Send Orders for Reprints to reprints@benthamscience.net

Current Pharmaceutical Design, **2014,** *20,* **000-000** **1**

GHB, GBL and 1,4-BD Addiction

Tibor M. Brunt[1,*], Jan G. C. van Amsterdam[2-4] and Wim van den Brink[3,4]

[1]*Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Da Costakade 45, 3521 VS Utrecht, The Netherlands;* [2]*Centre for Health Protection, National Institute of Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands;* [3]*Academic Medical Center University of Amsterdam, Department of Psychiatry, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands;* [4]*Amsterdam Institute for Addiction Research, Academic Medical Center, P.O. Box 75867, 1070 AW Amsterdam, The Netherlands*

Abstract: A growing body of evidence shows that gamma-hydroxybutyric acid (GHB) is an addictive substance. Its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) show the same properties and may pose even more risks due to different pharmacokinetics. There are indications that problematic GHB use is increasing in the European Union. This review investigates the existing literature on the neurochemistry of GHB and its precursors, their acute toxicity, addiction potential and withdrawal, the proposed molecular mechanism underlying addiction and the treatment of withdrawal and addiction. Current evidence shows that GHB and its precursors are highly addictive, both in humans and animals, probably through a $GABA_B$ receptor related mechanism. Severity of withdrawal symptoms can be considered as a medical emergency. Recent studies suggest that benzodiazepines are not very effective, showing a high treatment resistance, whereas detoxification with pharmaceutical GHB proved to be successful. However, relapse in GHB use is frequent and more research is warranted on relapse prevention. This might aid medical practitioners in the field and improve general understanding of the severity of addiction to GHB, GBL and 1,4-BD.

Keywords: GHB, GBL, 1,4-BD, GABA, dopamine, illicit drugs, addiction, dependence, withdrawal.

1. INTRODUCTION

Gamma-hydroxybutyric acid (GHB), a precursor of gamma-aminobutyric acid (GABA), was developed as an anesthetic in the early 1960s [1]. This application was possible because, unlike GABA, GHB can pass the blood brain barrier. However, GHB became obsolete as an anesthetic due to undesirable side effects such as vomiting and severe cramps and its narrow dose-response margin [2]. In 2005, GHB was approved by the FDA (United States Food and Drug Administration) for the treatment of narcolepsy and in some countries it is also used in the treatment of withdrawal symptoms in alcoholics [3-6]. Since the 1990s, GHB has been increasingly recognized as a substance of abuse in recreational settings, due to its euphoric and sexually stimulating effects [2, 7]. As a consequence, GHB was listed as an illegal drug in several countries [8]. Not much later, the GHB precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) emerged as legal alternatives to GHB exerting similar effects. These GHB-like psychotropic effects are induced because both compounds are rapidly converted to GHB [9, 10], following oral use of GBL [10-12] or 1,4-BD [13, 14]. GHB, GBL and 1,4-BD are cheap and easily purchased via the Internet [15].

GHB and its precursors show a biphasic effect pattern, the stimulant-like effects and euphoria are quickly followed by sedation as blood concentrations rise. There is a fine line between the dose where desired effects are experienced and overdose symptoms occur [16]. Overdose symptoms include ataxia, seizures, vomiting, cardiac-, respiratory- and CNS depression and, eventually, reversible coma [17]. It is therefore not surprising that inexperienced use of GHB and its precursors has led to a worldwide documentation on their toxicity [11, 17-22]. Furthermore, the probability of intoxication increases when other sedatives are combined with GHB, e.g. alcohol or ketamine [23-25].

*Address correspondence to this author at the Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Da Costakade 45, 3521 VS Utrecht, The Netherlands; Tel: (+) 31.30.2959325; Fax: (+) 31.30.2971111; E-mail: TBrunt@trimbos.nl

Last year prevalence (current use) of GHB in the Netherlands in 2009 was about 0.4% (70,000) [26]. Estimations from Australia and the United Kingdom indicate lower prevalences of current use of 0.1% among the general population [27, 28]. However, there are indications that problematic GHB (and GBL) use is rapidly increasing in the European Union [15]. In the Netherlands, emergency department (ED) presentations of GHB intoxications increased from 300 ED treatments in 2004 to 1200 in 2009 [26]. A similar trend, albeit more modest, was seen in the United Kingdom between 2006 and 2010 [29]. Also, in general, the nature of GHB intoxications at EDs was more serious than that with most other drugs of abuse, like ecstasy or cannabis [30]. Likewise, the number of information requests for GHB and GBL intoxication has risen steeply and ranks second after cannabis in 2011 and, especially, information requests by medical practitioners about GBL intoxication increased sharply from 5% in 2008 to 14% in 2011 [26]. In addition, various international ED studies reported GHB/GBL intoxication as one of the major forms of drug overdosing [31-35]. Despite these hazards, GHB and its precursors are generally considered as cheap, safe and harmless by recreational drug users [36, 37]. Moreover, GHB was long considered not to be addictive [38].

However, there is convincing evidence now that frequent GHB use can rapidly cause dependence and withdrawal [39, 40]. First of all, preclinical evidence of the dependence potential of GHB and its precursors has recently been accumulating based on animal studies [41-45]. Similarily, in humans, physical dependence has been described within weeks of frequent and heavy use [46]. Without treatment, withdrawal is characterized by symptoms of variable severity and in order to avoid these symptoms users may end up taking GHB around the clock [38, 39, 47-50].

This review investigates the existing literature on the neurochemistry, addiction potential and treatment of GHB, GBL and 1,4-BD addiction. Starting with the basic metabolism, pharmacokinetics and pharmacodynamics of these substances, the review will then briefly show current clinical applications of these substances as well as their recreational use that followed and acute toxicity. The main focus of this review is on the addictive properties of these substances, the molecular mechanisms involved in GHB addiction

1381-6128/14 $58.00+.00

supported by the most recent evidence and the treatment of withdrawal in patients with GHB, GBL and 1,4-BD addiction. The purpose of this review is to improve understanding of the severity of addiction to GHB and its precursors and a critical appraisal of current evidence.

2. METABOLISM OF GHB, GBL AND 1,4-BD

GHB is structurally related to GABA, the main inhibitory neurotransmitter in the CNS. It occurs naturally in the brain and is both a "precursor" and a metabolite of GABA [38]. It is found at very low concentrations in the brain [51, 52]. It is derived from its metabolic precursor GABA by conversion into succinic semialdehyde via GABA transaminase (Fig. (**1**)) [38]. Succinic semialdehyde is subsequently converted into GHB by succinic semialdehyde reductase. In a metabolic feedback loop, GHB may be degradated by the action of GHB dehydrogenase into succinic semialdehyde and then converted by GABA transaminase into GABA again. Nevertheless, the primary degradation pathway of GHB seems to be into succinate through the conversion of succinic semialdehyde by the enzyme succinic semialdehyde dehydrogenase [17]. Additional GHB can be formed by the oxidation of 1,4-BD via alcohol dehydrogenase into gamma-hydroxybutyraldehyde, which is metabolized by aldehyde dehydrogenase to GHB [53]. Also serving as a prodrug, exogenous GBL is converted into GHB by a lactonase that is present in liver and serum, but not in the brain [17].

3. PHARMACOKINETICS

After oral intake, GHB is easily absorbed and peak concentrations in the blood and brain occur within 1 hour. The half-life is 30-60 minutes, while GHB is usually fully eliminated from the blood within 6 hours [54]. Although the subjective effects of GBL and 1,4-BD seem more or less equivalent to those of GHB, they show a different pharmacokinetic profile. GBL is even more easily absorbed than GHB [10] and is converted rapidly in the periphery, resulting in a higher bioavailable level of GHB after administration of GBL than an equivalent dose GHB [55]. Because of its higher bioavailability and more rapid absorbtion, GBL is regarded to be more potent than GHB, but with a shorter duration of effects. Conversely, due to somewhat slower elimination, it has been suggested that 1,4-BD has a longer duration of effects than GHB [56, 57]. Like GHB, it is rapidly absorbed with a peak concentration of GHB after 25 minutes in healthy human volunteers [54]. In baboons, both GBL and 1,4-BD were shown to give a higher maximum concentration of GHB and shorter time to reach this concentration than GHB itself [58]. Pharmacokinetic differences could imply that users of GBL or 1,4-BD are at different risks of overdosing than users of GHB because the speed of action of these substances is different . In addition, GBL is more lipophilic than GHB and the enzyme lactonase can vary genetically between individuals, which means that GBL can display even more unpredictable results, especially in first-time users [59].

4. NEUROBIOLOGICAL TARGETS: GHB- AND GABA RECEPTOR SYSTEMS

GHB has been proposed as a neurotransmitter or neuromodulator in the brain [51, 60]. In both rodent and man, receptors have been identified to which GHB binds with high affinity [61, 62]. GHB receptors were shown to be abundant in the hippocampus and cortex [61-63]. These are likely to be G-protein-coupled receptors and respond to micromolar (physiological) concentrations of GHB, but rapidly desensitize at doses exceeding these physiological concentrations [62]. In these micromolar concentrations, the presynaptic GHB receptor probably inhibits GABA release and its action is thus excitatory [38, 64]. In addition, glutamate release is also affected through presynaptic GHB heteroreceptors and glutamatergic NMDA receptors appear to be downregulated by GHB, impairing spatial learning [38]. The precise biological function of the GHB receptor remains unknown.

