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REVIEW

Evaluating the risk of toxicity and adverse drug interactions involving recreational GHB use and prescribed drugs

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ABSTRACT

Introduction: GHB is a small molecule and is present in the human CNS. Exogenously, GHB is administered orally in the form of sodium oxybate to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy, and to manage alcohol withdrawal and detoxification in alcoholics. GHB shows a biphasic effect and dose-dependent pharmacokinetics and may interact with neuronal systems different from GABAergic one. The compound is also highly abused among bodybuilders and is associated with drugs of abuse.

Areas covered: This article provides an overview of the risks associated with the recreational consumption of GHB and its analogues, including pharmaceuticals mostly encountered in GHB-related emergency department admissions and postmortem investigations. A literature search was performed using PubMed, Scopus, Google Scholar, and Web of Science databases to identify scientific reports concerning the recreational use of GHB and analogs with prescribed drugs. Further articles were retrieved after consulting international health and regulatory authorities' reports.

Expert opinion: Due to its dual nature, interpreting and distinguishing GHB concentrations in biological fluid represents a challenge in forensic toxicology. To demonstrate recent exposure, a quick collection of samples is necessary to maximize the chance of detecting an exogenous GHB intake, especially in cases of GHB-facilitated sexual assaults.

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Drug–drug interaction; GHB; GBL; poisoning; prescribed drugs; recreational use; sodium oxybate

1. Introduction

γ-Hydroxybutyrate (GHB) is a short-chain fatty acid present in the mammalian central nervous system (CNS), and to a lesser extent, in peripheral tissues [1,2]. The main pathway of GHB production entails the conversion of γ-aminobutyric acid (GABA), the major inhibitory neurotransmitter, to succinic semialdehyde (SSA) followed by its catalysis via cytosolic SSA reductase [3,4]. SSA is further metabolized to succinic acid by SSA dehydrogenase and, ultimately, enters in Krebs cycle in mitochondria where it is converted in water and carbon dioxide (Figure 1). A minor alternative GHB formation pathway involves the partial oxidation of 1,4-butanediol (1,4-BD) originated from brain deaminated polyamines ornithine, spermine, spermidine, and putrescine [3,5].

GHB was firstly synthesized in 1874, but it was included in clinical studies starting from the 1960s when it was found to be structurally related to GABA [6]. At higher than physiological concentrations, GHB competes with GABA for the activation of the metabotropic $GABA_B$, a Gi-coupled-protein receptor, producing inhibitory responses at both presynaptic and postsynaptic sites in the cortex, hippocampus and amygdala [7,8]. GHB also affects other neuromodulatory systems enhancing dopamine and dynorphin release in the striatum and dampening norepinephrine signaling in the hypothalamus with the same neurobiological mechanism of addictive drugs [6,9]. GHB is a peculiar biphasic modulator, low doses produce euphoria and relaxation similar to alcohol while higher dosages are associated with nausea and vomiting, headache, vertigo, impaired speech, hallucinations, aggression, delirium, bradycardia, hypothermia, amnesia, respiratory depression, seizure or clonic movements and non-reactive coma [10,11].

GHB shows a dose-dependent pharmacokinetics. It is absorbed very rapidly after oral administration, although its bioavailability is affected by the saturation of transport process across the intestine and first-pass metabolism. Maximum plasma concentrations are reached after 25 to 45 minutes [12,13]. In vitro studies indicate limited or absent bond to plasma proteins, however, due to its amphoteric nature, GHB easily crosses placenta and brain-blood barrier [14]. Alcohol dehydrogenase has been postulated to contribute to GHB metabolism in human liver, albeit phase II metabolites such as GHB-glucuronide and GHB-4-sulfate may also be detected after chronic exposure [8,15,16]. The average elimination half-life after single doses ranged from 30 to 50 minutes and increases at higher concentrations. At low doses 1–5% of GHB is excreted unchanged in the urine and its detection window is about 12 hours post-administration [17]. In case of overdose, higher percentages are eliminated due to saturation of transporter-mediated re-absorption in the proximal tubule [17,18].

