2.5 hours after the patient's last self-administration of illicit GHB. It was a low dose to avoid the risk of intoxication (0.75-1.5 gram/gift < the second dose). The second dose, administered after a three-hour interval, was 70% the equivalent of the reported self-administered illicit GHB dose (e.g. for 3.3 gram illicit GHB, 2.3 gram pharmaceutical GHB was provided). The pharmaceutical GHB dose was adjusted every three hours according to the patient's self-reported symptoms and the nurse/doctor's observations. This took place until the patients reported an acceptable level of WS and the monitored vital signs were stable within the normal range. The following day, pharmaceutical GHB was tapered off according to a daily fixed schedule.

2.3.2 Study Procedure

Participants meeting the inclusion criteria of the GHB Monitor study were approached by their addiction treatment counsellor. If they chose the inpatient detoxification, they were approached again two weeks before a possible admission and details of the study were reviewed with them. Written informed consent for the treatment procedure was obtained, as well as the off-label prescription of pharmaceutical GHB, and use of the obtained data for research purposes. Participants were required to stop use of all other drugs by/before admission for detoxification. They were asked to use their morning dose of illicit GHB and to be present at the addiction care centre around 9.00am. Within the first hour of admission for detoxification, the participants underwent a review of their medical history and a physical examination by an addiction physician. Upon admission, breath blood alcohol concentration measurement (BAC) and urine samples for drug testing were taken. The exact recent concomitant substance abuse pattern was confirmed by means of the patient's self-report, with emphasis on the last 3 days prior to admission. Once the medical screening had been conducted and 2.5 hours had passed since the reported last illicit GHB ingestion, participants were asked to fill out the Subjective Withdrawal Scale SWS list (first measurement moment = T1), just before administration of a low dose of pharmaceutical GHB. To determine any change in the WS, patients were asked to complete the SWS list again 30 minutes before administration of the second dose, or 2.5 hours after administration of the low pharmaceutical GHB dose and 5 hours after the last illicit GHB ingestion (second measurement moment = T2).

The objective monitoring measures were blood pressure (BP) and heart rate (HR) and were acquired at admission manually by the addiction physician only. BP and HR were obtained at T1, half an hour after T1 and at T2 by the nursing staff only, measured in sitting position in both arms.

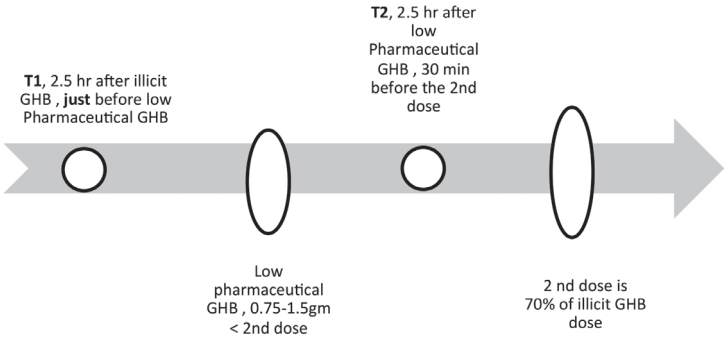

Figure 1: Time line measurements

2.3.3 Instruments

Measurement of Addicts for Triage and Evaluation (MATE), is a Dutch instrument designed to aid in the diagnosis of substance use disorders according to the DSM-IV axes[23]. For the present study, section 1 of this instrument (substance use) was used to define the participants' lifetime substance use and current use within the last thirty days (frequency and quantity) as a partial assessment of the degree of substance dependence.

The GHB questionnaire, a self-report instrument, describes the pattern of GHB misuse, indicating reasons, place, years, complications, dose, interval and frequency of use.

The Subjective Withdrawal Scale measures subjective WS. The SWS is based on the format of the Subjective Opiate Withdrawal Scale[24] and its Dutch translation proved to have good psychometric quality[25]. The SWS consists of all the subjective criteria as described in the chapter on substance-related disorders in the DSM-IV-TR under the subheadings of WS. The resulting SWS consists of 33 items, rated on a scale from 0 to 4 (0 = not at all, 1 = a little, 2 = moderate, 3 = severe, 4 = extremely severe). The total SWS score ranges between 0 and 132. To divide the SWS into related symptom clusters for further analysis, the SWS scores reported by all the patients included in the GHB monitor (n= 229), obtained during the first titration day before administration of the pharmaceutical GHB dose, were analysed. Firstly, items with a mean score <.40 were excluded (epilepsy (.05), fever (.09), visual or auditory hallucinations (.17), hyperlacrimation (.40), runny nose (.40), nausea (.40), vomiting (.21) and diarrhea (.36)). For this study the four items referring to sleeping problems were excluded as the measurement moments of interest were only during daytime. To examine the underlying factor structure of the symptoms with a mean score ≥ .40 and not assessing the sleep pattern an explorative factor analysis was performed. Principal component analysis (PCA) was conducted with Varimax rotation and extraction if the eigenvalue > 1.0. The EFA Kaiser-Meyer-Olkin measure was .90 ('superb') and all values for the remaining 20 individual items were > .72. Bartlett's test of sphericity, $p < .001$, indicated that correlations

between items were sufficiently large for PCA. The PCA of the remaining 20 SWS items (GHB-SWS) revealed four factors. The GHB-SWS symptoms and all factors had a Chronbach's alpha ≤ 0.80 except cluster 4, α = 0.61 (see supplementary Table A). The resulting symptom clusters were named as follows (Table 2): Factor 1 consists of seven symptoms which are labelled 'Psycho-autonomic distress'; Factor 2 consists of six symptoms labelled 'Psycho-motor stress'; Factor 3 consists of five symptoms labelled 'Psycho-motor retardation'; and Factor 4 consists of two symptoms labelled 'Appetite'.

Supplemental Table A

Item	Psycho-autonomic distress	Psycho-motor stress	Psycho-motor retardation	Appetite symptoms
Diaphoresis	**,787**	-,045	,052	,096
Hot flashes	**,704**	,213	,118	,105
Tremors	**,673**	,302	,171	-,108
Craving	**,533**	,331	,308	-,015
Rapid pulse	**,533**	,208	,233	,149
Cold flashes	**,500**	,425	,320	-,151
Goose flesh	**,413**	,365	,341	-,248
Muscle twitches	,244	**,768**	,146	,113
Muscle aches	,137	**,753**	,124	,215
Abdominal pain	,101	**,627**	,182	-,052
Restlessness	,481	**,563**	,056	,192
Agitation	,505	**,513**	,057	,151
Anxiety	,336	**,497**	,295	-,086
Apathy	,083	,163	**,851**	,154
Psychomotor retardation	,138	,160	**,793**	,159
Fatigue	,098	,155	**,708**	,186
Dysphoria	,308	,409	**,549**	,020
Yawing	,303	-,019	**,541**	-,121
Extreme eating	,108	,011	,154	**,783**
Hunger	,008	,172	,087	**,758**
Eigenvalue	3.57	3.14	3.08	1.55
% of variance	17.87	15.69	15.42	7.77
α	0.826	0.813	0.805	0.609

3. STATISTICAL ANALYSIS

Differences in demographic variables between the patients included in this study (n=95) and all GHB monitor participants (n=229) were analyzed with chi-square tests for categorical data and t-tests for continuous data. Descriptive analysis of the GO, GSE, and GST groups' baseline characteristics were carried-out. Comparisons between the groups were performed using ANOVA for continuous data and chi-square tests for categorical data.

Means and standard deviations (SD) at T1 and T2 were calculated for each withdrawal symptom and whole SWS scale for all participants and per group. To conduct a comparison per factor according to EFA, a factor mean score was calculated by dividing the sum of mean scores of the included items by their number. The total score of all factors was also calculated. To evaluate the WS in time within each group, paired t-tests were performed per factor, individual symptoms and total GHB-SWS. The effect of concomitant abuse at T1 and T2 was analysed in a stepwise fashion. The add-on effect ,with GO as the reference group, was tested at factor scores level with ANOVA where Bonferroni and Games-Howell post hoc test were performed. To identify which symptoms attributed to the differences, and taking into account the interaction between these symptoms, MANOVA was performed. Calculated mean (standard deviation) of the BP and HR measurements were also analysed via paired t-tests and MANOVA. A two-sided *p*-value of <.05 was considered statistically significant. Analysis was performed using IBM® SPSS® Statistics version 19 for Windows.

4. RESULTS

4.1 Participant characteristics

Generally, there were no significant differences between the 95 patients included and all GHB monitor participants (n=229) with regards to their age, gender, education and duration of GHB abuse. The sample consisted of 40 GO, 38 GSE and 17 GST patients. Characteristics of this sample are shown in Table 1. The average age was 29.1 (SD=8.2). GST patients were significantly younger than both the GO and the GSE groups (Table 1). Males accounted for 66.3% of the patients. There was no association between gender (rpb =.16, *p*=.124), or age (r=.03, *p*=.76), and drug co-abuse. The average amount of low dose pharmaceutical GHB used 2.5 hours before T2 was 2.3 g (SD=1.2).

GSE and GST patients reported dependence on sedatives and stimulants respectively. All GST patients stated co-use of stimulants till the day prior to admission, sometimes to late in the night. It is not clear if the patients co-used stimulants just before admission or up to 2.5 hours prior to the assessment. The average number of days of co-use of other drugs in the 30 days prior to admission is reported by group in Table 2. Despite that urine drug tests and blood

alcohol content measurements were obtained regularly at admission at all the involved institutes to confirm the self-reports accuracy, limited data was available for further analysis.

Table 1: Baseline characteristics of participants for the different groups

Characteristics	GO (n =40)	GSE (n =38)	GST (n =17)	F	p
Age, mean (sd)	28.2 (9.4)	31.6 (7.8)	25.8 (3.5)	3.6	0.03
Years of GHB misuse, mean(sd)	4.0 (2.7)	5.0 (2.7)	4.3 (2.9)	1.2	0.31
GHB dose in gram/d *, mean (sd)	49.9 (31.1)	59 (43)	70 (54.1)	1.4	0.25
GHB dose interval in hours, mean (range)	1.88 (1-3)	1.85 (1-3)	1.84 (1-4)	0.03	0.97
				X^2	
Male, n (%)	23 (57.5)	27 (71.1)	13 (76.5)	2.56	0.28

GO=GHB only abusers, GSE=GHB plus sedatives co-abusers, GST=GHB plus stimulants co-abusers.
*GHB dose is calculated based on street illicit GHB average concentration of 650mg/milliliter.

Table 2: Co-use of other drugs per group , mean (sd)

Co-use	GO	GSE	GST
Mean days alcohol co-use	8.3 (4.3)	20.3 (9.7)	4.8 (2.0)
Mean days cocaine co-use	3.8 (3.1)	3.7 (9.8)	14.0 (10.1)
Mean days amphetamine co-use	4.5 (3.2)	7.5 (9.6)	23.2 (10.5)
Mean days cannabis co-use	11.1 (2.1)	13.1 (3.6)	14.0 (10.1)
Mean days co-use benzodiazepines	12 (10.4)	24.8 (9.6)	6.4 (3.2)

GO=GHB only abusers, GSE=GHB plus sedatives co-abusers, GST=GHB plus stimulants co-abusers

4.2 GHB withdrawal symptoms by group

The GO patients reported the highest WS severity on the psycho-motor retardation factor at both T1 and T2 due to high apathy and dysphoria scores. Despite the lower score on the other factors, craving along with agitation and restlessness at T1 and anxiety at T2 were noticeably high (Table 3). The factor scores and total GHB-SWS score showed no significant change in time, apart from a significant decrease in the individual WS diaphoresis and rapid pulse (Table 3).

Table 3: The reported withdrawal symptoms divided in factors. Per individual symptom, per factor, and total GHB-SWS score is the mean score and standard deviation(SD) reported, at T1 and T2, by each group of participants defined by co-abuse.

Withdrawal Symptoms	GO n=40 mean (SD)	GSE n=38 mean (SD)	GST n=17 mean (SD)	GO n=40 mean (SD)	GSE n=38 mean (SD)	GST n=17 mean (SD)
	T1	T1	T1	T2	T2	T2
Psycho-autonomic distress	1.21(0.81)	1.25(0.82)	1.70(0.78)	1.11(0.74)	1.14(0.84)	1.09*(0.94)
Diaphoresis	1.40 (1.48)	1.08 (1.21)	1.57 (1.38)	0.85* (0.88)	1.16 (1.02)	1.14 (1.09)
Hot flashes	1.19 (1.27)	1.19 (1.26)	1.81 (1.32)	0.92 (1.21)	1.03 (1.17)	1.24 (1.24)
Tremors	1.03 (1.16)	1.24 (1.24)	1.56 (1.09)	1.08 (1.02)	1.25 (1.07)	1.00 (1.15)
Craving	2.20 (1.42)	2.24 (1.32)	2.76(1.20)	2.32 (1.43)	2.03 (1.33)	2.00 (1.66)
Rapid pulse	1.00 (1.20)	0.84(1.07)	1.61 (1.54)	0.46* (0.60)	0.78 (0.97)	1.07 (1.33)
Cold flashes	1.08 (1.25)	1.49 (1.28)	1.43 (1.39)	1.51 (1.38)	1.03 (1.20)	0.71 (1.20)
Goose flesh	0.56 (1.04)	0.76 (1.05)	1.07(1.16)	0.70(1.09)	0.68(0.88)	0.41*(0.87)
Psycho-motor stress	1.02(0.80)	1.20(1.10)	1.57(1.01)	0.92(0.80)	0.93(0.80)	1.26(0.89)
Muscle twitches	0.62 (0.85)	1.32 (1.51)	1.75 (1.57)	0.82 (1.31)	0.78 (1.09)	1.06 (1.36)
Muscle aches	1.05 (1.16)	1.21 (1.32)	1.75 (1.61)	1.03 (1.38)	1.07 (1.12)	1.00 (1.31)
Abdominal pain	0.51 (0.85)	0.61 (1.05)	1.08 (1.34)	0.43 (0.72)	0.59 (1.11)	0.32**(0.70)
Restlessness	1.38 (1.40)	1.57(1.52)	2.29 (1.59)	0.92 (1.09)	1.21 (1.17)	2.20 (1.37)
Agitation	1.45 (1.46)	1.49(1.48)	1.57 (1.83)	0.97 (1.20)	1.09 (1.21)	2.00 (1.41)
Anxiety	1.13 (1.26)	1.09(1.19)	1.24 (1.35)	1.43 (1.34)	1.03 (1.24)	1.13 (1.30)
Psycho-motor retardation	1.34(1.01)	1.08(0.86)	1.48(0.78)	1.34(0.84)	1.10(0.93)	0.96*(0.77)
Apathy	1.75 (1.29)	1.30 (1.13)	1.50 (1.32)	1.43 (1.09)	1.32 (1.22)	1.00 (1.00)
Slow reaction	1.10 (1.13)	0.92 (1.14)	0.94 (1.44)	1.00 (1.00)	1.00 (1.23)	0.81 (1.16)
Fatigue	1.37 (1.33)	1.08 (1.18)	1.71 (1.53)	1.33 (1.37)	1.21 (1.32)	1.50 (1.26)
Dysphoria	1.53 (1.56)	1.55(1.43)	1.75(1.39)	1.70 (1.45)	1.29(1.33)	1.00*(0.87)
Yawning	0.98(1.25)	0.65(0.98)	1.38(1.26)	1.10(1.03)	0.82 (1.06)	0.59*(0.71)
Appetite symptoms	0.81(0.99)	0.96(0.89)	1.16(1.08)	0.69(1.04)	0.70(0.86)	0.53*(0.67)
Extreme Eating	0.95(1.17)	1.03 (1.15)	1.06 (1.57)	0.63(1.00)	0.70(0.91)	0.53(0.80)
Hunger	0.68(1.05)	0.89(1.13)	1.25(1.13)	0.67(1.14)	0.63(0.80)	0.53(0.80)
Total Factors score	4.38(2.7)	4.50(2.8)	5.75(2.5)	4.06(2.4)	3.86(2.5)	3.85**(2.4)
Total GHB-SWS score	22.85 (14.22)	23.35 (15.19)	30.67 (12.22)	21.36 (12.51)	20.37 (14.06)	21.08** (14.23)

GO= GHB only abusers, GSE= GHB plus sedatives co-abusers, GST= GHB plus stimulants co-abusers *,** Indicates significant change in time (difference between T1 and T2, paired dependent T-test) in the withdrawal severity per individual symptom, factors or total GHB-SWS in every group. Significance p≤ .05*, p≤ .01**.

The GSE patients reported the highest severity on the psycho-autonomic distress factor, mainly attributable to higher craving, cold flashes and tremors at T1, and to increased craving at T2. Despite lower scores on the other factors, intense restlessness, agitation and dysphoria at T1 and dysphoria and apathy at T2 were reported (Table 3, supplementary Table B). No significant change was detected in intensity through time at factor levels, individual WS or on the total GHB-SWS score.

The GST group reported greatest severity at T1 in the psycho-autonomic distress factor (all included symptoms), followed by the psycho-motor stress factor (restlessness, muscle aches and twitches). At T2, the psycho-motor stress factor was the highest due to the strongly experienced restlessness and agitation, in addition to craving (Table 3, supplementary Table B). In time, this group reported a significant decrease in their factor scores due to a decrease in intensity of psycho-autonomic distress, psycho-motor retardation and appetite factors. Also a noticeable decrease in some individual important symptoms such as abdominal pain and dysphoria was scored. They also showed a significant decrease in the total GHB-SWS score.

4.3 Add-on effect of concomitant abuse

4.3.1 At T1

No significant add-on effect on factor levels and total GHB-SWS scores was detected. With MANOVA, no significant add-on effect in the severity of the symptoms expressing psycho-autonomic distress, psycho-motor retardation or appetite was identified. In terms of psycho-motor stress symptoms, a significant add-on effect was detected (Wilks Lambda F (12,194) =1.83, p=.048). This was mainly attributable to higher muscle twitches in both the GST (p=.003) and the GSE groups (p=.018) than in the GO group.

4.3.2 At T2

Analysis showed no significant co-use effect on factor levels and total GHB-SWS score. MANOVA showed that co-use led to a significant effect on the severity of WS indicating psycho-autonomic distress (Wilk's Lambda, F (14,150) = 3.47, p =.027). The GST group reported higher intensity of rapid pulse (p=.034) and lower intensity cold flashes (p= .038) than the GO group. A highly significant add-on effect was detected in the severity of psycho-motor stress symptoms (Wilk's Lambda, F (12,168) = 2.21, p=.014) as the GST group experienced more agitation (p=.009) and restlessness (p=.001) than the GO group. No difference was detected between the GO and GSE groups. In terms of psycho-motor retardation symptoms and appetite symptoms, there were no significant add-on effects at T2.

4.3.3 Blood pressure and heart rate

In GO, GSE and GST groups BP measurements were high with a mean of 139/90 mm Hg at T1 and 141/89 mm Hg at T2. A high BP measurement of 230/140 mm Hg was detected by one

patient in the GSE group at T2. HR had a mean ranging from 86 to 90 beats per minute (bpm) at T1 and 85 to 93 bpm at T2 (see table 4). There were no significant changes in BP or HR in time per group, or due to co-use add-on effect detected.

Table 4: Blood pressure (BP) and Heart Rate (HR)

variable	T1			T2		
	GO	**GSE**	**GST**	**GO**	**GSE**	**GST**
	M (sd)	**M (sd)**	**M (sd)**	**M (sd)**	**M (sd)**	**M (sd)**
HR	86.0 (14.2)	88.5 (18.1)	90.6 (10.9)	89.1 (15.1)	85.2 (14.5)	92.6 (14.6)
Systolic BP	139.3 (17.7)	139.4 (21.9)	139.2 (20.5)	139.8 (14.5)	139.3 (24.7)	143.8 (20.4)
Diastolic BP	89.6 (11.1)	89.9 (12.9)	89.9 (12.9)	90.6 (13.4)	86.9 (15.8)	89.5 (10.7)

The table shows from the left to the right:
Mean scores and standard deviation(SD) reported per sign at T1 and T2 by total participants (n= 95)

5. DISCUSSION

To our knowledge, no previous studies have investigated the effect of psychoactive substance co-use on GHB withdrawal within the first five hours after illicit GHB cessation. Our results showed that the withdrawal symptoms differed with co-use. Whilst GHB-only users principally reported psycho-motor retardation, especially apathy and dysphoria, sedative co-users experienced psycho-autonomic distress symptoms within the first five hours. Stimulant co-users stated that psycho-autonomic distress in the first 2.5 hours was predominated by psycho-motoric stress symptoms after five hours. Of particular interest is that all three groups reported high craving levels.
In a period of five hours, GO and GSE groups showed stable general withdrawal state intensity, despite the decrease in severity reported by GO of some symptoms such as diaphoresis and rapid pulse. A significant decrease in the severity of the total withdrawal state of the GST was detected. This could be due to the effect of the low dose of pharmaceutical GHB administered after 2.5 hours. It seems that these patients were more sensitive to the sedative effect of GHB in the absence of stimulants.
In general, the reported withdrawal symptoms supports earlier case reports and studies[4,6,26]. Nevertheless, precarious symptoms such as visual or auditory hallucinations and epilepsy were rarely reported within the first 5-6 hours. This would provide clinicians with a time window to start adequate therapy and avoid complications.

The add-on effect of co-occurring substance use of stimulants or sedatives on the GHB withdrawal syndrome was established. In the first 2.5 hours after self-administration of illicit GHB and before any medication supplements, the add-on effect was limited in both GST and

GSE to intense muscle twitches. This limited effect can be related to the dominant influence of GHB withdrawal as GHB has a short duration of action and is rapidly eliminated[26]. The signs and symptoms of GHB abstinence appear rapidly, starting generally within one hour after the last dose[27,28]. After a period of five hours of illicit GHB cessation, co-occurring_sedative use induced no detectable add-on effect. Based on the reinforced similarity of neurobiological pathways, an increase in the severity of withdrawal would be expected further in time, as the peak of alcohol and benzodiazepine withdrawal usually starts within 6-24 hours of cessation. Another possibility is that the low GHB dose administered regulated the add-on withdrawal symptoms caused by sedative abuse. This outcome supports the stated therapeutic influence of GHB in the management of alcohol withdrawal, where 3-7 g GHB was provided per day in 3-6 administrations[29,30]. Hence, given an average of 2.3 g GHB was provided, 2.5 hours before T2 in this study, this might explain the minimal to absent sedative co-use withdrawal add-on effect. These findings suggest it may be a good treatment strategy to apply pharmaceutical GHB as withdrawal treatment for combined GHB and alcohol/sedative substance use disorder.

Co-users of stimulants were at greater risk of developing increases in agitation, restlessness, muscle twitches and tachycardia than GHB-only users. A possible explanation would be that stimulants, such as cocaine and amphetamine, are known to produce an effect that declines and returns to baseline within 3-4 hours despite substantial plasma concentration[31]. Furthermore, although there was no significant statistical difference in the used dose of illicit GHB between groups, it is important to consider that stimulant abusers consumed relatively higher doses (mean 70g versus 49.9g in GO) possibly resulting in later onset and appended levels of WS.

Combining GHB and stimulants could increase the severity of withdrawal, possibly due to an intersection rise in extracellular dopamine and noradrenaline during withdrawal from chronic GHB use, in addition to the acute effect of stimulants use. However, other evidence suggests that chronic self-administration of and abstinence from psychostimulants dysregulates serotonin receptors and dopamine receptors[32]. This is in combination with an increase in serotonin caused by chronic GHB use[33], which possibly will persist during the withdrawal phase, and could suggest a trigger for a wider range of WS over time, e.g. extreme agitation or psychosis/delirium. When needed, it is advised to provide these patients, in time with higher doses of pharmaceutical GHB or extra benzodiazepines.

BP measurements were relatively high for the young participants with a mean of 140/90. There was no significant add-on effect of co-abuse on HR and BP. However, blood pressure measurements as high as 230/140 and a pulse of 124 bpm were reported in a member of the GSE group and the patient required medical attention.

Despite the fact that not all admitted patients were included in the study, this sample was representative of the whole inpatient group treated within the GHB monitor and can be generalized to GHB-dependent inpatients. The potential limitations of the study include the self-report nature of the data and the lack of complete data from the toxicological tests performed to confirm the self-reports. Evidence supports the accuracy of substance use self-reports, but

indicates that patients often report more than is detected in urinalysis[34,35,36]. The absence of an assessment of GHB plasma concentration and the exact drugs/alcohol doses co-used by the included patients is a limitation to be addressed. Restricted to the daytime measurements, sleeping problems were not assessed within the GHB-SWS. The effect of co-use over time could not be assessed without regarding the entire influence of medication due to the administration of a low pharmaceutical GHB dose within 2.5 hours of last illicit GHB use and we could not assess the delayed onset withdrawal effect of co-use of sedatives. Both of these issues were unavoidable as it is unethical to postpone the treatment required in order to avoid complications.

In conclusion, GHB withdrawal can be affected by co-occurring substance use. There may be an add-on effect to the GHB withdrawal related to either withdrawal from the co-used drugs (sedatives or stimulants) or even the actual acute effect of the drugs themselves, specially by co-use of cocaine and amphetamine. Physicians should be alert and prepared for confounding intensified symptoms such as restlessness, agitation, muscle twitches, cold flashes, and dysphoria, aggravating the withdrawal syndrome. This should influence the clinical decision-making during detoxification regarding medication choices and doses. It is safe to provide limited medication support for GHB-dependent patients within the first 2.5-5 hours of GHB cessation. In case of stimulant co-use, increasing the usual doses of withdrawal treatment medication is recommended.

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Chapter 5

GHB DETOXIFICATION BY TITRATION AND TAPERING

A - Detoxification in GHB dependent patients with GHB titration and tapering: Results of the first pilot

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ABSTRACT

Objective: To determine the effectiveness and safety of a new detoxification procedure in gamma-hydroxybutyrate (GHB) dependent patients. GHB is an endogenous inhibitory neurotransmitter and anaesthetic agent that is being abused as a club drug. In many GHB dependent patients a severe withdrawal syndrome develops that does not respond to treatment with high dosages of benzodiazepines and often requires an admission to an Intensive Care Unit.

Methods: Based on the knowledge of detoxification procedures in opioid and benzodiazepines dependence we developed a titration and tapering procedure. A consecutive series of 23 GHB dependent inpatients were transferred from illegal GHB (mostly self-produced) in various concentrations to pharmaceutical GHB. They were given initial doses that resulted in a balance between sedation and withdrawal symptoms. After this titration period, patients were placed on a one week taper.

Results: We have found that after titration the patients experienced a low level of withdrawal symptoms. During tapering these symptoms decreased significantly and no patient developed a delirium or a psychosis. None of the patients had to be transferred to a medium or intensive care unit.

Conclusions: This detoxification procedure proved to be safe and convenient in patients with moderate to severe GHB dependence.

1. INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a gamma-amino butyric acid (GABA) metabolite and agonist with central nervous depressive activity. GHB is approved for clinical use in the treatment of narcolepsy with catalepsy and is used in the treatment of alcoholism. GHB and its analogues (gamma-butyrolactone and 1, 4-butanediol) are popular drugs of abuse in the United States, Australia and Europe. The popularity of GHB can be related to the reported desirable effects such as being euphoric, aphrodisiac, sociable, relaxing, and the lack of a hangover after GHB intoxication. Easy accessibility and the possibility of self-production of the drug [e.g. via internet recipes] also contribute to its use. The prevalence of use is increasing and so does intoxication, dependence and withdrawal[1-3].

GHB is also rapidly absorbed within 15–30 minutes after oral administration and absorption is dose-dependent. The most documented clinical effects associated with use of gamma-hydroxybutyrate are dose related, such as anxiolysis (10 mg/kg); euphoria, drowsiness, somnolence, and dizziness (20- 30 mg/kg); abrupt onset of sleep, enuresis, hallucinations, myoclonic jerks (30-40 mg/kg); induction of anaesthesia (40–50 mg/kg); coma (>60 mg/kg)[4]. There are no accurate data about dose related effects in addicted patients. Withdrawal from GHB is characterised by autonomic instability and significant changes in mental status. The most common withdrawal symptoms in probability of occurrence are tremor, hallucinations, tachycardia, insomnia, anxiety and hypertension. Other symptoms include agitation, diaphoresis, paranoia, confusion, delusions, delirium, nystagmus, rhabdomyolysis and seizures[4-6]. Case reports indicate that dependent users can develop a rapidly deteriorating course, resembling alcohol withdrawal. It results frequently in delirium, which can be potentially life threatening[7, 8]. In general the GHB withdrawal syndrome is treated with high dosages of benzodiazepines, preferably in inpatient facilities[5]. Cases of outpatient treatment were also reported[9]. However many patients proved to have developed an extreme high tolerance for the sedative effect of benzodiazepines and needed frequent and very high dosages because of benzodiazepines resistance[7]. In some outpatient cases baclofen is used successfully[10].

Our own experience with GHB detoxification by means of benzodiazepines in two patients was not successful and was in fact the starting point of developing a new GHB detoxification method. One of these patients is presented her to illustrate our experiences.

A 28 year old male was admitted to the addiction unit for GHB detoxification. He reported a continuous use of GHB for 15 months. He ingested 5 to 8 ml every two hours including throughout the night. He reported previously failing attempts to stop GHB by substituting with alcohol and sometimes benzodiazepines. His withdrawal signs and symptoms included tremor, palpitations, headache, nausea, vomiting, auditory and visual hallucinations. The patient reported irregular use of cocaine and cannabis. His medical history, examination and routine blood test on admission were unremarkable. The patient was started 6 hours after the last self-administration of GHB, on a high dose of diazepam, according to the following schedule: 6x 10 mg oral and 2x

20 mg IM and haloperidol 7.5 mg within 24 hours. That would be reduced according to our unit protocol. Patient was initially stable. However and in spite of repeating the pervious mentioned regime, within less than 36 hours of admission the patient became agitated and psychotic with visual hallucinations. He lost orientation to time, place and person. He required restrain to administer IM haloperidol and diazepam. He had tremors, substantial hypertension and pyrexia. Facilities to deal with emergency and life threatening situations were insufficient. Therefore the patient was transferred to the first aid unit of a general hospital for medical management because our detoxification is a low care unit concerning medical support. In the hospital higher doses of benzodiazepines were applied up to 230 mg diazepam. Due to the complications in the form of rhabdomyolysis and acute renal insufficiency the patient was transferred to the ICU for intubation, general anaesthesia with propofol and mechanical ventilation.

In our opinion and as a result of the experiences with cases like this, our detoxification protocol had to be revised. We therefore developed a GHB detoxification protocol according to the principle used in case of opioid or benzodiazepines dependence. Withdrawal strategies are based on substitution with a long acting opioid (methadone)[11] or benzodiazepine (diazepam) [12] and gradually tapering the dosage. In our new protocol GHB detoxification is performed by using pharmaceutical GHB as a substitute and the daily dose of administered GHB is reduced in one week according to a tapering regime.

The aim of this explorative pilot study was to evaluate the effectiveness of this procedure by means of the subjective withdrawal severity and the safety for the patients. The safety was measured with the number of patients referred to be treated in a general medical ward emergency unit, or an intensive care unit.

2. METHODS

2.1 Sample and setting

The GHB titration and tapering was executed in a consecutive series of 23 patients (male/female: 15/8; mean age: 26.4, SD 5.9) admitted to the detoxification unit of an addiction treatment facility. All 23 patients were addicted to GHB according to the DSM IV-TR general criteria for dependence of a psychoactive substance[13]. We considered these general criteria for dependence as appropriate for formulating a diagnosis, knowing that GHB dependence as such is not mentioned in the DSM IV-TR. None of them used GHB analogs [GBL or 1.4-BD].