GHB also binds to the $GABA_B$ receptors, but with low affinity [38, 62]. Endogenous concentrations of GHB are too low to activate these receptors. However, when concentrations of GHB in the brain rise as a result of systemic administration (like in settings of drug use or involuntary administration in rape assault cases), the GHB receptor desensitizes and GHB acts as a competitive agonist at the presynaptic $GABA_B$ receptors. These presynaptic $GABA_B$ receptors can be subdivided into autoreceptors, at which GHB has an inhibitory effect on GABA release, and heteroreceptors, which inhibit the release of most other neurotransmitters [38]. It is mainly through

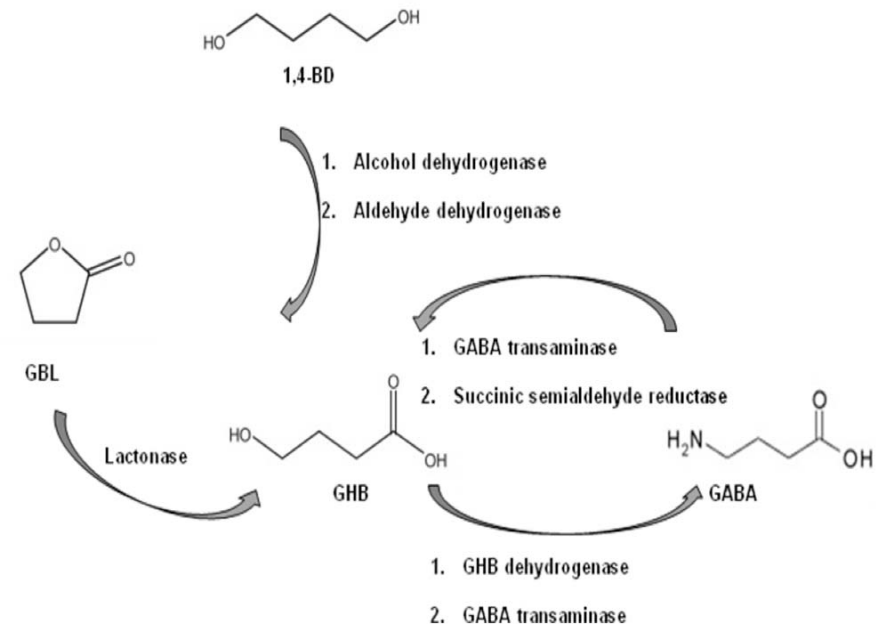

Fig. (1). Metabolism of GHB, GBL and 1,4-BD.

the $GABA_B$ receptor that exogenous GHB exerts its typical pharmacologic, clinical, behavioral, and toxicologic effects [17, 38]. This was ascertained by experiments where it was shown that $GABA_B$ antagonists, but not GHB antagonists, provided protection from GHB's typical effects in rodents, like sedation, hypothermia, distorted coordination, hypolocomotion and absence seizure-like activity [64, 65]. Moreover, these effects were completely absent in $GABA_B$ knockout mice after GHB or GBL application [66]. In animals and humans, the dual actions at these two receptor systems could explain the sudden awakening after several hours of GHB-induced deep sleep, because over time the concentration of GHB in brain decreases to a level at which predominantly GHB receptors are activated and excitation remains [52]. Also, in animal drug discrimination studies, mainly $GABA_B$ agonists, like baclofen, were able to evoke the same responses as GHB [67]. Discriminative stimulus effect studies can be used to study whether or not different substances evoke similar effects or whether certain substances can (partially) replace other substances. These studies can also be used to uncover common mechanistic pathways.

Selective $GABA_B$ antagonism diminished these discriminative stimulus effects, whereas antagonists of the GHB receptor did not. However, the difference in effects between baclofen and GHB has led researchers to hypothesize about the possibility for two receptor subtypes of $GABA_B$. Additional complexity of GHB's actions is added by the fact that it is partly degraded into GABA in the brain. So, it was argued that GHB activates the GABA system in at least three independent ways: (1) as low-affinity $GABA_B$-ergic agonist, (2) promoting GABA release and (3) as a precursor of GABA [38]. Figure **2** tries to capture the interactions of GHB with its respective receptor systems.

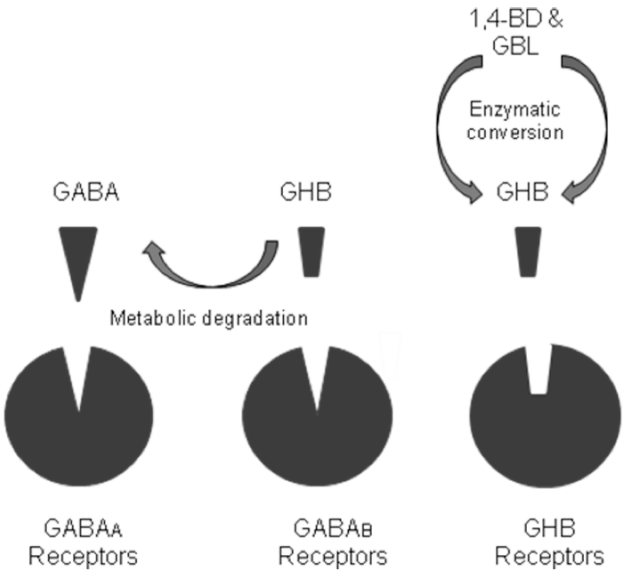

Fig. (2). The pharmacodynamics of GHB and its putative targets in the brain. Exogenously administered 1,4-BD and GBL are metabolized into GHB via enzymatic pathways in the body. GHB is an agonist at both the GHB- and $GABA_B$ receptors. GHB is degraded and metabolized downstream into GABA, which subsequently binds to its own receptors, $GABA_A$ and $GABA_B$.

5. CLINICAL APPLICATIONS OF GHB

Nowadays, GHB is not commonly used as an anesthetic anymore. However, there are some other medical applications for its use, GHB (as Xyrem®) is indicated to treat insomnia in narcolepsy patients [68] and alcohol withdrawal symptoms in alcohol dependent patients [4]. GHB reduces the symptoms of narcolepsy by stimulating the slow-wave, "deep sleep" with no effect on REM sleep [69]. The typical dose for this clinical indication is 4.5 g/ daily p.o., divided over two doses of 2.25 g at bed time and 4 hours later [70]. In some countries, GHB has also been used for the treatment of opioid withdrawal symptoms, alcohol withdrawal symptoms and for the prevention of relapse to alcohol use in alcohol dependent patients [40, 71, 72]. Clinical trials demonstrated that GHB, from three to six daily administrations (50-100 mg/kg), was able to suppress alcohol withdrawal and facilitated abstinence from alcohol [4]. However, serious concern was expressed in another systematic review about the risk of developing GHB dependence, which was not adequately investigated in those previous clinical trials [73].

The virtual absence of abuse liability of GHB in clinical trails of narcolepsy patients or alcoholics remains a challenging issue [4, 74, 75]. Approximately, only one case for every 2,600 narcolepsy patients treated fulfilled DSM-IV criteria for substance abuse [76]. There could be a number of possible explanations for this. Pharmaceutical GHB use for narcolepsy is prescribed in a medical setting of strictly nightly doses of up to 4.5 g to 9.0 g/ a day, fairly low doses compared to the doses used by frequent recreational users. Another proposed explanation is that there are important differences between illicit GHB and the pharmaceutical product in accessibility and purity [76]. Illicitly synthesized GHB often contains uncontrolled, and sometimes substantial higher than expected, concentrations or might still contain a considerable amount of GBL for instance. This could have profound effects on its potency and abuse liability. Also, combined use of alcohol and other CNS depressants is strongly discouraged in narcolepsy patients, whereas recreational and problematic users usually combine GHB with other substances [77-79]. Finally differences in addiction vulnerability between medical and recreational users may play an important role.

For the treatment of alcoholism, craving for GHB was found to be more frequent, although still a limited phenomenon (about 10%) [74]. Interestingly, when craving for and abuse of GHB was investigated among different types of alcoholics, craving for GHB was higher in those with previous cocaine dependence than in "pure" alcoholics, but craving for GHB did not differ between "pure" alcoholics and those with previous heroin dependence. According to the current insights, this may be due to effects on the dopamine (DA) system. Chronic exposure to cocaine reduces $GABA_B$ receptor activity in the mesocorticolimbic system [80, 81]. GHB may upregulate DA in these former cocaine using alcoholics through reactivation of the $GABA_B$ receptor, with a higher propensity for developing craving for and abuse of GHB.