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Article highlights

- Knowledge of the potential interactions of GHB and its analogues with prescribed drugs is crucial to minimize potential acute GHB toxicity.
- Prescribed drugs that are more frequently involved in GHB-related intoxications are hypnotics/sedatives, opioids/opiates, and antiepileptics.
- Central nervous system depression is the principal symptom encountered in GHB and prescribed drugs overdose.
- Polydrug and polypharmacy in recreational GHB users is an added risk factor that can lead to misdiagnoses of symptoms and misinterpretation of the cause of death.

The first therapeutic use of GHB was to produce anesthesia [7]. However, the absence of a significant analgesic effect and the tendency to induce seizures and vomiting limited its use to a narrow number of medical applications [19]. In July 2002 the GHB salt, sodium oxybate (Xyrem), was approved by the United States Food and Drug Administration (US FDA) for the treatment of cataplexy in narcoleptic patients and listed in Schedule III of the Controlled Substance Act [20,21]. Meanwhile, in Italy and in Austria, sodium oxybate (Alcover) was approved for the management of alcohol withdrawal and detoxification in alcoholics [1,22].

GHB has a long history of misuse and abuse. In the 1980s, it was largely touted as dietary supplement to manage insomnia, depression, alcohol addiction and sexual dysfunction, gaining also in popularity among bodybuilders for its supposed muscle-growing and fat-burning properties [23,24]. However, after several notifications of adverse events, the US FDA banned the nonprescription sale of the compound [25]. By that time, GHB emerged as a recreational drug. Sold illicitly and under attractive names such as 'Easy Lay,' Georgia Home Boy", 'Juice,' 'Liquid Ecstasy,' 'Mils,' 'G,' 'Liquid X,' 'Liquid G' and 'Fantasy,' GHB started to be involved in a rising number of impaired driving cases, drug-facilitated sexual assaults (DFSA) and deaths [26,27]. Since 2000, illicit GHB has been classified in Schedule I of the Controlled Substances Act and, starting from 2001, in Schedule IV of the 1971 Convention of Psychotropic Substances for its abuse and life-threatening potential [28]. As a consequence of these restrictions, pushers and users switched illicit sale and purchase from GHB to alternative legal precursors like γ-butyrolactone (GBL) and 1,4-BD [29,30]. These prodrugs are converted in vivo in GHB (Figure 1) and quickly replaced it because they are cheaper and easier to obtain [31]. For this reason, in 2009, GBL and 1,4-BD were included in the UK Misuse of Drugs Act. Italy has also included GBL in its Table IV of the Narcotics Act (Presidential Decree 309/90) but not 1,4-BD [32]. Although there are no significant differences in the clinical presentation, GBL is more lipophilic than GHB, it is absorbed faster and has higher bioavailability [33,34].

According to the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), GHB and analogs are used both in private and nightlife settings often with psychotropic drugs of abuse (DOA) and diverted prescribed drugs (PD) [35]. In certain contexts, such as rave parties and gay nightclubs, GHB is used by men who look for intentional sex with other men (men who have sex with men, MSM), alone or in combination with other psychoactive drugs to increase libido and facilitate muscle relaxation during sexual sessions [36,37]. This phenomenon is called 'chemsex' and represents a hidden health emergency. Chemsex is associated with engagement