Table 1 shows that there is wide range of substance abuse and dependence in this group of patients with a remarkable number of patients with abuse or dependence of stimulants (18/23). Most of the patients (86.9 %) reported using minimally one substance besides GHB on average of 20.5 days in the month. Attention deficit and hyperactivity disorder was diagnosed in 5 patients. Patients were admitted receiving a wide range of psychotropic drugs in varying daily doses and in different combinations (2: venlafaxine (75 mg), 2: trazodon (100 mg), 1: paroxetine

(20 mg), 3: mirtazepine (15 - 30 mg), 1: sertraline (100 mg), 2: risperdal (4mg), 6: quetiapine (50 - 100 mg), 1: dipiperon (40mg), 1: olanzepine (10 mg), 1: domperidon (40 mg), 2: akineton (2 mg), 1: topiramate (75 mg) and 1: methylphenidate (30mg)). Four of them took medication for physical disorders: ibuprofen (1200 mg), cetirizine (10 mg), loratidine (10 mg) and moxifloxacine (400 mg).

Table 1: Sociodemographic characteristics, daily GHB dose and concomitant psychiatric and substance use disorders in 23 patients

Gender: male/female	15/8
Mean age in years (sd)	26.4 (5.9)
Estimated mean daily GHB dose in grams before admission (sd; range)	16.9 (7.4; 6 - 36)
Concomitant psychiatric disorders	
Attention Deficit/Hyperactivity Disorder	5
Posttraumatic Stress Disorder	2
Anxiety disorder NOS	1
Anorexia Nervosa	1
No other psychiatric disorder	14
Concomitant substance use disorders *	
Alcohol abuse	3
Alcohol dependence	2
Amphetamine abuse	4
Amphetamine dependence	8
Benzodiazepine dependence	4
Cannabis abuse	1
Cannabis dependence	4
Cocaine abuse	4
Cocaine dependence	2
Ketamine abuse	1
No other substance use disorder	0

* One patient can have more SUD's; notable is the number of stimulants users, patients report the use of amphetamine as self-medication against ADHD symptoms

2.2 Study design and procedure

We used an open label design with uncontrolled observations. Two weeks before admissions the details of the study were reviewed with the patients and informed consent on the procedure

and the off-label prescription of pharmaceutical GHB was obtained. At admission the addiction physician and the psychiatrist determined the patients concomitant substance use disorders and actual co morbid psychiatric disorders by standard clinical evaluation. Patients were asked to bring in their GHB preparations for qualitative analysis. The testing revealed a mean GHB concentration of 600 mg/ml.

2.3 Instruments

The measurement of withdrawal symptoms took place with the Subjective Withdrawal Scale (SWS).The SWS is based on the format of the Subjective Opiate Withdrawal Scale[14] which proved to have good psychometric quality [15]. All the subjective criteria from all DSM-IV-TR withdrawal syndromes are added to the SWS. The SWS consists of 35 items, rated on a scale from 0 to 4 (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). The total SWS score ranges between 0 and 140. The nursing staff reported their observation using the Objective Withdrawal Scale (OWS), which is a translation and extension of the Objective Opiate Withdrawal Scale (OOWS), which originally is also a scale for opioid withdrawal signs [14]. The OOWS contains 13 objectively observable physical signs that reflect common motoric and autonomic manifestations of opiate withdrawal. We extended the OOWS in the Dutch translation with all observable manifestations of withdrawal from other psychoactive substances including alcohol withdrawal symptoms as presented in the DSM-IV-TR [13]. The OWS finally consist of 22 signs. Each item is rated as present or absent during a 10-minutes observation of the patient by nursing staff. Because the subjective and observable criteria from all DSM-IV-TR withdrawal syndromes are added to the SWS and the OWS these instruments are applicable not only for opioid withdrawal. Based on the fact that GHB serum levels peak 35–45 min after oral ingestion (1, 2, and 8) patients filled in the Subjective Withdrawal Scale (SWS) half an hour before and half an hour after the GHB dose.

2.4 Data analysis

Frequencies and descriptive data were calculated. To test differences for the mean total subjective withdrawal score in time the general linear model with repeated measures was conducted. The independent t-test for continuous outcomes was used for differences in withdrawal severity between male and female. The Pearson correlation coefficient was used to analyze the relation between age and withdrawal severity. For all statistical analyses SPSS version 15.0 was used.

2.5 Procedure of titration and tapering

All patients entering the inpatient treatment were stabilized on pharmaceutical GHB [150 mg/ml] produced by the licensed clinical pharmacy ZALV [ZiekenhuisApotheek en Laboratorium Venray] with the following contents: gamma-hydroxybutyric acid, methylparahydroxy benzoate, distillated water, saccharine and orange essence. The GHB starting dose was established via a titration method and then tapered off on a daily fixed schedule. All patients started with a

titration phase of one or maximally two days. Patients had been using GHB for an average of 1.6 year continuously on a daily basis. On average patients reported self-administration of 2.5 ml to 7 ml (2 to 4.2g) illicit GHB per dose before admission. Illicit GHB taken by the patients had an average concentration of 600-650 mg per ml; our pharmaceutical GHB had a concentration of 150mg /ml. We made the choice to administrate 70% of the calculated dose to start with. This means that a patient using 5ml illicit GHB per dose gets 14 ml of pharmaceutical GHB during the titration phase in our study (dose before admission: 5 ml = almost 5x 600 mg= 3000mg dose leads to 70 % of 3000 mg = 2100 mg/ 150 = 14 ml). The frequency of GHB self-administration varied between 45 minutes to 2.5 hours. After admission to the hospital all patients were treated with oral GHB dose within 1.5-2 hours after the last patient self-administration dose. Based on earlier clinical experience with dose finding, patients seemed to react efficiently on a dose that was almost 60-70% of the calculated dose equivalent to what the patients used to administer themselves at each interval, using the average GHB concentration of 600mg/ml as referential value. The administered first dose in the patients varied between 6-15 ml (0.9- 2.25 g), we chose to start with a rather low dose to avoid the risk of intoxication because our patients tend to under report their daily use. According to the observation by the nurse, the doctor and the self-report of the patient the stabilization dose of pharmaceutical GHB was increased or decreased by 3 to 8 ml [0.45 - 1.2 g] every 3 hours. Adjusting the dose took place until the patients had reported experiencing an acceptable level of withdrawal symptoms and the monitored blood pressure, heart rate and temperature were stable and within the normal range. Next each dose was tapered by 2-3 ml [0.3- 0.45 g] of GHB per medication dose each day. The nursing staff gave the SWS to the patient and observed the patient while he was filling in the questionnaire half an hour before and after GHB administration. They reported their observations by means of the Objective Withdrawal Scale (OWS) and measured blood pressure and heart rate. In cases of withdrawal symptoms, such as anxiety, uncontrollable tremors, hypertension or long lasting insomnia, patients were given on indication and not daily, metoprolol, diazepam or temazepam consequently in low doses and not simultaneously with GHB. All other psychotropic drugs prescribed before admission were kept on the same dosage during stabilization and tapering. All benzodiazepines were replaced with an equivalent dose of diazepam.

3. RESULTS

The mean score of the subjective withdrawal symptoms per day during eight detoxification days as follows is shown in figure 1. The sedation at the start of the tapering was done with a minimum of 7ml [1.05 g] and a maximum of 35 ml [5.25g]. This dose can be regarded as an estimate of illicit GHB abuse. The mean daily GHB dosage resulting in mild sedation was 14.1 ml (sd 6.2; range 5 – 30) resulting in a mean daily dose of 16.9 gram (sd 7.4; range 6 – 36) in the stabilization phase.

None of the patients developed a delirium or a psychosis in this study. The withdrawal symptoms as measured with the mean daily SWS scores were moderate at the start with a mean of 26.0 (range: 6.4 - 109.9). At the end of the eight-day tapering period there proved to be a significant decrease of withdrawal symptoms ($F = 16.88$; $p < .0001$) over time. At the eight day of the tapering the mean of the SWS was 5.9 (range: 0-26). There was no difference between the subjective withdrawal symptoms as measured with the SWS between male and female. No correlation was found between the age of the patient and the start dosage of titration.

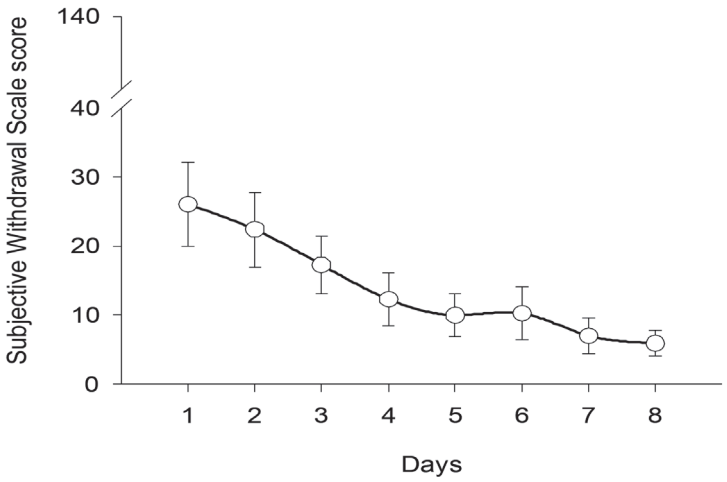

Figure 1: Subjective withdrawal symptoms during GHB detoxification (mean and STD error)

The most reported objective observations withdrawal signs in the OWS were fatigue, agitation, tremors and sweating (table 2).

The dose of medication at admission was not changed during the detoxification period. Sixteen patients experienced uncomfortable withdrawal symptoms at the end of the three hours period between two GHB doses, mostly in the first 3 days. Because most patients were poly-drug users these symptoms could also be attributed to withdrawal of the accompanying drugs such as cannabis, benzodiazepines or alcohol .Therefore, to offer relief from these symptoms patients were given when it was needed diazepam and not daily in a dose of 5 mg (eight patients), 10 mg (five patients), 15 mg (two patients) and 40 mg (one patient) per day. Because of severe insomnia 8 patients received temazepam 10 mg with a maximum of three administration days. Four patients received metoprolol 100 mg because of a diastolic blood pressure above 120 with a minimum dose of 50mg/day and a maximum of 150 mg/day with a maximum of two administration days. None of the patients developed severe somatic or psychiatric complications during the tapering period. None of the patients became psychotic or delirious. All of them could be treated within

the low medical care unit in the addiction treatment facility and none of them had to be referred to another higher care facility or dropped out of treatment.

Table 2: Withdrawal signs in patients, as measured with the Objective Withdrawal Scale (OWS) by the nursing staff

Observation of withdrawal signs*	**Patients**
Fatigue	15
Agitation	15
Craving (desire to use)	15
Tremors	14
Sweating	14
Anxiety	9
Sleepy	9
Change in perception of temperature [Warm and Cold]	8
Looks depressive	8
Muscle twitches	6
Pupil dilatation	5
Running nose	4
Abdominal pain	3
Vomiting	3

* Signs in the OWS such as yawning, goose flesh, watering eyes, general restlessness, nausea, epileptic seizures, dullness or slowness were not observed

4. DISCUSSION

The 23 patients in this series used to take high daily dosages of illegal GHB based on the dosage of pharmaceutical prepared GHB needed at the start of the tapering (mean 16.9 gram per day). They took GHB very frequently during the day. Despite this fact the titration with pharmaceutical GHB resulted in a condition in which patients subjectively perceived only minor withdrawal symptoms with a mean of 26.0 on a scale of 0 - 140 and none of them developed a delirium or a psychosis. We have found that there was a steady and significant decrease of subjective withdrawal symptoms in GHB dependent patients who were tapered off with pharmaceutical GHB. In comparison with patients treated for narcolepsy our patients used to take higher dose and more frequently. The additional dose of administrated benzodiazepines (diazepam in our study) was very low compared with patients described in the literature[4, 5], and with our experience in our previous admitted patients. Most of the patients were using other psychotropic drugs at

admission. The question cannot be answered her whether the patients were really in need for psychotropic drugs or that they presented a series of symptoms without revealing their GHB addiction to their prescribing physician before admission in our treatment facility.

Antipsychotics, antidepressants or anxiolytics were prescribed during titration in our clinic according to the dose at admission and during the detoxification period. During the one week of tapering they gradually experienced a significant and clinically relevant decrease of withdrawal symptoms. None of them developed serious psychiatric or somatic complications and no one needed more than low medical care. None of the patients had to be treated within a moderate or high care unit. If the frequency of concomitant substance use disorders are taken into account the results are even more promising.

This study has several limitations. Given the small sample size, our pilot study had of course limited power. Besides, we did not use a control condition as a comparative treatment for our newly developed method. In the literature there was no standard treatment protocol that we could use as a comparison. Because of the frequently described benzodiazepines resistance in these patients we decided not to use a dosage schedule of high benzodiazepines. We used the SWS and the OWS as instruments for measuring subjective and objective withdrawal symptoms while these instruments are not yet psychometrically evaluated well. Furthermore, it is difficult to assert that all the withdrawal symptoms presented by the patients were attributable only to GHB, because of their poly-drugs dependence . The number of patients in our study population is too small to take into account especially the effect of withdrawal from alcohol. Concerning withdrawal from benzodiazepines we have chosen to stabilize the dose and start the detoxification form benzodiazepines after the GHB detoxification.

More research is clearly needed to determine the best treatment for GHB dependent patients following detoxification, but titration and tapering with pharmaceutical GHB is a good candidate for a good start. We conclude that the method of GHB titration and tapering seems to be safe and convenient especially for the inpatient treatment of the withdrawal syndrome in GHB dependent patients.

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Chapter 5

GHB DETOXIFICATION BY TITRATION AND TAPERING

B - Detoxification with titration and tapering in gamma-hydroxybutyrate (GHB) dependent patients: the Dutch GHB monitor project

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Dijkstra , Kamal et al, 2015, Detoxification in GHB dependent patients with GHB titration and tapering: The Dutch monitor project. In review

ABSTRACT

Background and aims: *Gamma*-hydroxybutyrate (GHB) detoxification methods have been insufficiently studied for effectiveness and safety. Based on case reports, benzodiazepines are generally regarded as first-choice agents in GHB detoxification. Results of detoxification with pharmaceutical GHB in an open-label consecutive case series of 23 GHB-dependent patients shows to be feasible, effective and safe. This study explored the feasibility, effectiveness and safety of this method in a large group of patients.

Design and setting: A large national wide open-label naturalistic multicentre study was carried out in six inpatient addiction treatment centres in the Netherlands.

Participants and intervention GHB-dependent patients (229 patients, 274 admissions) were titrated on and tapered off with pharmaceutical GHB.

Findings: Successful detoxification was achieved in 85% of cases. Detoxification was carried out in 12.5 days in most patients. The advised Detoxification by Titration and Tapering (DeTiTap) regime proved to be feasible and significantly reduced the experienced withdrawal symptoms and craving ($p \leq .001$). Several symptoms were found to influence the course of subjective withdrawal symptoms. During detoxification, psychopathology, such as depression, anxiety, and stress also decreased ($p \leq .05$). The main complications were hypertension and anxiety. Six patients were sent to the general hospital for observation, but all returned to the addiction treatment centres to continue detoxification. Most patients (69%) relapsed within three months after detoxification.

Conclusion: The DeTiTap method using pharmaceutical GHB seems a safe alternative to benzodiazepines as a GHB detoxification method. However, the high relapse rate warrants further investigation.

Keywords: Y-Hydroxybutyrate, GHB, dependence, detoxification, abstinence, withdrawal, treatment

1. INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that naturally occurs in the human brain and acts as a neuromodulator and neurotransmitter[1]. Since the mid-nineties, GHB has become popular as a recreational drug[2-4]. It has relaxing, euphoric, and sexually stimulating effects at low doses[5]. In the Netherlands, the average 'street' concentration of illicit GHB is 650 mg/ml and is produced using gamma-butyrolactone (GBL). GBL has a different pharmacokinetic profile[6] and when used in pure form it is rapidly converted to GHB in the body.

Withdrawal symptoms may occur when GHB is used more than four times daily for two to four weeks at doses of over 18 grams per day[6]. Case reports, mainly from the United States, described relatively mild symptoms like insomnia, tremors, and anxiety after stopping daily use of high doses of GHB. The symptoms appeared to resemble those of alcohol withdrawal syndrome, but with a much more sudden onset. The duration of withdrawal symptoms in these cases varied from five to 12 days[7-10]. Some case-studies showed successful treatment of GHB withdrawal with low doses of benzodiazepines[11, 12]. In contrast, other patients developed severe GHB withdrawal symptoms, including delirium, psychosis, autonomic instability, rhabdomyolysis, seizures, and agitation, despite high-dose benzodiazepine treatment and/or additional pentobarbital[10,13-17]. Nevertheless, benzodiazepines are still considered first choice agents in reviews and case reports[18].

Already in 2001, Miotto and Roth [19] concluded that GHB detoxification methods had been insufficiently studied for effectiveness and safety. We developed a Detoxification procedure by Titration and Tapering (DeTiTap) with off-label use of pharmaceutical GHB as an alternative treatment option in which monitoring in a high-care medical setting would be no longer necessary. The results of a previously-conducted open-label consecutive case series of 23 GHB-dependent patients were promising[20]: the DeTiTap seemed to be feasible, effective and safe. This justified a large, nationwide, naturalistic study[21] in a large group of patients that requested professional treatment for their GHB addiction.

In this paper we report on 274 GHB-dependent patients treated with DeTiTap in six different Dutch Addiction Treatment Centres (ATC). The objectives of the study were as follows: First, to evaluate the feasibility of the DeTiTap by compliance with the detoxification protocol; Second, to evaluate the effectiveness by means of completion rates, the subjective and objective withdrawal severity, craving, psychological symptoms, and the need for co-medication; Third, to assess the safety of the detoxification procedure in terms of the occurrence of complications; Fourth, to assess relapse rates at follow-up after three months.

2. METHOD

2.1 Study design

We conducted an open-label, naturalistic, multicentre study in which GHB-dependent inpatients underwent detoxification according to the DeTiTap method using pharmaceutical GHB with a follow-up at three months after detoxification. This Dutch GHB monitor 1.0 was conducted from March 2011 to December 2012 in six ATCs in the Netherlands, with ethical approval from the Medical Ethical Research Committee (METC Twente). A preliminary report of the main results of the study have been published in a Dutch journal (Weert-van Oene de et al., 2013).

2.2 Participants

Patients were monitored in six participating ATCs (Novadic-Kentron, Tactus, IrisZorg, Victas, Verslavingszorg Noord Nederland, and Brijder). Patients were between 18 and 60 years old when admitted to the detoxification unit. They were diagnosed with GHB and/or GBL dependency according to the Diagnostic and Statistical Manual of Mental Disorders IV-TR [22] general criteria for psychoactive substance dependence. Pregnant women were excluded. All participants provided written informed consent for off-label use of pharmaceutical GHB and use of anonymized data for research purposes.

2.3 Treatment protocol

Pharmaceutical GHB was used off-label and produced by different pharmacies (depending on the ATC) with a concentration between 100 to 500 mg/ml GHB. The GHB detoxification procedure followed the standardized practice-based protocol by Kamal *et al.* [23]:

- After admission patients received the initial dose of pharmaceutical GHB within 2.5 hours after the last self-administered dose to prevent withdrawal. To avoid the risk of intoxication this first dose was calculated by taking 70% of the equivalent of the reported self-administered illicit GHB dose (based on an average 'street' concentration of 650 mg/ml) minus 0.75 – 2.25 g (depending on medical history, clinical state, plausibility of the patient's reported doses and level of the calculated dose).
- The second dose was administered after an interval of two to three hours (depending of the interval of GHB use) and contained 70% of the last reported dose (see Figure 1 for example). In case of concomitant alcohol dependence, an additional 0.75 – 1.5 g per GHB dose was advised. Low doses of long-acting benzodiazepines (mostly diazepam, max. 20 mg/day) could be prescribed in case of dependence on benzodizepines, cocaine, cannabis, or amphetamine, and kept stable during DeTiTap.
- During the titration phase the pharmaceutical GHB dose was adjusted every two to three hours depending on the patient's self-reported symptoms and observations by the nurse and physician. Consecutive GHB doses were adjusted until the patient experienced an

acceptable level of withdrawal symptoms and their blood pressure and heart rate were stable and within the normal range.

- The detoxification phase followed the day after titration by tapering the GHB on a fixed daily schedule consisting of two to three hour dose intervals. The dose was tapered by 2.4 to 3.6 g GHB each day (see Figure 1). Additional medication was provided in case of hypertension (metoprolol 50 – 100 mg), extreme anxiety (diazepam 5 – 10 mg), or insomnia (temazepam 10 mg for maximal two consecutive nights).

Example: Patient 1

Male, 23 years old.
History of social anxiety disorder. Uses home-brewn GHB since 4 years daily.
Every 60-90 min 12 ml. 2 doses during the night.

Detoxification schedule Patient 1: 12 ml X 0.65 X 70%= 5.46 g minus 1 g= 4.5 g starting dose. Dosing every 3 hours, including 2 nightly doses.

Time schedule		Detoxification day														
	T	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
08:00 am	4.5	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
11:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
14:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
17:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
20:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
23:00 pm	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
02:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
05:00 am	4.8	4.5	4.2	3.9	3.6	3.3	3.0	2.7	2.4	2.1	1.8	1.5	1.2	0.9	0.6	0.3
Total (g GHB)	38.1	36	33.6	31.2	29	26.4	24	21.6	19.2	16.8	14.4	12	9.6	7.2	4.8	2.4

Figure 1: Example of calculating titration dose and consecutive detoxification schedule based on self-reported illicit GHB use

2.4 Procedure

Detailed information about GHB use, dependence and mental wellbeing was acquired at baseline (see instruments). In case of emergency admission this information was acquired at admission. Upon admission the information about GHB use was confirmed and physical examination was performed by an addiction physician. Subjective and objective withdrawal scales were completed 30 minutes before GHB dose by both patient and nurse. Baseline blood pressure and heart rate were recorded. Patients also reported on withdrawal 30 minutes after the GHB dose during titration days. Craving visual analogue scales (VAS) were recorded daily at 10.30 pm.

At discharge additional measurement instruments were administered. After discharge, patients received treatment as usual. These treatments varied from short individual cognitive behavioural treatment intervention to extensive multidimensional therapy. At three month follow-up patients were questioned about their GHB use by means of self-report.

Table 1: Overview of instruments administered during the study

Instruments	T1. Baseline	T2. Admission	T3. Discharge	T4. Follow-up
MATE	X			X
DASS	X		X	
EuroQol-5D*	X		X	
BSI*	X		X	
GHB questionnaire	X			
Follow-up questionnaire				X
Medication list		X	X	
SOS	X	X	X	
OOS	X	X	X	
Craving (VAS)	X	X	X	

Measurement of Addicts for Triage and Evaluation(37), Depression Anxiety Stress Scale (DASS), Brief Symptom Inventory (BSI), Subjective Withdrawal Scale (SWS), Objective Withdrawal Scale (OWS).

2.5 Instruments

Table 1 presents a detailed overview of the instruments administered during the study.

Measurement of Addicts for Triage and Evaluation. The MATE [24] is designed as a diagnostic aid of relevant patient characteristics. For the present study sections 1 and 4 were used to define participants' current substance use (last thirty days), lifetime substance use, and GHB and/or GBL dependency according to the DSM-IV-TR.

GHB questionnaire. The GHB questionnaire is a self-developed questionnaire about the pattern of GHB use consisting of the number of years of use, total daily dose in grams, grams per dose and interval between doses.

Depression Anxiety Stress Scale (DASS). The DASS is a 21-item self-report instrument measuring depression, anxiety and stress over the past week on a four-point Likert-scale, from 'not at all or never' (0) to 'very much/most of the time' (3) [25, 26]. Scores for depression, anxiety and stress were calculated by summing the scores for the relevant items and multiplying by two (range between 0 and 42). Recommended cut-off scores for severity labels are shown in Table 3.

Brief Symptom Inventory (BSI). The BSI measures the levels of psychopathology and is a shortened form of the Symptoms Checklist-90-revised (SCL-90-r) [27]. The BSI is a 53-item self-report symptom scale measuring nine dimensions (Table 3). The score per dimension ranges from 'not at all' (0) to 'extremely' (4) [28, 29].

EuroQol-5D (EQ-5D). Patient's reported quality of life [30, 31] was measured with the EQ-5D, a 5-item self-report instrument with a three-point scale (1 = no problems, 2 = some problems, and 3 = extreme problems). The EQ-5D index was calculated according to the Dutch algorithm for

the general population, ranges from .594 to 1 (1 being perfect health). Participants self-rated their health on a vertical, visual analogue scale (EQ-5D VAS) where the endpoints are labelled from 'Best imaginable health state' (100) to 'Worst imaginable health state' (0) [30].

Subjective Withdrawal Scale (SWS). The SWS measures withdrawal symptoms experienced by the patient and is based on the format of the Subjective Opiate Withdrawal Scale [32] and proved to have good psychometric quality [33]. All subjective criteria from DSM-IV-TR withdrawal syndromes were added to the SWS. The SWS consists of 33 items, rated on a scale from 0 to 4 (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a bit, 4 = extremely). The total SWS score ranges between 0 and 132.

Objective Withdrawal Scale (OWS). The nursing staff reported their observations using the OWS, based on the Objective Opiate Withdrawal Scale (OOWS) [32]. The OOWS contains 13 objectively observable physical signs that reflect common symptoms of opiate withdrawal. We extended the OOWS in the Dutch translation with all observable withdrawal symptoms from other psychoactive substances including alcohol as included in the DSM-IV-TR [22]. The resulting OWS finally consisted of 22 items, rated as present or absent during a 10-minute observation by the nursing staff.

2.6 Data analysis

Frequencies and descriptives were calculated for patient characteristics. One-way ANOVA and Pearson's chi-square tests were performed to analyse differences between included and excluded patients, one or more admissions, and between abstinence and relapse at follow-up. Compliance to the protocol was evaluated by the duration of the titration and detoxification phase and titration doses of GHB.

Effectiveness was evaluated by detoxification completion rates, experienced subjective (SWS) and objective withdrawal symptoms (OWS), craving (VAS), psychological symptoms (BDI, DASS) and use of concomitant medication. Paired t-tests were performed to analyse the difference in withdrawal 30 minutes before and 30 minutes after each GHB dose. To illustrate the course of withdrawal during DeTiTap only the results before GHB doses are reported. For this, the mean scores per patient per day were calculated and because of the multiple responses and missing values, a restricted maximum likelihood Linear Mixed Model (LMM) was used to assess change in SWS scores over time and to relate the changes to covariates (fixed effects). The intercept and subjects were added as random effects. Prior to analysis the severity of withdrawal symptoms was normalized using log transformation. Change in general symptoms (BSI and DASS) were analysed by paired t-tests.

The safety of the detoxification procedure was evaluated by describing the occurrence of hospital admissions.

GHB abstinence three months after detoxification was defined as a self-reported total abstinence of GHB use in the last 30 days. If patients reported GHB use they were defined as non-abstinent.

All statistical tests were two-sided; p-value was considered statistically significant at the 0.05 level (2-tailed). IBM® SPSS® Statistics version 19 for Windows was used for all the computations.

3. RESULTS

3.1 Patient characteristics

From February 2011 to August 2012, 354 inpatient GHB detoxifications were performed, of which 278 were monitored according to the study protocol (78.5%). Absence of the research nurse was the main reason for un-monitored detoxifications and this differed significantly between ATCs. Unmonitored patients did not differ in age, amount of detoxifications or detoxification outcome, but they had fewer emergency indications. Four patients were excluded because they underwent a benzodiazepine tapering as their GHB use was very low. Of the 274 detoxifications, 16% included re-admissions (9 patients had been re-admitted three to four times during the study period), hence a total of 229 unique patients were involved in this study. Table 2 provides the characteristics of these patients. Daily GHB doses ranged from 10 – 312 gram (Mean=58.8, SD=41.6). 10% (also) used GBL.

One fourth of the admissions were emergency admissions, most of the emergency admissions were re-admissions. Comparing patients with re-admissions and those with a single admission for detoxification, the former group reported significantly more prior GHB-related emergency room (ER) admissions (76.9% versus 47.2%, F=12.8, p≤.001) and intensive care unit (ICU) admissions (50.0% versus 20.3%, F=15.3, p≤.001) and used significantly more GHB (M=72.4, SD=45.3) compared to patients without re-admissions (M=56.0, SD=40.3) during the study period (F=5.6, p=.02). They did not differ in years of GHB use, age or gender. A small proportion of the admissions were involuntarily (6.2%).

3.2 Course of the detoxification procedure with pharmaceutical GHB

The titration phase took an average of 1.9 (SD=1.0) days. Mean duration of completed detoxification was 10.6 (SD=6.3) days. Of 274 detoxifications, 39 (14.2%) were incomplete. Twenty-one patients discontinued detoxification voluntary due to different reasons. Nine drop-outs were involuntarily discharged due to aggression, nine to confirmed drug abuse during admission. There was a suspicion of illegal substance abuse (mostly supplementary illegal GHB) during detoxification in 20.9% of the patients, and it was confirmed in 13.2%. Almost one third left the ATC immediately after detoxification (recovery days M=3.0; SD=4.3). The mean number of admission days of all patients was 14.9 days (SD=8.0).

In most detoxifications the dose for titration and detoxification was in line with the protocol. Mean first and second titration doses were respectively 2.7 g (SD=1.1) and 2.9 g (SD=1.2) with a range of .75 – 7.5 g, respectively 67.5% and 72.5% of the reported self-administered illicit dose. During the titration day(s) the median stabilisation dose was 3.2 g (SD=1.2), 80% of the illicit

GHB dose. The first and second titration doses appeared to be the exact stabilisation dose for 40.9% and 57.1% of the detoxifications, respectively. Most of the patients however (56.5% versus 41.9%) received higher stabilisation doses. Figure 2 presents a graphical representation of the GHB doses.

