Risk assessment of GBL as a substitute for the illicit drug GHB in the Netherlands. A comparison of the risks of GBL versus GHB

Jan van Amsterdam a,b,* , Tibor Brunt c, Ed Pennings d, Wim van den Brink a,b

a Amsterdam Institute for Addiction Research, Academic Medical Center University of Amsterdam, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
b Amsterdam Institute for Addiction Research, Academic Medical Center, P.O. Box 75867, 1070 AW Amsterdam, The Netherlands
c Trimbos Institute (Netherlands Institute of Mental Health and Addiction), Da Costakade 45, 3521 VS Utrecht, The Netherlands
d The Maastricht Forensic Institute, P.O. Box 616, 6200 MD Maastricht, The Netherlands

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ABSTRACT
In the Netherlands, γ-hydroxybutyric acid (GHB) was recently banned, but γ-butyrolactone (GBL) was not. As such, GBL remained a legal alternative to GHB. This review compares the risks of GBL and GHB.

Pure GBL is per unit of volume about threefold stronger and therefore threefold more potent than cur-
rently used GBL-preparations in the Netherlands. Like GHB, GBL use hardly leads to organ toxicity, although, as with GHB, frequent GBL use may lead to repeated comas that may result in residual impairments in cognitive function and memory. Little is known about the prevalence of GBL use in Europe, but the recent increase in improper trading in GBL confirms that users of GHB gradually switch to the use of GBL. This shift may result in an increase in the number GBL dependent users, because the dependence potential of GBL is as great as that of GHB. Severe withdrawal symptoms and a high relapse rate are seen following cessation of heavy GBL use. GBL-dependent users seem to be severe (dependent, problematic) GHB users who started using GBL, the legal GHB substitute. Subjects who are solely dependent on GBL are rarely reported. About 5–10% of the treatment seeking GHB dependent subjects also use GBL and this subpopulation forms a vulnerable group with multiple problems. Fatal accidents with GBL are rarely reported, but non-fatal GHB (or GBL) overdoses frequently occur for which supportive treatment is needed. It is recommended to monitor the recreational use of GBL, the rate of GBL dependence treatment, and the improper trading of GBL.

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1. Introduction

In the Netherlands, GHB was rescheduled in May 2012 from List II to List I of the Opium Act in 2012. GBL was not banned at that time so that GBL remained a legal alternative to GHB as it is rapidly converted in the body to GHB following its ingestion; in fact, GBL is a legal pro-drug of illegal GHB. Other legal alternatives for GHB are 1,4-butanediol (BDO) and gamma-hydroxyvaleric acid (GVH) (Carter et al., 2005), which will be no further discussed here. That GHB can be substituted for by GBL has not escaped the attention of the WHO which is currently carrying out a risk assessment for GBL. Relevant data about GBL were retrieved by PubMed using the following search string: ‘’GBL’’[Majr] OR ‘’gamma-butyrolactone’’[Majr] OR ‘’GHB/toxicity’’[Majr] OR ‘’GHB/adverse effects’’[Majr] OR ‘’GHB’’[ti] OR ‘’GBL’’[ti] OR ‘’gamma-butyrolactone’’[ti] AND (toxicity[ti] OR prevalence[ti] OR fatal[ti] OR addiction[ti] OR abuse[ti] OR misuse[ti] OR adverse[ti] OR intoxication[ti] OR poisoned[ti] OR poisoning[ti] OR toxic[ti] OR toxicolog* [ti]) AND (english[la] OR dutch[la] OR german[la] OR french[la]). In addition, the free text search string (“gamma-butyrolactone” OR GBL) was used. Finally, the reference lists of the retrieved papers were used to trace data not retrieved via the search string.