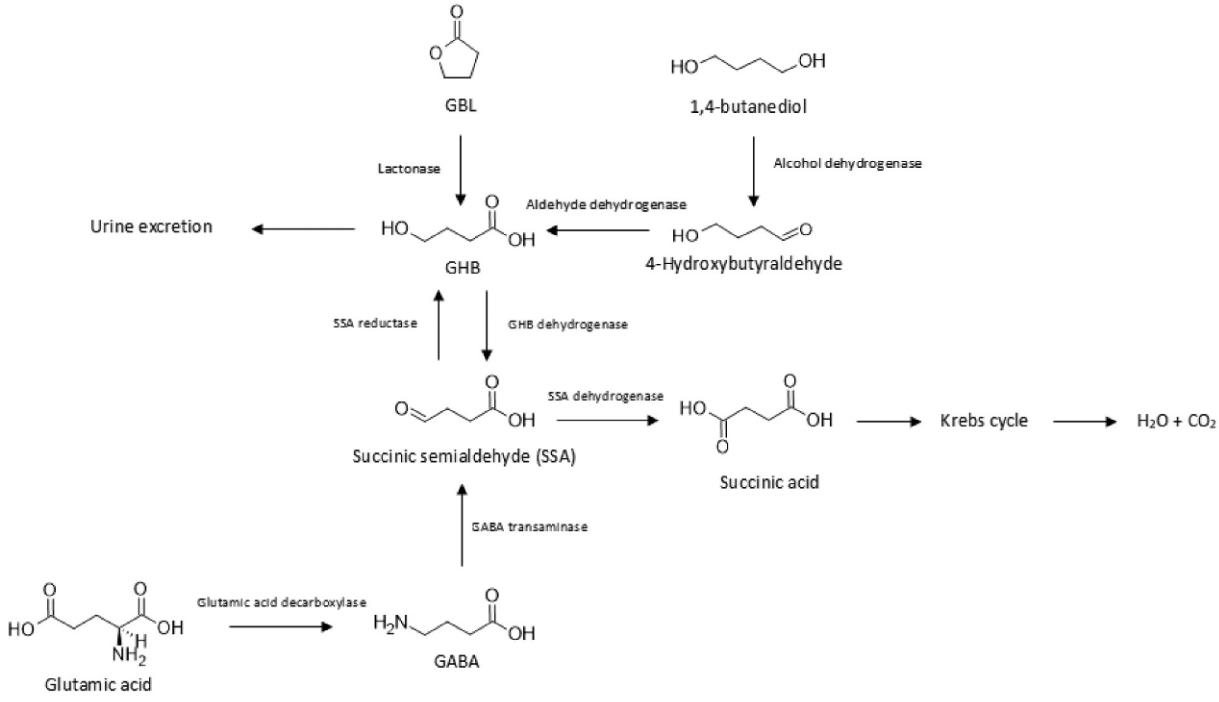

Figure 1. Metabolic pathway of GHB.

in sex groups, multiple sexual partners, and high-risk sexual behaviors like condomless anal intercourse or the practice to inject drugs and sharing injecting equipment, known as 'slamming' [38–40].

The role that some PD play in GHB overdoses and deaths is often unknown and masked by the presence of narcotic and depressant DOA. Health practitioners are first in line to attend intoxicated patients during hospitalizations but, sometimes, misdiagnose a CNS depression toxidrome since polypharmacy is the rule, rather than the exception, with symptoms appearing in a non-univocal manner [41].

The aim of this mini review is to describe the symptoms and the risks represented by the concomitant recreational use of GHB/analogs and PD, reporting the recent cases of admissions to the emergency departments (ED) and postmortem investigations (PMI), with the objective to differentiate the clinical presentation from other conditions often misdiagnosed.

2. Data search and selection method

A comprehensive literature search was performed using PubMed, Scopus, Google Scholar, and Web of Science bibliographic databases to identify scientific reports concerning the recreational use of GHB and analogs with PD. Database-specific search features with truncations, represented by an asterisk, and multiple keywords, represented by quotation marks, were employed. The search terms employed were: 'drug-drug interaction*' OR 'recreational use' OR chemsex OR toxicity OR 'adverse effect*' OR 'intoxication*' OR 'prescribed drug*' OR poisoning OR overdose) AND (GHB OR GBL OR 'sodium oxybate' OR 1,4-butanediol OR Xyrem OR Alcover). Further studies were retrieved from the reference list of selected articles and from reports of international institutions such as the World Health Organization, the EMCDDA, the European Medicines Agency (EMA), the US Drug Enforcement Administration and the US FDA. Articles written in English and only one in Spanish were included. Databases were screened through July 2021 and references were independently reviewed by the authors to determine their relevance to the present article.

3. Results and discussion

Of 1151 potentially relevant reports, 1139 were excluded because they did not describe intoxications related to the recreational use of GHB and analogs along with PD. No relevant reports were found for 1,4-BD. A total of 42 cases describing 9 ED admissions and 33 deaths are summarized in Table 1. Age, sex, observations (i.e. symptoms, death scene information, etc.), detected concentrations in biological matrices and co-exposure concentrations are also displayed.