Table 2: Baseline characteristics of unique patients (n = 229) at first admission

Characteristics		**n**
Age in years, mean (SD)	28.8 (7.2)	229
Gender		229
Male	69.0%	
Female	31.0%	
Country of birth		216
The Netherlands	96.8%	
Other	3.2%	
Living situation		215
Living alone	34.9%	
Living with husband partner and/or children	24.7%	
Living with parents	26.5%	
Other	14.0%	
GHB use, mean (SD)		
Mean age at first GHB use	25.0 (7.4)	206
Mean years of GHB use	4.2 (3.3)	216
GHB use last 30 days	29.7 (1.4)	218
Estimated GHB dose at a time, gram	3.88 (2.1)	205
Esimated mean daily GHB dose before admission, gram	56.0 (40.3)	207
Concomitant substance use, mean (SD)		207
Alcohol use last 30 days	13.1 (11.6)	118 (57%)
Cannabis use last 30 days	17.0 (12.1)	88 (43%)
Opioid use last 30 days	13.7 (11.6)	4 (2%)
Cocaine use last 30 days	09.1 (10.7)	63 (30%)
Stimulant use last 30 days	14.8 (12.2)	86 (42%)
Sedative use last 30 days	21.5 (11.2)	74 (36%)
Other drug use last 30 days	26.2 (08.3)	123 (59%)

* *P* value is statistically significant at the 0.05 level (2-tailed)

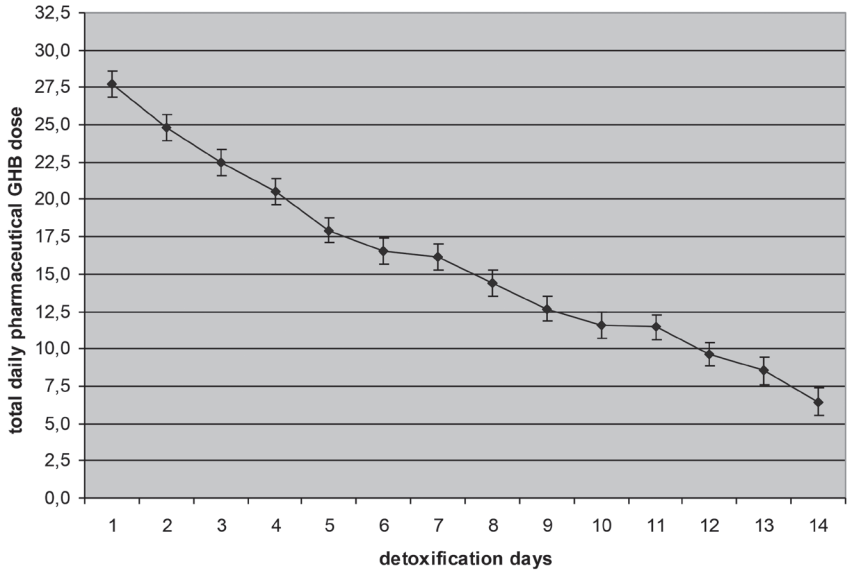

Figure 2: Total pharmaceutical GHB dose per detoxification day (mean and standard error of the mean)

3.3 Symptoms

3.3.1 Subjective withdrawal symptoms

The mean SWS score before the first titration dose was 29.4 (SD=18.1), decreasing to 24.7 (SD=16.3) at the end of the first titration day. During titration days the SWS differed significantly (t=18.2, p≤.001) 30 minutes before (M=22.5, SD=16.9) and 30 minutes after GHB dose (M=16.9, SD=14.1). The SWS (Figure 3a) decreased significantly over time (F=11.3; p≤.001). Patients with higher doses of pharmaceutical GHB (F=10.0; p≤.01), more detoxifications in the past (F=8.4; p≤.01), higher level of reported depression (F=23.4, p≤.001), anxiety (F=10.3, p≤.01) and stress (F=27.3, p≤.001) at baseline experienced higher levels of SWS. Women experienced higher levels of SWS than men (F=7.3; p≤.01), as did patients with an emergency admission (F=6.5; p=.01). In contrast to what we expected, significantly (F=4.0, p=.02) less severe SWS were found for patients that self-cooked their GHB compared to those who obtained GHB from a dealer or friend. We could not detect significant differences between GHB and GBL users due to the low number of GBL users. Readmission (F≤0.01, p=.92) and the amount of pre-admission GHB consumed, both per dose (F=0.2, p=.66) and per day (F=3.3, p=.07) showed no significant differences in terms of SWS. Finally, patients with higher SWS at the titration phase experienced more severe SWS during the detoxification phase (Pearson r=.7, p≤.001).

3.3.2 Objective withdrawal symptoms

Patients started the titration phase with a mean OWS score of 3.5 (SD=2.9). The OWS score differed significantly (t=12.5, p≤.001) 30 minutes before (M=3.6, SD=2.8) and 30 minutes after GHB dose (M=16.9, SD=14.1) during titration days. The course of OWS (Figure 3b) changed over time (F=7.4, p≤.001).

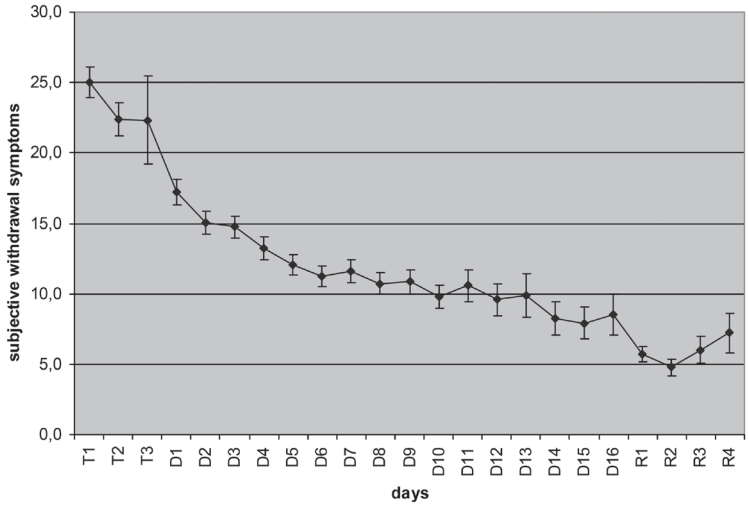

Figure 3a: Mean (and standard error of the mean) severity subjective withdrawal symptoms (SWS) per day during titration (T), detoxification (D), and recovery phases (R). Scores for this figure are calculated and presented when n > 20.

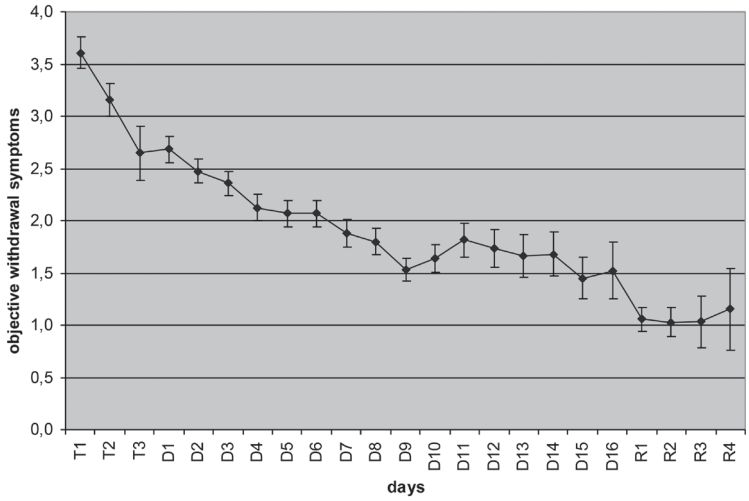

Figure 3b: Objective withdrawal symptoms (OWS) score per day during titration, detoxification, and recovery phases (mean and standard error of the mean). Scores for this figure are calculated and presented when n > 20.

3.3.3 VAS craving

At baseline patients reported a mean VAS craving score of 5.2 (SD=3.0), whilst on the first titration day the mean VAS craving score was 6.0 (SD=2.8). As shown in Figure 4 the mean VAS craving score significantly decreased over time ($F=7.3$, $p \leq .01$).

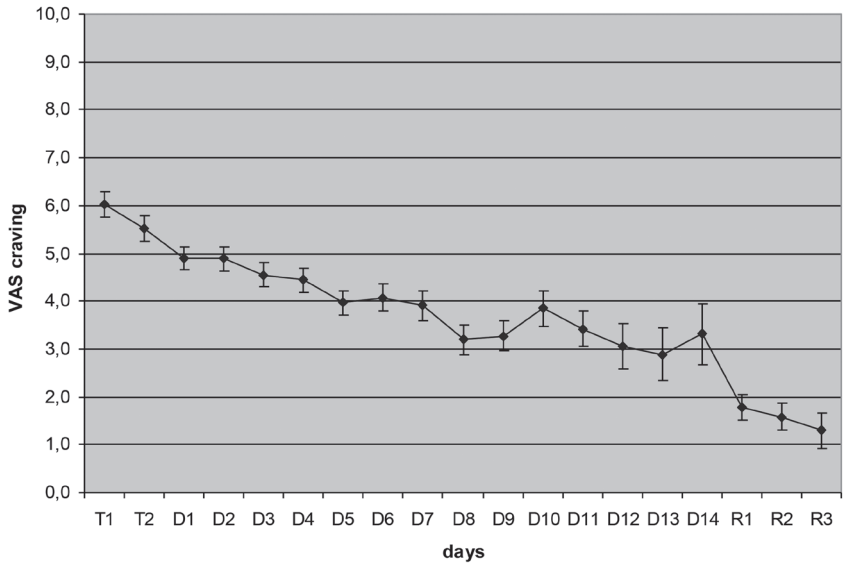

Figure 4: Experienced craving (measured with a VAS scale) per day during titration, detoxification, and recovery phases (mean and standard error of the mean). Scores for this figure are calculated and presented when n > 20.

3.3.4 Change in general symptoms

Patients reported high (DASS) or above average (BSI) symptoms of psychopathology compared to psychiatric outpatients. DASS and BSI symptoms decreased significantly during detoxification (Table 3). Although few patients still scored 'very high' on the BSI at discharge (15.7%, vs. 52.9% at admission), 47% scored 'high to very high'. The same was seen for severe/extremely severe anxiety on the DASS (30.5% of the patients, vs. 50.2% at admission). Fewer patients experienced stress (from 36.4% to 15.6%) and depression (from 38.5% to 17.9%) on the DASS at discharge.

Table 3: DASS and BSI

	Baseline		Discharge				
	mean	**(sd)**	**mean**	**(sd)**	**t-test**	**df****	**p-value**
BSI	n=211		n=134				
Somatisation	1.56	1.01	.62	.58	9,55	114	≤0.001
Cognitive problems	2.01	1.106	.99	.88	11,84	114	≤0.001
Interpersonal sensitivity	1.47	1.18	.60	.82	8,98	122	≤0.001
Depression	1.78	1.13	.87	.88	11,28	113	≤0.001
Anxiety	1.75	1.04	.91	.83	8,56	114	≤0.001
Hostility	1.29	1.05	.48	.45	9,05	114	≤0.001
Phobic anxiety	1.23	1.15	.54	.72	7,58	114	≤0.001
Paranoid ideation	1.51	1.13	.67	.72	9,15	110	≤0.001
Psychoticism	1.36	1.05	.65	.71	9,06	113	≤0.001
General psycho-pathology (total score)	1.60	.95	.74	.60	11.03	109	≤0.001
DASS*	n=215		n=134				
Depression	18,03[3]	(11,71)	12,21[2]	(10,26)	4.91	94	≤0.001
Anxiety	16,14[4]	(10,25)	11,73[3]	(9,08)	4.09	94	≤0.001
Stress	20,48[3]	(10,50)	14,32[1/2]	(9,89)	5.21	94	≤0.001
Total	54,72	(29,47)	38,25	(25,62)	5.49	94	≤0.001

1= normal, 2 = mild, 3 = moderate, 4 = severe, 5 = extremely severe
* Cut-off scores for DASS severity labels are as follows for depression (normal 0-9, mild 10-13, moderate 14-20, severe 21-27, extremely severe ≥28), anxiety (normal to mild ≤9, moderate 10-14, severe 15-19, extremely severe ≥20), and stress (normal 0-14, mild 15-18, moderate 19-25, severe 26-33, extremely severe ≥34).
** Baseline information did not differ significantly between patients with both baseline and discharge measurement on the DASS and BSI and patients with no or one measurement on the DASS and BSI.

3.3.5 Complications and concomitant medication

Before admission the majority of the patients used psychotropic medication, such as benzodiazepines (22.3%), antipsychotics (14.0%), antidepressants (4.3%) and hypnotics (14.0%; Table 4b).

During DeTiTap 17 patients (7.4%) developed hypertension. Hypertension was treated mostly with metoprolol (25-150 mg) given once or twice (see Table 4a). Fifty patients (23.7%) developed anxiety and/or agitation, which was treated mostly with diazepam (5-30 mg). Five patients (2.1%) developed psychosis, extreme restlessness and/or delirium and received antipsychotics or

benzodiazepines (see Table 4a for a detailed overview of co-medication). Four of those were sent to the general hospital (GH). Two other patients were sent to the GH due to intoxication. Five patients returned to the ATCs the same day, one patient was admitted to the psychiatric ward for two days. All patients continued detoxification at the ATCs.

Table 4b: Co-medication for symptomatic treatment during titration and detoxification phase

Withdrawal Symptoms	Titration	Detoxification	Total unique patients
Hypertension	**n=10**	**n=11**	**n=17**
	n=1 treated with metoprolol (50-150 mg)	n=3 treated with metoprolol (100 mg)	
	n=5 treated with metoprolol (50 mg)	n=7 treated with metoprolol (50 mg)	
	n=4 treated with metoprolol (100 mg)	n=1 treated with propranolol (10 mg)	
Anxiety	**n=17**	**n= 26**	**n=31**
	n=16 treated with diazepam (5-20 mg)	All were treated with diazepam (5-30 mg)	
	n=1 treated with oxazepam 25 mg		
Agitation	**n=4**	**n=9**	**n=12**
	n=3 treated with biperiden (2-4 mg)	n=7 treated with diazepam (5-30 mg)	
	n=1 treated with diazepam (10 mg)	n=1 treated with quetiapine (50 mg)	
		n=1 treated with dipiperon (20 mg)	
Anxiety + agitation	**n=6**	**n=3**	**n=7**
	n=4 treated with diazepam (5-40mg)	n=2 treated with diazepam (5-30 mg) (n=1 switched from diazepam	
	n=1 treated with biperiden(4 mg)	5-10 mg to oxazepam (100mg) + biperiden (2 mg)	
	n=1 treated with beperiden (2 mg) + oxazepam (100 mg)	n=1 treated with oxazepam (25 mg)	
Psychosis and/or Delirium and/or Extreme Agitation	**n=2**	**n=4**	**n=5**
	Patients were treated besides GHB increase with haloperidol (2-4 mg) + biperiden (1-2 mg)	n=3 treated with haloperidol (2.5-4 mg) + diazepam 10-20 mg + biperiden (1-2 mg)	
		n=1 treated with with halo-peridol (2.5 mg) + dipiperon (40 mg) + lorazepam (3-4 mg) + patient used also diazepam (30-40 mg)	

Table 4b: Co-medication related to co-abuse or pre-diagnosed psychiatric or somatic problems before admission per unique patient

Indication	**n** **applied medication**
Hypertension	**n=6**
	n=1 treated with nifedipine (60 mg)
	n=3 treated with metoprolol (100 mg)
	n=2 treated with propranolol (40-80 mg)
Psychosis	**n=32**
	n=4 treated with olanzapine (15-20 mg)
	n=3 treated with haloperidol (2.5-5 mg)
	n=2 treated with abilify (10-15 mg)
	n= 23 treated with quetiapine (150-300 mg)
Depression	**n= 10**
	n=2 treated with citalopram (30 mg)
	n=2 treated with venlafaxine (75-188 mg)
	n=1 treated with escitalopram (15 mg),
	n=3 treated with paroxetine (20 mg)
	n=1 treated with amitriptyline (25 mg)
	n=1 treated with agomelatine (25 mg)
Intestinal	**n=26**
	n=11 treated with omeprazole (20-40 mg)
	n=15 treated with loperamide (2-10 mg)
Co-abuse	n=51
	n=44 used diazepam (5-60 mg)
	n=2 treated with chlordiazepoxide (30-60 mg)
	n=3 treated with oxazepam (50-300 mg)
	n=2 switched between diazepam (5-40 mg) and domperidone (20 mg)
Sleep disorders	**n= 32**
	n=10 treated with quetiapine (25-100 mg)
	n= 6 treated with nozinan (12.5-25 mg)
	n= 4 treated with mirtazapine (15-30mg)
	n= 6 treated with melatonin (5 mg)
	n= 6 treated with promethazine (25 mg at night)

Table 5: Overview of hospital admissions

Case (age/ gender)	Prominent withdrawal symptoms/ complications	GHB dose	Day	Management	Medication
Case 6 (32/m)	Intoxication even before start of the detox	15 ml	T1	Check up in GH	No medication
Case 2 (24/m)	Admitted in ATC with delirium and aggression	14 ml	T1	After consult GH back to ATC the same day	Increase GHB
Case 4 (18/f)	Intoxication due to abuse outside the prescription: severe sedation and anxiety	6 ml	D1	Only observation for few hours in GH, detox continued at ATC	Diazepam 10 mg
Case 3 (38/m)	Delirium	Start 15 ml, at time of complication 13 ml	D3	Treated in ATC after a quick check in GH	Increase GHB
Case 1 (37/m)	Delirium, anxiety and agitation	Start 21 ml, at time of complication 15 ml	D4	After examination GH back to the ATC the same day	Increase GHB, diazepam 15 mg, zyprexa 20 mg
Case 5 (39/m)	Delirium	18 ml, when the patient needed 30 ml	D7	Admitted to psychiatric ward ofGH for three days, then continued treatment in ATC	Lorazepam 2.5 mg/d, haloperidol to 10 mg/ day, then increase GHB + diazepam when needed up to 30 mg/d

GH = general hospital; ATC = Addiction Treatment Center

3.4 Relapse rate

Of the 274 detoxifications, 96 (35.0%) were lost to follow-up. Those who were lost to follow-up did not differ significantly on baseline variables and detoxification outcome from patients with follow-up assessments. Of the remaining 178 patients, 64.6% relapsed into GHB use during the three months after detoxification. Of these patients, 26.7% reported relapse immediately after detoxification. Mean duration of abstinence was 8.4 weeks (SD=4.2). Daily GHB use was reported by 36.5% of the patients at follow-up. Half of the patients reported current GHB use at follow-up (21.5 days (SD=11.5) out of 30). Patients also reported the use of alcohol (51.5%), benzodiazepines (37.4%), cocaine (26.9%), amphetamines (26.9%), and cannabis (23.4%) at follow-up.

4. DISCUSSION

In this open-label multicentre study, we found that successful detoxification from GHB was achieved in 85% of the cases using the DeTiTap method with pharmaceutical GHB. In most patients, detoxification was achieved in 12.5 days. During titration and detoxification the withdrawal symptoms and craving, as well as symptoms of depression, anxiety and stress significantly decreased over time. Several symptoms were found to influence the course of subjective withdrawal symptoms. Main complications were hypertension and anxiety. Six patients were sent to the GH for observation, but all returned to the ATCs to continue detoxification. Relapse rates were high at 69% at three month follow-up.

Although the prevalence of GHB abuse and dependence has increased in recent decades, there have been no clinical trials investigating GHB withdrawal treatments[18]. Published case-reports mostly present acute unplanned detoxifications complicated by severe withdrawal syndromes that are difficult to manage in GH settings. Benzodiazepine administration still appears to be the first-line treatment, with, if necessary, barbiturates, baclofen, or propofol as second line management options, combined with monitoring in an ICU[18].

This open-label study with off-label use of pharmaceutical GHB came about due to the absence of studies and guidelines on safe and effective detoxification methods in ATC settings, complicated withdrawal studies, and a rapid increase in the number of GHB users[23]. The advised titration and detoxification regime proved to be feasible and we confirmed the effectiveness and safety of the DeTiTap method using pharmaceutical GHB in a large group of patients that requested professional treatment for GHB addiction in different Dutch ATCs. Substantial co-medication was given during DeTiTap, partly because of comorbid substance use and psychiatric symptoms at baseline. Extra medication to treat anxiety and/or agitation was necessary in about 25% of the cases in relatively low doses. Due to the risk of severe and complicated withdrawal syndromes, the expertise of relevant healthcare practitioners was and is necessary.

The naturalistic multicentre design meant we relied on the resident nurses and physicians to provide data. Absence of the research nurse caused missing data and this could have influenced our results, although no meaningful differences were found between patients with and without missing data.

In our protocol, GHB detoxification was performed by using short-acting pharmaceutical GHB as a substitute, as no long-acting GHB was available. We chose GHB because of the various multiple neurological properties of GHB, like (in)direct binding to GHB, GABA(A), and GABA(B) receptors[6], however alternatives should also be investigated. One case study showed positive results for the GABA(B) agonist baclofen[34], although the overlap in the neurobiological pathway and intoxication symptoms of GHB and baclofen can cause a serious and dangerous state of intoxication[35]. Another option could be dexmedetomidine, used for other withdrawal syndromes[18]. More systematic research should be performed with pharmaceutical GHB in

which the efficacy and safety will be assessed, as compared to other potential treatments, e.g. benzodiazepines and/or baclofen.
The daily amount of illicit GHB use in this study population was strikingly high, as well as the high percentage of prior ER and ICU admissions, emergency detoxification admissions, and the high prevalence of reported symptoms of depression, anxiety, and stress. General sociodemographic characteristics were nevertheless similar to GHB-dependent patients treated in Dutch ATCs[36], although unmonitored patients had fewer emergency indications and underwent fewer detoxifications in total. The high relapse rates immediately after detoxification and at three month follow-up require attention in future research and practice.

In conclusion, the DeTiTap method seems a feasible and safe alternative for GHB detoxification with benzodiazepines, although randomized controlled trials with different agents should be performed to establish efficacy and safety. Detoxification is part of a total treatment program aimed at the maintenance of abstinence and the high relapse rate warrants further investigation.

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Declaration of interest

The authors report no conflicts of interest. The content and writing of the paper are the sole responsibility of the authors.

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Chapter 6

Pharmaceutical gamma-hydroxybutyrate in patients with severe benzodiazepine-resistant gamma-hydroxybutyrate withdrawal in the hospital

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ABSTRACT

Background: With an increase of gamma-hydroxybutyrate (GHB) abuse as a party-drug in the past decades, the addictive properties of GHB and the complications of intoxications and severe withdrawal-syndromes have become apparent. Abrupt cessation of intensive GHB-use often results in severe and potentially life-threatening withdrawal syndromes. Treatment of these withdrawal syndromes has not been systematically investigated. In case-reports, treatment consisting of high-dose benzodiazepines and supportive measures is advised. However, in clinical practice, these treatments sometimes appear to be ineffective. In many Dutch addiction treatment centers GHB-detoxification occurs by titrating and tapering of pharmaceutical GHB following a standardized protocol.

Method: We describe three patients admitted to our hospital with severe acute GHB-withdrawal syndromes, resistant to high-dose benzodiazepines, who were treated according to this protocol.

Results: In all three patients symptoms rapidly improved after titration with pharmaceutical GHB.

Discussion: Although systematic evidence is still lacking, practice-based experience suggests that in patients with a benzodiazepine-resistant severe GHB-withdrawal syndrome, treatment with pharmaceutical GHB may be effective. Further studies are necessary to establish efficacy, safety and superiority to other treatments.

1. INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a gamma-aminobutyric acid (GABA) precursor and metabolite that naturally occurs in the human body. It has found a limited medical use as an anaesthetic agent, in the treatment of narcolepsia, and alcoholism and has recently been rediscovered as a possible antidepressant agent.[1,2] Moreover, it is a popular drug of abuse in Europe, Australia and the United States.[3] GHB has a biphasic effect due to dopamine (DA)-release in the striatum and cortex as a result of binding to GHB-receptors in lower concentrations, whereas in higher concentrations, DA-release is inhibited due to binding to $GABA_B$-receptors.[4] The exact mechanisms of action and interaction with GHB receptors are still being studied. Due to its narrow 'therapeutic' window intoxications frequently occur and often result in coma and respiratory depression.[1,5] GHB intoxications may frequently be indistinguishable from other drug overdoses (e.g. ethanol, benzodiazepines) or medical conditions resulting in a coma.[1] Although the absolute prevalence of GHB-abuse remains low, the increase of its abuse over the past decades has resulted in alarming reports of GHB-related deaths due to intoxications and occasionally due to complications of withdrawal.[6,7,8,9] The GHB-precursors gammabutyrolactone (GBL) and 1,4-butanediol (1,4-BD) are being used with more or less the same (side-) effects.

In the Netherlands, the number of patients admitted to addiction treatment centers (ATCs) for GHB-detoxification has quadrupled in the past years.[4] In addition, many patients with symptoms of GHB-withdrawal present to emergency departments (EDs) of general hospitals every year. GHB-withdrawal syndromes are medical emergencies, in severe cases characterized by extreme agitation, delirium, and rhabdomyolysis.[3,8] Treatment of GHB-withdrawal has not been systematically investigated. The literature consists of reviews and case-reports in which high doses of benzodiazepines are recommended as treatment for GHB-withdrawal syndromes.[1,8] However, this approach appears to be often ineffective.[3,8] Until recently, elective GHB-detoxification using benzodiazepines was the standard of practice in the Dutch ATCs. In 2011, a new GHB-detoxification protocol based on titration and tapering with pharmaceutical GHB has been developed by De Jong et al.[3] This protocol appears to be safe and effective in ATCs, where patients are treated for an elective GHB-detoxification.[3,10] Data on 229 GHB dependent patients have recently been published. Intramural detoxification in ATCs using this new protocol was successful in 86% of the patients. 21 patients (8%) aborted treatment, and 18 (6%) were discharged because of the use of street-GHB on the ward.[10]

In ATCs, admissions for GHB detoxifications are often elective and planned. In general hospitals however, patients often present with acute and unwanted withdrawal syndromes that can be extremely difficult to stabilize, even in intensive care units (ICUs).[1,11,12]

Here we present three cases of GHB-dependent patients admitted to the general hospital with severe GHB-withdrawal syndromes. In all cases, pharmaceutical GHB was successfully administered after failure to stabilize the patient with high-dose benzodiazepine treatment.

2. CASES

2.1 Case #1

Ms. B was a 28-year-old woman with a history of current GHB dependence, previous supervised GHB detoxification followed by relapse shortly after discharge, and two reported episodes of GHB-withdrawal seizures during unsupervised detoxification. She had been dependent upon GHB for several years, and also abused amphetamines, cannabis and alcohol. She was referred to our hospital by her addiction specialist because of suicidal ideations. She had required a GHB detoxification in the ATC, but she was found to be 'too unstable' to continue detoxification. Her current use was reported as 10 ml (approx. 7 g) of 'home-cooked' GHB, 45 minutes apart and several nightly doses. She reported feeling 'haunted' by everybody, a feeling which made her exhausted and longing for rest. She had become too tired to maintain the tight dosing schedule and had deliberately overdosed the GHB combined with amphetamines during the days prior to admission. She reported feelings of agitation and inner tension, despite the fact that she took her last dose of GHB just before arrival to the hospital. Physical evaluation revealed a blood pressure (BP) of 150/104 mmHg, a tachycardia of 111 beats per minute (BPM), a body temperature of 37,9 degrees Celcius (°C), and profound sweating. Initial laboratory evaluation showed no abnormalities. Ethanol levels were <0.1 g/l and additional tox-screens had not been performed. Lorazepam 2 mg p.o. was administered twice in the first hour, followed by 1-2 mg lorazepam per hour. Despite the lorazepam, Ms. B quickly developed a severe GHB-withdrawal syndrome characterized by tremor, muscle rigidity, dysarthria, motor agitation and delirium with disorientation, visual hallucinations and disturbance of consciousness. The vital functions remained stable. Laboratory evaluation the following day showed a hypokalemia of 3.0 mEq/l and potassium chloride syrup was started. After treatment with 22 mg lorazepam in 12 hours without any effect on the delirium, we administered pharmaceutical GHB in order to stabilize the patient. Within 15 minutes after the first titration dose of 6 grams sodium oxybate, the motor agitation decreased. After the second dose, two hours later, the delirium started to resolve. The heart rate decreased to 84 bpm. We continued this pharmaceutical GHB dose every two hours, resulting in a quick remission of the delirium. The next day, Ms. B was referred to the regional ATC for a regular intramural detoxification with pharmaceutical GHB. She did not experience side effects from the pharmaceutical GHB.

2.2 Case #2

Mr. Z, a 33-year-old male with GHB-dependence, a prior ICU admission with a GHB intoxication, attention deficit hyperactivity disorder (ADHD), mood disorder, poly-substance abuse and mild cognitive impairment, presented to the ED of our hospital after a suicide attempt by cutting his wrists and throat with a bread-knife. According to his mother, he had developed auditory hallucinations, paranoid delusions, agitation and anxiety after abrupt cessation of intensive GHB abuse three days before admission. She was unable to provide information about his daily

GHB doses. In the ED, he was very anxious, agitated and psychotic. His vital functions were stable, with a BP of 135/77 mmHg, a pulse of 105 BPM, and a body temperature of 37.9 °C. Laboratory evaluation showed a hyperkalaemia of 7.7 mEq/l and a creatine phosphokinase (CPK) of 10.969 U/l. A urine tox-screen was negative for GHB, cocain, amphetamines, cannabis and benzodiazepines. Ethanol levels were <0.1 g/l. Under suspicion of the clinical diagnosis of GHB-withdrawal syndrome, an insulin/glucose intravenous drip was started, as well as lorazepam 2.5 mg after he refused to take pharmaceutical GHB. While the patient was still in the ED, the plastic surgeon was able to treat his injuries without additional sedation. The patient was admitted to the psychiatry ward where he quickly became more agitated despite three consecutive doses of 2.5 mg lorazepam. Because of uncontrollable aggression and psychosis progressing into a delirium with reduced ability to focus and sustain attention, and disorientation, he was transferred by an ambulance to an isolation room at the local mental health clinic. There, treatment with lorazepam was continued with assistance of a local police team, that was consulted because of extreme agitation. He was administered zuclopenthixol acetate 50 mg without any effect. In 24 hours, he had received a total of 38 mg lorazepam. Finally, he became sedated. In his agitation in the isolation room, unfortunately he had developed a head trauma. He was transferred back to the hospital and immediately admitted to the ICU. He had a EMV-score of 3-5-3, made murmuring sounds, and opened his eyes after a painful stimulus. His pupils were isocore and reactive to light. A brain CT-scan showed a small subdural haematoma, right parietotemporal. His vital functions were monitored and pharmaceutical GHB was started in order to prevent further escalation; 1.5 g sodium oxybate per two hours via nasogastric tube. This was continued for two days and nights. He slowly recovered from his delirium and the pharmaceutical GHB was tapered off. Three days later, the delirium was in complete remission. His vital functions were stable with a heart rate of 95 bpm and a BP of 129/76 mmHg. The neurologist concluded that there were no abnormalities in neurological examination and that second brain scan was not indicated. Blood potassium and CPK levels had normalized. He had an amnesia for the events during the past week. He was discharged and further treated by his addiction specialist and outpatient psychiatrist.

2.3 Case #3

Mr. B, a 42-year-old male with a history of GHB-dependence and several prior unsuccessful supervised GHB-detoxifications, presented to the ED of our hospital with symptoms of acute GHB-withdrawal upon abrupt unsupervised cessation of GHB after 5 years of abuse. He reported a current dose regimen of multiple doses of home-cooked GHB per day of unknown quantity, and no other drugs. In the ED, tremors, mild dysarthria and profound sweating were noted, with stable vital parameters: a BP of 126/88 mmHg, a heart rate of 90 BPM, and a body temperature of 36,8 °C. On psychiatric evaluation, Mr. B. had a clear consciousness, intact orientation and concentration. There were no psychotic features nor mood disturbances. Laboratory evaluation showed a hyperkalemia of 5.6 mEq/l. A tox-screen had not been performed. After admission to the psychiatry ward, diazepam 10 mg per hour p.o. was administered. Nevertheless, the

withdrawal symptoms quickly progressed into a full-blown GHB withdrawal syndrome, consisting of a delirium, with disorientation, incoherence, fluctuating consciousness, hallucinations, and agitation. After 3 doses of 10 mg diazepam without any clinical effect, we started with 1.5 g sodium oxybate .The agitation, tremor, and sweating diminished 15 minutes after administration. We continued 1.5 g sodium oxybate every 2.5 hours, after which the delirium and agitation quickly improved. One day after admission, the delirium was in remission and the potassium level had normalized. His pulse was 84 bpm and his BP 119/86 mmHg. He still experienced mild residual symptoms of withdrawal: tremors and sweating. The sodium oxybate was continued in dose schedule of 1.5 g per 2 hours without any side effects. After three days, Mr. B was referred to a regional ATC for detoxification by means of titration and relapse management.