6. RECREATIONAL USE OF GHB

6.1. Prevalence of use

Since the 1990s, GHB, GBL and 1,4-BD have been increasingly used as recreational drugs [2] for its increased euphoria, relaxation, increased sociability and enhanced sensuality [72]. For instance, in the Netherlands the use of GHB gradually increased over the last decade and became the most popular recreational anesthetic drug with a last year prevalence of 0.4% in the general population in 2009 [26, 82]. GHB users are generally young adults (18-30 years) [32, 83, 84]. In the ESPAD study, a population survey performed amongst 15-16 year old European college students, a life-time prevalence of GHB use was reported ranging from 1% to 2% [85]. Lifetime and last month prevalence of GHB use in the Australian population aged 14 years or older was 0.5% and 0.1%, respectively with a peak between 20 and 29 years [28, 86]. However, GHB use appears to start at a much younger age (16-17 years) [87] than in 2001, when the average starting age was 24 years [88]. Moreover, European surveys among partygoers show higher prevalence rates of GHB use than in the general population. In a recent survey among visitors of parties and festivals in the Netherlands, last month prevalence of GHB use was 4.6% and lifetime use 14% with a mean age of 23 yrs [89]. A recent survey carried out in the United Kingdom of a group of 2000 clubbers revealed a lifetime

prevalence of 15.2% for GHB and 5.8% for GBL use, with last month prevalences of 1.7% and 1.6%, respectively [90]. Between 2005 and 2006, last 4 months prevalence of GHB use among clubbers (mean age 24 yrs) in New York was 5% [91]. In summary, recreational GHB use is on the rise with general GHB use and start of use at a young age.

6.2. Characteristics of Ghb Users

In a typology of club drug users in New York City, users of GHB were often characterized as extensive polydrug users with a tendency for sensation seeking and high risk behaviours [77]. Extensive polydrug use was supported by ED studies done in Western Europe [21, 29, 35] and Australia [33]. These studies suggested that these users were rather indiscriminatory of the drugs they used, as long as they got their high. In the Netherlands, in recent years, the use of GHB has shifted from partygoers in the larger cities to a, less typical, broader group of users spread out over more rural areas and use more often outside the party scene [92, 93]. A worrying phenomenon is that these users frequently report passing out (coma) after an unintentional overdose, at home or with friends, and rarely indicate this as problematic [87]. This is supported by previous emergency department (ED) studies, showing frequent hospitalization after a GHB overdosis [21, 36, 94]. The subjects under study reported using GHB several times a week and even several times a day [21]. This also raises the question whether these users may be compulsive users or addicted.

Research into the source of obtaining GHB revealed that most users get it from friends or make it themselves [79, 87, 95]. It may very well be that the relative ease to manufacture GHB and the free accessibility of its components through internet wholesale (cleaning products, usually pure GBL) leads the drug to be around in abundance and its use relatively unrestrained. Finally, GHB is a very cheap drug (0.5 euro per dose) and often handed out for free by friends. Partners, colleagues or friends are often unaware of heavy use of GHB by their peers as frequent users are able to function normally and generally show no physical signs of use, letting frequent use go virtually undetected. Therefore, it could be that this may have led to a certain group that was vulnerable for the development of GHB abuse and addiction.

7. PROBLEMATIC USE: ACUTE TOXICITY

7.1. Clinical Symptoms

GHB, GBL, and 1,4-BD have all been described as toxic substances [17, 31]. In the cases of GBL and 1,4-BD this is largely ascribed to the pharmacological conversion to GHB. GBL is a biologically inactive compound and 1,4-BD has proven to have a moderate toxicity by itself. From a large body of international case studies, clinical intoxication symptoms have been reported [19, 22, 31-35]. Most commonly seen were CNS depression associated with bradycardia, hypotension and hypothermia. In addition, other symptoms include aggression, ataxia, amnesia, vomiting, somnolence, apnoea, seizures, asphyxia and coma [31, 38, 96]. Most of these symptoms usually resolve within 4 to 8 hours, probably due to the short elimination time of GHB and its precursors and metabolites [54]. Some of the symptoms that were reported in cases of GHB toxicity may be related to the polydrug use, mainly concurrent use of ethanol has been described to pose more risks than the use of GHB or its precursors alone [31]. Users who combined GHB with ethanol showed more severe complications related to GHB use, both in the clinic [21] and in a double-blind, placebo-controlled, study [54]. Increased toxicity was not the result of a pharmacokinetic interaction between GHB and ethanol. Similarly, the probability of inducing a coma may be increased by combined use with other sedatives [24]. On the other hand, sedative effects of GHB might be counteracted by the combined use of stimulants, such as cocaine or amphetamine.

7.2. Clinical Case Studies and Epidemiology

Many ED case studies mention GHB related overdose and subsequent coma as major reason for drug use related hospitalization [19, 22, 31-35]. In the Netherlands, it is estimated that 20% of all drug related hospitalizations was due to GHB [26]. This is a very high percentage, considering that prevalence of GHB use in relatively modest in comparison with other drugs. In Melbourne, Australia, 618 GHB-related ambulance attendances were recorded during 2001 to 2005 with an increase of 4% per month, a higher rate of increase than for heroin overdoses [97]. In addition, 90% of patients were hospitalized, compared to 21% for heroin. However, in most countries estimates are hard to come by and many cases of GHB intoxication are probably overlooked anyway. Many patients and their friends will not report to an ED for assistance and rather "sleep it off" [31]. Also, many cases of GHB intoxication will be misdiagnosed as result of unfamiliarity with the symptoms or confused with ethanol intoxication or another sedative.

A Spanish ED study describing cases from 2000 to 2007 showed that 72% of GHB-intoxicated patients scored ≤ 12 on the Glasgow Coma Scale (GCS) [35]. If a low score on the GCS is also accompanied by vomiting, aspiration might follow and aspiration pneumonia, due to the lack of protective airway reflexes [31]. The state of non-responsive coma is defined by a GCS of 3 and this is frequently seen in these ED case series. Usually, monitoring of vital signs suffices and most patients awake rapidly from non-responsive coma to consciousness without hangover or headache. Currently, there is no antidote for GHB overdose symptoms and treatment of acute intoxication is mainly supportive. Intubation and mechanical ventilation are rarely needed in these patients [98], unless the respiratory system is severely hampered by CNS depression or when patients show clinical indications for it, like vomiting or seizures [31]. Due to the quick absorption of GHB, gastric lavage is not very useful. Administration of extra oxygen has been described and atropine for bradycardia [17]. Sudden awakening and agitation are characteristics that follow after overdose, sometimes sedatives are required to calm the patient down [25]. It has been proposed that physostigmine might reverse some of the clinical symptoms of GHB intoxication, but others have concluded there wasn't enough evidence to recommend this as a clinical therapy. Moreover, the use of physostigmine was even associated with serious adverse events, like atrial fibrillation, bradycardia, pulmonary infiltrates and hypotension [99, 100].

In addition to these clinical findings, several hundreds of deaths have been mentioned in two different studies from the United States and Europe as a consequence of GHB toxicity and its precursors [19, 22]. Presumably, the actual number is considerably higher, but in many of these cases combined use of GHB with other substances is involved and it is very hard to detect GHB in post-mortem fluids [31]. Therefore, it is difficult to determine a direct causal relation between GHB intoxication and death. In most cases, the cause of death was aspiration and respiratory arrest.

8. PROBLEMATIC USE: GHB ADDICTION

8.1. Addiction Liability in Humans

Regular GHB use may cause severe dependence and serious withdrawal symptoms upon abrupt discontinuation of chronic, frequent use [39, 40, 46, 101]. Studies on recreational users revealed a high dependence liability in frequent, heavy GHB users [36, 102]. In clinical trials with human subjects GHB displayed greater abuse liability than ethanol [16, 103]. It has been described that intensive/frequent GHB use (i.e. > 4 times per day, 2-4 weeks and in higher doses) can lead to physical dependence within a few weeks [46]. According to Miró *et al.* [104], the dose of GHB associated with dependence is about 18 g per day (with one dose on average being 2.5-3.5 g) and for GBL this is 10 g per day. Interestingly, the majority of patients in treatment for GHB dependence only had a brief

history of GHB use, often one or two years, suggesting that dependence to GHB indeed develops rapidly [12, 39, 46, 49].

8.2. Withdrawal in Humans

Upon drug discontinuation moderate GHB, GBL or 1,4-BD users will usually experience a mild withdrawal syndrome, but withdrawal can be more severe in chronic and heavy users of GHB, GBL or 1,4-BD. The withdrawal symptoms of GHB and its precursors start quickly (1 to 6 hours after the last dose) and can last 5-21 days in severe cases [50, 106]. This withdrawal syndrome is much more serious than previously assumed and certain symptoms are similar to that seen with other CNS depressants, like benzodiazepines, alcohol or barbiturates [40, 47-49]. In frequent and heavy users withdrawal symptoms include tremors, cardiac arrhythmias, hypertension, delirium, hallucinations and seizures [107-109]. Dependence severity was strongly associated with sleep problems [79], which may persist for weeks after GBL detoxification [110]. In terms of subjective severity, GHB withdrawal is often experienced to be just as severe as withdrawal from heroin and alcohol [39, 111]. However, the objective risks and symptoms of GHB withdrawal may vary substantially from those associated with heroin withdrawal, since GHB withdrawal has been associated with a rapid onset of life-threatening complications in some occasions [47, 107, 109]. The rapid onset of GHB withdrawal can at least partly be explained by its short half-life ($T_{1/2}$ of 20-45 min). The severity of withdrawal symptoms can urge users and clinicians treating GHB withdrawal by maintaining their GHB levels by redosing every two hours, around the clock (GHB intake every 30 minutes has been reported) [38].