Most patients and victims were young individuals of both sexes, often with a previous history of substance abuse and mental illness. Acute intoxications and deaths related to GHB and analogs in combination with PD and DOA were reported in Australia, Italy, Netherland, Spain, Sweden, UK and US. GHB, analogs, and other drugs were detected and quantified in biological matrices using GC-FID, GC-MS, and LC-MS/MS.

All subjects in this sample were taking prescribed psychoactive medications, mostly hypnotics/sedatives (34 cases), antidepressants (15 cases), opioids/opiates (9 cases), phenothiazines (5 cases), phenylethylamine (3 cases), antipsychotics (1 case) and antiepileptics (1 case), often in combination with DOA and new psychoactive substances, such as amphetamine-like stimulants, cocaine, ethanol, dissociatives, MDMA, opiates, and synthetic cathinones which were detected in the 86% of the cases. There was an overlap between GHB blood concentrations found in ED admissions [49] and deaths [] [43,50,52]. This may reflect differences in tolerance developed after frequent drug exposure. In other cases, there is too little information or analytical data to improve our knowledge about the contribution of GHB and analogs in drug overdoses [42,44,45,47,48] and since polypharmacy dominates this scenario, it is not possible to assign causality to a single drug as the death was due to the multiple drug toxicity 43,50–53

3.1. GHB-drug interactions

3.1.1. Hypnotics/sedatives

Benzodiazepines are the PD more frequently associated to the use of GHB and analogs, notably diazepam and alprazolam [54]. Unlike barbiturates and meprobamate, that activate directly the ionotropic $GABA_A$ receptor, benzodiazepines are positive allosteric modulators and enhance the binding affinity of the $GABA_A$ receptor for GABA, depending only on GABA endogenous availability [55]. Due to this controlled neuronal inhibition, the risk of CNS depression is substantially avoided, but it increases exponentially if other CNS depressants, such as GHB, ethanol or opioids, are simultaneously consumed [45]. In these cases, flumazenil, a competitive $GABA_A$ antagonist, may be successfully used to revert benzodiazepines overdose [47]. These latter drugs are widely used for the management of anxiety, panic attacks, sleep disorders, epilepsy, and as myorelaxants, but are also highly abused to reinforce opioid euphoric effects and to alleviate the 'crash' following stimulant abuse [56–58]. Flunitrazepam, marked in Europe under the brand name Rohypnol®, is a potent incapacitating benzodiazepine which is administered surreptitiously, alone or in combination with GHB, to perpetrate DFSA and robberies. Due to its anterograde amnesic properties, the victim cannot recall events that took place while under the influence of this drug [59,60]. The combined use of GHB and sedative drugs such as Z-drugs (e.g. Zolpidem or Zopiclone), barbiturates and meprobamate may also result in similar clinical signs and symptoms on ED admission [61,62].

3.1.2. Opiates/opioids

Narcotic analgesics can be grouped into synthetic compounds and natural/semi-synthetic substances which are related to alkaloids naturally occurring in poppy seeds. The first category includes synthetic opioids, for example, fentanyl, methadone, and tramadol while the second is composed by codeine, morphine, and their semi-synthetic analogs buprenorphine, dihydrocodeine, heroin, hydrocodone, hydromorphone, oxycodone, and oxymorphone [63]. Death due to overdose of

Table 1. GHB and analogs case reports.