3. DISCUSSION

Due to the increase in prevalence of GHB abuse, there is an increase in the number of patients presenting to EDs with severe GHB-withdrawal syndromes. These syndromes are medical emergencies that require aggressive multidisciplinary treatment. Treatment of the GHB-withdrawal syndrome has not been systematically investigated, and most authors of case-reports suggest high doses of benzodiazepines as drugs of first choice in the treatment of GHB-withdrawal.[1,5,8,11,13] Benzodiazepine resistance is common, especially when patients are used to high doses of GHB. This is probably due to the fact that benzodiazepines are $GABA_A$-agonists and GHB is a $GABA_B$-agonist.[14] Antipsychotic agents are also considered to be ineffective.[8,9] Sedation with other agents, such as barbiturates or baclofen are sporadically reported.[9] These case-series illustrate that when severe GHB-withdrawal syndromes are resistant to high doses of benzodiazepines, patients could be stabilized with pharmaceutical GHB. The detoxification by titration and tapering protocol was the first publication in which the use of pharmaceutical GHB for detoxification was described.[3] This procedure was developed by ATC Novadic-Kentron in the Netherlands, and proved to be effective and safe.[10]

Based on this experience with the detoxification protocol in elective detoxifications in ATCs, and our first experiences with successful administration of pharmaceutical GHB in patients with severe acute GHB-withdrawal syndromes, we developed practice-based recommendations for management of acute GHB-withdrawal syndromes in the hospital. These recommendations include the following steps:

1. Intoxication or withdrawal?

Symptoms of GHB intoxication tend to resolve in several hours, where withdrawal develops in a few hours after the last dose in dependent patients. This change in symptoms makes evaluation complex. Prominent symptoms of GHB intoxication are: amnesia, somnolence, dizziness, nausea, agitation, bradycardia, coma, hypoventilation.[1] Common symptoms of GHB withdrawal include:

fatigue, tremors, perspiration, mild anxiety, nausea, restlessness in mild cases. In more severe cases, agitation, confusion, hallucinations, severe anxiety, hypertension, tachycardia, seizures, rhabdomyolysis and delirium may be present, although no formal criteria have been established.[1,8] Withdrawal symptoms are likely to develop in patients that use more than three doses every day (i.e an interval of ≤ 8 hours between GHB doses), where most dependent patients use every 1-4 hours 'around the clock'.[1,8] Management of acute GHB intoxication consists of monitoring and supportive care.[1,8] Detailed review of the management of GHB intoxication is beyond the scope of this paper. See for example Mason and Kerns, 2002.[15] Management of GHB withdrawal depends on the pattern of GHB use (e.g. frequency, dose) and the need for hospital admission.[16]

2. Pattern of GHB-use

Obtaining information about the pattern of GHB use is of utmost importance, because it may predict the severity of withdrawal symptoms. This information should be obtained by medical history taking of the patient and close friends or relatives. Important questions are: what is the interval of use? How many milliliters per dose? Has the patient been previously admitted to the ED or ICU with intoxications or withdrawal? If possible, the concentration of the patient's GHB should be measured. In the Netherlands, common concentration of 'street-GHB' is about 650 mg/ml.

3. Need for admission?

The next step in the evaluation of a patient with symptoms of GHB withdrawal is to determine whether hospital admission is necessary for another somatic or psychiatric indication. In that case, clinicians should be aware of the possible development of a severe GHB withdrawal syndrome in patients with a history of intensive GHB-abuse or dependence. Since withdrawal symptoms usually emerge within one to two hours after the last dose,[8,9,13] immediate action should be taken to prevent escalation. Multidisciplinary collaboration is important and the patient should preferably be treated on the ICU, psych-med unit, or on the psychiatry ward with the possibility for ICU in case the patient cannot be stabilized.[8,11,12]

4. Indication for pharmaceutical GHB?

In treatment of a patient with symptoms of GHB withdrawal with a need for hospital admission, the daily GHB amount of the patient should be taken into account. Based on the literature, experience in Dutch ATCs and our experience in the general hospital, in low daily doses of GHB use, benzodiazepine treatment may be sufficient. In dependent patients who are used to taking extreme high doses, benzodiazepine treatment may not be sufficient. In patients who use more than 15 g or 20-25 ml GHB/day, and in patients who do not respond to high doses of benzodiazepines, we advise to consider the off-label use of pharmaceutical GHB. However, literature that supports these thresholds is not yet available.

5. GHB dose-titration and tapering

If there is an indication for treatment with pharmaceutical GHB, the patient should first be adequately stabilized by titration of pharmaceutical GHB. In most general hospitals, sodium oxybate is available for treatment of narcolepsy. The concentration of sodium oxybate is 500 mg/ml. A flowchart with suggestions for titration, based on the protocols used in several Dutch ATCs is presented in figure 1.[3,10] It is important to consider the fact that GHB-withdrawal in the general hospital, contrary to planned detoxification in ATCs, is most often acute and unplanned. Therefore, in a patient with acute GHB withdrawal on the ED the exact pattern of GHB-use is often unknown, complicating titration on pharmaceutical GHB and stabilization of the patient. In all circumstances adequate monitoring of the vital functions is necessary. If the patient is familiar with abuse of other substances, including GBL or 1,4-BD, a GHB expert should be consulted to adjust the schedule if necessary. The titration phase may take one or two days, and doses are provided every 2-3 hours. Doses may be increased or decreased according to evaluation of withdrawal symptoms by nurse, doctor and patient (See figure 1). If the patient has been adequately titrated on pharmaceutical GHB, it could be either gradually tapered off in 7-10 days, with a decrease in dose of 0.3-0.45 g sodium oxybate per day,[3] or kept stable until the patient is transferred to an ATC.

Growing experience in Dutch ATCs and preliminary experience in general hospitals suggests that titration and tapering with pharmaceutical GHB may be a safe and effective method.[3,10,17] However, it is important to stress that the proposed algorithm is preliminary and that more systematic research (for example, head to head comparison with benzodiazepine or baclofen treatment) should be performed to establish safety and efficacy. In the meantime, since no guidelines exist, practice-based experience could be used to treat patients presenting with acute GHB withdrawal syndromes in the hospital.[15]

Disclosures

The authors report no conflicts of interest.

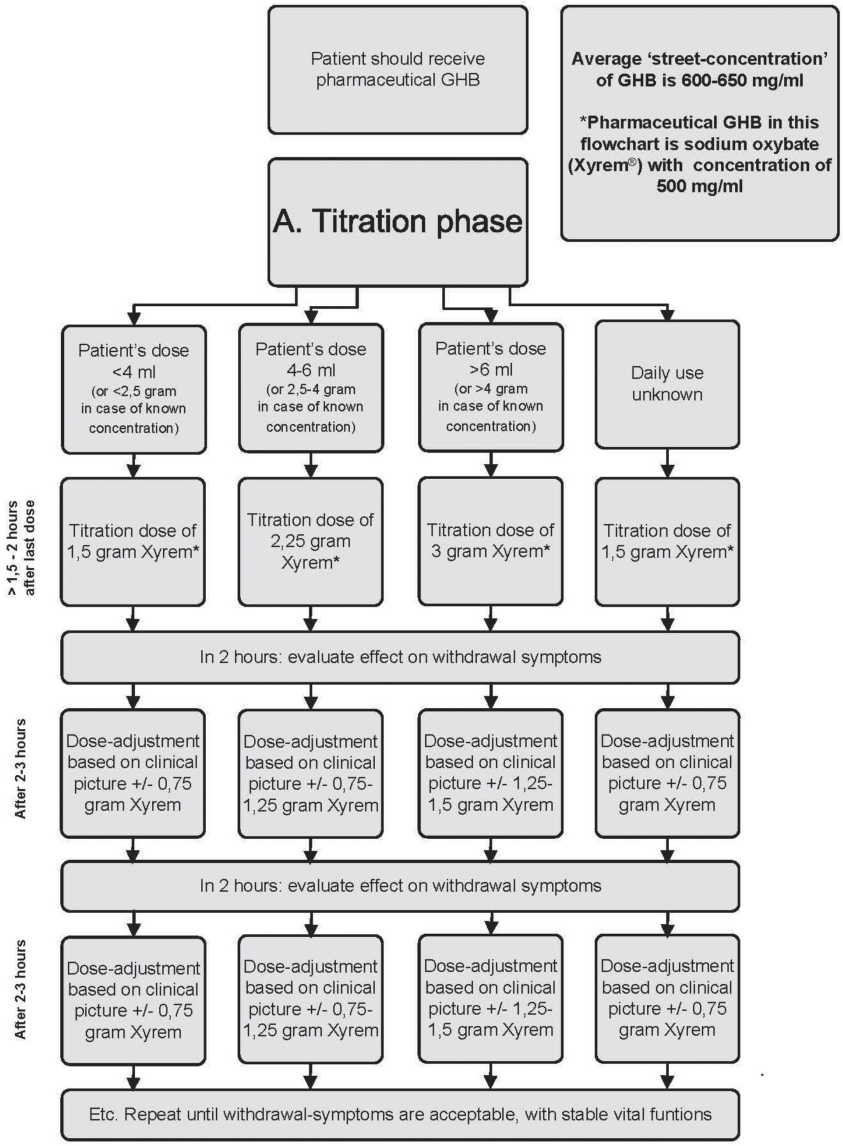

Figure 1: Suggested practice-base recommendation of titration with pharmaceutical GHB (Xyrem® 500 mg/ml) in patients with severe acute GHB-withdrawal syndrome in the general hospital. These recommendations are based on expanding experience in Dutch ATCs with patients admitted for elective GHB-detoxifications.

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Chapter 7

Decision Rules for Outpatient GHB (Gamma-hydroxybutyric acid) Detoxification

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ABSTRACT

Background: GHB dependent patients can suffer from a severe and sometimes life-threatening withdrawal syndrome. Therefore most of the patients are treated within inpatient settings. However, some prefers an outpatient approach to treatment. The aim of this study was to develop decision rules for addiction physicians to determine whether an outpatient or inpatient setting should be chosen for a safe GHB detoxification.

Methods: A prospective vignette study was performed. Forty addiction medicine specialists from various treatment settings and residents of the Addiction Medicine postgraduate Master training were asked to contribute vignettes of GHB dependent patients. A focus group of 15 psychiatrists and addiction medicine specialists was asked to recommend an outpatient or inpatient setting for GHB detoxification treatment, per vignette. Finally, five addiction medicine specialists, experts in GHB dependence treatment in the Netherlands, assessed the bio-psychosocial reasons for the choices of the focus group and formulated the recommended criteria.

Results: Based on the bio-psychosocial state of twenty vignette patients, addiction physicians and psychiatrists established the criteria and conditions recommended for the indication of an outpatient GHB detoxification. Intensity of addiction, [GHB dose ≤ 32 gram/d and frequency of abuse ≤ 2 hours], was stated as the primary criterion in determining the setting as well as the complexity of the psychiatric comorbid disorders. The importance of a stable support system was emphasised.

Conclusion: The vignette study resulted in a set of criteria with which addiction medicine specialists can make a weighted decision as to an outpatient or inpatient setting for GHB detoxification.

Keywords: Gamma-hydroxybutyric acid; GHB; Detoxification; Outpatient; Vignette Study

1. INTRODUCTION

GHB (Gamma-hydroxybutyric acid) use has increased in recent years in Europe and the Netherlands[1] due to its positive effect on libido and its euphoric and anxiolytic effect. Regular abuse of GHB can lead to dependence, and abrupt discontinuation can cause a severe and sometimes life-threatening withdrawal syndrome. Increased levels of dopamine after GHB cessation is probably the main cause of the complex GHB withdrawal symptoms which take the form of agitation, anxiety, psychotic symptoms and delirium[2, 3].These withdrawal symptoms occur within 1-6 hours, run their course over a week, after which they decrease in intensity[4, 5]. In the Netherlands, despite the fact that different methods have already been established for inpatient GHB detoxification[6-8], some patients prefer an outpatient approach to treatment. Nevertheless, outpatient GHB detoxification creates a dilemma because it is known that even at a low GHB dosage and frequency of abuse, withdrawal can be accompanied by complications[2]. .The course of GHB outpatient detoxification can be variable and difficult to predict in advance. In addition, patients cannot be observed medically and the risk of relapse is higher in their home setting. Although there is an increasing demand for outpatient treatment of GHB-withdrawal, there is also uncertainty as to which criteria are decisive in choosing between an inpatient or outpatient approach to treatment. In the Netherlands, existing directives were based on local clinical experience with inpatient GHB detoxification and repeatedly showed a lack of consensus and a high degree of variation in the identification and management of GHB abuse in outpatient practice. The Dutch guideline on detoxification in substance related disorders focused on bio-psychosocial criteria for making decisions as to an outpatient or inpatient setting for detoxification[9], but it did not include GHB.

Bell and Collins (2011) mentioned indication criteria for GBL withdrawal treatment for a case series within an outpatient clinic setting. The criteria mentioned were: no co-abuse of other drugs at the time of detoxification, having someone at home who is aware of the possible withdrawal symptoms, and the ability of the patient to come to the clinic in the first two days for medication dose adjustment and to undergo medical examination. There was no obvious method as to how these criteria were stated. The only management aim mentioned was the avoidance of withdrawal delirium[10]. Addolorato (1999) did not seem to consider alcohol dependence treatment simultaneous with GHB abuse treatment, as a contraindication for outpatient GHB detoxification. In that specific case, this opinion was based on the reported history of GHB discontinuation without withdrawal symptoms[11]. These criteria did not address the somatic and psychiatric condition of the patients treated, which can predispose to life-threatening withdrawal symptoms. We considered all the foregoing as a limited and non-decisive answer to the stated question.

Qualitative research provides in-depth analysis data from direct fieldwork observations, studying real-world settings to generate rich narrative descriptions which can yield unknown patterns[12] Vignettes are brief descriptions of hypothetical situations, designed and constructed in most

studies by researchers, to be evaluated by respondents and to elicit comment or opinion as to these typical scenarios[13, 14] and are used as an instrument in qualitative research. We decided to perform a vignette study because vignettes accurately capture actual practice, represent real-life responses, reflect clinical complexity[15] and research has documented that they can be a measure of knowledge [16]. Vignettes are a valid tool in situations where case-mix variation is a concern[17, 18], and should contain evidence-based scoring criteria to express improved health outcomes. Vignettes were used and found to be suitable for quality assessments of clinical practice e.g. in psychiatry[19] and treatment decisions by physicians e.g. diagnosis of foot problems [20] and chronic illness care[21].

These factors and the fact that information from literature was limited were valid arguments in favour of the utility of vignettes for our study. The aim of this study was to provide clinicians with practice-based recommended decision criteria to determine the setting, outpatient or inpatient, for effective, safe and comfortable GHB detoxification.

2. METHODS

2.1 Design

A prospective vignette study was conducted among experts on GHB detoxification in the Netherlands, as part of the Dutch National GHB Monitor project. In a clinical cohort study, the GHB monitor evaluated the titration and tapering method with pharmaceutical GHB in six Dutch addiction treatment facilities from 2010 to 2012.

2.2 Participants

Addiction medicine specialists, residents and psychiatrists, working in different addiction care and mental care facilities in the Netherlands, were approached in March 2012.

2.3 Procedure

2.3.1 Step1: Construction of vignettes

Forty addiction medicine specialists and residents of the Addiction Medicine Master training (MIAMs) of various treatment settings throughout the Netherlands, were asked by mail to contribute a vignette. Each vignette had to be of an anonymized real patient with a GHB abuse problem, in which they had to decide on a detoxification treatment setting: inpatient or outpatient. They were asked to state for each vignette the bio-psychosocial factors of interest, such as duration, dosage and frequency of GHB use, co-abuse of other psychoactive substances, medical history, psychiatric or somatic disorders, and the contributing social factors. They were also asked to report briefly on the treatment history, and the extent of previous withdrawal symptoms.

2.3.2 Step 2: Recommendation of detoxification setting

Fifteen other psychiatrists and addiction medicine specialists who were not involved in providing any of the previously mentioned vignettes were selected and asked to participate in a focus group. They were selected due to their participation in the Dutch National GHB Detoxification Monitor and the fact that they were frequently confronted with new patients in need of GHB detoxification. Both the psychiatrists and addiction medicine specialists were nominated by their institutes as being responsible for the treatment of GHB dependent inpatients. The vignettes were sent by mail to the focus group. The focus group members were asked to recommend a type of GHB abuse detoxification treatment for each vignette patient as done by Kunins and colleagues, where respondents recommended the type of substance abuse treatment for the opioid dependent vignette patient[22] . They rated their decision about the submitted vignettes by filling in a visual analogue scale (VAS) with a quantitative score from -5 to 5 (figure 1). A score of -5 meant that the addiction physician or psychiatrist was absolutely certain of an outpatient detoxification as indication, and +5 meant that an inpatient admission for GHB detoxification should definitely take place. A score of 0 meant that no choice could be made. The focus group members were also asked to indicate three main reasons for their choice for each vignette.

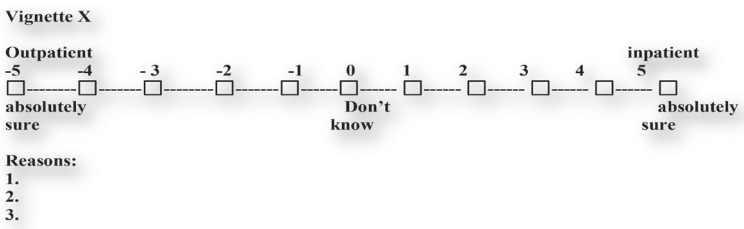

Figure 1: The VAS scale rating the choice of an in- or outpatient detoxification setting

2.3.3 Step 3: Determination of decision rules

Ten qualified addiction medicine specialists with more than six years' work experience, also within Dual Diagnosis departments, who were considered to be experts in GHB dependence treatment in the Netherlands, were invited to a meeting to discuss the response of the focus group. Their expert's status was estimated by: the number of GHB dependent patients they personally treated; their knowledge of the subject of GHB withdrawal, measured by the coaching they provided for other professionals working in the field (psychiatrist, addiction physicians, emergency doctors and nurses); their experience with scientific evidence- based medicine research. Over the course of their careers, they were collectively responsible for treating more than 500 GHB dependent patients. Four members of the considered and invited ten qualified addiction medicine specialists were asked earlier also to participate in the focus group. The expert group members were asked to assess the reasons stated by the focus group and to determine the decision criteria and rules for selecting the best option for a GHB detoxification treatment setting.

2.4 Data analysis

Data was processed and analysed using the Statistical Package for the Social Sciences (SPSS), version 18. A descriptive analysis of the focus group's VAS rating was carried out per vignette. A mean rating score greater than or equal to +3 (inpatient) or less than or equal to -3 (outpatient) was classified as an indication of an acceptable level of decision certainty. Secondly, the percentage (frequency) of the focus group members' scores within the average range ³ +3 to+5 or £ -3 to -5 was also calculated for each vignette. A score of 60% or higher per vignette was considered to indicate an adequate level of consensus between the focus group members over their choice of detoxification treatment setting. The decisive criteria were determined by means of interpretive recursive abstraction qualitative analysis of the previously mentioned bio-psychosocial factors of the vignettes.

3. RESULTS

3.1 Results step 1:

Twenty-one out of 40 participants responded. Seven of them stated that they had no patients in their caseload to enable them to provide a vignette. The rest of the 14 participants provided twenty vignettes; one to four patient vignettes per individual. All vignettes were included and were based on bio- psychosocial criteria of interest such as dosage and frequency of GHB use, medical history, psychiatric or somatic disorders, and social factors such as family support or employment. (In box 1,) Two vignettes are presented in box 1. All vignettes are available on the NISPA website[23]. http://www.nispa.nl/onderzoek/ghb/protocollen.

Box 1: Examples of vignette

Vignette 2

A 35-year old man has been suffering from GHB dependence for 10 years. For the last two months, he has been using 10 millilitres of illicit GHB every 1.5 hours, with a daily dose of 160 ml (104 g). There is no report of other psychoactive drugs abuse. In the past, the patient has repeatedly attempted to stop; twice through an inpatient treatment in an addiction care facility and several times at home with support of diazepam ordered over the internet. Patient is known to experience extreme withdrawal symptoms with history of repeated withdrawal delirium. He lives with his parents, has financial problems (5000 euro deb). Parents are supporting him in his treatment journey. There is no known other psychiatric or somatic comorbidity.

Vignette 7

A 26-year-old woman has been using for four years, 15 millilitres of GHB (9.75 gram) divided into 2 or 3 doses at night. She has no history of treatment from GHB dependence or abuse of other psychoactive substances. Patient suffered from anxiety symptoms which were related to her past as a prostitute, leading to sleep problems. She uses GHB as self-medication to avoid these symptoms. Patient is following a treatment for anorexia nervosa at a mental health institution. There is no somatic comorbidity. Patient lives with her mother and, except for a small student loan, she has no debts.

Table 1: Descriptive results per vignette scored by the focus group members (n=11).

Vignette* n=20		Min	Max	Mean	SD	≥+3%**	≤-3 %**
1	man 43 year old with no supporting network	-2	5	2.91	2.17	72.7	0
2	man 35 year old with history of withdrawal delirium	4	5	4.64	0.51	100	0
3	woman 34 year with BPD and recurrent inpatient admissions	-5	5	-1.00	3.13	18.2	45.5
4	man 33 year with low GHB dose and oxazepam misuse	-5	0	-3.27	1.79	0	63.6
5	woman 24 year with supporting network	-4	4	0.27	3.00	36.4	27.3
6	man 23 year had earlier successful inpatient detoxification attempts	-5	1	-2.82	2.09	0	63.6
7	woman 26 year with anorexia nervosa	-5	5	-2.73	3.29	9.1	72.7
8	man 24 year with BPD,ADHD and psychotic disorder	-5	3	-3.45	2.25	9.1	90.0
9	man 24 year with several intoxication incidents	-5	5	-0.82	3.71	27.3	45.5
10	woman 38 year with alcohol abuse living with her parents	-5	3	-1.64	2.80	9.1	45.5
11	man 24 year student with alcohol misuse at the weekend	-5	4	-0.82	2.79	9.1	27.3
12	man 40 year with depression	0	5	2.91	1.64	45.5	0
13	man 32 year no social support, irresponsible use of GHB	-3	5	1.36	2.66	36.4	18.2
14	woman 21 year with GHB dependence has a clothing store	-3	4	2.55	2.34	81.8	9.1
15	woman 28 year has relation problems and her own web shop	2	5	3.45	1.29	63.6	0
16	woman 26 year with hallucinations	2	5	4.00	1.18	81.8	0
17	man 28 year frequently sick	-5	-1	-3.00	1.18	0	63.6
18	woman 17year skipping school ,parents pushing treatment	-4	5	1.82	2.60	45.5	9.1
19	woman 43 year with a GHB dependent son	3	5	4.73	0.65	100	0
20	man 36 year with GHB dependence working as builder	-4	4	0.18	3.13	18.2	36.4

* The most prominent biological or psychosocial character per vignette is given.
** Frequency percentage score for the setting per vignette: outpatient (from ≤ -3 to -5) or inpatient (from ≥ +3 to +5). Numbers in Italic indicate that the percentage of scores ≥ +3 or ≤ -3 was ≥ 60% per vignette.

3.2 Results step 2:

Of the 15 addiction medicine specialists and psychiatrists invited to participate in the focus group, 11 of them responded. The mean rating scores, standard deviation (SD) and range of rating scores are shown for each vignette in table1. The focus group members rated most of the vignettes within a wide distribution. Some were convinced of completely opposite choices, represented in the rating score -5 (outpatient) and +5 (inpatient). The SD in most vignettes was high relative to the value of the mean score. The fit of the mean (X) was assessed, assuming that the actual rating score should be in the range of -5 to +5. The estimated rating score ($\hat{X}$) can be calculated (with 95% confidence interval) according to the following equation: $\hat{X} = X \pm (SDx2)$. It was found that most of the vignettes had estimated mean rating scores outside the range of the data, indicating that the mean and SD were only partly informative. Eleven of the 20 vignettes were rated by ³ 60 % of the focus group members at £ -3 or ³ +3 (table 1).

This frequency percentage represents the extent to which the focus group members were collectively convinced whether the detoxification should take place in an outpatient setting (score £ -3) or an inpatient setting (score ³ +3). In one vignette (vignette 12),10 of the 11 members of the focus group chose an inpatient detoxification setting and one member did not make a choice at all, with a mean score 2.91, SD 1.64 (table 1). In response to this vignette, the focus group members achieved consensus for (an) inpatient treatment (table 2) in spite of the fact that they scored a 45.5% frequency rate between ³ +3 to +5 (table 1). In the other eight vignettes, we could state that it was unclear for them whether an outpatient or inpatient detoxification should take place (table 3) [high SD and frequency rate below 60%](table 1). Members of the focus group stated three reasons for their choice of an outpatient or inpatient detoxification setting for each vignette. The criteria mentioned for the twelve vignettes which were considered relevant due to clarity of a treatment choice (table 2), were subjected to further analysis.

Table 2: Criteria given by the focus group members for each significant vignette (12 from the 20) to motivate their choice for an outpatient or inpatient detoxification setting.

Vignettes	Motivation for choice of a detoxification setting	Choice of setting
Man with no supporting network	High GHB dose, psychiatric comorbidity, ADHD, lack of support system.	Inpatient
Man with history of withdrawal delirium	High dose, long duration of addiction, history of withdrawal delirium, failed outpatient attempts.	Inpatient
Man with low GHB dose and oxazepam misuse	Low dose, presence of a support system, no relevant psychiatric comorbidity, low dose co-abuse.	Outpatient
Man had earlier sucessful inpatient detoxfication attempts	Low dose, no psychiatric or somatic comorbidity, family support.	Outpatient
Woman with anorexia nervosa	Low dose, extensive social network, due to the anorexia nervosa would not fit in group therapy.	Outpatient
Man with BPD, ADHD and psychotic disorder	Limited GHB use,supporting system, psychiatric comorbidity ;psychotic symptoms.	Outpatient
Woman with sleeping problems and job stress	High dose, unstable social network; friend is also a GHB abuser, simultaneous alcohol abuse.	Inpatient
Woman with alcohol abuse, anxiety and relation problems	High dose, failed previous outpatient attempt to stop with GHB , fors sleeping disorder.	Inpatient
Woman experinced withdrawal hallucinations	High dose, hallucinations during previous detoxfication attempt, anxiety symptoms.	Inpatient
Man with job problemes, supporting network	Low dose, no previous detoxification attempt, supporting system.	Outpatient
Woman with anxiety and a GHB dependent son	High dose, cardiac problems , son also GHB abuser.	Inpatient
Man with depression	Psychiatric comorbidity in the form of depression and suicidal risk, High dose, long history of GHB abuse.	Inpatient

Table 3: Non-consensus between the focus group members in eight vignettes.

Vignette no	decisive outcome	reasons outpatient *	reasons inpatient**
3	woman 34 year with BPD and recurrent inpatient admissions	No night dose. Borderline personality disorder. Social support. Repeated inpatient admissions.	High GHB dose. Borderline personality disorder. Unsucessful repeated inpatient admissions. Co-abuse of benzodiazepins.
5	woman 24 year with support netwerk	Presense of support system. No psychiatric comorbidity. Good Phsycial condition.Work and day activity.	High dose. Single living alone. Long history of GHB abuse. Working in a bar.
9	man 24 year with several intoxication incidents	Limited GHB use. In work. No complex withdrawal symptoms in the past.	External motivation. Multiple GHB intoxication incidents. Co-abuse of cannabis. Possible Social phobia.
10	woman 38 year with alcohol abuse living with her parents	Social support. Low dose. Sucessful outpatient detoxification. No psychiatric comorbidity.	Frequency of GHB use > 3 dd. Co-abuse of alcohol. Possible use of GHB against craving for alcohol.
11	man 24 year student with alcohol misuse at the weekend	Mild GHB abuse. Having work. High Intellegnce. No history of treatment.	Frequency GHB abuse of > 5 dd. Anxiety symptoms. Alcohol co-abuse.
12	man 40 year with depression	No reason was mentioned.	High GHB dose . Long duration GHB abuse. Depression.
13	man 32 year no social support, irresponsable use of GHB	Relativly low dose. No psychiatric or somatic comorbidity.	Social isolation. GHB abuse frequency > 3 dd.
18	woman 17year skipping school, extern motivation	Supportive Stable family. Young age.	High dose. Young age. History of depression. Anxiety symptoms.
20	man 36 year with GHB dependence working as builder	Social support. No psychiatrisc or somatisc comorbidity.	High dose.

** Stated criteria to choose for an outpatient setting
*** Stated criteria for the choice an inpatient setting

3.3 Results Step 3:

Of the ten experts approached, five were present during the consensus meeting. Four of the five were also members of the focus group. Recommended criteria for the indication of GHB detoxification in an outpatient setting were formulated. These were based on the reasons mentioned by the focus group members within the vignettes where ³ 60% consensus was achieved (table 2). The criteria were divided into 3 categories related to the bio-psychosocial model: biological, psychological and social criteria. Finally, the conditions for ensuring a safe detoxification were also suggested.

The biological criteria warranting outpatient detoxification are: a limited degree of GHB dependence as specified in table 4; patients who have no history of severe withdrawal symptoms e.g. delirium or physical aggression; limited co-abuse of other psychoactive substances and patients who are not suffering from severe somatic disorders. Pregnant women should be admitted for inpatient treatment.

The psychological criteria are: patients with mild to moderate intensity of personality disorders and/or symptoms of anxiety and mood disorders and patients with a stable severe psychiatric condition (table 4). These patients should be properly supervised during the detoxification. Serious psychiatric illnesses which are inadequately controlled are considered to be criteria for an inpatient treatment approach. For patients with Attention Deficit Hyperactivity Disorder (ADHD) receiving medication e.g. Ritalin, an inpatient detoxification would be safer, due to the add-on effect of the increase of dopamine during GHB withdrawal, which can predispose patients to psychoses or delirium.

The social criteria are: patients who are socially integrated (with a job, a social network, minimal financial problems etc.), who have a stable support system and a suitable residence during the outpatient detoxification (preferably with no children at the patient's residence) (table 4). The patient's preference for a detoxification setting should also be taken into consideration.

Several treatment preconditions are needed to perform safe outpatient GHB detoxification. There must be a coach in the home situation to guide and look after the patient and to accompany them to medical consultations during the detoxification process. This coach should not be an abuser of any psychoactive substances and should be in a position to provide that support full-time. It should be possible for the patient to be examined by the addiction physician or the family doctor at least three times a week. Furthermore, the physician should be able to use withdrawal and craving monitoring scales to follow the detoxification process. In case of complications, facilities for an inpatient admission should be available.

Table 4: Recommended Bio-Psycho-Social criteria for indication of an outpatient or inpatient detoxification setting.

Precondition for an outpatient approach	
Full time Coach.	
Physician contact three times a week	
Use withdrawal monitoring scales	
Available facilities for an inpatient admission	
Criteria for indication outpatient detoxification	**Criteria for inpatient treatment**
Biological criteria	**Biological criteria**
Somatic	*Somatic*
GHB abuse ≤ 32 g/d	Pregnancy
≥2 hours frequency .	Severe somatic disorder e.g.
Limited or no night GHB abuse	Hepatic impairment
Limited psychoactive substances co-abuse	Renal impairment
No history of severe withdrawal symptoms	Cardiovascular- and Pulmonary complications
No severe somatic disorders	Epilepsy
Psychiatric	*Psychiatric*
Psychiatric disorders ; stable or in a mild form e.g.	Psychiatric disorders as e.g.
*Personality disorders	*Depression
*Mild anxiety and mood disturbance symptoms	*Psychotic disorders
*Attention Deficit and Hyperactivity Disorder	*Bipolar disorder
*Anorexia and bulimia nervosa	*Severe anxiety disorder
*Insomnia	ADHD treated with medication
Psycho-Social criteria	**Psycho-Social criteria**
Socially integrated	Social dis-integration
Stable supporting system	Drugs abuse in the system
Residence	Rambling

4. DISCUSSION

This prospective vignette study was conducted in order to create practice- based decision rules to determine whether GHB dependent patients should follow detoxification in an outpatient or inpatient setting and to ensure an effective, safe and comfortable outpatient detoxification process.