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2 Pharmacokinetics of GBL

Following oral consumption and absorption in the gastrointestinal tract, GBL is rapidly (within minutes) converted by lactonase in serum and the liver (but not in the brain) into GHB which can then enter the brain. Even though GBL is a pro-drug of GHB, it has a faster onset of effects (at about 10–15 min) and a higher bioavailability than GHB (Goodwin et al., 2009; Andreason et al., 2011; Kohrs and Porter, 1999; Lettieri and Fung, 1978; Roth et al., 1966), because GBL has a higher lipophilicity than GHB. For the same reason GBL also penetrates rapidly into tissues before being hydrolyzed, and as such serves as a sink explaining its prolonged action (Roth et al., 1966). Maximum concentrations of GHB in serum were measured 20 min after oral consumption of GBL (Schröck et al., 2014). Following oral administration of GBL in baboons, higher values of $C_{\text{max}}$ and shorter values of $t_{\text{max}}$ were observed as compared to GHB (Goodwin et al., 2009). Based on these pharmacokinetic differences, GBL has a faster onset and a longer duration of the effects (Hurlbut and Silverstein, 2000; Irwin, 1996), but it is slightly more potent as compared to GHB (Goodwin et al., 2009). This may explain the relative higher addiction potential of GBL (Goodwin et al., 2009).

2.2 Differences between GHB and GBL

GBL is a colorless, slightly oily liquid and has a similar appearance as an aqueous GHB solution. As such, GBL is indistinguishable to the eye from a GHB solution. GHB tastes slightly salty, while GBL has an unpleasant ‘chemical/synthetic’ taste. In addition to its bad taste, the hygroscopic GBL has – especially in undiluted form – a corrosive effect on the mucous membranes of the esophagus and stomach. For these reasons, on drug fora users are advised to convert GBL to GHB or to dilute GBL with water or juice before intake (Erowid, 2009; Drugs Forum, 2013).

GBL preparations, purchased in the Netherlands for recreational use and offered by users in 2012 for testing to the Drugs Information and Monitoring System (DIMS), contained on average 0.42 g GHB per ml (DIMS, 2013). An oral dose of 0.6–1.3 ml of pure GBL gives the desired euphoric effect (HSDB, 2000) and is equivalent to 0.7–1.4 g GBL, i.e., 10–20 mg GBL per kg bodyweight in a person of 70 kg. Based on the density of pure GBL (1.13 g/ml) and the amount of GHB in GHB solutions (approx. 0.4 g/ml), pure GBL is approximately 3 times stronger (and more potent) than the currently used GHB preparations. Moreover, due to its higher lipophilicity the intake of GBL results in a faster and higher blood peak level than an equimolar dose of GHB (Kohrs and Porter, 1999; Lettieri and Fung, 1978).

Like GHB, GBL has a narrow safety margin, i.e., a small margin between the dose for the desired effects and the dose leading to a coma. Compared to GHB, the risk of overdosing is increased by the higher density of pure GBL requiring smaller – more difficult to measure – volumes in dosing. On the other hand, GBL is seldom swallowed in undiluted form for the reasons described above. Secondly, the effects of GBL may vary among users because of differences in genetic background of lactonase activity and due to enzyme induction first-time users can show a slower onset of the effects of GBL followed by headaches (Arena and Fung, 1980).

2.3 Prevalence of use

No solid data are available on the prevalence of use of GBL in the Dutch population, because (1) most reports refer to GHB use and not to GBL use; (2) GBL is a legal product; (3) until recently there were no indications for the abuse of GBL; and (4) GBL cannot be detected in body specimen because it is rapidly converted into GHB. Some studies report about the prevalence of GHB/GBL use without further distinction between the two.

In the Netherlands around 22,000 people (15–64 years) used GHB in 2009 (prevalence rate of 0.2%) and 1.3% have ever used GHB (van Rooij et al., 2011), which is very similar to the European average at that time. Data about the use of GBL are not available, though the use of GBL among clubbers seems to be rare (Benschop et al., 2013). Similarly, it is not known how many people buy GBL to convert it at home into GHB. A Dutch internet survey of the among a convenience sample of young recreational users (Van Laar, personal communication) showed that some 10% occasionally used GBL.