8.3. Experimental Evidence: Animal DATa

Early drug discrimination studies indicated GHB as an addictive substance; GHB, GBL and 1,4-BD elicited similar responses in rats as reinforcers like ethanol or diazepam, known $GABA_A$ agonists [57, 112, 113]. $GABA_B$ agonists, like baclofen, were also able to partly mimick responses to GHB. Nevertheless, animals were clearly able to distinguish ethanol, baclofen or diazepam from GHB, and no other substance could really substitute for GHB, indicating that multiple receptors were probably involved in these discriminative stimulus effects in rats [76, 114]. Animals also showed conditioned place preference after chronic administration of GHB, which suggests reinforcing effects of GHB [115]. Other lines of evidence showed that GHB is readily self-administered by rats and mice, and rats that were chronically administered GHB showed tolerance and withdrawal [116-118]. Tolerance to GHB has been demonstrated after 3-6 days of daily administration in rats [117, 118]. In addition, GHB and alcohol showed cross-tolerance [105].

Perhaps the most compelling evidence for GHB, GBL and 1,4-BD as addictive substances comes from experiments executed in the laboratories of Weerts and colleagues from the John Hopkins University. They did a series of experiments in baboons, a non-human primate that shows a close genetic proximity to humans. Physical dependence was shown after chronic intragastric administration of GHB, GBL and 1,4-BD [41-44]. Chronic GHB (350-750 mg/kg), GBL (400-600 mg/kg) or 1,4-BD (600 mg/kg) decreased feeding behavior, disrupted performance and produced sedation and muscle relaxation. In these experiments, discontinuation of administration and $GABA_B$ antagonism produced abrupt withdrawal, not antagonism of the benzodiazepine site of the $GABA_A$ receptor with flumazenil. In more recent experiments, self-administration was established in baboons that were offered GHB (3.2-178 mg/kg/injection), GBL (10-130 mg/kg/injection) and 1,4-BD (10-100 mg/kg/injection) [43, 45].

8.4. GHB Addiction and Dopamine: Molecular Targets

Converging evidence suggests that virtually all known addictive substances induce their reinforcing properties through activation of the mesocorticolimbic dopamine (DA) system, so this brain circuitry has been a logical target for GHB's actions [38, 119]. The mesocorticolimbic DA circuitry is composed of the ventral tegmental area, nucleus accumbens and prefrontal cortex. GHB alters dopaminergic activity in the brain, either by increasing or decreasing the amount of DA released [120-122], and it decreases firing of dopaminergic neurons in the striatum [123, 124]. Chronic treatment of rats with GHB results in an increase of mRNA expression of dopamine D_1 and D_2 receptors in brain regions that are rich in GHB receptors [125] and the development of tolerance to the effect of GHB on brain dopamine levels. In rats, low doses of GHB (50-400 mg/kg) increase dopaminergic cell firing in the substantia nigra, whereas higher doses (1000-1500 mg/kg) inhibit dopaminergic cell firing [126]. However, in rats, after an initial inhibitory phase, DA release increases, probably due to GHB receptor re-activation [52]. This complex mechanism could partly explain the dual effects of GHB observed in recreative users i.e. both sedation and stimulation. Although some of the actions on the DA system are mediated through high affinity of GHB to the GHB receptor, most of it is thought to be mediated via the low affinity of GHB to the $GABA_B$ receptors in the mesocorticolimbic DA system [41, 44, 119, 127].

Classically, addictive drugs cause an increase in the neuronal activity of mesocorticolimbic DA system [119]. However, as was mentioned above, there is an intriguing paradox in GHB's actions on DA as it exerts two opposing actions: at low concentrations GHB stimulates DA release whereas at higher and enduring levels it inhibits DA release [128-130]. The solution of this apparent paradox lies in the interaction of GHB with $GABA_B$ receptors in the mesocorticolimbic dopamine (DA) system. The coupling between the $GABA_B$ receptors and the G protein-gated inwardly rectifying potassium channels was found to be more decreased in DA neurons as compared to GABA neurons [131, 132]. This renders GABA neurons more sensitive to GHB's actions than DA neurons. GHB administration may therefore preferentially inhibit GABAergic neurons and the release of GABA in the ventral tegmental area through presynaptic $GABA_B$ receptors. The result would be a disinhibition of DA neurons of the ventral tegmental area with increased dopaminergic activity within that circuitry (Fig. (**3**)). This mechanism was also supported in a study whereby direct injection of GHB into the ventral tegmental area, but not the nucleus accumbens, induced rewarding properties [42]. It is this disinhibition, leading to DA release, which is thought to be responsible for the addictive properties of GHB and its precursors. However, repetitive exposure to GHB (1) increases the $GABA_B$ receptor-potassium channel coupling of DA neurons, which inhibits DA release and (2) causes tolerance to GHB. GHB may even become aversive, which may offer an explanation for its efficacy in treatment of alcohol withdrawal symptoms [74].

This differential action of GHB on DA and GABA neurons might also help explain why GHB is addictive and baclofen is not [133]. In fact, it does explain various properties of GHB that have remained elusive previously. It explains the limited efficacy of treatment of GHB dependent patients with benzodiazepines. Importantly, it also offers additional avenues for addiction treatment of GHB and its precursors, like preliminary treatment results with baclofen promises [134]. Similarly, $GABA_B$ receptor antagonsim may also prove to be useful in treating respiratory depression resulting from GHB overdoses or withdrawal [135]. However, while the GABAergic mediated DA disinhibition hypothesis is plausible for many reasons, there could be alternative routes by which GHB may disinhibit DA neurotransmission, such as the modulation of GHB of the locus coeruleus norepinephrine neurons [136]. Finally, GHB-derived GABA interacts with both subtypes of the GABA receptor, which may provide for added complexity of GHB's addictive effects [38].

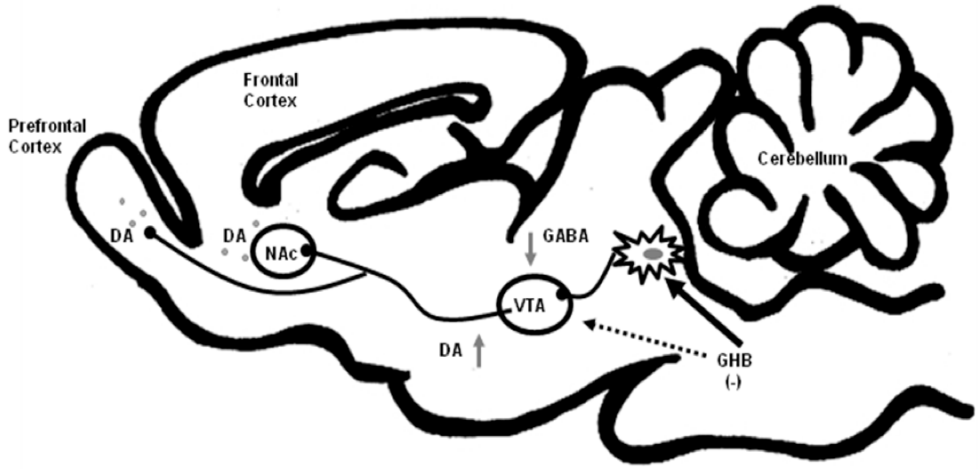

Fig. (3). The putative mechanism whereby GHB increases dopaminergic activity in the mesocorticolimbic circuitry. As indicated by the bold arrow: GHB preferentially inhibits GABAergic neurons and the release of GABA in the ventral tegmental area through presynaptic $GABA_B$ receptors. As indicated by the dotted arrow: dopaminergic neurons are relatively left unscaved, thereby causing DA disinhibition.
NAc, nucleus accumbens, VTA, ventral tegmental area, DA, dopamine.

9. TREATMENT OF GHB ADDICTION

Recently, most data about clinical treatment has been assembled in the Netherlands [26, 78, 79, 137]. Probably due to the serious lack of awareness of the risks of GHB, previous to 2009, treatment for GHB dependence was not registered in the Netherlands. But the number of requests for GHB dependence treatment has rapidly increased from 60 in 2007 to 761 in 2011 [137], leading to public health concern and scientific interest. Most subjects, seeking help for their GHB dependence, were young adults (mean age of 28 yrs; 32% younger than 25 yrs), and relatively more women were dependent on GHB compared to clients that are addicted to other substances of abuse (33%) [137]. This was also confirmed in a sample of 75 inpatients treated for GHB dependence (DUDIT dependence score > 25) where 73% was male and the mean age was 26.8 yrs. In addition, most patients were low educated (78%) and half of them (48%) was unemployed [79]. This unemployement rate was also found for users of GBL in a British study. Ages of these patients were between 21 and 37 years (mean 27.9) and 17 of 19 were male, mostly gay men [110]. All reported daily 'round the clock' use of GBL. Strikingly, almost half of GHB dependent clients in the Netherlands was known by the police for some criminal offence [95].