We found that the participating physicians could reach consensus on a suitable detoxification setting in 60% of the twenty cases, with a percentage of agreement between 63 to 100% per

patient vignette. They selected an outpatient detoxification approach in five out of the twenty patient vignettes. This probably reflects the fact that it is still new for addiction physicians in the Netherlands to endorse GHB outpatient detoxification treatment, due to the lack of protocols and guidelines for this approach. Based on the analysis of the vignettes and their own clinical knowledge, the experts determined criteria which underlined the stability of the patient's biological, psychological, and social status. The intensity of addiction, reflected by the GHB dose and frequency of abuse, was stated as the most prominent reason in determining the detoxification setting. Thus, when the patient abuses GHB in a dose of less than 32 grams over long intervals during the day, with limited concomitant abuse of other psychoactive substances, detoxification in an outpatient setting can be considered. An outpatient detoxification indication would be eligible only when a medical history of no severe somatic disorders and/or a stable psychiatric condition such as controlled anxiety, mood disturbance and mild personality disorders has been diagnosed. There is also emphasis on the importance of social integration and a stable support system in the success of an outpatient approach. Pursuant to the literature[10], rapid access to an inpatient admission facility in case of complications should be provided.

Our qualitative research in this area is important due to the absence of other systematic procedures to aid physicians. One merit of the study is the vignettes method, as vignettes have been found to be more accurate than chart reviews in weighing physician choices[24, 25]. However, to avoid presenting a series of hypothetical scenarios constructed by researchers[26], we chose non-standardized patient vignettes, devised by physicians relating to actual clinical practice and the patients' personal background details. This approach offered insights into variation in complexity and characteristics, indicating a wide range of GHB abuse and psychiatric co-morbidity among these patients. Nevertheless, we acknowledge that the use of patient vignettes may not completely cover all actual clinical situations where decision making or treatment recommendations are needed. A limitation of the study is the intersection between members of the focus group and those of the expert group. This problem is related to the limited number of addiction physicians and psychiatrists who have relevant experience with GHB dependence treatment in the Netherlands, which made the overlap in participant groups unavoidable. This also accounted for the low participant rate for this study. Our results are generally applicable in the Netherlands but may not be in all international addiction management facilities.

5. CONCLUSION AND FUTURE RECOMMENDATIONS

This is one of the first studies to provide criteria to determine the GHB detoxification setting. Our results are not yet tested in daily clinical practice but an algorithm based on these recommended criteria can now be created. The next step is to test the predictive value of that algorithm on a new group of patients. The results of such a study can provide physicians and patients with an empirically-based guideline for the start of a safe and comfortable GHB detoxification.

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Chapter 8

RELAPSE PREVENTION

A - Baclofen as relapse prevention in the treatment of Gamma-Hydroxybutyrate (GHB) dependence: a case series

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ABSTRACT

In the last decade gamma-hydroxybutyrate (GHB) abuse and dependence have increased. It has been reported that GHB dependence has a high rate of relapse, serious complications of intoxication, and a potentially life-threatening withdrawal syndrome. Nevertheless, in clinical practice there is no known medical treatment to support GHB relapse prevention. We describe a case series of patients who were supported through an off-label treatment with baclofen to avoid a relapse into GHB abuse, for a period of 12 weeks. Nine out of eleven patients did not relapse while taking a dose ranging from 30 to 60 mg per day, one patient relapsed after 5 weeks, and one stopped after 7 weeks. Baclofen was well tolerated, patients reported mild side-effects such as fatigue, nausea, dry mouth, excessive sweating and depressive feelings. Although systematic evidence is still lacking, our practice-based experience suggests that treatment with baclofen to assist abstinence might be effective in patients with GHB dependence. Further systematic controlled studies are necessary to establish the exact efficacy and safety of baclofen as relapse prevention for GHB dependent patients.

Keywords: GHB dependence, baclofen, relapse prevention, relapse management, abstinence

1. INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that is an endogenous precursor and metabolite of gamma-aminobutyric acid (GABA) [1]. Systemically administered GHB can cross the blood–brain barrier, resulting in central nervous system mediated effects such as sedation, sleep, abnormal electroencephalogram, and anesthesia [2]. It is rapidly absorbed with a peak blood concentrations within 1 hour. GHB is metabolized primarily in the liver with a 20 – 60 minute half-life and complete elimination within 4 – 8 hours. GHB acts both directly as a partial GABA-B receptor (GABA-BR)[3] and α4-GABA-A receptor agonist[4] and indirectly through its metabolism to form GABA[3]. GHB is approved in Austria and Italy to treat alcohol dependence and withdrawal (Alcover®)[5]. However, GHB tolerance develops rapidly when patients use it on a daily basis, leading to physical dependence, which can produce severe withdrawal symptoms and may be life-threatening at higher doses [6]. It can result in tremors, nausea, vomiting, tachycardia, insomnia, anxiety, and delirium with auditory and visual hallucinations, hypertension, coma and even death. Seizures and massive diaphoresis have also been reported as part of the GHB withdrawal syndrome.[7,8] In the Netherlands, a sharp increase in the number of GHB dependent patients admitted to addiction treatment facilities was indicated.[8,9] Although many patients attempted to reduce GHB use or to abstain completely, they often remain vulnerable to reusing GHB and report craving[9]. Data in the Netherlands has shown that 45% of GHB dependent patients had previously been in treatment for the same addiction.[8,9] Furthermore, in our previous monitor study the relapse rate was as high as 64%, three months after detoxification (unpublished data). To date, management of GHB dependence consists of detoxification approaches such as replacement by benzodiazepines[10] or by GHB tapering[11] followed by cognitive behavioral therapy. To the best of our knowledge, systematic studies on GHB medical relapse prevention are still lacking.

Preclinical studies have revealed that acute administration of both direct and indirect GABA-BR agonists possesses anti-motivational effects and decreases the spontaneous self-administration of several drugs of abuse[12-16]. High affinity GABA-BR agonists such as baclofen decrease dopamine release in the mesolimbic reward circuitry[17,18]. These dopamine mediated anti-craving properties of baclofen could induce beneficial effects on relapse, as observed in studies with alcohol dependent patients[19-21]. Indeed, animal data has shown baclofen to effect GHB self-administration[22], which suggests that it might be particularly suitable for treating GHB dependence.

In this paper we present a case series of patients who were treated with baclofen as medication to prevent relapse into GHB use. The main objective of this case series was to examine the feasibility of a future randomized controlled trial (RCT) with baclofen treatment for GHB-dependence. To achieve this aim we tried firstly to assess whether baclofen would have an effect in supporting abstinence and on craving in GHB-dependent patients; secondly, to explore the margins of the safe and tolerable required dose of baclofen to achieve this goal; and finally, to determine the procedures for baclofen administration and frequency of the measurements required to monitor such a treatment.

2. METHODS

2.1 Patients

Patients were nominated by their regular clinician for GHB management treatment within Novadic-Kentron addiction care institute. Patients were asked to participate if they were ≥ 18 years, met the DSM-IV criteria for substance (GHB) dependence, abused GHB daily during a minimum period of 12 weeks prior to detoxification, expressed the wish and the motivation to stop this abuse, and were able to understand and sign written informed consent. All patients followed an inpatient GHB detoxification program by means of titration and tapering of pharmaceutical GHB[11,12], where diazepam was added (max 20 mg/d) only in case of associated benzodiazepines dependence or severe abuse of more than 2 g/d amphetamine or cocaine. Patients were abstinent from GHB before starting with baclofen. Diazepam was also tapered and stopped. Patients were excluded if a safety concern was present (e.g. cirrhosis, renal insufficiency, unstable hypertension, diabetes mellitus, seizure disorder), if they had a history of any clinically significant severe psychiatric illness, suicidal ideation, concurrent use of anticonvulsants/ insulin/oral anti-diabetic drugs, and in case of pregnancy. As we are reporting the results of ongoing treatment with an off-label regular patient care, submission to the institutional ethical review committee was not necessary. Nevertheless all patients gave written informed consent to participate in the procedures.

2.2 Procedure

During the inpatient GHB detoxification treatment phase, an information consultation was provided by the addiction physician in which patients were informed about the nature of the off-label treatment, the benefits, the possible outcome, and also the possible side effects and risks of baclofen. Patients were notified that they were free to discontinue their participation at any time. When the addiction physician was convinced that the patient understood the implications of this treatment, the patients were asked to give their written informed consent within one week before starting treatment. To assess baclofen safety and tolerability, patients were required to fill out a side-effect checklist 3 times a day during the first 2 weeks, then daily for 3 weeks, followed by a weekly list for the rest of the treatment. The treating addiction physicians were asked to score the observational part during consultation visits. To assess the effect on craving, patients were asked to fill out a VAS 2 times a day during the first week, then daily for 11 weeks and the OCDS list on a weekly basis during the entire study.

2.3 Baclofen treatment

This treatment was carried out by addiction physicians during structured counselling sessions. In the first week, patients had consultation 2-3 times, then weekly for 2 weeks and then on a 3-weeks basis for the remainder of the treatment period. Each consultation included an examination of

the general functioning, vital signs, and cardio-pulmonic functions. In week 6, blood tests were required to evaluate liver and renal functions.

Baclofen was started at 5 mg 3 times a day. Patients were instructed to take their medication with some liquid during their daily meals, preferably at 8:00, 13:00 and 18:00 hrs. Guided by the craving level reported by the patient baclofen was gradually built up with 15 mg daily every 3 days minimally to reach the required daily dose needed to support abstinence by the second week. This maintenance dosage was continued for a period of 12 weeks (3 months). In case of relapse, defined by GHB abuse at least 3 times on the same day or by taking single doses on more than 3 consecutive days, baclofen treatment was immediately tapered off. The baclofen dose was decreased to 0 mg per day in 2 weeks. Patients who wished to continue the baclofen treatment were offered outpatient counselling and medication by their physician.

2.4 Measurements

The Side effect check list (SEC) consisting of the most prevalent side effects of baclofen (supplementary figure 1), derived from the most prominent published side effects of baclofen. Side effects were partly self-monitored (21 items) and partly observed by the physician (8 items). Every item is scored on a five point scale: never (0), seldom (1), sometimes (2), frequently (3) or always (4).

Levels of craving for GHB were assessed by means of a visual analogue scale (VAS), patients were asked to rate their craving for GHB on a vertical line ranging from 0 to 100 (no craving at all = score 0 to extreme craving = score 100). the 14 questions Obsessive Compulsive Drinking Scale (OCDS) [23] filled out on a weekly basis. Several studies suggest that the OCDS is predictive of relapse during active treatment [24] and it has also been found to be sensitive to change during anti craving treatments [25]. This Dutch OCDS version is translated from the original OCDS [26] and has been adapted for GHB (OCDS-GHB). Questions are scored in a scale of intensity from 0 to 4. A total OCDS-GHB score is the sum of all items adjusting for combined items (maximum score 40).

Baclofen Side-effect list patient

Date:

Name:

Do you feel that this medicine helps you? Circle the answer which suits you the best.

No	I do not think so	I think so	Yes

Baclofen Side-effect list

Give a rating on how often you have experienced following complaints:

never (0) seldom (1) sometimes (2) frequently (3 always (4)

Drowsiness	0 1 2 3 4
Fatigue	0 1 2 3 4
Nausea	0 1 2 3 4
Vomiting	0 1 2 3 4
Light-headedness	0 1 2 3 4
Dizziness	0 1 2 3 4
Tremor	0 1 2 3 4
Headache	0 1 2 3 4
Vision dysfunction	0 1 2 3 4
Constipation	0 1 2 3 4
Diarrhoea	0 1 2 3 4
Dry mouth	0 1 2 3 4
Excessive sweating	0 1 2 3 4
Skin eruption	0 1 2 3 4
Urination problems	0 1 2 3 4
Muscle pain	0 1 2 3 4
Muscle weakness	0 1 2 3 4
Euphoric feelings	0 1 2 3 4
Depressive feelings	0 1 2 3 4
Hallucinations	0 1 2 3 4
Epileptic seizures/attacks	0 1 2 3 4

Others (report when did it start)

-	0 1 2 3 4
-	0 1 2 3 4
-	0 1 2 3 4

Figure 1: Example of baclofen side effects list

3. RESULTS

Fourteen patients were potentially eligible for the off-label treatment. Two were excluded due to their severely unstable psychiatric state. One dropped out at day one. Eleven patients received the baclofen treatment between January 2010 and October 2012, 6 men (54.5 %) and 5 women (45.5 %). Their ages varied from 20 to 33 years (mean age of 25.4 years, sd= 4.0). These patients suffered from chronic dependence on GHB, repeated ER /ICU admissions. Ten patients had been admitted several times for GHB detoxification treatment (mean 2.1 times, sd = 0.83), with sever withdrawal symptoms, and high relapse rate (see Supplement Table B). Self-reported use of liquid GHB before detoxification varied from 39 to 90 grams a day (street or home cooked GHB average concentration in Netherlands determined by regular GHB sample analysis, is 650mg/ml), with a mean of 58.5 g/d (sd = 16.2).

Supplement table A: Summary demographic characters of the eleven cases

	Gender/ age	Work/student	Somatic	System
1	m/24	Student	No known problems	supporting parents and partner
2	m/29	On benefits, due to somatic problems	Acquired brain injury (ABI)	No support system (avoiding) parents
3	w/25	student	No known problems	no support system
4	m/27	unemployed	No known problems	Supporting parents
5	w/33	work (own online shop)	Oedematous hands and feet	Supporting mother, abusive partner (domestic violence)
6	w/22	student	No relevant symptoms	Supporting mother
7	m/20	works as logistician	Urine infection, intensive unprotected sex	Supporting parents
8	w/23	student + work in retail store	Recurrent urine Sexual transmitted infections, increase weight almost 25 kl in 2 years	Supporting father, partner is GHB abuser
9	w/21	on benefits	No relevant symptoms	Supporting mother, all friends GHB abusers
10	m/27	No source of income	No relevant symptoms	Parents
11	m/30	work, own one man company	Constant headache, short memory problems	Partner and child

3.1 Clinical Cases

The following cases describe the type of patients included in the case series (see table 1 and Supplement Table A and B for characteristic details and demographic data of all patients).

3.1.1 Case #1

Mr. B is a 24 year old student using 59-60 grams of home-cooked GHB daily, a dose every 45 min, and several doses during the night, associated with oxazepam 50 mg/d. He had been admitted several times to the ICU due to GHB intoxications and withdrawal delirium, and twice for GHB detoxification where he relapsed within days of his discharge despite the start of the needed psychological therapy. Patient is co-diagnosed with generalized anxiety disorder and abuse of amphetamine and cannabis. On the third day after detoxification, he was started with baclofen 15 mg/d. Guided by his craving level reports during the outpatient consultations, the dose was increased to 30 mg within 4 days, and a week later to 45 mg. He reported tremors then diaphoresis and dry mouth as side-effects, which disappeared within 2 weeks. During the 3 months treatment period, abstinence from GHB was maintained, craving decreased, but the patient still had depressive and erratic feelings and used 0.5 g amphetamine twice and alcohol once (BAC 1.7). The patient chose to continue baclofen treatment for another 2 months. Compliance for adjuvant therapy was evident and patient was able to resume his education activities.

3.1.2 Case #4

A 27- year old man, using 12 ml of GHB every 2.5 hours with a total dose of 75 g/d. In 2 years GHB abuse he was admitted twice to the emergency room, had several unsuccessful self-attempts, and two admissions for detoxification with tremors, hypertension, anxiety and hallucinations as withdrawal symptoms. He was taking 50 mg Seroquel as treatment for insomnia when baclofen 15 mg/d was started, inpatient, three days after detoxification. He occasionally reported sedation, fatigue and a dry mouth. After discharge and within 7 days, baclofen was increased to 30 mg resulting in more frequent sedation and fatigue, less dry mouth intensity, and 3 days of intense diarrhoea. Due to the positive but not optimal impact on craving, dose was increased within another 10 days to 45 mg/d. However, the patient stated this dose resulted in euphoria which simulated the GHB effect and lead to his 5 ml (3.3g) GHB abuse once without repetition. Treatment was continued at 40 mg/d without relapse or side effects and he acknowledged decreased craving for GHB (Supplement Table C and Figure 2). Urine tests twice were negative for cocaine, amphetamine, cannabis, and GHB, but he reported use of diazepam 10mg in three different occasions. He was able to follow music, relation and cognitive therapy and also started voluntary work.

Supplement table B: Pattern of GHB abuse 11 patients

Case(m/w)	Years GHB abuse	Number Emergency admision last year(where)	Aided detoxifica-tions	Withdrawal symptoms	Abstinence after detox	Co- Therapy / change during treatment
Case 1(m)	4 y	several (ICU)	2	Delirium, agitation, insomnia and depressive feelings	several days	Relapse prevention, Lifestyle training/ resumed his study.
Case 2 (m)	6 y	3(ER), several (MHI)	3	Anxiety, muscle pain, diarrhoea and depressive feelings	2-3 weeks	Relapse prevention, cognitive therapy, and job coaching
Case 3 (w)	2	Non	2	Agitation, tremors and insomnia	1 week	Occupational therapy, cognitive therapy
Case 4 (m)	4.5 y	2 (ER)	2	Anxiety, visual hallucinations, hypertension and tremors	2 weeks	Drama therapy, cognitive therapy, relation therapy / started voluntary work
Case 5 (w)	3 y	2 (ER), 1(ICU)	4	Paranoid psychosis with visual hallucinations and convul-sion attacks	3 days -1 week	Started relapse pre-vention therapy group, assertiveness training, psychotherapy (EMDR)
Case 6 (w)	2 y	Non	2	Anxiety, tremors and diaphoresis	max 3 weeks	Occupational therapy, residence training, Family therapy and intense sport activities /start with Job coaching
Case 7 (m)	2 y	2 (ER)	2	Visual hallucinations, muscle pain and itching	several days	Prevention therapy, cognitive therapy sessions and family therapy / start reinte-gration, followed by 7 month abstinence and stop addiction treatment
Case 8 (w)	6 y	Non	2	Anxiety, tremors, agitation and visual and auditory hallucination	3 weeks	Social capacity training, occupational therapy, Psychological diagnose and money budgeting
Case 9 (w)	5y	1 (ER)	4	Agitation, panic and insomnia	4 weeks	Psychotherapy
Case 10 (m)	4 y	1 (ER)	4	Tremors and diaphoresis	1-2 weeks	Started counselling appointments
Case 11 (m)	3y	2 (ER)	3	Anxiety, depressive feelingssweat, insomnia, paranoid	2 weeks	Psychotherapy

3.2 Relapse rate

Nine patients (81%) did not report relapse into GHB use during the 12 weeks of treatment. Five were completely abstinent in this period, ingesting baclofen in doses between 30 and 60 mg per day. The other four patients used GHB on several occasions as illustrated in table 1, but they did not reach the predefined relapse criteria. Average baclofen dose used by these 9 patients was 42.2 mg (sd= 10.3). One patient relapsed into GHB abuse. One stopped the treatment for no apparent reasons, but did not report relapse into GHB use during the 7 weeks of treatment.

3.3 Frequency measurements needed for monitoring

The patients experienced the required frequency of measurements as intensive and unnecessary, especially in the last 4 weeks. Five patients filled out the VAS at least once per week, the OCDS-GHB list almost weekly during their treatment period and the SEC list was minimally once per week in the first 5 weeks, in the case of dose adjustment or before the doctors consultation visit from week six. The other 6 patients were not consistent in filling out the lists except for the SEC list during titration of baclofen, Their available data was documented with or without filling out a list in the treating addiction physician consultation subsequent reports in the electronic patient's dossier (EPD) during the 12 weeks treatment period. For these patients, we are able to report the highest baclofen dose used, the side effects and the relapse rate (see table 1), but no exact craving rates.

3.4 Effect on craving

We were only able to report the exact impact of baclofen on craving by the 5 patients who filled in the VAS and OCDS-GHB lists and stated a decrease in craving scores (see supplement table C and figure 2). Five of the other 6 patients reported a decrease in craving documented in the EPD by the addiction physician. One patient stated experiencing no change in craving for GHB.

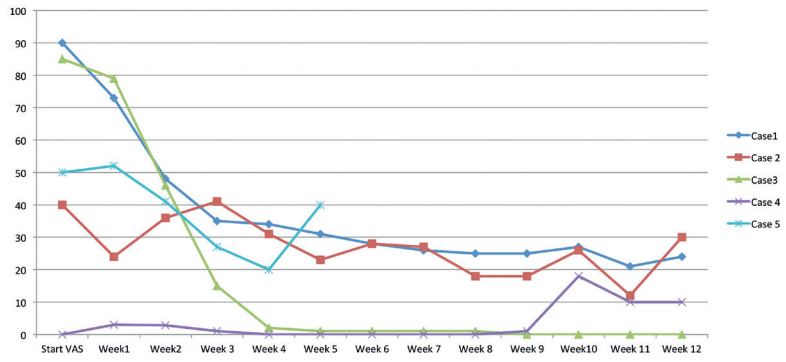

Figure 2: Average craving level represented by the VAS score per week reported by the five cases (filled out list plus report by the doctor)

Table 1: Description of the baclofen treatment by the eleven patients

case	Psychiatric diagnose	GHB dose g/day	Co-abuse	Baclofen dose mg / day (period upload)	Setting	Relapse into GHB	Side-effects (scale)	Abuse other drugs in 12 w	Other medication in 12 w
1	generalized anxiety disorder, (ADHD ?)	59-60	Amphetamine, irregular Cocaine and cannabis	45 (10 days)	outpatient	Abstinence for 12 w	Dry mouth, tremors, diaphoresis (all 1)	Amphetamine (0.5 g twice), alcohol once (BAC 1.7)	Melatonin 5 mg/d, Mirtazapine 15 mg/d
2	suicidal thoughts, anxiety	59	Cocaine, amphetamine, alcohol max IL beer/d	55 (8 w)	1 w inpatient, 11 w outpatient	Used 6 g divided in two doses in the same day	Fatigue, diaphoresis, headaches (all 2), euphoria (1)	cocaine on 3 occasions	Paroxetine 20 mg/d
3	social anxiety, borderline PD	39-40	Cocaine, cannabis, ketamine, alcohol	60 (18 days)	2 w inpatient, 10 w outpatient	Abstinence for 12 w	Dizziness, fatigue, drowsiness, diaphoresis (all 2),dry mouth (3)	XTC(2 tab), cocaine (1 g once) Alcohol 3-4 times	Promethazine 25 mg/d
4	Not yet diagnosed (PTSD?)	75	Cocaine	40(21 days)	1 w inpatient, 11 outpatient	Used 3.3 g once in one dose	Fatigue, dry mouth, diaphoresis(all 2), euphoria (3 by 45mg)	Diazepam 10 three times	Seroquel 50 mg/d
5	ADHD and Dependant PD	63	Diazepam, Sporadic alcohol and cocaine	30 (7days)	outpatient	Relapsed after 5 w into daily abuse, a dose every 2 hours	No side-effects	After week 7, irregularly cocaine	Ritalin 45 mg/d, Mirtazapine 30 mg/d, diazepam 10mg/d
6	ADD	39	Cannabis , weekly Amphetamine, irregular cocaine	45 (23 days)	4 w inpatient, 8 w outpatient	Abstinence for 12 w	Drowsiness, dry mouth (both 3), fatigue, muscle pain, diaphoresis, depressive feeling(all 2)	No co-abuse	Diazepam 5 mg /d sporadically when needed
7	Pathological gambling	90	Alcohol, irregular cocaine	30(3 days)	5 w inpatient, 7w outpatient	Abstinence for 12 w	Fatigue, muscle pain, depressive feeling(all 2)	Diazepam 5 mg irregular not daily	None
8	Not yet diagnosed	47	Non	40 (53 days)	inpatient, with standard rehabilitation days at home	Abstinence for 12 w	Dry mouth, diaphoresis(all 3), depressive feeling (2)	No Co-abuse	None
9	Mentally challenged (IQ = 84)	80	Amphetamine	30 (7 days)	inpatient	Used GHB once dose unknown	Dry mouth (3)	No Co-abuse	None
10	Pervasive Developmental Disorders not otherwise specified, ADHD	42	Cannabis and cocaine	45 (20 days)	outpatient	Stopped with baclofen after 7weeks	No side-effects	Once cocaine 1 g	Seroquel 50 mg/d, Melatonin 5 mg/d
11	Depression with paranoid symptoms Borderline PD	85	Cannabis and benzodiazepines	35(28 days)	1 w inpatient, 11 outpatient	Used GHB 3 times a +/- 3g dose within 2 days	No side-effects	No Co-abuse	Levomepromazine 12.5-25 mg/d, diazepam 10-20 mg/d, Mirtazapine 40 mg/d

3.5 Side effects

None of the patients reported side effects at severity 4 (always during the day). The most prominent side effect was dry mouth, reported frequently (severity 3), by 7 patients. Five patients reported diaphoresis, tremors and fatigue, both in severity 2. Four patients reported sometimes feeling drowsiness and sedation (severity 2), as illustrated in table 1. Three patients did not report any side effects. There was no relation between the occurrence of the side effects and the baclofen dose provided.

4. DISCUSSION

This naturalistic case series aimed to assess whether off-label baclofen could be a feasible treatment for GHB dependence, and eligible to be explored throughout a randomised controlled trial (RCT). Our results illustrated that administration of baclofen was associated with low relapse rates. Out of the eleven patients included within a period of 12 weeks, one had relapsed into GHB abuse and another stopped at 7 weeks. A dose ranging from 30 to 60 mg baclofen per day was enough for nine patients to avoid relapse into GHB use. It is unknown whether the other two patients were in need of a daily dose higher than 30 and 45 mg respectively to achieve their goal. Based on the side effects experienced by the patients and the physicians' clinical observation, baclofen (30-60 mg/d) can be considered safe and suitable as relapse prevention aid. Baclofen was well tolerated by our patients, in line with statements in earlier alcohol studies [27]. The patients reported relatively mild side-effects such as fatigue, nausea, dry mouth, excessive sweating and depressive feelings. A higher dose of baclofen did not lead to a structural rise in the reported side-effects. However, it is impossible to conclude that the 'side effects' reported were caused only by the use of baclofen. The treatment with baclofen was started immediately after the GHB detoxification. It is possible that these 'side effects' were actually residual complaints from the withdrawal phase or due to other physical complaints which existed before and were masked by GHB abuse. To avoid this uncertainty about the physical complaints reported, it is advisable in a future trial to require a baseline measurement of the side effect checklist before starting the baclofen treatment and to consider an add-on effect of baclofen. Thus, baclofen was well tolerated by our patient group and higher doses were not needed to support abstinence for a period of 12 weeks. The pharmacological overlap between baclofen and GHB as GABA-BR agonists, advocates suggesting that the relatively long acting baclofen (half-life up to 4 hours) may act as a substitute for the short acting GHB (half-life 30-60 minutes). Despite the fact that the exact data for craving was limited to only five cases, the overall reported decrease in craving for GHB in time with this low dose of 30-60 mg is interesting. The intensive measurement requirement was not practical and formed a burden for the patients. Our patients seemed to prefer reporting directly to their addiction physician. This could be minimized by decreasing the frequency of measurement and relating it to the addiction physician consultations to ensure

accuracy and relevance for the medical treatment monitoring and to avoid a great amount of missing data. This case series had several limitations. Abstinence from GHB was not confirmed with consistent or systematic urine or blood tests. This was related to the narrow time frame of 6-8 hours in which GHB can be detected [3], as a result of the short half-life of GHB, this besides the lack of financial support to repeatedly perform these tests. This was difficult to establish, especially in an outpatient setting. It is not possible to conclude exclusively that the decreased scores on the VAS and OCDS-GHB were only due to the treatment with baclofen, because the patients were attending adjuvant psychological treatment. Considering all of the above and despite the limitations, we can suggest that the GHB dependent patients could benefit from treatment with baclofen to maintain abstinence. A low daily dose between 30-60 mg would be required. Baclofen in this dose range is tolerated by the patients as no serious neuropsychiatric adverse events where reported and safe as it would not be expected to cause co-intoxication in combination with GHB.. It also seems to decrease craving for GHB. Nevertheless, providing the treatment with baclofen should be managed by specialized medical teams and should be monitored carefully taking in consideration the possible health risks of high dose baclofen such as for example lowering the threshold for seizures[28], experiencing withdrawal symptoms by abrupt discontinuation of baclofen[29], when used for several months or even intoxication[30]. It would be relevant to start a controlled study on the efficacy of baclofen in GHB dependence treatment. The use of technological tricks to make filling in short questionnaires easier is to be recommended. The proposed RCT should be able to answer with certainty the question whether baclofen can be helpful in bringing about a decline in the high relapse rate encountered in GHB addiction.

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Chapter 8

RELAPSE PREVENTION

B - Baclofen as relapse prevention in the treatment of Gamma- Hydroxybutyrate (GHB) dependence: an open label study

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ABSTRACT

Background: GHB dependence is a growing health problem in several western countries, especially the Netherlands. Attempts to stop using GHB are often followed by relapse shortly after successful detoxification. Craving for GHB use and co-morbid psychiatric symptom levels are thought to be the major factors contributing to the high relapse rates. Given its pharmacological profile, baclofen might prove an effective anti-craving agent for patients with GHB dependence. The aim of the current study is to assess the potential of baclofen as an anti-craving agent relapse prevention intervention in GHB dependent patients.

Methods/Design: In an open label non-randomized trial treatment with baclofen to a maximum of 60 mg/day will be compared with treatment as usual (TAU) in recently detoxified GHB dependent patients (n=80). The primary outcome measure will be the level of GHB use. Secondary outcome measures are craving levels, psychiatric symptom levels and quality of life. Questionnaires will be administered during 12 weeks of baclofen treatment and at follow-up (six months after the start of treatment).

Discussion: It is hypothesized that baclofen treatment compared to TAU will be associated with significantly reduced GHB use. In addition, we hypothesize that baclofen treatment will be associated with decreased craving and anxiety levels, and higher quality of life. If results are in line with our hypotheses, further studies on the efficacy of baclofen using placebo controlled designs and long term follow-up are warranted.

Trial registration: The Netherlands Trial Register with number NTR4528. Registered 19 April 2014.

Keywords: Baclofen, Gamma- Hydroxybutyrate, GHB dependence, relapse, craving

1. INTRODUCTION

GHB use is a growing public health issue in several Western countries, including the Netherlands[1]. Recreational use of GHB has gained popularity over the past decades[2]. As a result, it's addictive potential has become more apparent[3]. Little is known about the exact prevalence of chronic GHB dependence in the USA and Europe due to the absence of surveillance and systematic reporting mechanisms[4]. Nevertheless the number of GHB users seeking help increased over the past years[5]. For example, the number of GHB dependent patients admitted in addiction treatment facilities sharply increased in the Netherlands, over the last five years from 60 in 2008 to almost 800 patients in 2013[6].