The EMCDDA does not routinely collect information about the use of GBL, because GBL is primarily seen as a precursor (EC, 2010). The most recent data collected by the EMCDDA date from 2008 (EMCDDA, 2008) and show that the use of GHB/GBL in the EU is generally low. For instance, the ever use of GHB/GBL by 15–16 year old students in 12 EU countries was 0.5–1.4%. There are, however, a number of subpopulations, like homosexuals, gay disco’s, night clubs, and dance and music settings where GBL use is considerable (Hunter et al., 2014; Wood et al., 2009, 2012; Yamamoto et al., 2013). A survey of the clubbers magazine ‘Mix-Mag’ carried out in 2010 in the UK showed a lifetime prevalence of GHB and GBL use of 11.8% and 5.6%, respectively (Winstock and Power, 2011). Another study performed in 2010 in the UK...
showed that the last month prevalence of GBL in two ‘gay-friendly’
dance clubs was 19% (Wood et al., 2012). Of 544 samples retrieved
in drug amnesty bins of gay-friendly nightclubs in South London,
160 (29.4% of total) contained GBL, whereas the remaining 38% of the liquid samples contained GHB (Yamamoto et al., 2013). Both
in the UK (EMCDDA, 2008) and Sweden (Mickelsson, 2005), the use of GBL increased following the ban of GHB in 2000. In the United
States the use of GHB, and by implication that of GBL, tends to decrease (Anderson et al., 2006), while in New South Wales life-
time GBL use increased in 5 years to 0.8% in 2010, although “recent use” remained constant at 0.1% (Whittaker et al., 2013).

2.4. User characteristics

As noted in the previous section, GBL in the UK is used by specific
subpopulations (Hunter et al., 2014; Wood et al., 2009, 2012; Yamamoto et al., 2013). In the Netherlands, the sparse data available indicate that the majority of GBL users are highly dependent on GHB (or GBL) and consume GBL as a substitute for GHB. Most GHB addicts seeking help for their GHB dependence are young adults (mean age 29 years, 32% were younger than 25 years) and two-thirds are male (Wisselink et al., 2013). Their number increased rapidly in the Netherlands from 80 in 2003 to 761 in 2012, but this still a relatively small number in a country with about 50,000 people annually seeking treatment for an alcohol or drug use disorder. In the first GHB monitor of NISPA on 270 GHB dependent patients in treatment, only 10 patients (3.7%) used GBL and 18 patients (6.6%) used both GHB and GBL (Dijkstra et al., 2013). The second survey among these patients (GBL monitor 2.0) showed that 4 out of 39 (10.2%) have ever used GBL. Two of these four subjects had used GBL only, one used both GBL and GHB, and one used only GBL if GHB was not available (Dijkstra and de Jong, 2014).

The characteristics of GBL users are not known, but they may resemble GHB-dependent patients; (1) the average age is 29.4 years, (2) half of the users has debts (>€10,000), (3) half is known to the police, (4) most have a low level of education, (5) 60% has a comorbid psychiatric disorder, and (6) half of them are poly-drug users (at least three different drugs) (Dijkstra et al., 2013).

2.5. Adverse effects of GBL

No major signs of chronic toxicity have been reported for GHB and GBL (Wood et al., 2011; Wong et al., 2004). The toxic, physiological and behavioral effects of GBL are fully attributable to the rapid and complete conversion of GBL into GHB; GBL itself is biologically inactive (Roth et al., 1966).

2.5.1. Toxicity of GHB and GBL

GBL taken in high dose has been reported to result in a severe metabolic acidosis and an asystolic cardiac arrest (Roberts et al., 2011).

The lethal oral dose of GHB (1–3 g/kg of body weight derived from the LD$_{50}$-value in dogs) (Lund et al., 1965) is high (Persson et al., 2001; Soderlund, 2004) and general anesthesia is achieved at a dose of about 60 mg/kg (Schoental, 1968). Given the complete conversion of GBL to GHB, these values are probably similar for GBL (see also Table 1). Most data on GBL intoxications refer to inci-
dents after an acute overdose. Although several fatal accidents following GBL consumption have been reported (see below) it is not possible to determine in blood whether GHB or GBL was used, because of the very rapid conversion of GBL to GHB. Secondly, GHB can be produced in urine samples stored or GHB can be redistrib-
uted postmortem in the body (Mazair-Prou and KERRIGN, 2005; LeBeau et al., 2007). Applying an inaccurate analytical procedure to assay GHB or GBL can therefore lead to incorrect results.