Compound	Study	Age; sex	Observations	Concentration†/dose	Co-exposure concentration(s)†		Ref.
					Prescribed drugs	Drugs of abuse	
GBL	ED	25; M	Gastrointestinal effects, Mood changes, Rebound insomnia	3X 15–30 mL/day + 2 sips at bedtime for 9 months	OXY occasional PAR occasional	COC occasional MDMA occasional NIC occasional THC occasional	[][42]
	PMI	NR; NR	Multiple Drug Intoxication	Blood 260 Urine 1300 Vitreous humor 130	DZP blood^{+} PHO blood^{+} ZPC blood^{+}	MEPH blood 0.21 TFMPP blood 0.02 MAMP blood 0.04 KET blood^{+} THCCOOH blood^{+}	[][43]
GHB/GBL	ED	23; F	Agitation, Delirium, Diaphoresis, Hallucinations, Paranoia, Tachycardia	Up to 36 mL/day for 2.5 years	DZP up to 25 mg/day for 2.5 years	MAMP up to 0.3 g/day for 2.5 years	[][44]
GHB	ED	37; F	CNS depression, Seizures	Blood 0.1 (after 8 h) Serum 42.5 Urine 32.8 (after 8 h)	BZD urine^{+}	AMP urine^{+} THC urine^{+}	[][45]
		23; M	CNS depression	Half bottle	BZD (3 tablets)	EtOH (3 pints of lager)	
		24; M	Apnea, Mild CNS depression, Mydriasis, Respiratory alkalosis, Seizures	Blood^{+}	DZP blood^{+} MTD blood^{+}	6-AM blood^{+}	[46]
		29; M	CNS depression, Coma, Mydriasis	Urine^{+}	BZD urine^{+}	EtOH urine^{+} COC urine^{+} THC urine^{+}	[][47]
		NR; F	Diaphoresis, Hypothermia, Loss of consciousness, Unresponsiveness	Serum^{+}	BZD serum^{+}	COC serum^{+} MAMP serum^{+} PCP serum^{+} THC serum^{+}	[][48]
		29; M	Chest pain, Dizziness, Severe headache, Shortness of breath, Sinus tachycardia	Blood 55.1 Urine 35.7	SIL blood 0.34, urine 1.27	-	[][49]
		34; M	Headache	Blood 37.8 Urine 15.5	SIL blood^{+}, urine 1.22	-	
	PMI	NR; NR	Possible multiple drug intoxication	Blood 10	MTD blood 0.34	EtOH blood 140 COC blood 0.01	[50]
		NR; NR		Blood 40	TRA NR OME NR	EtOH NR COC NR	
		NR; NR		Blood 21	FLX blood 0.05 ZPC blood 0.01	EtOH blood 620 MOR blood 0.10	
		35; M	Multiple drug intoxication	Blood 230 Urine 8200	PHEN blood 0.1	MDMA blood^{+}	[][51]
		23; M	Accidental overdose	Blood 770	COD blood 0.06 Nor-DZP blood 0.07 PAR blood 4	COC blood 0.09 BE blood 2.4	[52]
		23; M		Blood 490 Urine 2300	DZP blood 0.4 Nor-DZP blood 0.5 MIR blood 0.1 PAR blood 7	AMP blood 0.2 BE blood 0.11	

(*Continued*)

Table 1. (Continued).

Compound	Study	Age; sex	Observations	Concentration†/dose	Co-exposure concentration(s)†		Ref.
					Prescribed drugs	Drugs of abuse	
		24; M		Blood 290 Urine 2300	COD blood 0.008 DZP blood 0.5 Nor-DZP blood 0.5 TRA blood 0.4	EtOH blood 110	
		30; M		Blood 260 Urine 1100	BUP blood 0.004 Nor-BUP blood 0.008 ZPC blood 0.02	-	
		20; F		Blood 230 Urine 1200	ASA blood 0.8 CIT blood 0.2	AMP blood 0.2 BE blood 0.14	
		46; M		Blood 170 Urine 1900	ALI blood 0.3 CMI blood 0.07 DZP blood 0.07 Nor-DZP blood 0.1	AMP blood 0.1	
		20; M		Blood 55 Urine 1200	CIT blood 0.1	EtOH blood 1000 MDMA blood 0.3	
		27; M		Urine 850	7-amino-FNZ blood 0.12	AMP blood 0.2 MOR blood 0.07 THC blood 0.0004	
		35; M		Urine 240	CAR blood 7.2 DZP blood 0.5 Nor-DZP blood 1.3 MPB blood 40 PMZ blood 0.1 PPZ blood 0.1	BE blood 0.04 MOR blood 0.02	
		33; M		Urine 200	7-amino-FNZ blood 0.03 DZP blood 0.3 Nor-DZP blood 0.1 MIR blood 0.2 Dihydro-PPZ blood 0.06	EtOH blood 670 MOR blood 0.02	
		23; M		Urine 100	7-amino-FNZ blood 0.09	EtOH blood 370 MOR blood 0.4	
		32; M	Multiple drug intoxication	Blood 11 Urine 210	CIT blood 0.09 PAR blood 4	AMP blood 0.5 BE blood 0.4 THC blood 0.003 MOR blood 0.02	
		29; M		Blood 200 Urine 4700	AMI blood 5 DZP blood 0.1 NTP blood 0.3 PAR blood 1 TRA blood 0.2	EtOH blood 170	
		21; M		Blood 190 Urine 2300	DZP blood 0.4 Nor-DZP blood 0.1 Dihydro-PPZ blood 0.06	-	
		31; M		Blood 170 Urine 300	Nor-DZP blood 0.2	EtOH blood 1700	
		30; F		Blood 140 Urine 620	FFA blood 0.3	EtOH blood 1600	
		24; F		Blood 34	ALI blood 0.2 CIT blood 0.3 PMZ blood 0.4	-	