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that is an endogenous precursor and metabolite of gamma-aminobutyric acid (GABA). GHB administered systemically can cross the blood–brain barrier where it acts both as neurotransmitter and a neuromodulator[7]. It has a plasma half-life of approximately 30-60 minutes[8]. GHB has high affinity for the GABA-B receptor and to a lesser extent for subtypes of the GABA-A receptor[9]. GHB has impact as neuromodulator via both GABA-ergic effects and direct effects on a wide variety of other neurotransmitters, including glutamate, dopamine, serotonin, noradrenaline, acetylcholine, opioids, and GABA[10-12]. GHB has various therapeutic applications, like general anesthesia[13], treatment of sleep disorders as narcolepsy[14], and the treatment of alcohol[15] and opioid withdrawal[16].

GHB tolerance occurs rapidly when used daily, inducing physical dependence at higher doses. Discontinuation of GHB can produce severe withdrawal symptoms as anxiety, delirium with auditory and visual hallucinations, seizers, and coma, which may be life threatening[17,18]. Recent studies have shown safety of strategies for the detoxification in GHB dependence, using tapering with pharmaceutical GHB or benzodiazepines[19]. Nevertheless, high relapse rates hamper long-term recovery, despite psychological treatment and counseling. Forty-five percent of the cases reporting to addiction care facilities had previously been in treatment for GHB dependence[19]. Indeed, short-term relapse rates up to 64% have been reported[20]. Self-reported reasons for relapse include social pressure, craving for and loss of control over GHB use and increased anxiety and depression after stopping GHB use[21].

Here we present a study protocol investigating the potential of baclofen in relapse prevention and its anti-craving properties in recently detoxified GHB dependent patients. Baclofen is a high affinity GABA-B receptor agonist with a half-life ranging from 2 to 6 hours[22]. The pharmacological overlap between baclofen and GHB suggests that the relatively long-acting baclofen may serve as a substitute for the short acting GHB. Moreover, baclofen is thought to modify brain reward function, through its indirect effects on dopamine, which has been suggested to be a key neurotransmitter for craving[23-25]. Finally, baclofen is thought to have anxiolytic effects through its agonist effects on the GABA-B receptor[26]. Overall, it could be speculated that baclofen may be effective in relapse prevention in GHB dependent patients. Indeed, animal data have shown beneficial effects of baclofen on GHB self-administration in mice[27].

1.1 Aims and hypotheses

The primary aim of the current study is to assess the potential of baclofen to prevent relapse in recently detoxified GHB-dependent patients. We hypothesize that administration of baclofen to GHB-dependent patients after detoxification is associated with decreased relapse rates as compared to treatment as usual (without baclofen). We also hypothesize that treatment with baclofen is associated with reduced levels of craving for GHB and reduced psychiatric symptoms levels, including anxiety, and increased quality of life. We expect baclofen treatment to cause minimal side effects in these patients. Finally, we expect a lower drop-out rate from adjuvant therapy (TAU) in the intervention group.

2. METHODS AND DESIGN

2.1 Study design

The design is of an open label non-randomized controlled clinical study in six addiction care facilities in the Netherlands. The study is part of the Dutch national GHB Monitor 2.0 and data collection will take place between May 2014 and December 2015. After successful detoxification of GHB, patients will receive either baclofen on top of treatment as usual (TAU + baclofen) or treatment as usual (TAU) only. Assignment is based on in- and exclusion criteria and on patient preference (informed consent).

2.2 Ethical considerations

The study was approved by the Medical Ethics Committee, Twente Medical School, Institute for Applied Scientific Research (METC/14015.kam) study number NL40321.044.13. Participants are informed about the trial and about the voluntary nature of their participation with both written and verbal communications. Participants are only included following the provision of informed consent.

2.3 Participants

2.3.1 Recruitment

Participants are GHB dependent patients in treatment for detoxification at six participating addiction care facilities. These GHB dependent patients will be informed by their physician about the possibility to participate in the current study before GHB detoxification. The physician will inform the research nurse per centre on potential participants for the study, who will provide further study information to the patients after the detoxification. After informed consent, a research physician will perform the medical screening. The intervention group will be compared with two control groups: recently detoxified GHB dependent patients included in the Dutch national GHB Monitor 2.0, but that do not want to use baclofen (TAU only); and a matched

historical control group from our previous work on GHB dependence (n=274) of whom follow-up data are available[20]. The historical control group will be matched on age, gender, GHB use (dose and years), and number of detoxification attempts.

2.3.2 In- and exclusion criteria

Patients are eligible to participate if GHB dependence (according to the DSM-IV general criteria of dependence) is their primary diagnosis[28] and their age is at least 18 years. All participants should be able to read and speak the Dutch language. Patients with any current somatic or psychiatric safety concerns are excluded. Exclusion criteria are liver cirrhosis and impaired renal function (as indicated by aspartate aminotransferase (AST)), alanine transaminase (ALT), or gamma-glutamyl transferase ((GGT) level >3 times the upper limit of normal (ULN); bilirubin > ULN; serum creatinine > ULN), unstable hypertension, unstable diabetes mellitus, seizure disorder including patients currently taking anticonvulsants, and pregnancy. Patients experiencing current severe mood disorder (bipolar disorder or major depressive disorder), current psychotic disorder (including schizophrenia), and/or suicidal ideations and patients suffering Parkinson's disease will be excluded too. Co-current use of anxiolytics, stimulants or hypnotics will not be permitted.

2.3.3 Sample size calculation

To date, there are no published studies on the effect of baclofen on relapse in GHB dependent patients. Therefore, we used the results of previous studies on the effect of baclofen in alcohol dependent patients and our previous work on GHB dependence, in order to estimate the required sample size. Two RCTs showed that baclofen was superior to placebo in increasing abstinence rates in alcohol dependent patients: 70% (14 out of 20) versus 21% (4 out of 19) within a period of 30 days [29] and 71% (30 out of 42 p) versus 29% (14 out of 42) within a period of 12 weeks[30]. These results indicate a potential increase in abstinence of 42-49% with baclofen treatment for alcohol dependence. Results of the previous national GHB project stated that 36% of the patients succeeded to avoid relapse in GHB within a period of 3 months after detoxification without any medical interventions[20]. Therefore, we will consider a percentage of importance difference in baclofen effect in the GHB dependent participants of 34% between the Baclofen + TAU group and the TAU only or the matched control group with an expected abstinence rate with baclofen of 70% as in the alcohol studies and of 36% without baclofen.

We used the following formula comparing two proportions to calculate the sample size, $n= [(Z\alpha/2 + Z\beta)^2 \times \{(p1 (1-p1) + (p2 (1-p2))\}] / (p1 - p2)^2$, $n= [(1.96+ 0.84)^2 \times \{(0.7(1-0.7) + (0.36 (1-0.36))\}] / (0.34)^2$, according to Dr. Steve Brooks sample size calculator, Exeter Initiative for Statistics. The calculation estimates that the minimal total samples size of 30 patients per group would be sufficient to detect a clinical difference of 34% in two-tailed z-test of proportions ($\alpha= 0.05$, $\beta =0.80$). In the alcohol studies and our previous work with GHB inpatients an attrition rate of 13-15 % was reported. We anticipate a slightly higher drop-out rate of 25%, due to the outpatient component of the baclofen treatment. Therefore we will include 40 participants in the baclofen treatment group.

2.4 Study intervention

2.4.1 Baclofen intervention

Clinical trials on baclofen for alcohol dependence treatment have used baclofen at a dose of 30 mg /d [29-31] over 30 to 120 days. This is within the low therapeutic range for muscle spasms. However, Garbutt and colleague's[32] suggested that 30 mg of baclofen per day may be an insufficient dose for some patients to achieve abstinence. Additionally, baclofen effectiveness for GHB dependence could be smaller, since tolerance may occur due to recent abuse of GHB and a possible substitution function (as treatment will be started immediately after detoxification).

Based on these results and the unpublished results of a small dose finding experimental treatment study in our treatment centre, where patients reported limited effect of baclofen 30mg per day, we decided to administrate a dose of 45 mg to a maximal dose of 60 mg per day orally to avoid the risk of (co) intoxication. In this study baclofen will be administrated orally three times daily as usually recommended[22] and started with a total dose of 15 mg per day. During the first 10 days baclofen will be gradually increased with 15 mg per day every 3 days up to the chosen minimum dose of 45 mg, or a maximum dose of 60 mg in case no effect is reported at 45 mg after 2 weeks. This dose will subsequently be maintained for a period of 10 weeks. Successively, baclofen will be tapered off to 0 mg in 2 weeks (see table 1). Patients will be asked to avoid abrupt termination of baclofen and will be guided by their physician to avoid complications of baclofen withdrawal. Patients who wished to continue the baclofen treatment will be offered an outpatient counselling and medication by their physician for another 3 months.

Compliance will be assessed based on self-report, urine test for GHB, and empty pill counts. The physician will make use of the BRENDA method, a psychosocial program designed to enhance medication and treatment compliance [33, 34] . In case of GHB use during baclofen treatment, participants are expected to contact the research physician. In case of relapse, immediate cessation of treatment will be considered to avoid intoxication hazards.

Table 1: Baclofen dose in mg/week

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Doses a day	15-30	45-60	45/60	45/60	45/60	45/60	45/60	45/60	45/60	45/60	45/60	45/60	30-45	15-30	15-0

2.4.2 Treatment as usual (TAU)

Patients included in the current study will undergo the usual treatment provided by their addiction treatment center (TAU). These can vary from short individual behavioral treatment intervention, inpatient treatment, Community reinforcement therapy, or extensive multidimensional therapy (like MDFT) with attention to psychological, social, relation, financial, and medical problems. During the study the psychological interventions applied will be monitored. For the historical

control group, reports on the adjunct psychological treatment interventions applied are unavailable.

2.5 Outcome and Instruments

2.5.1 Primary outcome measures

The primary study outcome is the relapse rate, in other words the level of GHB use as indexed by the total number of abstinent days, the duration of continued abstinence after detoxification (CAD), time before relapse, and intensity of substance use over a period of 3 and 6 months (Timeline Follow-back Method).

2.5.2 Secondary outcome measures

The secondary outcomes as listed below are;

1. The craving level, as indexed by self-report using the Desire for Drugs Questionnaire (DDQ) and a visual analogue scale (VAS). The DDQ is validated instrument[35] which measures an instant desire, triggered by internal or external cures (instant craving). Franken and colleagues (2002) identified three factors as underlying dimensions, namely 'desire and intention' (seven items), 'negative reinforcement' (four items), and 'control' (two items) with a scale from 1 (totally disagree) to 7 (totally agree). The total score exists of 14 items with a sum score between 14 and 98[36] . In addition to that patients were asked to rate craving for GHB by means of a visual analogue scale (VAS) on a Vertical line from no craving at all (at the bottom) with a score of 0, to extremely strong craving (at the Top) with a score of 100. The result is a score on a continuous scale ranging from 0 to 100.
2. A change in psychiatric symptoms will be measured by means of the Mini International Neuropsychiatric Interview-plus (MINI-plus) and Depression Anxiety Stress scale (DASS). A trained therapist or physician will apply the MINI-plus. It is a structured interview to assess the main Axis I psychiatric disorders based upon the DSM–IV and ICD-10 criteria. It is used to determine current and lifetime psychiatric disorders[37]. The MINI is shown to have good psychometric properties and is reliable for the detection and classification of psychiatric comorbidity[38]. The DASS self-report will be used to measure psychiatric symptom levels and the related negative emotional states along the 3 axes of depression, anxiety and stress. It is a 21-item self-report instrument. Participants are asked to use a 4-point severity scales to rate the extent to which they have experienced each state over the past week. Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. For each scale threshold values are proposed and are interpreted in 5 severity intensities: normal, mild, moderate, severe and extremely severe. Thresholds as (for Depression ≥ 21; for Anxiety ≥15; for Stress ≥ 26) indicate a severe or extremely severe distress state [39, 40].

3. The EuroQol-5D (EQ-5D) will be used to measure changes in patients health-related quality of life. For the overall quantification of health status as a single index we will use the standard EQ-5D classification system developed by the EuroQol Group[41]. The EQ-5D is a widely used multi-attribute system available to determine health state preferences (utilities). It is a simple self-report instrument which assesses 5 domains of general health and functioning: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This is along a 3-point scale (1= no problems, 2=some problems and 3= extreme problems). Based on the descriptive classification of the EQ-5D system a preference index (utility) can be estimated that expresses the overall preference of the classified health status[42] [the Netherlands algorithm will be used to calculate the index]. This EQ-5D index measures objective quality of life and is a societal-based numerical quantification of the patients' health status in a scale from-.594 to 1 (perfect health), 0 is (as bad as being dead). In addition, participants will be asked to rate the overall health related quality of life, by means of a visual analogue scale (EQ-5D VAS). The VAS is a 100-mm vertical line from worst (0) to optimal of health (100). The EQ-5D VAS represents the subjective quality of life.
4. Safety of baclofen will be assessed by the number and intensity of reported side effects, using weekly report of adverse effects on a checklist and standardized medical assessments. The side-effects checklist is based on published side effects of baclofen in the treatment of Multiple Sclerosis[43]. Side-effects are partly self-monitored (21 items) and partly observed (8 items) by a doctor or nurse practitioner. Every item is scored on a five-point Likert scale: never (0), seldom (1), sometimes (2), frequently (3) or always (4). Examples of items are vomiting, nausea and diarrhea. The checklist also contains 5 parameters measured by a doctor or nurse practitioner. Examples of parameters are body temperature and heart rate frequency.

2.5.3 Additional measures

Addiction physicians will be asked to monitor withdrawal symptoms when tapering baclofen, using standard questions. These include a short check of the most reported withdrawal symptoms in the literature[44, 45].

We will monitor the use of other substances over the last thirty days (number of days and quantity) using section 1 of the Measurement of Addicts for Triage and Evaluation (MATE) before and after detoxification and at follow up (3 months). The MATE is a Dutch instrument designed as an aid in the diagnosis of clinically relevant patient characteristics in substance use disorders according to the DSM-IV axes[46].

At 6 month period we will also report on the needed period of treatment with baclofen to maintain abstinence by monitoring relapse (Timeline Follow back) and craving assessment (DDQ, VAS) within the intervention group between those who used baclofen for 3 month only and those who choose to continue the treatment further.

2.6 Procedure and Data collection

Patients in all treatment conditions (baclofen + TAU or TAU only) will be assessed by research assistants identically in the following time points. Before detoxification, the intensity of GHB abuse (MATE), Quality of life (EQ-5D) and psychiatric comorbidity (DASS) will be assessed. At the end of the detoxification treatment (baseline) and at follow up (three months after start of detoxification) craving (VAS, DDQ), psychiatric comorbidity (MINI plus, DASS), and Quality of life (EQ-5D) will be assessed.

The addiction physician will monitor the participants in the baclofen condition during regular medical check-ups for potential side effects (side effect checklist) and craving (VAS, DDQ), see table 2. During the follow-up (six months after start of detoxification) the DDQ, DASS, MINI-plus, EQ-5D will be repeated. In summery self-report questionnaires will be administered at the start of detoxification; start of baclofen treatment (week 0), baclofen titration and stabilization (week 1+2) and maintenance treatment (week 3-12). Add to that, three months after the end of the baclofen treatment, a follow-up measurements will take place. The research assistant will build up an online Client Record Form from all the questionnaires filled in by the patients. A summary of the medical records will be added by the physician to the electronic patient file.

Table 2: Time measurements

Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**24**
Measurement	T0-baseline	T1											T2				T3
MATE section 1	xx				x								xx				x
EQ-5D	xx												xx				x
DASS	xx												xx				x
MINI-PLUS	xx												xx				x
Blood	xx						x						x				
Urine	xx						x						xx				x
Medical consult	2x	2x	2x	x	x			x			x		x	x	x		
Baclofen (mg)	0	15-30						45-60						30-45	30-15	15-0	0
Baclofen Side effect	x	2x	2x	x	x			x			x		x				
VAS	xx	x	x	x	x			x			x		xx				x
DDQ	xx	x	x	x	x			x			x		xx				x
Baclofen with-drawal checklist														x	x	x	
Timeline Follow back													xx				x

xx = baclofen group and control group TAU only, x = baclofen group, T0 = end of GHB detoxification
T1 = start baclofen treatment, T2 = follow-up TAU only and end of baclofen therapy, T3 = follow-up baclofen group

2.7 Statistical analyses

Descriptive analysis will be executed for all measurements and will include the mean, SD and frequencies of events with confidence intervals. Descriptive statistics will be used to compare the basic characteristics of the participants in the experimental group and the control groups. To assess any difference in relapse rates between the experimental group and the control groups (TAU group and matched historical group) at 3 month after detoxification Pearson Chi-squared test will be used for the dichotomous abstinence rates. ANOVA will be carried out on continuous variables, such as the total number of abstinent days, the maximum duration of continued abstinence, time before relapse (relapse defined as ≥ 3 times GHB use per day, for 2 subsequent days), and level of substance use over a period of 3 months. At 6 months period participants who continued baclofen will be compared to those who have stopped with baclofen (after 3 month) on relapse into GHB abuse or abstinence corrected for craving. The numbers of patients maintaining abstinence will be analysed with the intention-to-treat principles. The difference in craving will be analysed by MANCOVA at 3 months between groups (abstinent experimental versus abstinent TAU or relapsed TAU) with DDQ and VAS craving as dependent variables and corrected for craving levels immediately after detoxification. The change in craving in time during the baclofen treatment will be analysed via repeated measures MANOVA. By means of MANCOVA at 6 months after detoxification the difference in craving among participants who are still using baclofen and those who have discontinued baclofen will be analysed corrected for craving after 3 months. The effect of baclofen on the psychiatric symptoms levels (DASS, MINI) and also quality of life (EQ-5D) will be analyzed similarly as for craving at 3 and 6 months. The effects of the different TAU approaches as potential confounders will be tested in a sensitivity analyses (changing one-factor-at-a-time) in an linear regression including TAU per center as covariates.

Safety of baclofen, as assessed by the number and intensity of reported side effects, will be analyzed in the following categories: acceptable or unacceptable adverse effect, clinically significant deterioration, and relocation. In all analyses socio-demographic characteristics such as age and gender will be considered as co-variates in the analysis. Two-sided p-value of >.05 is considered statistically significant. The statistical software package SPSS will be used for all the computations.

3. DISCUSSION

This study protocol presents the design of an open label clinical trial evaluating the efficacy of baclofen to prevent relapse, reduce craving and anxiety, and to assess the safety profile of baclofen in GHB dependent patients. To date, there are no reports on the potential of baclofen to prevent relapse in GHB dependent patients. We expect that baclofen will increase abstinence rates, reduce craving and will be well tolerated. In addition, baclofen may improve psychiatric symptoms

such as anxiety and depression, as suggested in several clinical trials in alcohol-dependent individuals[29, 30, 47].

Several risks of baclofen use are taken into account in the current study. In patients with neuropsychiatric disorders, such as schizophrenia, severe depression, mania, Parkinson's disease and cerebrovascular diseases, exacerbations of these conditions may occur, when the dose of baclofen is rapidly increased. It may lower the threshold for seizures in epileptic patients[43]. To limit these risks in the current trial, baclofen will be uploaded gradually, over a period of minimally 10 days. Moreover, patients previously diagnosed with any of the mentioned diseases will be excluded from the study.

Abrupt discontinuation of baclofen, when used for several months, can be associated with a withdrawal syndrome which resembles benzodiazepine and alcohol withdrawal . Several symptoms are reported such as hallucinations, fever, confusion, delirium, agitation, insomnia, and muscle stiffness and spasms[48]. Therefore, patients will be advised to taper down slowly when discontinuation is needed.

Intoxication with baclofen has been reported in doses above 100 mg[49]. This risk increases if patients combine baclofen with GHB. Intoxication is not expected when baclofen is administered at a low dose (< 30 mg per gift), as applied in the current study. Patients will however, be informed repeatedly of this potential risk and the treatment will be discontinued immediately in case of relapse.

The current study does have several limitations. First, the study is not randomized, nor placebo controlled. However, we will compare patients receiving baclofen with a control group matched for gender, age and the pattern of GHB use, in order to control for potential confounding factors. Second, the accompanying treatment as usual (TAU) is not identical in all participating addiction care facilities. This may confound our results. The impact of TAU will be checked with a sensitivity analysis compare patients' results from the different centers conforming the add-on baclofen effect.

Given these methodological limitations the current study should be considered explorative in nature. Given the currently rather limited information from both preclinical and clinical studies of GHB such an explorative approach seems justified. We would also like to test the GHB substitution effect of baclofen (as a GABA-B agonist) hypothesis. It is important to evaluate of this effect is clinically recognized and obvious for the participants, and may define placebo use as non-beneficial. We need to be able to determine the margins of the required treatment dose. All forgoing justify this setup of an open label trail before a large placebo controlled randomized trial.

Implications for practice

If our study confirms the potential of baclofen to reduce relapse and craving without serious adverse events in GHB-dependent patients, this warrants large scale randomized controlled trials in order to draw more firm conclusions. If baclofen showed to have beneficial effects on psychiatric symptoms in these patients, baclofen might be specific interest for the treatment of those GHB dependent patients with co-morbid high levels of anxiety and depression.

Competing interest

All authors declare they have no conflict of interest.

Authors' contributions

RK wrote the initial idea for the study protocol and was responsible with BD and AS for determining the design of the study. RK wrote the study protocol and prepared the first draft of this manuscript. AS and BD edited the study protocol and various drafts of the current manuscript. CdJ supervised the process of study design and protocol preparation; and provided feedback on the manuscript. All authors read and approved the final version of the manuscript.

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Chapter 8

RELAPSE PREVENTION

C - Baclofen and GHB (Gamma hydroxybutrate) a Dangerous Combination

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ABSTRACT

Baclofen is a GABA – β receptor agonist with a muscle relaxant effect. It increases GABA (gamma aminobutyric acid) activity and reduces the production of glutamate and dopamine. The GABA precursor GHB has gained popularity as a drug of abuse. For the first time we report a case of a GHB-dependent patient who ingested several days' doses of baclofen (80 mg) simultaneously with 0.3 L (215 gram) of illicit GHB. Baclofen (40 mg /d) was prescribed to prevent relapse following a successful detoxification. The patient developed a rapid coma (E2M5V1 with oxygen support), bradypnea and hypotonia. Physicians should be alert to the danger of this combination because of the hazards of coma and respiratory distress.

1. INTRODUCTION

Baclofen is a lipophilic derivative of gamma aminobutyric acid (GABA), used clinically as an anti-spasticity agent in, for example, spinal cord injury, cerebral palsy and multiple sclerosis[1]. It has an anti-nociceptive effect[2]. GHB, on the other hand, is a neurotransmitter and neuromodulator that occurs naturally in the human brain. Exogenously administered GHB is assumed to act as a partial agonist of the GABA - β receptors[3]. Baclofen intoxication includes symptoms such as nausea, hypotension, dizziness, respiratory depression, coma, heart rhythm disorders, seizures and EEG abnormalities[4]. An intoxication with GHB is presented by drowsiness, confusion, convulsions, collapse, hypostatic pneumonia with respiratory depression and coma[5]. The overlap in the clinical presentation of GHB and baclofen intoxication is obvious.

Baclofen and GHB gained popularity as candidates in the pharmacotherapy for treating substance abuse disorders such as detoxification or relapse prevention e.g. for alcohol dependence[6,7], GHB dependence[8] and polydrug abuse[9]. This is based on their anxiolytic and sedative properties. In this article we present a patient with a combined intoxication.

2. CASE REPORT

Patient (N) is a 21 year-old woman with a four-year history of GHB dependence and amphetamine dependence in full remission. She was admitted three times for GHB detoxification by means of titration and tapering of pharmaceutical GHB. Over the last year she developed a pattern of relapse in the weekends, using around 125 ml (82 gram) within two days. She described life without drugs as boring. She noticed that her memory was deteriorating, she became disorganized, remembered things incorrectly, forgot important appointments and lost a lot of her belongings. Psychological examination revealed the patient's tendency for socially desirable reactions, with an avoidance of unwanted feelings and frequent confrontations with others. After the fourth successful GHB

detoxification process in the inpatient medium care setting, baclofen was prescribed as an experimental treatment in the process of relapse prevention. After an increase of the daily dose from 30 mg to 40mg/day she was transferred to a supervised, shared, residential, and therapeutic environment where she maintained abstinence for a period of two months.

Following a short conversation with one of the nurses, the patient fell to the ground and proved to be unconscious. A bottle was found in her pocket containing approximately 100ml of GHB. Her blood pressure (125/75) and pulse (72/min) were stable, however she developed bradypnea. The patient was placed in the recovery position. The respiratory rate was difficult to count due to short apneas in between. Neurological examination revealed dilated isocoric pupils, muscular hypotonia and decreased knee and ankle jerks bilaterally. She responded only to painful stimuli on the chest, which triggered her breathing until the ambulance arrived. Vital parameters recorded at that time were: RR 130/90, pulse 70 / min, blood sugar of 6.00, respiratory rate 4/min, 97 % blood saturation, regular width pupils reacting normally to light, Glasgow E2M5V1. The

patient was transferred to the general hospital emergency room with oxygen inhalation support. In the hospital, the vital signs were: RR 132/81, pulse 76/min, saturation 98 % without oxygen, respiratory rate 16/min. E4M6V1, later maximal EM and V4, Glucose 6.0, temperature 35.6 degrees. Right side lung rhonchi were heard which disappeared as the patient started to resume normal breathing. No other neurological, cardiac, or abdominal irregularities were detected. A thorax X-ray showed no abnormalities. The patient was transferred back after two hours of observation to the addiction treatment inpatient ward. The patient admitted inconsistencies in taking baclofen as medication, setting aside tablets to be used in a higher dose for the purpose of sedation and as an anxiolytic. The patient also stated that she had relapsed into illicit GHB (0.33 liter = 215 gram) abuse for several hours without any problems until it was accompanied with the consumption of 80 mg of baclofen.

3. DISCUSSION

Several cases are published describing intoxication with GHB in combination with other sedative drugs, such as alcohol and/or ketamine[10]. This case report presents, for the first time, a dangerous intoxication as a result of the abuse of illicit GHB in combination with baclofen. The combined intoxication was characterized by a rapid onset coma associated with bradypnea or respiratory distress as major symptoms, with normal blood pressure and heart rate.

The rapid development of the clinical condition can be explained by certain neurobiological pathways. Despite the involvement of extrasynaptic GABA-A receptors subtypes in the hypnotic GHB effect[11,12], the GHB-induced toxicity, especially respiratory depression (due to a decrease in respiratory rate), seems to occur via a prominent GHB activation of GABA-B receptors and a negligible effect of GABA agonism at GABA-A receptors[13]. A rise in GABA in selective regions of the brain after GHB administration via increased GABA release and conversion of GHB into GABA was reported by a number of investigators [12,14,15], but it was found to take place with a rather long delay of 40 to 160 min after GHB administration[14], which is inconsistent with the rapid onset of the toxicological effects of administered GHB. Then again, an initial decrease in total GABA levels was observed with GABA levels which did not correlate with the offset of the toxic sedative effect[16]. However, this data is drawn from animal studies which makes it difficult to prove a statement about humans. Thus, the influence of high administered doses of GHB on GABA concentrations remains controversial and unclear. In conclusion, GHB activation of GABA-B receptors has contributed to the intoxication inhibitory state observed in the presented case. Therefore, agents which increase GHB clearance as monocarboxylate transporter (MCT) inhibitors, including L-lactate, in combination with a low-dose GABA-B antagonist are suggested to be a potential treatment for GHB intoxication[13]. There is a narrow dose response margin between the desired relaxing response, the sedative effects and reaching coma[5]. There is no linear relationship between plasma GHB concentration and that sedative

effect, which supports the steepness of the dose-response relationship[16]. High doses of GHB, ingested orally, cause a prolonged high plasma concentration[13].

Baclofen has a rapid and complete absorption, Tmax = 0.5-1.5 hours and half-life of 3-4 hours. If ingested in higher doses its gastrointestinal absorption becomes prolonged with extension of the serum baclofen and elimination half-life (Agabio et al., 2013). In higher doses it will also penetrate the blood brain barrier and exerts a central effect with slower degeneration and sustained effect[2]. As a selective agonist, baclofen activates GABA-B receptors in the CNS, and can result in a decrease in the release of glutamate and several other excitatory neurotransmitters [17-19], causing depression of cortical activity. There is evidence that the subtypes of GABA-B receptors mediating the behavioural effects of baclofen and GHB are not identical[20], which can support the assumption of increased danger and a quick progression to a state of intoxication. Additionally, animal studies have shown that higher doses of baclofen can directly depress the medullary inspiratory neurons[21]. Baclofen, as a muscle relaxant, inhibits the mono-and polysynaptic reflex transmission in the afferent nerve terminal at spinal level and weakens the reflex activity and in intoxication doses also causes depression of both gamma and alpha motor neurons which in turn causes decreased muscular tone[4]. In summary, patients may present, as in this case, with acute baclofen intoxication with respiratory depression, muscular hypotonia and hyporeflexia.

In our case, baclofen, even at a dose within the therapeutic margin (20-80 mg/d), enhanced the agonist role of GHB. The overlap in the neurobiological pathway and intoxication symptoms emphasizes the danger of uncontrolled ingestion of GHB and prescribed baclofen, even though the outcome of GHB or baclofen intoxication is generally good, even after episodes of coma[22]. A combined intoxication may be life-threatening. Management of oral baclofen and GHB intoxication is still primarily based on active symptom supportive treatment. GHB coma can be accompanied by vomiting[23] , which can lead, especially when reinforced with the associated weak reflex activity as a result of ingestion of baclofen, to aspiration and asphyxia. In addition to that, GHB toxicity is unpredictable because of its variable concentration, so lethality will be high when co-ingested with other depressant substances such as baclofen in our case, or if emergency medical services are not provided on time[23].

4. CONCLUSION

Although this seems to be a rare event, it is important with the widespread and increased usage of baclofen as well as of GHB, that, where baclofen is prescribed, physicians are aware of the danger of intoxication in patients using GHB. Frequent medical consultations are required to observe compliance, to educate and to inform patients about the consequences of the combination of baclofen and GHB use.