The major toxic effect of GBL (at 20–30 mg/kg p.o.) is inhibition of the central nervous system, which translates into bradycardia, a shallow and slow respiration, nausea, drowsiness, seizure-like activity, changes in the pupil reflex, uncontrolled movements, and confusion. At an oral dose of about 20 mg GBL per kg body weight (the usual recreational dose) anxiety (no acute effect) and insomnia may be induced, whereas a 3-fold higher dose already leads to loss of consciousness (acute coma). In the same dose range GHB or GBL induce coma, a life threatening event, especially if the comatose patient suffocates during vomiting or if respiratory depression arises. Moreover, repeatedly comas (by GBL) may lead to brain damage, resulting in poorer cognitive functioning and impaired memory function similar to the effects that may occur after anesthesia of patients during a medical procedure (Van Amsterdam et al., 2012). Indeed, users of GHB have reported peri-
ods of anterograde amnesia whilst on the drug (Duff, 2005; Barker et al., 2007) and animal studies indicate neurotoxicity following repeated treatment with high doses of GBL (Van Amsterdam et al., 2012).

2.5.2. Poisonings following GBL use

In general, GBL intoxications are just as dangerous as GHB intoxications (Knudsen et al., 2005). No data are available about the number of visits to emergency departments after GBL use, because GBL and GHB poisoning are very similar and GBL poisoning is not registered separately. Finally, users of GHB/GBL have impaired motor skills, e.g. they are less able to drive a car (Kim et al., 2007) and have an increased risk to fall or to be injured. However, users are in general well aware of the dangers of driving under the influence of GHB (Barker et al., 2007).

2.5.3. Documented GBL intoxications

Occasionally, fatal overdoses have been reported due to a suicide attempt (Lenz et al., 2008; Roberts et al., 2011), accidental overdosing (Lenz et al., 2008; Dupont and Thornton, 2001; Duer et al., 2001; Dargan et al., 2009) or due to an accidental exchange of the bottle of GBL and the bottle of diluent (Fieguth et al., 2009). In the UK, in the period 1995–2006, a total of 44 GHB/GBL-related deaths have been reported (EMCDDA, 2008). In four out of the 44 cases, GBL was definitely involved (usually in 2005–2006), including one case with GBL only (EMCDDA, 2008).

Furthermore, in Germany from 1998 to 2011, 19 users of GHB (37%) or GBL (63%) were treated in the emergency department because of severe withdrawal symptoms or coma; three of the 19 patients were dependent on GBL (Freudemann et al., 2013). In the Netherlands, only two well documented near-fatal cases after GBL intake have been reported (Van Vugt and Hofhuizen, 2012). A retrospective study of 65 GHB and GBL poisonings in a Swiss emergency department showed that 63% of the poisonings had occurred in young men who also (65%) consumed alcohol, MDMA or cocaine. Most were in coma (83%), but the proportion of GBL was not described (Lieti et al., 2006). A British report on 158 emergency department recordings in 2006 showed that only 8 (5.1%) of GHB/GBL related cases concerned GBL (self-report) (Wood et al., 2008). Various cases have reported incidents after unintended GBL overdosing, followed by successful treatment in the intensive care unit (Dupont and Thornton, 2001; Supady et al., 2009; Eiden et al., 2011; Chwaluk and Rejmak, 2011; Kashyap and Patel, 2011; Rambourg-Scheppens et al., 1997; Andersen and Netterstrom, 1992; Lenz et al., 2008; Bhattacharya et al., 2011; Savage et al., 2007; Brown and Nanayakkara, 2005; Fogh et al., 2004; Higgins and Bronson, 1996).