The withdrawal syndrome of GHB, GBL or 1,4-BD closely resembles that of other sedative-hypnotic agents [48, 138]. GHB withdrawal is known to cause autonomic dysfunction with severe CNS symptoms [11, 50]. A systematic review [109] on withdrawal from GHB, 1,4-BD and GBL included 27 studies with 57 cases with withdrawal: GHB in 36 cases (63%), 1,4-BD in 3 cases (5%) and GBL in 18 cases (32%). Withdrawal features, similar for all three agents, consisted of tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), anxiety (46%) and hypertension (44%). Seizures and rhabdomyolysis each occurred in 7% of the cases, and death occurred in one patient withdrawing from GHB [50]. In such severe cases of GHB withdrawal, intense treatment with high doses of sedative hypnotics, mostly benzodiazepines, was generally indicated [138].

Whereas in some instances, GHB withdrawal has responded well to a treatment with benzodiazepines, many patients still showed severe manifestations of withdrawal symptoms and treatment resistance to high doses of benzodiazepines [39, 48, 49, 109, 139]. The doses of diazepam or oxazepam could amount to up to 230 mg or 300 mg a day, respectively [49, 78]. In some cases with treatment resistance to benzodiazepines, pentobarbital proved successful and treatment with antipsychotic agents was sometimes considered if severe delirium or hallucinations were reported [138, 139]. Finally, baclofen may be useful to treat GHB withdrawal, as it decreased severe withdrawal symptoms in one case without complications [134].Also, baclofen is able to antagonize GHB self-administration in mice [140].

Because of the frequently observed treatment resistance of withdrawal symptoms to high dose benzodiazepine regiments and the many co-occuring complications during the standard GHB detoxification procedures, there has been a revision of the GHB detoxification protocol in the Netherlands, modelled as a scientific research program: the GHB-monitor of the Nijmegen Institute for Scientist-Practitioners in Addiction (NISPA) [95]. The new protocol was based on a similar principle as the opioid withdrawal therapy with opioids [141]. The new detoxification protocol basically treats GHB withdrawal with pharmaceutical GHB (Xyrem®) in a daily titration and tapering scheme. The first results of this new detoxification procedure are promising: patients were started with a very high dose of pharmaceutical GHB (mean 16.9 g/day), which was then titrated to the usual dose of their illicit GHB and from there slowly tapered to zero [78]. Preliminary results indicate that 90% out of 226 patients have been detoxified successfully in this way [26, 95]. Titration with pharmaceutical GHB resulted in minor withdrawal symptoms with a mean of 26 on a scale of 0–140 and no delirium or psychosis were experienced by any of the patients.

However, this is a novel and pioneering detoxification procedure, unique to the world to our knowledge, and randomized controlled clinical trials (RCTs) have not been performed yet to provide scientific evidence for clinical efficacy of this treatment. For instance, comparisons with the benzodiazepines detoxification procedures are not available yet and no cost-effectiveness studies have been conducted.

Equally important, a considerable percentage of detoxified patients relapsed into GHB use within 3 months follow-up, only about one third had ceased GHB use completely, whereas the rest relapsed into incidental to frequent use and also turned back to some form of mental health or addiction treatment [95]. A necessary step by the researchers is to identify predictors that are important for relapse prevention, such as the high co-morbidity with other mental disorders that was found for many of these GHB addicted patients [95].

10. CONCLUSIONS AND FUTURE DIRECTIONS

The available evidence shows that GHB, GBL and 1,4-BD are all substances with a considerable addiction potential and a potentially severe withdrawal symptomology. Most human evidence consists of case studies, hardly any systematic study or clinical studies were found of larger groups in addiction treatment. Similarly, most evidence for treatment efficacy is derived from case studies; virtually no solid RCTs for effective treatment are available. More appropriate studies are, however, underway. For instance in the Netherlands, where GHB and GBL use causes increasing health problems with rising numbers of users in addiction treatment, treatment guidelines have been developed [95]. These relatively large new groups of users in addiction treatment have also led to new research and scientific insights [79]. However, GHB addiction is still a relatively novel concept and is faced with new challenges in therapy and indicators for relapse prevention, similar issues that have been investigated a lot longer and more extensive for other addictive substances [142-144]

Whereas GHB exerts some of its stimulating actions directly through the GHB receptor, most studies point towards the GABA system as the most probable candidate for GHB's actions on DA response, and thereby the circuitry for reward and addiction. However, this $GABA_B$ mediated DA disinhibition hypothesis must be tested further, by creating GHB receptor knockout mice or with the use of more specific agonists or antagonists. As it is, it does explain many of the elusive properties of GHB in the past, like the limited efficacy of treatment of GHB dependent patients with benzodiazepines and it offers promising avenues for GHB addiction treatment, like treatment with baclofen for instance or $GABA_B$ receptor antagonists. They may also prove to be useful in treating GHB overdose symptoms [135].

One of the probable reasons for its increased use and, therefore, associated problems is the relative ease to manufacture GHB and easy accessibility of its precursors through internet (pure GBL). Until recently, GHB was classified as a Schedule II drug under the Dutch Opium Act, but its apparent great potential for harm and addiction has led the Dutch Minister of Health to execute another risk assessment. The overall risk potential of GHB use was now assessed as moderate to high and the government decided to upgrade GHB's status to a Schedule I drug ("hard drug") [8]. This will result in stronger law enforcement and the cracking down on illegal manufacture of GHB in the Netherlands. This shift in legal status might lead to an increase in the direct purchase and consumption of GBL as has already been suggested in studies from other countries where GHB's legal status became stricter, such as the United Kingdom or Switzerland [31]. As mentioned, GBL is a chemical with slightly different pharmacokinetics and a greater potency than GHB [58]. This may lead to differences in toxicity or addiction potential [59]. In addition, other analogues of GHB, such as gamma-hydroxyvaleric acid (GHV) for instance, have also been mentioned as possible replacements for GHB and they are sold as dietary supplements or other misleading products on the internet [145]. Because these substances differ in various aspects and toxicology, they might pose their own unique risks [146].

For experts in the addiction field, it is important to keep track of these quickly changing customs in drug use nowadays, in light of the often unpredictable and severe effects of certain substances, such as GBL and GHB. For medical practitioners, it is important to realise the urgency of withdrawal symptoms associated with GHB addiction and together with new insights into treatment and relapse will hopefully lead to an improvement in handling the complications with this substance and its precursors.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

Declared none.

ABBREVIATIONS

1,4-BD	=	1,4-Butanediol
CNS	=	Central Nervous System
DA	=	Dopamine
DSM-IV	=	Diagnostic and Statistical Manual of Mental Disorders, Fourth edition
DUDIT	=	Drug Use Disorders Identification Test
ED	=	Emergency department
FDA	=	United States Food and Drug Administration
GABA	=	Gamma-aminobutyric acid
GBL	=	Gamma-butyrolactone
GHB	=	Gamma-hydroxybutyric acid
GHV	=	Gamma-hydroxyvaleric acid
NISPA	=	Nijmegen Institute for Scientist-Practitioners in Addiction
RCT	=	Randomized controlled clinical trials

REFERENCES

[1] Laborit H. Sodium 4-hydroxybutyrate. Int J Neuropharmacol 1964; 3: 433-51.

[2] Kam PC, Yoong FF. Gamma-hydroxybutyric acid: an emerging recreational drug. Anaesthesia 1998; 53: 1195-8.

[3] Gallimberti L, Spella MR, Soncini CA, *et al.* Gamma-hydroxybutyric acid in the treatment of alcohol and heroin dependence. Alcohol 2000; 20: 257-62.

[4] Caputo F, Vignoli T, Maremmani I, *et al.* Gamma hydroxybutyric acid (GHB) for the treatment of alcohol dependence: a review. Int J Environ Res Public Health 2009; 6: 1917-29.

[5] Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006; 29: 939-46.

[6] Black J, Pardi D, Hornfeldt CS, *et al.* The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. J Clin Sleep Med 2010; 6: 596-602.

[7] Sumnall HR, Woolfall K, Edwards S, *et al.* Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). Drug Alcohol Depend 2008; 92: 286-90.

[8] van Amsterdam JGC, van Laar M, Brunt TM, *et al.* Risk assessment of gamma-hydroxybutyric acid (GHB) in the Netherlands. Regul Toxicol Pharmacol 2012; 63: 55-63.

[9] Hurlbut KM, Silverstein S. Gamma butyric acid and related compounds. Hurlbut KM, Silverstein S. Eds. poisindex. In: Toll LL & Hurlbut KM (Eds): POISINDEX® System. MICROMEDEX, Inc., Greenwood Village, Colorado (Edition expires 6/2000). 2000.

[10] Irwin RD. NTP Summary Report on the Metabolism, Disposition, and Toxicity of 1,4-Butanediol. NIH Publication No. 96-3932. United States Departement of Helath and Human Services, Public Health Sevice, National Institute of Health. Available from: ntp.niehs.nih.gov/ntp/htdocs/ST_rpts/tox054.pdf. [Accessed 2 April 2013]. 1996.