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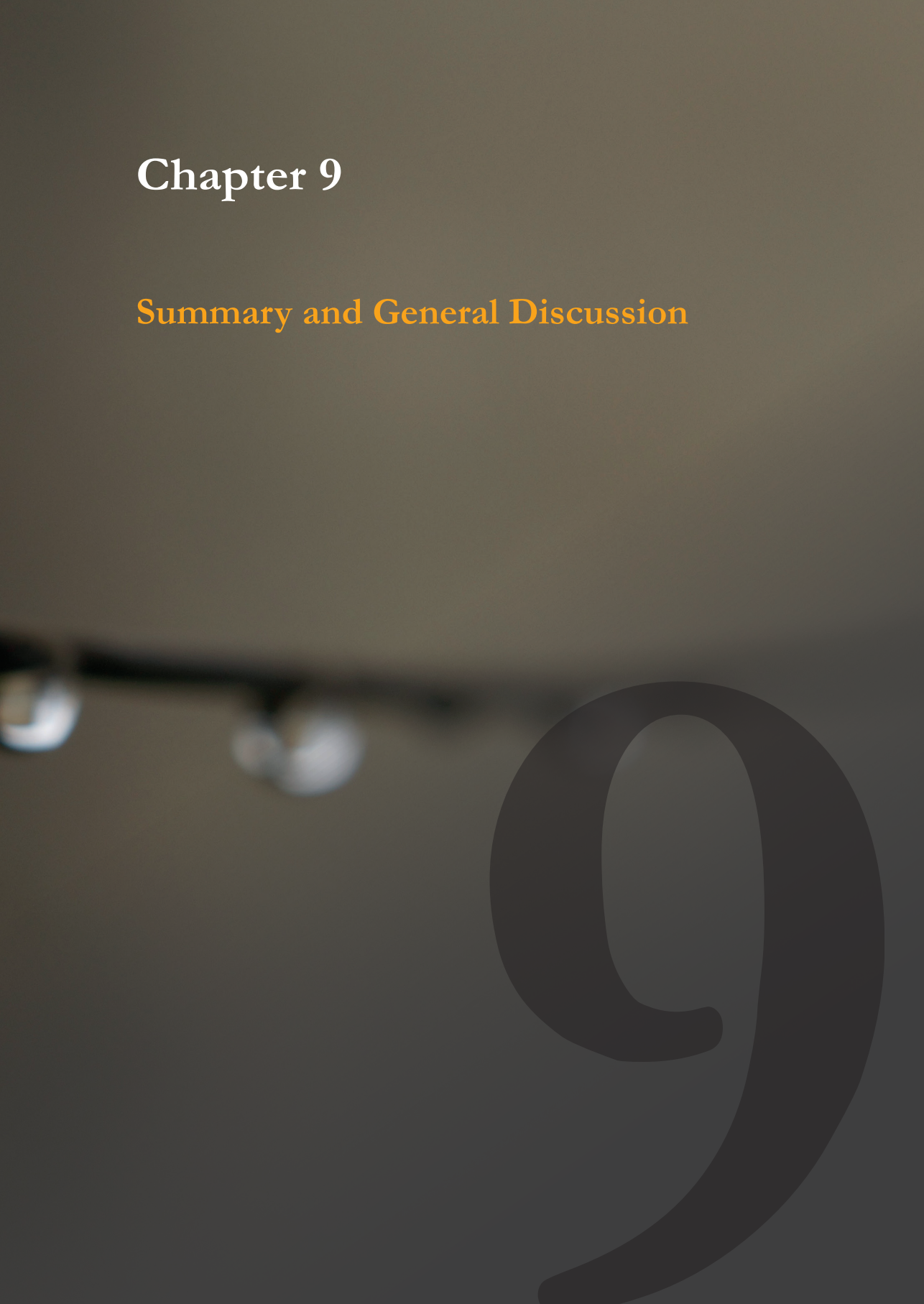
Chapter 9

Summary and General Discussion



SUMMARY AND GENERAL DISCUSSION

GHB dependence has been a growing public health issue over the last decade in the Netherlands. In this thesis I focus on the medical management of the GHB withdrawal syndrome without the need for intensive care (IC) admissions. Abrupt cessation of regular GHB use can result in severe withdrawal symptoms, which could need special medical care. These symptoms include varying degrees of anxiety, agitation, elevated blood pressure, hallucinations (auditory and/or visual), and delirium. When we started our investigations, evidence-based protocols addressing GHB withdrawal treatment did not yet exist.

In this thesis, I apply an evidence-based approach in order to develop and investigate new treatment strategies, aiming at the prevention of severe complications and Intensive Care Hospital admissions in patients with GHB dependence. First, I reviewed current literature on the neuropharmacology of GHB (**chapter 2**). This was to understand the effect of chronic GHB use, the complex withdrawal syndrome from GHB, and the pharmacological options for medical support during detoxification. Secondly, I investigated the prevalence of psychiatric comorbidity in this group of patients and its impact on their pattern of GHB use/abuse and their quality of life (**chapter 3**), which may influence the state and presentation of withdrawal during the detoxification phase. Next, I characterized the GHB withdrawal syndrome in a group of GHB-dependent patients, in order to explore the effect of co-abuse of other substances on the GHB withdrawal syndrome (**chapter 4**). Based on neuro-pharmacological insights, a new treatment approach was proposed to minimize, and possibly avoid, complications. The titration and tapering method using medical GHB is described in **chapter 5a**. Next, the effectiveness and safety of this new treatment approach were tested using an inpatient open label clinical trial. The results of this trial are summarized in **chapter 5b**. I also investigated the effectiveness of this approach to treat complications in cases of benzodiazepine-resistant acute withdrawal within a high-care general hospital setting (**chapter 6**). Finally, I explored the potential for outpatient GHB detoxification, by asking experienced clinicians for their assessment of clinical vignettes (**chapter 7**). During our monitoring activities, exceedingly high relapse rates were observed after detoxification. As an add-on to the main topic of this thesis (management of GHB withdrawal) I explored the effect of baclofen as a relapse prevention medication in a case series presented in **chapters 8a** and **8b**. Moreover, I developed a study protocol for a clinical trial with baclofen as a relapse prevention medication, which is outlined in chapter 8c. In this general discussion the main results of this thesis are summarized. Subsequently, the strengths, limitations, clinical implications, and suggestions for future research will be discussed.

KEY FINDINGS

Neurobiological pathways of GHB dependence are complex

The administration of GHB stimulates the endogenous GHB signalling systems in the brain. As such, illicit GHB achieves its central effects through binding to the same receptors as endogenous GHB, namely GABA-A, GABA-B, and GHB receptors. GHB leads to the suppression of the spontaneous activity of the GABA neuron and disinhibition of the mesolimbic dopamine neurons, especially in the VTA. As a result, GHB has possible anxiolytic and depression modulating effects, as well as analgesic and sedative effects.

The central effects of GHB contribute to its strong abuse potential. In the case of chronic GHB abuse, adaptations occur in several neurotransmitter pathways. For example, there are indications that GABA-receptors are down-regulated, while there may be up-regulation of Dopamine D1 and D2 receptors and NMDA receptors. Changes within the serotoninergic, noradrenergic and cholinergic circuitries have also been reported. Due to this complex interaction between different neuro-circuitries and the short half-life of GHB, acute cessation of GHB abuse will induce a rapid withdrawal syndrome characterized by a variety of clinical symptoms. As such, the GHB withdrawal syndrome cannot be attributed to a single dominant neurobiological mechanism. This may explain why treatment with conventional anti-withdrawal medication, such as benzodiazepines, is often insufficient to prevent complications. This may be of particular relevance when high doses of GHB are used[1-3]. Moreover, treatment alternatives such as antipsychotic agents have been associated with neuroleptic malignant syndrome during GHB withdrawal[26]. Given the complex neurobiology of GHB dependence and withdrawal, I investigated the application of GHB titration and tapering as a detoxification method.

High prevalence of psychiatric comorbidity, psychological distress, and poor quality of life

GHB-dependent inpatients showed high levels of comorbid psychopathology, both current and lifetime (chapter 3). Anxiety and mood disorders were the most prevalent comorbid psychiatric disorders. These results may be supported by the assumed anxiolytic and antidepressant effects of GHB[4, 5]. particularly at low doses. However, with chronic use tolerance develops and higher doses are needed. It has been hypothesized that higher doses of GHB are anxiogenic and depressogenic. Lifetime psychosis was common among GHB-dependent patients (observed: 22%; self- reported: 74%). GHB-dependent patients with co-occurring mood and psychotic disorders used higher doses of GHB (chapter 3) and reported more severe withdrawal syndromes (chapter 5b). In general, GHB-dependent patients reported a low quality of life, despite the often short duration of abuse (average 4 years). Moreover, psychiatric comorbidity was associated with further reductions in quality of life. Taken together, these results emphasize the importance of psychiatric symptomatology among GHB patients and their poor quality of life.

GHB withdrawal differs with and without co-use of psychoactive drugs

Tolerance occurs when it takes the patient a higher dose of the drug to achieve the same level of response achieved initially[6]. It seems that GHB-dependent patients had developed tolerance for GHB as the patients included abused significantly high doses of GHB. These patients were repeatedly admitted to the ER with intoxication symptoms and were also subjected to several admissions for detoxification treatment (chapter 5b). Patients who needed higher doses of pharmaceutical GHB , who had experienced more detoxifications in the past , who reported higher levels of depression, anxiety and stress, all experienced higher levels of withdrawal symptoms. Women experienced higher levels of withdrawal than men (chapter 5b). In our studies we attempted to report characteristics of the pure withdrawal syndrome from illicit GHB in the first hours before any or with very limited medication intervention. In the first 5 hours of withdrawal the most prominent symptoms observed were high apathy and dysphoria along with agitation and restlessness. Autonomous dysregulation was detected in the form of tremors, tachycardia, and hypertension. These symptoms were stable in intensity for 5-6 hours and indicated the need for detoxification. GHB-dependent patients are mostly poly-drug users (73 % of the patients included in the research used another drug besides GHB) (chapter 5b). Concomitant abuse of substances, especially of stimulants such as cocaine and amphetamine, had an add-on effect on the withdrawal symptoms, as indicated by higher levels of agitation, restlessness, muscle twitches and tachycardia detected within the first 5 hours of withdrawal. Severe withdrawal symptoms such as visual or auditory hallucinations were minimally reported, and seemed to be mostly auditory or light sensitivity. Convulsions were not observed within the first 5-6 hours of withdrawal, with or without co-abuse of other psychoactive drugs.

Detoxification by means of titration and tapering of pharmaceutical GHB is a safe practical method

In our detoxification studies, GHB-dependent patients were titrated on 72.5% of the reported self-administered illicit GHB dose. The use of a 2-hour interval regime did not limit the severity of the withdrawal more than a 3-hour interval regime despite the higher dose of pharmaceutical GHB provided. The use of a 3-hour regime is recommended as it still showed reports of limited complications for the several different types of patient (in crisis, with comorbidity, complication, but also stable) and is practical in terms of implementation.

The withdrawal symptoms were moderate at the start (first 3 days), as measured with the mean daily SWS scores, with a significant decrease in intensity over time. In both studies, with a total of 254 unique patients, limited complications were observed. Only 6 patients developed severe somatic symptoms, e.g. severe hypertension or psychiatric complications such as delirium or a psychosis, and were sent to the high-care general hospital for treatment. One of these patients was admitted to a psychiatric ward for 2 days where the detoxification with titration and tapering (DeTiTap) treatment regime was provided along with treatment with antipsychotics (haloperidol) and lorazepam. All patients returned to the addiction treatment centre to complete

their detoxification process. We can conclude that detoxification by the titration and tapering method seems to be safe and convenient for inpatient treatment indications within the addiction treatment centre setting. This even applied to emergency admissions, as was the case for almost 30% of the patients included in this study (chapter 5b).

Most patients reporting abuse of high doses of GHB can develop a withdrawal state which is characterized by agitation, aggression, delirium and psychosis that does not resolve without medical intervention within hours and could make transferral to a general hospital necessary (chapter 6). Due to the lack of experience with GHB detoxification in general hospitals in the Netherlands and repeated encounters with life- threatening acute withdrawal status, a practice-based recommendation protocol for management of acute GHB-withdrawal syndromes in the hospital was developed. These recommendations can be summarized in the following steps: 1) Obtaining information about the GHB abuse or dependence through medical history is crucial; 2) Immediate action, within 3 hours, should be taken to prevent escalation in the form of admission to a psych-med unit with the possibility for intensive care unit admission /referral; 3)For patients who use more than 15 g or 20-25 ml GHB/day (average concentration 650mg/ml) and patients who do not respond to high doses of benzodiazepines, it is recommended to consider the off-label use of pharmaceutical GHB and follow the same concept of detoxification by titration and tapering as described earlier; 4) In all circumstances adequate monitoring of vital functions is necessary; 5) If the patient is familiar with the abuse of other substances, including GBL or 1,4-BD, a GHB expert should be consulted to adjust the schedule if necessary.

Outpatient GHB detoxification can be provided

Determining the detoxification setting is a crucial element in the process to increase the patient's compliance and reach successful results. Experts in GHB detoxification in the field indicated, through a vignette study, that safe outpatient detoxification treatment can be provided according to several practice-based decision rules or criteria. These criteria underlined several aspects to consider, namely the intensity of the GHB abuse and the stability of the patient's biological status (stable/no medical history of somatic disorders), psychological status (stable psychiatric condition such as controlled anxiety, mood disturbance, and mild personality disorders), and social and support system (presence of a coach) . The outpatient detoxification could be provided with the support of long-acting benzodiazepines such as, for example, diazepam. The importance of providing facilities for an addiction physician or the family doctor to give intensive guidance to their patients, and in the case of complications admit them for inpatient treatment, is emphasised. In all other conditions, the recommendation is to resort to an inpatient detoxification approach. Knowledge of GHB and its treatment is still limited and in development, especially GHB outpatient detoxification treatment, due to the lack of protocols and guidelines for this approach.

Baclofen can be considered and tested as relapse prevention treatment aid

Baclofen, with a dose range from 30 to a maximum of 60 mg per day, was found to be helpful in decreasing relapse rates. Baclofen was well tolerated by the 12 patients included. This assumption was based on physicians' clinical observation and the patient's reported craving and experienced side effects (chapter 8a). The baclofen dose administered was associated with low relapse rates, as only 1 patient relapsed into abuse of GHB within a period of 12 weeks. There was no direct relationship detected between the dose of baclofen and the level of craving. A higher dose of baclofen did not lead to a structural rise in reported side-effects. Nevertheless, the role of an adjuvant psychological treatment should not be dismissed in the interpretation of these findings. Considering all of the above, we can suggest it would be beneficial to start a future study, testing the exact impact and efficacy of baclofen to reduce craving and prevent relapse in a larger group of GHB-dependent patients. This study protocol presents the design of an open label study (chapter 8c), where we expect that baclofen will be well tolerated, reduce craving and increase abstinence rates and possibly improve mood and anxiety. These findings would encourage starting a future large-scale RCT (randomized controlled trial) which can be transferred to practice immediately with almost no delay.

Despite the aim of studying baclofen as a relapse prevention medication, we encountered a case in which the overlap of GHB and baclofen use caused a serious and dangerous intoxication state (chapter 8b). The overlap in the neurobiological pathway and intoxication symptoms emphasizes the danger of uncontrolled ingestion of GHB and prescribed baclofen. Even though the outcome of separate GHB or baclofen intoxication is generally good[7], a combined intoxication may be life-threatening.

Clinical implications and directions for future research

In the treatment of a chronic process of drug seeking and abuse, medical detoxification is an important step[8]. Physicians can provide outpatient detoxification for GHB-dependent patients when certain essential preconditions are met (see chapter 7). Of particular importance is the possibility of scaling up to an inpatient treatment facility without any delay. Policy makers in health care should be aware of the importance and need to provide these facilities to avoid life-threatening consequences. In acute situations, health professionals have a time frame of 5-6 hours to provide medication before a potentially dangerous withdrawal syndrome occurs. During GHB detoxification, unpredictable and severe withdrawal symptoms are often detected. The outcome of GHB detoxification might be affected by a high level of psychiatric comorbidity and psychological distress. These patients also reported more panic attacks, somatization symptoms, social anxiety and suicidality, as compared to those without psychiatric comorbidity (chapter 3). GHB-dependent patients with psychiatric comorbidity use higher doses of GHB within shorter time intervals, associated with severe withdrawal symptoms, as shown in chapter 5b. The symptoms could be related to the effect of the high dose of GHB used (chapter 3) or

the associated psychiatric state. Patients with psychiatric comorbidity therefore require inpatient detoxification. Early screening for psychiatric symptomatology is crucial in this respect. Several screening instruments can be applied, such as the Depression, Anxiety and Stress Scale (DASS). DASS scores above the thresholds (21 for Depression, 15 for Anxiety and 26 for Stress) can indicate expected psychiatric comorbidity[9]. These patients should undergo a thorough psychiatric assessment, taking into consideration the pattern of substance use, as well as behavioural and personality disorder dynamics. Even though psychiatric assessment will be coloured by the effect of GHB use as an anxiolytic/ antidepressant or sometimes a reverse effect of apathy and insomnia related to the continued pattern of abuse (chapter 2), psychiatric assessment before detoxification remains of vital importance in order to provide a safe and effective treatment. Co-occurring substance use is another important factor affecting the GHB withdrawal syndrome, e.g. the use of psychostimulants (chapter 3). For these patients, an inpatient detoxification setting is necessary and higher doses of supplementary medication (pharmaceutical GHB or benzodiazepines) are recommended to avoid severe agitation and possible psychosis. When using pharmaceutical GHB for detoxification, 5-15 ml (3.3- 9.8 gram) extra GHB per dose would be needed in the case of alcohol, cocaine and amphetamine co-abuse (chapter 5b).

Detoxification by means of Titration and Tapering of pharmaceutical GHB (DeTi-Tap method) can be used in several settings and different clinical situations, but it is highly recommended in the following clinical situations:

- Planned detoxification within medium-care facilities with no direct access to intensive care level support, when a high dose of GHB is abused, anxiety disorders or psychosis are diagnosed or suspected.
- Cases of acute GHB withdrawal presentations when psychosis (chapter 6) or other complication, e.g. rhabdomyolysis, is observed (chapter 5a), with or without the availability of an accurate medical history of abuse. Take into consideration the fact that antipsychotics play a limited to almost no role in the treatment of GHB withdrawal related psychosis/ delirium.
- When the last use of illicit GHB is more than 6 hours before admission.

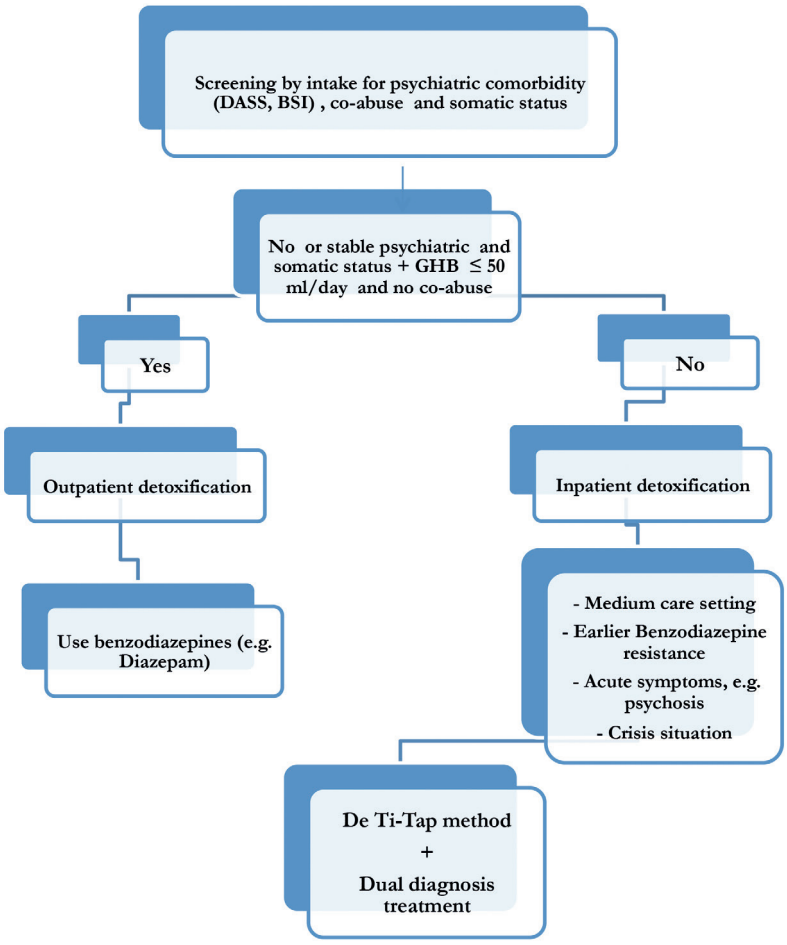


Figure: Summary recommendation

It is highly relevant that physicians, particularly addiction medicine physicians, general practitioners and psychiatrists, expand their knowledge concerning GHB dependence and withdrawal (recognition and treatment), given the rapid appearance of severe withdrawal symptoms (chapter 4) and complications in these patients (chapter 5a and 6). The lack of knowledge can lead to unnecessary complications and sometimes death of patients[10].

This thesis resulted in several protocols, which can be implemented in addiction care centres, mental health facilities and general hospitals, in order to prevent life-threatening complications and intensive care unit (ICU) admissions (available online at the NISPA site: http://www.nispa.nl/onderzoek/ghb/protocollen). However, it is important to stress that the proposed algorithm in these protocols is preliminary, given the limited evidence currently available. For example, head-to-head comparison between the DeTi-Tap method and frequently used treatment alternatives,

such as benzodiazepine or baclofen-assisted detoxification is lacking. Such comparison is important to establish the safety, efficacy and cost- effectiveness of these treatment methods.

GHB-dependent patients are usually described as difficult to control, with high craving, quick and high relapse rates shortly after GHB detoxification treatment, and lack of insight. Such impulsive behaviour, characterised by impatience to delayed rewards and an increased likelihood of premature responding[11], as explained in chapter 2, could be related to a state of dopamine receptors up-regulation and an abnormal increase in dopamine transmission [12, 13] and serotonin dis-balance [14] besides manipulations of the noradrenergic system[15] and the decreased GABA levels[16]. Thus, several neurobiological changes related to SUDs may mediate the high relapse rates. This neurobiological process is suggested to be present before and during the GHB withdrawal phase and may persist for weeks (chapter 2). However, we still do not know what exact neurobiological changes contribute to the extremely quick and high relapse rates as observed in GHB-dependent patients when compared to other substance use disorders. This, in addition to the fact that some GHB-dependent patients also suffer from anxiety, could be translated hypothetically into an impaired capacity to resist feelings of craving or temptation, leading to a relapse in GHB abuse in the early weeks of abstinence. The confrontation of the patients with their environment and the resulting pressure at the beginning of the treatment is also a high risk factor that they must overcome to maintain abstinence from GHB[25]. Therefore, it may be of interest to investigate whether treatment in a closed inpatient setting, for example for a period of 6 weeks, would confine anxiety, impulsivity and relapse rates and add to the commitment and participation in treatment. More information and studies supporting this hypothesis and this treatment approach are required. It is also highly relevant to explore the personal views of these patients as well, concerning their GHB dependence and potential causes and factors contributing to relapse. Such insight could help in understanding the behaviour of these patients and develop optimal therapy approaches. Concomitant treatment of existing psychiatric comorbid disorders should be provided and implies the presence of psychiatric expertise within the professional staff. Because, as mentioned earlier, these patients report low quality of life, it can be suggested to constantly evaluate the therapy provided in terms of improvement of the quality of life of the patients (EuroQol-5D). Quality of life is considered a good parameter in estimating the impact and success of treatment[24], and EuroQol-5D is also a simple self-report instrument which can be easily filled in by the patient, encouraging their commitment to follow-up.

Finally, the neurobiological evidence available has shown the complexity of GHB pharmacology and dependence, including the involvement of various neurotransmitter systems in the brain (chapter 2). However, there is limited information on the impact of chronic GHB abuse on the brain pathways. Neuroimaging techniques could be used to assess the long-term effects and potential neurological damage related to chronic GHB use. Similarly, studies on cognitive impairment, such as learning and memory, would be of importance to assess the long-term clinical effects of GHB use in humans as stated in animal data[18-20].

General issues

The current thesis should be seen in the light of its strengths and weaknesses. A major strength of this thesis is its innovative nature. To our knowledge, this is the first multicentre (nationwide) systematic approach to address GHB detoxification with structured monitoring. It provides the first stone in a safe recovery pathway for these patients, improving their quality of life and decreasing emergency interventions and life- threatening complications. This thesis also provides a picture, for the first time, of the psychiatric comorbidity and psychological distress as a crucial factor affecting the pattern of GHB abuse and choice for detoxification. Given the collaboration of several addiction care facilities throughout the Netherlands, it can be expected that the population under survey is a representative sample of GHB-dependent patients in treatment. Another major strength is that the results of the current studies were translated into a treatment protocol which was implemented in different clinical addiction centres in the Netherlands. Moreover, in the current studies I translated insights from basic science on the neuropharmacology of GHB to the clinic, in order to support the treatment of severe GHB withdrawal syndrome and prevent relapse. As such, the current thesis covers a wide range of clinical aspects of GHB dependence.

However, several limitations should also be considered. In this thesis the results were based on observational and cross-sectional studies. With this method it is difficult to find causal relationships, we cannot check all influencing variables, thus the results should be interpreted with caution. We did not compare our sample with a control group of patients with other SUDs, nor did we conduct Randomized Clinical Trials to compare the efficiency of the detoxification with pharmaceutical GHB versus, for example, treatment with benzodiazepines or baclofen. Therefore, the results of the current studies should not be considered as definitive answers to research questions such as, for example: how does GHB dependence differ from other SUDs? Is GHB-assisted detoxification better than benzodiazepine-assisted detoxification for GHB dependence? A comparison RCT study between the DeTi-Tap method and benzodiazepine or baclofen medication supplements as a detoxification aid would be important to be able to answer this last question. For the studies in chapter 4, 5 and 8a, we fully relied on self-reports of substance use which were not confirmed by blood or urine toxicological tests.

Another issue of concern is the missingness in the data: not all of the participants completed all the research instruments and several (37%) were not available for follow-up. For example, psychiatric comorbidity was reported in only 50% of the included patients. As a result, our estimations of the prevalence of psychiatric comorbidity may not be accurate and possibly an underestimation of the real problem.

Also our findings in chapter 6 can be criticized as they were based on a limited number of patients. We cannot confirm that detoxification with the titration and tapering (DeTiTap) treatment regime is the only/best method in cases of benzodiazepine resistance. Collecting more data through implementation of the suggested protocols might provide more insight in the future. In assessing baclofen as a means of relapse prevention in chapter 8a, the inclusion of

highly motivated patients cannot be ruled out, which could have biased our results.
Finally, it is important to note that our results should not be generalized to all GHB users, because the studies were restricted to patients undergoing inpatient GHB detoxification at addiction care facilities. It would be relevant to compare the characteristics of our patients with recreational GHB users or those with dependence unknown in the addiction care facilities. It also remains to be studied whether our findings are in line with international populations of GHB-dependent patients.

Conclusion

This dissertation has clearly illustrated that GHB withdrawal is a complex syndrome related to multiple neurobiological pathways. The high percentage of psychiatric comorbidity and co-abuse by GHB-dependent patients should be taken into consideration in the choice for a detoxification approach. It is recommended to provide systematic early screening (psychiatric and somatic), which would add to the efficacy of detoxification. Some of the patients are eligible for outpatient detoxification. The DeTi-Tap method is feasible and can be provided safely in inpatient medium-care settings, with no or limited need for the addition of other medication. It has also provided good results in general hospital settings and is recommended as treatment medication in benzodiazepine-resistant cases. This dissertation also emphasizes that relapse in GHB use is a serious problem which should and will be addressed in future research.

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SAMENVATTING EN ALGEMENE DISCUSSIE

In de afgelopen tien jaar is de afhankelijkheid van GHB een groeiend probleem in de volksgezondheid. In dit proefschrift richt ik mij op de medische behandeling van GHB zonder gebruik van Intensive Care (IC) opnames. Abrupte stopzetting van het reguliere GHB-gebruik kan leiden tot ernstige ontwenningssymptomen, die vragen om bijzondere medische behandeling. Deze symptomen kunnen variëren van angst, agitatie, verhoogde bloeddruk, hallucinaties (auditieve en/of visuele) en een delirium. Dit in verschillende mate van intensiteit. Bij de start van dit onderzoek waren er geen evidence-based protocollen bekend als het gaat om de onthouding van GHB.

In dit proefschrift heb ik een evidence-based benadering gebruikt om nieuwe therapeutische strategieën te ontwikkelen en te onderzoeken. Die zijn gericht op het voorkomen van ernstige complicaties en Intensive Care ziekenhuis opnames voor patiënten met GHB afhankelijkheid. Ten eerste, heb ik een review van de huidige literatuur over de neurofarmacologie van GHB verricht (hoofdstuk 2). Dit was om het effect van chronische GHB, het complex GHB onthoudingssyndroom, en de farmacologische mogelijkheden voor medische ondersteuning tijdens detoxificatie te begrijpen. Ten tweede heb ik onderzoek gedaan naar de prevalentie van psychiatrische co-morbiditeit bij deze groep patiënten, de impact hiervan op hun patroon van GHB-gebruik en misbruik, en de kwaliteit van leven (hoofdstuk 3). Dit zijn factoren die de presentatie van onthoudingssymptomen tijdens de detoxificatiefase kunnen beïnvloeden. Vervolgens heb ik het GHB ontwenningssyndroom in een groep van GHB afhankelijke patiënten gespecifieerd met als doel het effect van co-misbruik van andere psychoactieve middelen op het GHB ontwenningssyndroom te onderzoeken (hoofdstuk 4). Gebaseerd op de neuro-farmacologische inzichten, werd een nieuwe benadering van de behandeling voorgesteld om complicaties te minimaliseren, en zo mogelijk te voorkomen. De titratie en methode van afbouw met behulp van medische GHB wordt beschreven in hoofdstuk 5a. De effectiviteit en veiligheid van deze nieuwe behandeling werd getest met behulp van een open-label klinische studie. De resultaten van deze studie zijn samengevat in hoofdstuk 5b. Ook heb ik onderzoek gedaan naar de effectiviteit van deze behandelingsaanpak bij complicaties ten gevolge van benzodiazepine-resistente acute onthouding binnen een high-care algemeen ziekenhuis (hoofdstuk 6). Tot slot, heb ik de mogelijkheden voor ambulante GHB detoxificatie onderzocht, door ervaren artsen hun klinische vignetten te laten beoordelen (hoofdstuk 7). Tijdens ons monitoringstraject, werd een zeer hoge terugval in GHB na detoxificatie waargenomen. Als toevoeging aan het hoofdonderwerp van dit proefschrift (de behandeling van GHB onthouding), heb ik het effect van Baclofen als medicatie voor terugvalpreventie onderzocht bij een serie patiënten, en beschreven in de hoofdstukken 8a en 8b. Bovendien heb ik een studieprotocol ontwikkeld om het effect van Baclofen als medicatie voor terugvalpreventie te toetsen. Dit protocol wordt beschreven in hoofdstuk 8c. In deze algemene bespreking worden de belangrijkste resultaten van dit proefschrift

samengevat. Vervolgens zullen de sterktes, de beperkingen, de klinische implicaties, en suggesties voor toekomstig onderzoek worden besproken.

BELANGRIJKSTE BEVINDINGEN

Neurobiologie van GHB afhankelijkheid is complex

Externe GHB inname stimuleert de endogene GHB signaleringssystemen in de hersenen. Illegale GHB realiseert de centrale effecten door aan dezelfde receptoren te binden als het endogeen GHB, namelijk GABA-A, GABA-B en GHB receptoren. GHB leidt tot de repressie van de spontane activiteit van het GABA neuron met als gevolg disinhibitie van de mesolimbische dopamine neuronen, vooral in de VTA (Area Tegmentalis Ventralis). Hierdoor heeft GHB anxiolytische en depressie modulerende effecten, alsook analgetische en sedatieve effecten.
De centrale effecten van GHB kunnen bijdragen aan het sterke potentieel tot misbruik. Bij chronisch GHB misbruik treedt er verandering en adaptaties op in verschillende neurotransmitter paden. Er zijn aanwijzingen dat GABA-receptoren neerwaarts-gereguleerd zijn, naast de opwaartse-regulatie van dopamine D1 en D2 receptoren en NMDA-receptoren. Veranderingen binnen de serotonergic, noradrenerge en cholinerge circuits zijn ook gemeld.
GHB leidt tot de repressie van de spontane activiteit van het GABA neuron met als gevolge disinhibitie van de mesolimbische dopamine neuronen, vooral in de VTA. Hierdoor heeft GHB anxiolytische en depressie modulerende effecten, alsook analgetische en sedatieve effecten.
Door deze complexe interacties tussen verschillende neuro-schakelingen en de korte halfwaardetijd van GHB, kan het acuut stoppen met GHB-gebruik leiden tot het snelle onthoudingssyndroom gekenmerkt door zijn diversiteit in klinische symptomen. Als zodanig kan het GHB onthoudingssyndroom niet worden toegeschreven aan een enkel dominant neurobiologisch mechanisme. Dit kan verklaren waarom de bekende methoden van behandeling, zoals benzodiazepinen, vaak onvoldoende complicaties kunnen voorkomen. Dit kan van groot belang zijn bij het gebruik van hoge doseringen van GHB [1-3]. Bovendien kan een alternatieve behandeling zoals antipsychotica, geassocieerd worden met het maligne neurolepticasyndroom tijdens de GHB onthouding [26]. Gezien de complexe neurobiologie van GHB afhankelijkheid en detoxificatie, heb ik onderzoek gedaan naar de toepassing van GHB titratie en afbouw als een methode van detoxificatie.