The Dutch National Poisons Information Center (NVIC) reported a stable number of questions from GPs about GHB/GBL.
Recreational users of GHB/GBL frequently and repeatedly fall into coma i.e. loss of consciousness while the subject does not awake while tapping in the face. For example, half of 76 Australian GHB users had experienced a GHB overdose in which they had lost consciousness (Degenhardt et al., 2002). Moreover, in the previously mentioned Dutch cohort of GHB dependent patients in treatment (Dijkstra et al., 2013), 80% had fallen into a coma at least once and 61% in the past month. Some could not recall the number of times they had fallen into a coma which exceeded the number of 50. GHB-dependent patients seem to show cognitive deficits (Dijkstra, personal communication), but this remains to be confirmed and if so whether these are caused by the heavy GHB use or by multiple comas.

2.5.4. Coma as adverse effect

Recreational users of GHB/GBL frequently and repeatedly fall into coma i.e. loss of consciousness while the subject does not awake while tapping in the face. For example, half of 76 Australian GHB users had experienced a GHB overdose in which they had lost consciousness (Degenhardt et al., 2002). Moreover, in the previously mentioned Dutch cohort of GHB dependent patients in treatment (Dijkstra et al., 2013), 80% had fallen into a coma at least once and 61% in the past month. Some could not recall the number of times they had fallen into a coma which exceeded the number of 50. GHB-dependent patients seem to show cognitive deficits (Dijkstra, personal communication), but this remains to be confirmed and if so whether these are caused by the heavy GHB use or by multiple comas.

2.5.5. GBL dependence

The study of Dijkstra et al. (2013) for instance shows that both GHB and GBL are substances with a considerable addiction potential and potentially severe withdrawal symptoms following heavy use. In terms of severity and risks, the withdrawal symptoms of GHB/GBL are similar to those of heroin and alcohol (McDonough et al., 2002). GHB dependence is based on GBL’s shorter onset of action, its greater potency, and this study was too low to allow comparison with GHB. However, some animal studies (drug discrimination studies) indicated that GBL has reinforcing properties that are similar to those of GHB (Carter et al., 2003, 2004; Beardsley et al., 1996) (for review see Brunt et al., 2014).

Clinical observations suggest that GBL and GHB have a comparable dependence liability, although GBL dependent patients are treated with a higher starting dose of GHB (followed by tapering off the dose) and show more symptoms of psychosis/delirium i.e. visual and auditory hallucinations as compared to GHB dependent patients (Kamal, personal communication). Though this observation suggests that GBL has a higher addictive potential, it may well be that the GHB using patients are in general more severely addicted to the drug as compared to those using GHB.

Severe withdrawal symptoms after abrupt discontinuation of GBL use have been reported (Sivilotti et al., 2001; Brunt et al., 2013; Dijkstra et al., 2013; Bell and Collins, 2011; Zept et al., 2009; Choudhuri et al., 2013), but the high relapse rate i.e. 85–89% in 191 GHB-dependent patients (Dijkstra et al., 2013; McDaniel and Miotto, 2001) is even more concerning. At follow-up, about 75% had a GHB-free period (average of 8 weeks), whereas the remaining 25% started to re-use GHB immediately after discharge from the clinic. The number of GBL dependent patients in this study was too low to allow comparison with GHB. However, based on GBL’s shorter onset of action, its greater potency, and longer duration of activity than GHB, its dependence potential may be somewhat greater than GHB itself (Goodwin et al., 2009).

2.6. Availability, illegal trade and legislation

GHB has no therapeutic application, but for chemical industrial purposes over 100 ktons of GBL are produced yearly (Couper and Marinetti, 2002; CCR, 2006). Dilutions of GBL (approximately 20–40% v/v) have been used in nail polish remover, paint stripper (graffiti), and to clean rims, although in the Netherlands cheaper alternatives for these applications have meanwhile been developed. According to unpublished police reports (personal communication Mr. Vijlbrief, Dutch National Police Force), there is an increasing trend to use GBL as a legal alternative to the illegal GHB as it can be easily converted to GHB.