[11] Zvosec DL, Smith SW, McCutcheon JR, *et al.* Adverse events, including death, associated with the use of 1,4-butanediol. N Engl J Med 2001; 344: 87-94.

[12] Gónzalez A, Nutt DJ. Gamma hydroxy butyrate abuse and dependency. J Psychopharmacol 2005; 19: 195-204.

[13] Lora-Tamayo C, Tena T, Rodríguez A, *et al.* Intoxication due to 1,4-butanediol. Forensic Sci Int 2003; 133: 256-9.

[14] Dart RC. Medical Toxicology. Medical Toxicology. Baltimore/London, Lippincott Williams & Wilkins, 3 ed. 2004; 1096-102.

[15] EMCDDA. European Information Centre and Database on New Drugs. EMCDDA Early Warning System about GHB. 2011.

[16] Abanades S, Farre M, Barral D, *et al.* Relative abuse liability of gamma-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. J Clin Psychopharmacol 2007; 27: 625-38.

[17] Wong CGT, Chan KFY, Gibson KM, *et al.* Gamma-hydroxybutyric acid: neurobiology and toxicology of a recreational drug. Toxicol Rev 2004; 23: 3-20.

[18] Elliott SP. Nonfatal instances of intoxication with gamma-hydroxybutyrate in the United Kingdom. Ther Drug Monit 2004; 26: 432-40.

[19] Knudsen K, Jonsson U, Abrahamsson J. Twenty-three deaths with gamma-hydroxybutyrate overdose in western Sweden between 2000 and 2007. Acta Anaesthesiol Scand 2010; 54: 987-92.

[20] Lenz D, Rothschild M, Kroener L. Intoxications due to ingestion of gamma-butyrolactone: organ distribution of gammahydroxybutyric acid and gamma-butyrolactone. Ther Drug Monit 2008; 30: 755-61.

[21] Liechti ME, Kunz I, Greminger P, *et al.* Clinical features of gamma-hydroxybutyrate and gamma-butyrolactone toxicity and concomitant drug and alcohol use. Drug Alcohol Dep 2006; 81: 323-6.

[22] Zvosec DL, Smith S, Porrata T, *et al.* Case series of 226 gamma-hydroxybutyrate-associated deaths: lethal toxicity and trauma. Am J Emerg Med 2011; 29: 319-32.

[23] Ricaurte GA, McCann UD. Recognition and management of complications of new recreational drug use. Lancet 2005; 365: 2137-45.

[24] Kim SY, Anderson IB, Dyer JE, *et al*. High-risk behaviors and hospitalizations among gamma hydroxybutyrate (GHB) users. Am J Drug Alcohol Abuse 2007; 33: 429-38.

[25] Zvosec DL, Smith SW. Agitation is common in gamma-hydroxybutyrate toxicity. Am J Emerg Med 2005; 23: 316-20.

[26] van Laar MW, Cruts AAN, van Ooyen-Houben MMJ, *et al.* Netherlands national drug monitor; NDM annual report 2011. Trimbos Institute, Utrecht, The Netherlands. 2012.

[27] Home Office. British Crime Survey. Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales (2nd Edition). http://www.statistics.gov.uk http://www.homeoffice.gov.uk/science-research. 2012.

[28] Degenhardt L, Dunn M. The epidemiology of GHB and ketamine use in an Australian household survey. Int J Drug Policy 2008; 19: 311-6.

[29] Wood DM, Greene SL, *et al.* Five-year trends in self-reported recreational drugs associated with presentation to a UK emergency department with suspected drug-related toxicity. Epub ahead of print. Eur J Emerg Med 2012.

[30] Vogels N, Croes E. Monitor Drugs Incidenten: factsheet 2011. Trimbos-instituut, Utrecht. 2012.

[31] Wood DM, Brailsford AD, Dargan PI. Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). Drug Test Anal 2011; 3: 417-25.

[32] Van Sassenbroeck DK, De NN, De PP, *et al.* Abrupt awakening phenomenon associated with gamma-hydroxybutyrate use: a case series. Clin Toxicol (Phila) 2007; 45: 533-8.

[33] Munir VL, Hutton JE, Harney JP, *et al.* Gamma-hydroxybutyrate: a 30 month emergency department review. Emerg Med Australas 2008; 20: 521-30.

[34] Krul J, Girbes ARJ. Gamma-hydroxybutyrate: Experience of 9 years of gamma-hydroxybutyrate (GHB)-related incidents during rave parties in The Netherlands. Clin Tox 2011; 49: 311-5.

[35] Galicia M, Nogue S, Miró O. Liquid ecstasy intoxication: clinical features of 505 consecutive emergency department patients. Emerg Med J 2011; 28: 462-6.

[36] Miotto K, Darakjian J, Basch J, *et al*. Gamma-hydroxybutyric acid: Patterns of use, effects and withdrawal. Am J Addict 2001; 10: 232-41.

[37] Zvosec DL, Smith S, Porrata T, *et al.* Case series of 226 gamma-hydroxybutyrate-associated deaths: lethal toxicity and trauma. Am J Emerg Med 2010; 29: 319-32.

[38] Snead OC, Gibson KM. Gamma-hydroxybutyric acid. N Engl J Med 2005; 352: 2721-32.

[39] McDonough M, Kennedy N, Glasper A, *et al*. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. Drug Alcohol Depend 2004; 75: 3-9.

[40] Gonzalez A, Nutt DJ. Gamma hydroxy butyrate abuse and dependency. J Psychopharmacol 2005; 19: 195-204.

[41] Weerts EM, Goodwin AK, Griffiths RR, *et al.* Spontaneous and precipitated withdrawal after chronic intragastric administration of gamma-hydroxybutyrate (GHB) in baboons. Psychopharmacology (Berl) 2005; 179: 678-87.

[42] Watson J, Guzzetti S, Franchi C, *et al.* Gamma-hydroxybutyrate does not maintain self-administration but induces conditioned place preference when injected in the ventral tegmental area. Int J Neuropsychopharmacol 2010; 13: 143-53.

[43] Goodwin AK, Kaminski BJ, Weerts EM. Self-administration of gamma-hydroxybutyric acid (GHB) precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in baboons. Psychopharmacology (Berl) 2013; 225: 637-46.

[44] Goodwin AK, Griffiths RR, Brown PR, *et al*. Chronic intragastric administration of gamma-butyrolactone produces physical dependence in baboons. Psychopharmacology (Berl) 2006; 189: 71-82.

[45] Goodwin AK, Kaminski BJ, Griffiths RR, *et al.* Intravenous self-administration of gamma-hydroxybutyrate (GHB) in baboons. Drug Alcohol Depend 2011; 114: 217-24.

[46] Perez E, Chu J, Bania T. Seven days of gamma-hydroxybutyrate (GHB) use produces severe withdrawal. Ann Emerg Med 2006; 48: 219-20.

[47] Veerman SRT, Dijkstra HN, Liefting-Kluft I. Levensbedreigende onthoudingsverschijnselen door gammahydroxyboterzuur. Tijdschr Psychiatrie 2010; 52: 411-6.

[48] van Noorden MS, Kamal R, de Jong CAJ, *et al.* [Gamma-hydroxybutyric acid (GHB) dependence and the GHB withdrawal syndrome: diagnosis and treatment] GHB-afhankelijkheid en -onthoudingssyndroom: diagnostiek en behandeling. Ned Tijdschr Geneeskd 2010; 154: A1286.

[49] van Noorden MS, van Dongen LC, Zitman FG, *et al*. Gamma-hydroxybutyrate withdrawal syndrome: dangerous but not well-known. Gen Hosp Psychiat 2009; 31: 394-6.

[50] Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. Ann Emerg Med 2001; 37: 147-53.

[51] Vayer P, Mandel P, Maitre M. Gamma-hydroxybutyrate, a possible neurotransmitter. Life Sci 1987; 41: 1547-57.

[52] Maitre M. The gamma-hydroxybutyrate signalling system in brain: organization and functional implications. Prog Neurobiol 1997; 51: 337-61.

[53] Snead OC, Furner R, Liu CC. *In vivo* conversion of gamma-aminobutyric acid and 1,4-butanediol to gamma-hydroxybutyric acid in rat brain. Studies using stable isotopes. Biochem Pharmacol 1989; 38: 4375-80.

[54] Thai D, Dyer JE, Benowitz NL, *et al.* Gamma-hydroxybutyrate and ethanol effects and interactions in humans. J Clin Psychopharmacol 2006; 26: 524-9.

[55] Andresen H, Aydin BE, Mueller A, *et al*. An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results. Drug Test Anal 2011; 3: 560-8.

[56] Palmer RB. Gamma-butyrolactone and 1,4-butanediol: abused analogues of gamma-hydroxybutyrate. Toxicol Rev 2004; 23: 21-31.

[57] Carter LP, Wu H, Chen W, *et al*. Effects of gamma-hydroxybutyrate (GHB) on schedule-controlled responding in rats: role of GHB and GABAB receptors. J Pharmacol Exp Ther 2004; 308: 182-8.