(*Continued*)

Table 1. (Continued).

Compound	Study	Age; sex	Observations	Concentration†/dose	Co-exposure concentration(s)†		Ref.
					Prescribed drugs	Drugs of abuse	
		24; M		Urine 650	CIT blood 0.4 DZP blood 0.3 Nor-DZP blood 0.1 MIR blood 0.2	EtOH blood 1900 AMP blood 0.5	
		30; M		Urine 580	ALP blood 0.09 CAR blood 3.5 SRT blood 0.08 PAR blood 94 ZOL blood 0.4	AMP blood 0.07 MOR blood 0.03	
		NR; NR	Multiple Drug Intoxication, Accidental overdose, Cardiac and/or respiratory complications	Blood 270 Urine 824	DZP blood 0.12 TMZ blood 0.01	EtOH blood 470 COC blood 1.6 MAMP blood 0.02	[43]
		NR; NR		Blood 22	DZP blood^{+} GBP blood^{+} PB blood^{+}	EtOH blood 150 AMP blood 0.0003 HER blood 0.16	
		NR; NR		Blood 800	TMZ blood^{+}	MDMA blood 7.69 MDA blood 0.09 MAMP blood 0.28 AMP blood 0.11	
		NR; NR		Blood 245	FLX urine 309	EtOH blood 2630	
		NR; NR		Blood 520 Urine 1300	DZP blood 0.38 CDP blood 0.23	EtOH blood 1560	
		NR; NR		Blood 2313	DZP blood 0.71 Desmethyl-DZP blood 0.46 OXZ blood 0.040 TMZ blood 0.11 FLX blood 0.06	EtOH blood 181 KET blood 0.15 MEPH blood 0.12	
NaGHB	PMI	52; M	Multiple drug intoxication	Blood 141	PHEN blood 0.26 ZOL blood 0.16 PRX blood 0.3	EtOH blood 0.02 g %	[53]
		44; M		Blood 110	ALP blood 0.16 Nor-DZP blood 0.081 QTP 0.045	–	
		43; F		Blood 3500	CPA blood^{+} BZD urine^{+}	MAMP blood 1.1 AMP blood 0.19 COC urine^{+}	

†Concentrations are expressed as µg/mL unless specified; $^{+}$ Positive screening.