For recreational use, GBL is purchased worldwide online (Thai et al., 2007; Palmer, 2004; Fernandez et al., 2005) and delivered at home (Miller and Sonderlund, 2010; EMCDDA, 2008). In the Netherlands, 39 websites which offered GBL were traced between January 2010 and December 2011; 60% of all webshops operated from the Netherlands (Pazos et al., 2013) and they mainly served customers in Germany and the UK. The price of GHB varies from €2 to €8/5 ml. Recently, however, it appeared that only one website is still active (GBL, personal communication). Danish youths bought pure GBL over the Internet in Germany, the Netherlands and Poland, because GBL in Denmark is for sale only in denatured form (Malmström, 2010). To avoid prosecution, pure GBL (99.9%) on the Internet is sold as a cleaning agent, wheel cleaner and paint remover with the explicit warning of the seller that the product is not intended for human consumption (Veenuk, 2011). In France, GBL is available as a solvent or paint stripper in specialty stores and on the Internet (Karila et al., 2009). Remarkably, at the time GBL was not yet classified as an illegal drug in the UK 66.2% of the 225 seized GHB samples, which were offered in London nightclubs, contained GBL rather than GHB (Wood et al., 2008). The rescheduling of GHB in the Netherlands from List II to List I (upgrading to hard drugs) did not affect the price of GBL. GBL currently costs €80–125/l or €500–750/10 l (Benschop et al., 2013).

The Dutch import large quantities of GBL from China and offer it worldwide over the internet. Of these, about 10–15 improperly sold GBL, i.e., with the presumed aim to produce GHB from GBL (KLPD, 2012). In 2012/2013 the Dutch Fiscal Investigation Service (FIOD) received 29 voluntary reports from home and abroad (covering a total volume of 57,700 kg and 3400 l of GBL) on suspicious orders of GBL in companies that are known as online shops. An increase in seizures of GBL in postal packages from the Netherlands, usually ordered over the Internet, is reported. In 2011, import of GBL from the Netherlands was reported by some 14 countries, including Germany, Greece, Hungary, Great Britain, Spain, New Zealand and Australia, Finland and Canada (NBI, 2011; KLPD, 2012; CBSA, 2010). No data from other countries about the trading in GBL for drug consumption are available, although the WHO reported hundreds of seizures of GBL (country not specified), Sweden and Norway reported notable increases in seizures of GBL (Mickelsson, 2005), and the European member states yearly report seizures (numbers and volumes) of GBL to the EMCDDA with GBL being more commonly seized than GHB (EMCDDA, 2013).

GHB is classified as Schedule IV under the Convention on Psychotropic Substances (1971) and banned in the USA and almost all European Countries (WHO, 2014). However, GBL is presently on the EU Voluntary Monitoring List of Non Scheduled Chemicals which only recommends the voluntarily report of unusual or suspicious transactions with GBL. As such, GBL is in The Netherlands still a legal compound. Because of the growing recreational use of GBL, several countries have, however, introduced national legislation to restrict the trading and use of GBL, either directly or as a precursor of the illicit GHB. In countries, like the UK (GOV, 2009), the USA, Latvia, Italy (EMCDDA, 2008), Canada (Atkins, 2012; DEA, 2000, 2010) and Sweden (Riksdagen, 2011), GBL is listed as an illicit drug while in other countries GBL is subjected to pharmaceutical regulations (e.g., Germany and Austria), prohibited in its pure form (e.g., France) or available in denatured form only (e.g., Denmark) (Jensen and Olsen, 2012). GBL is not regulated in Poland (Krajewska et al., 2012), and finally in Switzerland one has to apply for a permit to import GBL (EDI, 2011).
3. Conclusion

GBL is effective as a legal alternative to the banned GHB as it virtually has an identical pharmacological profile and risk potential as GHB. Recent police reports about improper trading in GBL (KLPD, 2014) confirm that after the ban of GHB, users of GHB gradually switched to the use of GBL. Because the dependence potential of GBL is as great as that of GHB, a growing prevalence of GBL use may result in an increased number of GBL dependent users, which show the same severe withdrawal symptoms and a high relapse rate following cessation of heavy GHB use. In contrast to GHB, GBL can, however, not be easily banned because of its wide commercial use. It is therefore recommended to monitor the recreational use of GBL, including problematic use, and the improper trading of GBL before further policy measures to limit the recreational use of GBL are taken.

References