Hoge prevalentie van psychiatrische co-morbiditeit, psychologische stress en slechte kwaliteit van leven

Klinisch opgenomen patiënten met een GHB-afhankelijkheid vertonen zowel een huidige als lifetime hoge mate van co-morbide psychopathologie (hoofdstuk 3). Angst- en stemmingsstoornissen waren de meest voorkomende co-morbide psychiatrische stoornissen. Deze resultaten worden ondersteund door de veronderstelde anxiolytische en antidepressieve

effecten van GHB [4, 5] met specifiek lage doses. Echter, met chronisch gebruik van GHB kan tolerantie ontwikkeld worden en zijn hogere doses nodig. De hypothese is dat hogere GHB doses anxiogeen en depressogeen zijn. Lifetime psychose was gebruikelijk onder GHB-afhankelijke patiënten (waargenomen: 22%; zelf gerapporteerd: 74%). GHB-afhankelijke patiënten met zowel stemmings- als psychotische stoornissen op hetzelfde moment, gebruiken hogere doses GHB (hoofdstuk 3) en rapporteren ernstige onthoudingssymptomen (hoofdstuk 5b). In het algemeen melden GHB-afhankelijke patiënten een lage levenskwaliteit, ondanks de korte duur van misbruik (gemiddeld 4 jaar). Bovendien werd psychiatrische co-morbiditeit geassocieerd met een verdere vermindering van de levenskwaliteit. Bij elkaar genomen benadrukken deze resultaten het belang van psychiatrische symptomatologie onder GHB patiënten en hun slechte kwaliteit van leven.

GHB onthoudingssyndroom verschilt met en zonder co-gebruik van psychoactive drugs

Tolerantie treedt op wanneer een hogere dosis van het geneesmiddel nodig is voor de patiënt om hetzelfde initiele effect te kunnen bereiken [6]. Het lijkt erop dat GHB-afhankelijke patiënten een tolerantie voor GHB hadden ontwikkeld wanneer de patiënten aanzienlijk hogere doses GHB misbruikten. Deze patiënten werden keer op keer opgenomen op de SEH/IC met vergiftigings symptomen en/of voor detoxificatiebehandeling (hoofdstuk 5b). Patiënten die hogere doses van farmaceutische GHB nodig hadden, die meerdere detoxificatie hebben doorgemaakt in het verleden, en hogere niveaus van depressie, angst en stress hebben gerapporteerd, ervaren allemaal ernstige ontwenningsverschijnselen. Vrouwen ervaren onthoudingsklachten intenser dan mannen (hoofdstuk 5b). In onze studies hebben we geprobeerd de kenmerken te beschrijven van het zuivere ontwenningssyndroom van illegale GHB in de eerste uren. Dit zonder of met ondersteuning van een lage dosis medicatie. In de eerste 5 uur na het stoppen met GHB zijn de meest prominent waargenomen ontwenningssymptomen: hoge apathie en dysforie, samen met agitatie en rusteloosheid. Autonome ontregeling in de vorm van trillingen, tachycardie en hypertensie werden gedetecteerd. Deze symptomen waren stabiel in intensiteit gedurende 5-6 uur en bevestigen de noodzaak voor een detoxificatie traject. GHB-afhankelijke patiënten zijn meestal polydrugsgebruikers (73% van de geïncludeerde patiënten in het onderzoek gebruikte een ander middel naast GHB) (hoofdstuk 5b). Gelijktijdig misbruik van psychoactieve middelen, en in het bijzonder van stimulantia zoals cocaïne en amfetamine, veroorzaakt een verhogend effect op de ontwenningsverschijnselen. Dit in de vorm van hogere niveaus van agitatie, rusteloosheid, spiertrekkingen en tachycardie gedetecteerd binnen de eerste 5 uur na het staken van GHB. Ernstige ontwenningsverschijnselen zoals visuele of auditieve hallucinaties werden minimaal gerapporteerd. Convulsies werden niet waargenomen binnen de eerste 5-6 uur van de ontwenningsfase, met of zonder co-misbruik van andere psychoactieve drugs.

Detoxificatie met titratie en afbouw van farmaceutische GHB is een veilige praktische methode

In onze detoxificatie studies werden GHB-afhankelijke patiënten getitreerd op 72,5% van de gerapporteerde eigen illegale GHB gebruikte dosis. Behandeling in een 2 uur interval regime heeft de ernst van de onthoudingssymptomen niet meer verminderd dan bij een 3-uur interval, ondanks verstrekking van een hogere dosis van farmaceutische GHB. Het gebruik van een 3 uur regime wordt aanbevolen in verband met melding van beperkte complicaties van verschillende patiënten (in crisis, met co-morbiditeit, complicatie, maar ook stabiel), en is praktisch in termen van implementatie.

De onthoudingsverschijnselen waren matig in de eerste 3 dagen, zoals gemeten met de gemiddelde dagelijkse SWS scores, met een significante afname in intensiteit in tijd. In beide studies, met een totaal van 254 unieke patiënten, zijn beperkte complicaties waargenomen. Slechts 6 patiënten ontwikkelden ernstige somatische klachten zoals ernstige hypertensie of psychiatrische complicaties zoals delirium of een psychose, zij werden naar de high-care van een algemeen ziekenhuis gestuurd voor behandeling. Een van deze patiënten werd 2 dagen opgenomen op een psychiatrische afdeling waar detoxificatie met farmaceutisch GHB titratie en afbouw (DeTiTap) als behandeling werd aangeboden, met toevoeging van antipsychotica (haloperidol) en lorazepam. Alle patiënten zijn teruggestuurd naar de Verslavingszorg om hun detoxificatieproces te voltooien. We kunnen concluderen dat detoxificatie met titratie en afbouw een veilige en geschikte methode lijkt om uit te voeren in klinische settingen binnen de verslavingszorg. Dit geldt zelfs voor spoedeisende opnames, zoals het geval was voor bijna 30% van de geïncludeerde patiënten in deze studie (hoofdstuk 5b). De meeste patiënten die hoge doses GHB misbruiken, melden een onthoudingssyndroom gekenmerkt door agitatie, agressie, delirium en psychose. Als deze symptomen zonder medische interventies niet binnen enkele uren verdwijnen, kan verwijzing naar een algemeen ziekenhuis nodig zijn (hoofdstuk 6).

Als gevolg van het gebrek in Nederland aan ervaring met GHB detoxificatie behandeling in algemene ziekenhuizen, en de herhaalde meldingen van levensbedreigende acute onthouding-status, is een praktijkgericht aanbevelingsprotocol voor de behandeling van acute GHB onthoudingssyndromen in het ziekenhuis ontwikkeld. Deze aanbevelingen kunnen worden samengevat in de volgende stappen: 1) Het verkrijgen van informatie over het GHB misbruik of afhankelijkheid gedurende de medische voorgeschiedenis is van groot belang; 2) Onmiddellijke actie moet binnen 3 uur worden genomen, om escalatie in de vorm Intensieve care of een opname op de PAAZ afdeling te voorkomen; 3) Voor patiënten die meer dan 15 g of 20-25 ml GHB per dag gebruiken (gemiddelde concentratie 650 mg/ml) en patiënten die niet reageren op hoge doses benzodiazepinen, is het raadzaam om de off-label inzet van farmaceutische GHB voor detoxificatie met titratie en afbouw zoals eerder beschreven te overwegen; 4) In alle gevallen is een adequate controle van de vitale functies noodzakelijk; 5) Als de patiënt bekend is met het misbruik van andere middelen, waaronder ook GBL en 1,4-BD, moet een GHB expert worden geraadpleegd om het schema aan te passen indien nodig.

Ambulante GHB detoxificatie kan worden verstrekt

Het bepalen van de setting van detoxificatie is een cruciaal element in het proces om de therapietrouw van de patiënt te verhogen en succesvolle resultaten te bereiken. Experts in GHB detoxificatie in het veld geven aan door middel van een vignet studie, dat een veilige ambulante detoxificatie behandeling kan worden uitgevoerd volgens verschillende practice-based beslisregels of criteria. Deze criteria onderstrepen verschillende aspecten die de behandelaar moet overwegen, met name de intensiteit van het GHB misbruik en de stabiliteit van de biologische toestand van de patiënt (stabiel/geen medische voorgeschiedenis van somatische aandoeningen), psychologische toestand (stabiele psychiatrische aandoening zoals gecontroleerde angst, stemmingsstoornis en milde persoonlijkheidsstoornissen), en het sociale en steun systeem (aanwezigheid van een coach). De ambulante detoxificatie kan worden uitgevoerd met de steun van langwerkende benzodiazepines zoals bijvoorbeeld diazepam. Er wordt benadrukt dat de verslavingsarts of de huisarts gefaciliteerd moet worden om intensieve begeleiding te kunnen bieden aan hun patiënten, en intramurale behandeling moet beschikbaar zijn in geval van complicaties. In alle andere omstandigheden, de aanbeveling is voor een intramurale detoxificatie aanpak te kiezen. Kennis van het effect van GHB en de methoden van behandeling, met name de ambulante detoxificatie behandeling, zijn nog beperkt en in ontwikkeling. Dit vanwege het ontbreken van protocollen en richtlijnen voor deze benadering.

Baclofen kan worden beschouwd en getoetst als steun bij de behandeling van terugvalpreventie

Baclofen, in een dosis van 30 tot maximaal 60 mg per dag, bleek nuttig te zijn in de vermindering van terugvalpercentages. Baclofen werd door de 12 geïncludeerde patiënten goed verdragen. Deze veronderstelling is gebaseerd op de klinische observatie van artsen en de door de patiënt gerapporteerde zucht en ervaren bijwerkingen (hoofdstuk 8a). De Baclofen dosis gebruikt in het onderzoek, werd geassocieerd met een lage neiging tot terugval. Slechts 1 patiënt is terugvallen in misbruik van GHB binnen de periode van 12 weken. Er was geen directe relatie waargenomen tussen de dosis Baclofen en het niveau van zucht. Een hogere dosis Baclofen heeft niet geleid tot een structurele toename van gerapporteerde bijwerkingen. Een adjuvans psychologische behandeling dient niet te worden afgewezen bij de interpretatie van deze bevindingen. Gezien de bovenstaande resultaten, kunnen we suggereren dat het gunstig zou zijn om een toekomstige studie te starten in een grotere groep GHB verslaafde patiënten welke de precieze impact en werkzaamheid van Baclofen op het voorkomen van terugval en zucht onderzoekt. Dit open label studie protocol wordt gepresenteerd (hoofdstuk 8c). De hypothese is dat wanneer Baclofen getolereerd zal worden, de zucht verminderd, de kans op abstinentie vergroot, en mogelijk stemmings- en angstklachten verminderen. Deze bevindingen zouden het starten van een toekomstige grootschalige RCT (gerandomiseerde gecontroleerde studie) aanmoedigen. Deze kan snel worden geïmplementeerd met vrijwel geen vertraging.

Ondanks het doel om Baclofen als medicatie voor terugvalpreventie te bestuderen, hebben we een geval waarin de overlap van het gebruik van GHB en Baclofen een gevaarlijke en ernstige vergiftiging tot gevolg had (hoofdstuk 8b). De overlap in de neurobiologische kenmerken en vergiftigings symptomen benadrukken het gevaar van een ongecontroleerde inname van GHB en voorgeschreven Baclofen. Ook al is de uitkomst van afzonderlijke GHB of Baclofen intoxicatie meestal goed[7], een gecombineerde intoxicatie kan levensbedreigend zijn.

Klinische implicaties en aanwijzingen voor toekomstig onderzoek

Bij de behandeling van een chronisch proces van drug bemachtigen en misbruik, medische detoxificatie is een belangrijke stap[8]. Artsen kunnen ambulante detoxificatie voor GHB-afhankelijke patiënten aanbieden wanneer aan bepaalde randvoorwaarden wordt voldaan (zie hoofdstuk 7). De mogelijkheid van opschaling naar een intramurale behandeling zonder enige vertraging is van bijzonder belang. Beleidsmakers in de gezondheidszorg moeten zich bewust zijn van het belang en de noodzaak om deze faciliteiten beschikbaar te stellen om levensbedreigende gevolgen te kunnen vermijden. In acute situaties, hebben behandelaars een tijdsbestek van 5-6 uur om patiënten te voorzien van medicatie voordat een potentieel gevaarlijk ontwenningssyndroom optreedt. Tijdens GHB detoxificatie zijn onvoorspelbare en ernstige ontwenningsverschijnselen vaak gedetecteerd. Het resultaat van GHB detoxificatie kan worden beïnvloed door een hoog niveau van psychiatrische co-morbiditeit en psychologische stress. Deze patiënten rapporteerden in vergelijking met mensen zonder psychiatrische co-morbiditeit meer paniekaanvallen, lichamelijk klachten, sociale angst, en suïcidaliteit (hoofdstuk 3). GHB-afhankelijke patiënten met psychiatrische co-morbiditeit gebruiken hogere doses GHB met kortere tijdsintervallen welke geassocieerd worden met ernstige ontwenningsklachten, zoals beschreven in hoofdstuk 5b. De symptomen kunnen worden gerelateerd aan het effect van de hoge dosis GHB (hoofdstuk 3) of de geassocieerde psychiatrische toestand. Patiënten met psychiatrische co-morbiditeit vereisen daarom intramurale detoxificatie. Vroege screening voor psychiatrische symptomen is in dit opzicht cruciaal. Verschillende screeningsinstrumenten kunnen worden toegepast, zoals de Depressie, Angst en Stress Scale (DASS). DASS scores boven de drempels (21 voor Depressie, 15 voor angst en 26 voor Stress) kunnen duiden op verwachte psychiatrische co-morbiditeit[9]. Deze patiënten moeten een grondig psychiatrisch onderzoek hebben, rekening houdend met het patroon van GHB gebruik als ook de gedrags- en persoonlijkheidsstoornis dynamiek. Hoewel psychiatrisch onderzoek gekleurd kan worden door het effect van GHB als een anxiolytische/antidepressivum of soms een omgekeerd effect van apathie en slapeloosheid gekoppeld aan het voortdurende patroon van misbruik (hoofdstuk 2), blijft het psychiatrisch onderzoek voorafgaand aan een traject van detoxificatie van vitaal belang om een veilige en effectieve behandeling te garanderen. Co-gebruik van middelen is een andere belangrijke factor die het GHB ontwenningssyndroom kan beïnvloeden, bijvoorbeeld het gebruik van psychostimulantia (hoofdstuk 3). Voor deze patiënten is een klinische omgeving voor detoxificatie noodzakelijk en hogere doses ondersteunde medicatie (farmaceutische GHB of benzodiazepinen) zijn

aanbevolen om ernstige agitatie en psychose te voorkomen. Bij detoxificatie met ondersteuning van farmaceutische GHB, zou 5-15 ml (3.3- 9.8 gram) GHB per dosis extra nodig zijn, in het geval van alcohol, cocaïne en amfetamine co-misbruik (hoofdstuk 5b). Detoxificatie door middel van titratie en afbouw van farmaceutische GHB (DeTiTap-methode) kan worden gebruikt in verschillende instellingen en therapeutisch situaties, maar het wordt sterk aanbevolen in de volgende situaties:

- Geplande detoxificatie binnen medium-care faciliteiten zonder directe toegang tot een intensieve care unit, wanneer een hoge dosis GHB wordt misbruikt, angststoornissen of psychose zijn gediagnosticeerd of vermoed.
- Acute GHB onthouding wanneer psychose (hoofdstuk 6) of andere complicaties, zoals rhabdomyolyse zijn waargenomen (hoofdstuk 5a), met of zonder de beschikbaarheid van een volledige medische voorgeschiedenis van GHB misbruik. Rekening houdend met het feit dat antipsychotica een beperkte tot bijna geen rol spelen in de behandeling van GHB onthouding gerelateerde psychose/ delirium.
- Wanneer het laatste gebruik van illegale GHB meer dan 6 uur is vóór de opname.

Het is zeer relevant dat artsen, met name verslavingsartsen, huisartsen en psychiaters, hun kennis over GHB afhankelijkheid en onthouding (herkenning en behandeling) uitbreiden, gezien het snelle optreden van ernstige ontwenningsverschijnselen (hoofdstuk 4) en complicaties bij deze patiënten (hoofdstuk 5a en 6). Het gebrek aan kennis kan leiden tot onnodige complicaties en soms tot de dood van deze patiënten[10].

Dit proefschrift heeft tot resultaat geleid dat er een aantal protocollen in de verslavingszorgcentra, geestelijke gezondheidszorg en algemene ziekenhuizen kunnen worden uitgevoerd. Dit met het oog op het voorkomen van levensbedreigende complicaties en intensive care unit (ICU) opnames (online beschikbaar op de NISPA website: (http://www.nispa.nl/onderzoek/ghb/protocollen).

Echter, het is belangrijk om te benadrukken dat gezien de beperkte informatie die momenteel beschikbaar is, het voorgestelde algoritme in deze protocollen voorlopig is. Er ontbreekt bijvoorbeeld een directe vergelijking tussen de DeTI-Tap methode en de frequent gebruikte alternatieven voor ondersteuning bij detoxificatie zoals benzodiazepines of Baclofen. Deze vergelijking is van belang om de veiligheid, werkzaamheid en kosteneffectiviteit van deze behandelingsmethoden te toetsen.

GHB-afhankelijke patiënten worden meestal omschreven als moeilijk te controleren, met een hoge zucht, snelle en hoge terugval in GHB gebruik kort na de detoxificatie, en een gebrek aan inzicht. Dit impulsieve gedrag, gekenmerkt door ongeduld met uitgestelde beloningen en een verhoogde kans op prematuur reacties[11], zoals beschreven in hoofdstuk 2, kunnen gerelateerd worden aan een staat van dopaminereceptoren opwaartse-regulatie en een abnormale verhoging van de dopamine transmissie[12, 13] en serotonine irregulariteit[14] naast manipulaties van de noradrenergic systeem[15] en de verminderde GABA levels[16]. Zo kunnen dus verschillende neurobiologische factoren de hoge recidieve beïnvloeden.

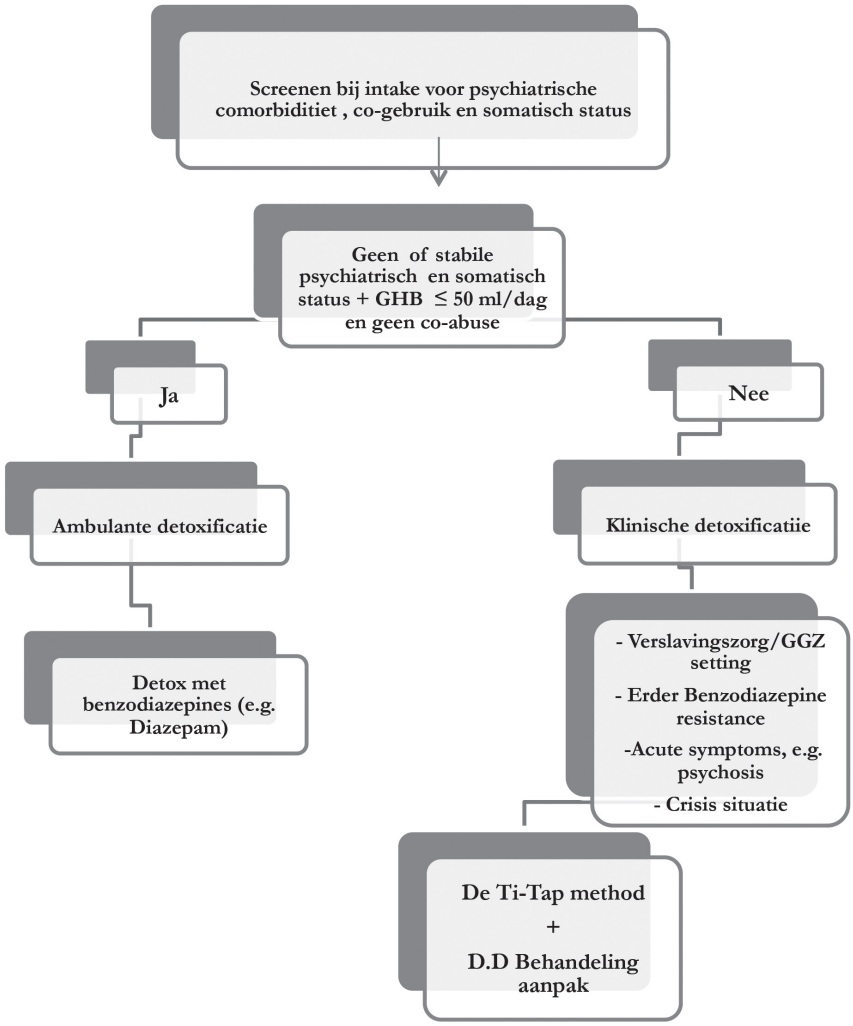

Figure: Samenvatting aanbeveling

Dit neurobiologische proces wordt verwacht aanwezig te zijn voor en tijdens de GHB onthoudingsfase en kan weken aanhouden (hoofdstuk 2). Maar we weten nog steeds niet wat de exacte neurobiologische veranderingen zijn die bijdragen aan de waargenomen extreem snelle en hoge terugval recidieve bij GHB-afhankelijken in vergelijking met aan andere middelen gebonden stoornissen. Dit, naast het feit dat sommige GHB verslaafde patiënten ook leiden aan angst, hypothetisch kan dit vertaald worden dat zij de gevoelens van zucht of verleiding minder kunnen weerstaan, wat leidt tot terugval in GHB misbruik in de eerste weken na detoxificatie. De confrontatie van de patiënten met de druk uitgeoefend door de omgeving aan het begin van de behandeling is een grote risicofactor die ze moeten overwinnen om abstinentie te handhaven[25]. Daarom kan het van belang zijn om te onderzoeken of een aangeboden behandeling in een gesloten intramurale instelling, bijvoorbeeld voor een periode van 6 weken, de angst, impulsiviteit en terugval beperken, en een toevoegde waarde heeft op de inzet en deelname aan behandeling. Meer informatie en studies om deze hypothese en behandelaanpak te ondersteunen, zijn vereist. Het is ook zeer relevant om de persoonlijke opvattingen, het gedrag, en verklaringsmodellen van deze patiënten met betrekking tot hun GHB afhankelijkheid te onderzoeken, en de mogelijke oorzaken en factoren die bijdragen aan terugval in misbruik. Dergelijke inzichten kunnen helpen bij het begrijpen van het gedrag van deze patiënten en om optimale benaderingen van therapie te ontwikkelen. Gelijktijdig geïntegreerde behandeling van bestaande psychiatrische co-morbide stoornissen moet worden aangeboden en impliceert de aanwezigheid van de nodige psychiatrische expertise binnen de professionele behandelteams.

Zoals eerder vermeld, deze patiënten melden een lage kwaliteit van leven, een regelmatige evaluatie van de ontvangen therapie met verbetering van de levenskwaliteit (EuroQol-5D) als parameter is geadviseerd. Levenskwaliteit wordt beschouwd als een goede parameter om de invloed en het succes van behandeling te beoordelen[24].

EuroQol-5D is een eenvoudig zelfrapportage instrument dat gemakkelijk kan worden ingevuld door de patiënt, en kan de inzet voor follow-up stimuleren.

Ten slotte, het neurobiologisch beschikbare bewijsmateriaal heeft de complexiteit van GHB farmacologie en afhankelijkheid bevestigd, net als de betrokkenheid van de verschillende neurotransmittersystemen in de hersenen (hoofdstuk 2). Er is echter weinig informatie over de gevolgen van chronisch GHB misbruik op de hersenanatomie en functie. Beeldvormende technieken kunnen worden gebruikt om de lange-termijn effecten en mogelijke neurologische schade gerelateerd aan chronisch GHB gebruik te beoordelen. Zo ook zijn er studies over cognitieve stoornissen, zoals leren en geheugen, van belang om de langdurige klinische effecten van GHB gebruik bij mensen te kunnen beoordelen zoals vermeld wordt vanuit dierenstudies[18-20].

Algemene kwesties

Het huidige proefschrift moet worden gezien in het licht van de sterke en zwakke punten. Een grote kracht van dit proefschrift is het innovatieve karakter. Voor zover wij weten, is dit de eerste multicenter (landelijke) systematische methode van GHB detoxificatie met een gestructureerde

monitoringsaanpak. Het biedt de eerste handreiking op een veilige herstelroute voor deze patiënten, het verbeteren van hun kwaliteit van leven, en het verminderen van crisisinterventies en levensbedreigende complicaties. Dit proefschrift biedt ook een beeld, voor het eerst, van de psychiatrische co-morbiditeit en psychologische stress als een cruciale factor die het patroon van GHB misbruik en keuze voor detoxificatie beïnvloed. Gezien de medewerking van verschillende verslavingszorgcentra in Nederland kan worden verwacht dat de geïncludeerde patiënten een representatieve steekproef zijn van GHB-afhankelijke patiënten in behandeling. Een ander belangrijk pluspunt is dat de resultaten van de huidige studie zijn vertaald in een behandelprotocol dat in verschillende klinische verslavingszorgcentra in Nederland is geïmplementeerd.

Bovendien is in de huidige studie de inzichten uit de basis wetenschap en preklinisch onderzoek op neurofarmacologie van GHB naar een klinische aanpak vertaald, ten gunste van de behandeling van het ernstige GHB onthoudingssyndroom en om terugval te voorkomen. Dit proefschrift omvat een breed scala van de klinische aspecten van GHB afhankelijkheid.

Er moeten echter verschillende beperkingen worden overwogen. In dit proefschrift worden de resultaten op basis van observationele en cross-sectionele studies vermeld. Met deze methode is het moeilijk om causale verbanden te vinden, alle beïnvloedde variabelen kunnen we niet controleren, waardoor de resultaten met voorzichtigheid moeten worden geïnterpreteerd. We hebben geen vergelijking met een controlegroep, noch een gerandomiseerde klinische studie uitgevoerd om de efficiëntie van de detoxificatie met farmaceutische GHB versus bijvoorbeeld de behandeling met benzodiazepinen of Baclofen te kunnen vergelijken. Dus de resultaten van de lopende studies moeten niet worden beschouwd als definitieve antwoorden op vragen zoals: hoe verschilt GHB afhankelijkheid van ander middelenmisbruik? Is GHB detoxificatie met ondersteuning van GHB beter dan met benzodiazepine?

Een vergelijkende RCT studie tussen de DeTi-Tap-methode en benzodiazepine of Baclofen medicatie supplementen als steun bij detoxificatie, zou belangrijk zijn om deze laatste vraag te kunnen beantwoorden. Voor de studies in hoofdstuk 4, 5 en 8a, was de data gebaseerd op de zelfrapportage van het middelengebruik zonder bevestiging door bloed of urine toxicologische testen.

Een ander punt van aandacht is de onvolledigheid van de data: niet alle deelnemers vulden alle onderzoeksinstrumenten in en een aantal (37%) waren niet beschikbaar voor follow-up. Zo werd psychiatrische co-morbiditeit gemeld in slechts 50% van de opgenomen patiënten. Hierdoor kan onze inschatting van de prevalentie van psychiatrische co-morbiditeit mogelijk een onderschatting zijn van het werkelijke probleem.

Ook onze bevindingen in hoofdstuk 6 kunnen worden bekritiseerd omdat ze zijn gebaseerd op een beperkt aantal patiënten. We kunnen niet bevestigen dat detoxificatie met de titratie en afbouw (DeTiTap) de enige/ beste methode van behandelingsregime is in geval van benzodiazepine resistentie. Het verzamelen van meer gegevens via de implementatie van de ontwikkelde protocollen geeft wellicht meer inzicht in de toekomst. Bij de beoordeling van Baclofen als een middel bij de preventie van terugval in hoofdstuk 8a, kan de geïncludeerde zeer gemotiveerde

patiënten niet worden uitgesloten, waardoor onze resultaten mogelijk beïnvloed kunnen zijn. Tenslotte moet opgemerkt worden dat de resultaten niet gegeneraliseerd kunnen worden naar alle GHB gebruikers, omdat de studies beperkt waren tot de klinisch opgenomen patiënten binnen de verslavingszorg. Het zou relevant zijn om onze patiënten te vergelijken met recreatieve GHB gebruikers of met afhankelijke patiënten die niet bekend zijn binnen de verslavingszorg. Het blijft ook te onderzoeken of onze bevindingen in lijn zijn met de kenmerken van GHB-afhankelijke internationale patiënten populaties.

Conclusie

Dit proefschrift heeft duidelijk aangetoond dat GHB onthouding een complex syndroom is, gerelateerd aan meerdere neurobiologische routes. Bij de keuze voor de aanpak van detoxificatie moet er rekening worden gehouden met het hoge percentage van psychiatrische co-morbiditeit en co-misbruik door GHB afhankelijke patiënten. Het wordt aanbevolen om systematisch vroegtijdig te screenen (psychiatrisch en somatisch), om het aanbod van detoxificatie te kunnen verbeteren en optimaliseren. Sommige patiënten komen in aanmerking voor ambulante detoxificatie. De DeTi-Tap-methode is haalbaar en kan veilig intramuraal worden uitgevoerd in medium-care-instellingen, met geen of beperkte toevoeging van andere medicatie. Het heeft ook goede resultaten in de algemeen ziekenhuis instellingen geboden en wordt aanbevolen als behandelingsaanpak bij benzodiazepine-resistente patiënten. Dit proefschrift benadrukt ook dat de terugval in GHB-gebruik een ernstig probleem is dat in toekomstig onderzoek moet en zal worden aangepakt.

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CURRICULUM VITAE

Rama Kamal grew up in the warm city Omdurman, Sudan. She attended Om-Amar High School in Abu-Dhabi, the United Arab Emirates. She acquired in 1993 her medical degree at Medical Faculty of Ain Shams University Cairo, Egypt and completed the post-graduation training required for permanent medical registration in Sudan. She stopped with her Registrar psychiatry position and travelled to the Netherland where she was introduced to the field of addiction medicine. Rama has been working at Novadic-Kentron addiction care institute since 2002, where she had the opportunity to occupy several positions, such as a clinical manager until 2014 in region north, Novadic-Kentron. She completed her training as an Addiction Medicine specialist at the Radboud University Nijmegen in 2009. She is a fellow in the Dutch Royal Medical Federation (KNMG) of Addiction Medicine physicians specialists and has been working as Consultant Addiction Medicine. This besides the function of head of the crisis unit in the period of 2009 to 2011. She is a lecturer in the National Addiction Medicine specialists training program, at Radboud Nijmegen University and was responsible for the Medical Training and Family Doctor Residency Program, region north at Novadic-Kentron tot 2014. She started in 2008 with developing the treatment line for patients addicted to GHB. Between 2011 and 2014 she was the Medical Supervisor of the first and second National GHB Addiction Monitor a project of Netherlands Ministry of Health and Welfare in collaboration with the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA). In line with this project, she also proceeded to start and continue her PhD in combination with the Senior Consultant Addiction Medicine function. In 2014 she started her training to become a psychiatrist at GGZE (the mental health treatment organization located in Eindhoven, the Netherlands) in combination with Maastricht University.

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