[58] Goodwin AK, Brown PR, Jansen EEW, *et al.* Behavioral effects and pharmacokinetics of gamma-hydroxybutyrate (GHB) precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) in baboons. Psychopharmacology (Berl) 2009; 204: 465-76.

[59] Arena C, Fung HL. Absorption of sodium gamma-hydroxybutyrate and its prodrug gamma-butyrolactone: relationship between *in vitro* transport and *in vivo* absorption. J Pharm Sci 1980; 69: 356-8.

[60] Tunnicliff G. Significance of gamma-hydroxybutyric acid in the brain. Gen Pharmacol 1992; 23: 1027-34.

[61] Andriamampandry C, Taleb O, Viry S, *et al.* Cloning and characterization of a rat brain receptor that binds the endogenous neuromodulator gamma-hydroxybutyrate (GHB). FASEB J 2003; 17: 1691-3.

[62] Andriamampandry C, Taleb O, Kemmel V, *et al.* Cloning and functional characterization of a gamma-hydroxybutyrate receptor identified in the human brain. FASEB J 2007; 21: 885-95.

[63] Hechler V, Gobaille S, Maitre M. Selective distribution pattern of gamma-hydroxybutyrate receptors in the rat forebrain and midbrain as revealed by quantitative autoradiography. Brain Res 1992; 572: 345-8.

[64] Castelli MP, Ferraro L, Mocci I, *et al.* Selective gamma-hydroxybutyric acid receptor ligands increase extracellular glutamate in the hippocampus, but fail to activate G protein and to pro-

duce the sedative/hypnotic effect of gamma-hydroxybutyric acid. J Neurochem 2003; 87: 722-32.
[65] Carai MA, Colombo G, Gessa GL. Protection by the GABAB receptor antagonist, SCH 50911, of gamma-hydroxybutyric acid-induced mortality in mice. Eur J Pharmacol 2004; 503: 77-80.
[66] Kaupmann K, Cryan JF, Wellendorph P, *et al.* Specific gamma-hydroxybutyrate-binding sites but loss of pharmacological effects of gamma-hydroxybutyrate in GABA(B)(1)-deficient mice. Eur J Neurosci 2003; 18: 2722-30.
[67] Carter LP, Koek W, France CP. Behavioral analyses of GHB: receptor mechanisms. Pharmacol Ther 2009; 121: 100-14.
[68] Black J, Pardi D, Hornfeldt CS, *et al*. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. Sleep Med 2009; 10: 829-35.
[69] Galloway GP, Frederick-Osborne SL, Seymour R, *et al*. Abuse and therapeutic potential of gamma-hydroxybutyric acid. Alcohol 2000; 20: 263-9.
[70] Mamelak M, Scharf MB, Woods M. Treatment of narcolepsy with gamma-hydroxybutyrate. A review of clinical and sleep laboratory findings. Sleep 1986; 9: 285-9.
[71] Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the alcohol withdrawal syndrome. Cochrane Database Syst Rev 2011; 15: CD008537.
[72] Sumnall HR, Woolfall K, Edwards S, *et al.* Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). Drug Alcohol Depend 2008; 92: 286-90.
[73] Leone MA, Vigna-Taglianti F, Avanzi G, *et al*. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database Syst Rev 2010; CD006266.
[74] Caputo F, Bernardi M. Medications acting on the GABA system in the treatment of alcoholic patients. Curr Pharm Des 2010; 16: 2118-25.
[75] Carter LP, Griffiths RR, Mintzer MZ. Cognitive, psychomotor, and subjective effects of sodium oxybate and triazolam in healthy volunteers. Psychopharmacology (Berl) 2009; 206: 141-54.
[76] Carter LP, Pardi D, GorslineJ, *et al*. Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): differences in characteristics and misuse. Drug Alcohol Depend 2009; 104: 1-10.
[77] Ramo DE, Grov C, Delucchi K, *et al.* Typology of club drug use among young adults recruited using time-space sampling. Drug Alcohol Depend 2010; 107: 119-27.
[78] de Jong CAJ, Kamal R, Dijkstra BAG, *et al*. Gamma-hydroxybutyrate detoxification by titration and tapering. Eur Addict Res 2012; 18: 40-5.
[79] Brunt TM, Brunt TM, Koeter MW, *et al.* Sociodemographic and substance use characteristics of gamma hydroxybutyrate (GHB) dependent inpatients and associations with dependence severity. Drug Alcohol Depend 2013.
[80] Xi ZX, Ramamoorthy S, Shen H, *et al.* GABA transmission in the nucleus accumbens is altered after withdrawal from repeated cocaine. J Neurosci 2003; 23: 3498-505.
[81] Jayaram P, Steketee JD. Effects of repeated cocaine on medial prefrontal cortical GABAB receptor modulation of neurotransmission in the mesocorticolimbic dopamine system. J Neurochem 2004; 90: 839-47.
[82] Nabben T, Benschop A, Korf DJ. Antenne 2009: trends in alcohol, tabak en drugs bij jonge Amsterdammers. Amsterdam: Rozenberg Publishers. Available from: www.dare.uva.nl/document/223193. [Accessed 3 April 2013]. 2010.
[83] Camacho A, Matthews SC, Murray CF, *et al*. Use of GHB compounds among college students. Am J Drug Alcohol Abuse 2005; 31: 6001-607.
[84] Moller JT, Cluitmans P, Rasmussen LS, *et al.* Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 1998; 351: 857-61.
[85] Hibell B, Guttormsson U, Ahlström S, *et al*. The 2011 ESPAD Report - Substance Use Among Students in 36 European Countries. http://www.espad.org/en/Reports--Documents/ESPAD-Reports/. 2012.
[86] Degenhardt L, Hall WD, Lynskey M, *et al*. Should burden of disease estimates include cannabis use as a risk factor for psychosis? PLoS Med 2009; 6: e1000133.
[87] Voorham L, Buitenhuis S. GHB-gebruik(ers) in beeld. Een typering van de GHB-gebruiker en hun bereikbaarheid. Trimbos-instituut, Utrecht, The Netherlands. 2012.
[88] Korf DJ, Nabben T, Leenders F, *et al.* GHB: Tussen Extase en Narcose, Rozenberg Publishers, Amsterdam. 2002.
[89] van der Poel A, Doekhie J, Verdurmen J, *et al*. Feestmeter 2008-2009: uitgaan en middelengebruik onder bezoekers van party's en clubs. Utrecht/Amsterdam: Trimbos-instituut/Bonger Instituut. Available from: www.trimbos.nl. [Accessed 3 April 2013]. 2010.
[90] Dick D, Torrance C. Mixmag drugs survey. Mixmag 225, pp. 44-53, 14 January 2010. 2010.
[91] Parsons JT, Grov C, Kelly BC. Club drug use and dependence among young adults recruited through time-space sampling. Public Health Rep 2009; 124: 246-54.
[92] Aarts M, van Melick D, Parlar D, *et al*. Onderzoeksrapport: GHB-gebruik in Noord-Limburg. Venray: GGZ Noord- en Midden-Limburg. 2010.
[93] de Jong M, Poelmans I, Linck H, *et al*. Tendens 2008: alcohol- en drugsgebruik bij jongeren en jongvolwassenen in Gelderland. Arnhem: IrisZorg. Available from: http://www.iriszorg.nl/sites/iriszorg.nl/files/field/attach/tendens_2008.pdf. [Accessed 3 April 2013]. 2008.
[94] Degenhardt L, Darke Sh, Dillon P. The prevalence and correlates of gamma-hydroxybutyrate (GHB) overdose among Australian users. Addiction 2003; 98: 199-204.
[95] Dijkstra BAG, de Weert van Oene G, Verbrugge CAG, *et al.* GHB Detoxificatie met farmaceutische GHB. Eindrapportage van de mi\onitoring van DeTiTap in de Nederlandse verslavingszorg. NISPA. Nijmegen. http://www.nispa.nl/sites/default/files/2013-03-18%20Presentatie%20GHB%20monitor%20 eindcongres%20BD.pdf. 2013.
[96] Devlin RJ, Henry JA. Clinical review: Major consequences of illicit drug consumption. Crit Care 2008; 12: 202.
[97] Dietze PM, Cvetkovski S, Barratt MJ, *et al.* Patterns and incidence of gamma-hydroxybutyrate (GHB)-related ambulance attendances in Melbourne, Victoria. Med J Aust 2008; 188: 709-11.
[98] Krul J, Blankers M, Girbes ARJ. Substance-related health problems during rave parties in the Netherlands (1997-2008). PLoS ONE 2011; 6: e29620.
[99] Zvosec DL, Smith SW, Litonjua R, *et al.* Physostigmine for gamma-hydroxybutyrate coma: inefficacy, adverse events, and review. Clin Toxicol (Phila) 2007; 45: 261-5.
[100] Traub SJ, Nelson LS, Hoffman RS. Physostigmine as a treatment for gamma-hydroxybutyrate toxicity: a review. J Toxicol Clin Toxicol 2002; 40: 781-7.
[101] Galloway GP, Frederick SL, Staggers FE, *et al.* GHB: an emerging drug of abuse that causes physical dependence. Addiction 1997; 92: 89-96.
[102] Stein LAR, Lebeau R, Clair M, *et al*. Preliminary web-based measures development for GHB: expectancies, functions, and withdrawal. Am J Drug Alcohol Abuse 2012; 38: 121-9.
[103] Johnson MW, Johnson MW, Griffiths RR, *et al.* Comparative Abuse Liability of GHB and Ethanol in Humans. Exp Clin Psychopharmacol 2013.
[104] Miró O, Nogué S, Espinosa G, *et al.* Trends in illicit drug emergencies: the emerging role of gamma-hydroxybutyrate. J Toxicol Clin Toxicol 2002; 40: 129-35.
[105] Colombo G, Agabio R, Lobina C, *et al.* Symmetrical generalization between the discriminative stimulus effects of gamma-hydroxybutyric acid and ethanol: occurrence within narrow dose ranges. Physiol Behav 1995; 57: 105-11.
[106] Schep LJ, Knudsen K, Slaughter RJ, *et al.* The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. Clin Toxicol (Phila) 2012; 50: 458-70.
[107] Kamal R. Afkicken van GHB: levensgevaarlijk. Ned Tijdschr Geneeskd 2010; 154: A1286.
[108] Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. Drug Alcohol Depend 2001; 63: 1-22.
[109] Wojtowicz JM, Yarema MC, Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. CJEM 2008; 10: 69-74.
[110] Bell J, Collins R. Gamma-butyrolactone (GBL) dependence and withdrawal. Addiction 2011; 106: 442-7.
[111] Freese TE, Miotto K, Reback CJ. The effects and consequences of selected club drugs. J Subst Abuse Treat 2002; 23: 151-6.

[112] Beardsley PM, Balster RL, Harris LS. Evaluation of the discriminative stimulus and reinforcing effects of gammahydroxybutyrate (GHB). Psychopharmacology (Berl) 1996; 127: 315-22.

[113] Carter LP, Flores LR, Wu H, *et al*. The role of GABAB receptors in the discriminative stimulus effects of gamma-hydroxybutyrate in rats: time course and antagonism studies. J Pharmacol Exp Ther 2003; 305: 668-74.

[114] Koek W, Carter LP, Lamb RJ, *et al*. Discriminative stimulus effects of gamma-hydroxybutyrate (GHB) in rats discriminating GHB from baclofen and diazepam. J Pharmacol Exp Ther 2005; 314: 170-9.

[115] Martellotta MC, Fattore L, Cossu G, *et al*. Rewarding properties of gamma-hydroxybutyric acid: an evaluation through place preference paradigm. Psychopharmacology (Berl) 1997; 132: 1-5.

[116] Colombo G, Gessa GL. Gamma-hydroxybutyric acid in alcohol preference, dependence and withdrawal. Addict Biol 2000; 5: 389-403.

[117] Bania TC, Ashar T, Press G, *et al*. Gamma-hydroxybutyric acid tolerance and withdrawal in a rat model. Acad Emerg Med 2003; 10: 697-704.

[118] Van Sassenbroeck DK, De Paepe P, Belpaire FM, *et al*. Tolerance to the hypnotic and electroencephalographic effect of gamma-hydroxybutyrate in the rat: pharmacokinetic and pharmacodynamic aspects. J Pharm Pharmacol 2003; 55: 609-15.

[119] Luscher C, Malenka RC. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. Neuron 2011; 69: 650-63.

[120] Gessa GL, Crabai F, Yargiu L, *et al*. Selective increase of brain dopamine induced by gamma-hydroxybutyrate: study of the mechanism of action. J Neurochem 1968; 15: 377-81.

[121] Aghajanian GK, Roth RH. Gamma-hydroxybutyrate-induced increase in brain dopamine: localization by fluorescence microscopy. J Pharmacol Exp Ther 1970; 175: 131-8.

[122] Walters JR, Roth RH. Effect of gamma-hydroxybutyrate on dopamine and dopamine metabolites in the rat striatum. Biochem Pharmacol 1972; 21: 2111-21.

[123] Erhardt S, Andersson B, Nissbrandt H, *et al*. Inhibition of firing rate and changes in the firing pattern of nigral dopamine neurons by gamma-hydroxybutyric acid (GHBA) are specifically induced by activation of GABA(B) receptors. Naunyn Schmiedebergs Arch Pharmacol 1998; 357: 611-9.

[124] Roth RH, Doherty JD, Walters JR. Gamma-hydroxybutyrate: a role in the regulation of central dopaminergic neurons? Brain Res 1980; 189: 556-60.

[125] Schmidt-Mutter C, Muller C, Zwiller J, *et al*. Gamma-hydroxybutyrate and cocaine administration increases mRNA expression of dopamine D1 and D2 receptors in rat brain. Neuropsychopharmacology 1999; 21: 662-9.

[126] Diana M, Mereu G, Mura A, *et al*. Low doses of gamma-hydroxybutyric acid stimulate the firing rate of dopaminergic neurons in unanesthetized rats. Brain Res 1991; 566: 208-11.

[127] Fattore L, Cossu G, Martellotta MC, *et al*. Baclofen antagonizes intravenous self-administration of nicotine in mice and rats. Alcohol Alcohol 2002; 37: 495-8.

[128] Crunelli V, Emri Z, Leresche N. Unravelling the brain targets of gamma-hydroxybutyric acid. Curr Opin Pharmacol 2006; 6: 44-52.

[129] Feigenbaum JJ, Howard SG. Naloxone reverses the inhibitory effect of gamma-hydroxybutyrate on central DA release *in vivo* in awake animals: a microdialysis study. Neurosci Lett 1996; 218: 5-8.

[130] Madden TE, Johnson SW. Gamma-hydroxybutyrate is a GABAB receptor agonist that increases a potassium conductance in rat ventral tegmental dopamine neurons. J Pharmacol Exp Ther 1998; 287: 261-5.

[131] Cruz HG, Ivanova T, Lunn ML, *et al*. Bi-directional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. Nat Neurosci 2004; 7: 153-9.

[132] Labouebe G, Lomazzi M, Cruz HG, *et al*. RGS2 modulates coupling between GABAB receptors and GIRK channels in dopamine neurons of the ventral tegmental area. Nat Neurosci 2007; 10: 1559-68.

[133] Chick J, Nutt DJ. Substitution therapy for alcoholism: time for a reappraisal? J Psychopharmacol 2012; 26: 205-12.

[134] LeTourneau JL, Hagg DS, Smith SM. Baclofen and gamma-hydroxybutyrate withdrawal. Neurocrit Care 2008; 8: 430-33.

[135] Morse BL, Vijay N, Morris ME. gamma-Hydroxybutyrate (GHB)-induced respiratory depression: combined receptor-transporter inhibition therapy for treatment in GHB overdose. Mol Pharmacol 2012; 82: 226-35.

[136] Szabo ST, Gold MS, Goldberger BA, *et al*. Effects of sustained gamma-hydroxybutyrate treatments on spontaneous and evoked firing activity of locus coeruleus norepinephrine neurons. Biol Psychiatry 2004; 55: 934-9.

[137] Wisselink DJKWG, Kuijpers WGT, Mol A. Kerncijfers verslavingszorg. National Information System on Alcohol and Drugs (LADIS), Stichting Informatie Voorziening Zorg (IVZ). http://www.sivz.nl/images/documenten/kerncijfers/kerncijfers%20verslavingszorg%202012.pdf. 2012.

[138] Tarabar AF, Nelson LS. The gamma-hydroxybutyrate withdrawal syndrome. Toxicol Rev 2004; 23: 45-9.

[139] Sivilotti ML, Burns MJ, Aaron CK, *et al*. Pentobarbital for severe gamma-butyrolactone withdrawal. Ann Emerg Med 2001; 38: 660-5.

[140] Fattore L, Cossu G, Martellotta MC, *et al*. Baclofen antagonises intravenous self-administration of gamma-hydroxybutyric acid in mice. Neuroreport 2001; 12: 2243-6.

[141] Amato L, Davoli M, Ferri M, *et al*. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev 2004; CD003409.

[142] Agboola S, McNeill A, Coleman T, *et al*. A systematic review of the effectiveness of smoking relapse prevention interventions for abstinent smokers. Addiction 2010; 105: 1362-80.

[143] Penberthy JK, Ait-Daoud N, Vaughan M, *et al*. Review of treatment for cocaine dependence. Curr Drug Abuse Rev 2010; 3: 49-62.

[144] Spanagel R, Vengeliene V. New pharmacological treatment strategies for relapse prevention. Curr Top Behav Neurosci 2013; 13: 583-609.

[145] Penberthy JK, Ait-Daoud N, Vaughan M, *et al*. Review of treatment for cocaine dependence. Curr Drug Abuse Rev 2010; 3: 49-62.

[146] Carter LP, Chen W, Wu H, *et al*. Comparison of the behavioral effects of gamma-hydroxybutyric acid (GHB) and its 4-methyl-substituted analog, gamma-hydroxyvaleric acid (GHV). Drug Alcohol Depend 2005; 78: 91-9.

Received: July 15, 2013 **Accepted: August 26, 2013**