6-AM – 6-acetylmorphine; ALI – Alimemazine; ALP – Alprazolam; AMP – Amphetamine; AMI – Amitriptyline; ASA – Acetyl salicylic acid; BE – Benzoylecgonine; BUP – Buprenorphine; BZD – Benzodiazepine; CAF – Caffeine; CAR – Carisoprodol; CDP – Chlordiazepoxide; CIT – Citalopram; CPA – Chlorpheniramine; CMI – Clomipramine; CNS – Central Nervous System; COC – Cocaine; COD – Codeine; DZP – Diazepam ED – Emergency Department; EtOH – Ethanol; F – Female; FEN – Fentanyl; FFA – Fenfluramine; FLX – Fluoxetine; FNZ – Flunitrazepam; GBP – Gabapentin; GBL – γ-Butyrolactone; GHB – γ-Hydroxybutyric acid; HER – Heroin; KET – Ketamine; M – Male; MAMP – Methamphetamine; MDA – 3,4-Methylenedioxyamphetamine; MDMA – 3,4-Methylenedioxymethamphetamine; MEPH – Mephedrone; MIR – Mirtazapine; MOR – Morphine; MPB – Meprobamate; NaGHB – GHB sodium oxybate; NIC – Nicotine; NR – Not reported; NTP – Nortriptyline; OME – Omeprazole; OXY – Oxycodone; OXZ – Oxazepam; PAR – Paracetamol; PB – Phenobarbitone; PCP – Phencyclidine; PHEN – Phentermine; PHO – Pholcodine; PMI – Postmortem investigation; PMZ – Promethazine; PPZ – Propiomazine; PRX – Paroxetine; QTP – Quetiapine; SIL – Sildenafil; SRT – Sertraline; TFMPP – 3-Trifluoromethylphenylpiperazine; TMZ – Temazepam; TRA – Tramadol; THC – Δ^{9}-Tetrahydrocannabinol; THCCOOH – 11-Nor-9-carboxy-THC; THCOH – 11-Hydroxy-THC; VEN – Venlafaxine; ZOL – Zolpidem; ZPC – Zopiclone

these compounds is characterized by respiratory arrest caused by the suppression of brainstem respiratory centers. This effect is expected to be addictive with others CNS depressants as in case of benzodiazepines [64,65]. Akins et al. described a fatal case of a 53-year-old woman with a medical history of narcolepsy, sleep apnea, and sarcoidosis found unconscious by her husband. The cause of death was established to be accidental and due to the combined effects of sodium oxybate, tramadol, carisoprodol, all within normal therapeutic ranges [62]. Gabapentin was also detected but it was not listed as contributory cause of death.

3.1.3. Antiepileptics

In epileptic patients, the safety and efficacy of sodium oxybate has not been fully established. The EMA and the FDA discourage the use of sodium oxybate with inhibitors of the GHB dehydrogenase such as sodium valproate, phenytoin, and ethosuximide. In particularly, the concomitant use of sodium oxybate and sodium valproate resulted in a 25% mean increase in systemic exposure to sodium oxybate and in a greater attention and working memory impairment [66–68].

A single, supposed pharmacokinetic interaction has been reported in a 52-year-old Swiss woman under treatment of sodium oxybate and topiramate [69]. The subject was hospitalized after developing confusion and headache followed by intermittent myoclonic jerks, meiosis and a rapid onset of coma, which was probably provoked by an excessive enhancement of the GABA signaling. A same interaction may be expected for gabapentin and pregabalin which increase the GABAergig signaling though increased synthesis of GABA and reduction of excitatory neurotransmitters release via calcium channel blockage [70]. It is therefore probable that gabapentin contributed to the cause of death of the patient reported by Akins et al., although authors did not list it (see paragraph 3.1.2 Opiates/opioids).

3.1.4. Other medications

Although their abuse potential is well documented in literature [71–74], interactions between GHB and antidepressants, antihistaminics, antipsychotics, or prescribed stimulants are not reported. Co-existing cardiac diseases may be exacerbated by the use of stimulants and tricyclic antidepressants or antihistaminics intake might cause the prolongation of the QT interval, leading to ventricular arrhythmias, syncope, and even cardiac arrest [66,75]. It has also been observed that hypertension, hyperlipidemia, obesity, diabetes, and obstructive sleep apnea are much more common in patients with narcolepsy [76]. Thus, stimulants, antidepressants and antipsychotics and preexisting pathologies might have played a key role in the three fatalities reported by Zvosec et al. [53] and possible interactions with GHB/sodium oxybate should not be excluded.

Furthermore, since GHB has previously been associated with 'gym culture,' additional studies on the non-medical use of androgenic anabolic steroids (AAS) together with GHB need to be undertaken. AAS are often self-administered without any medical prescription among athletes and bodybuilders to increase body performance and promote muscle growth, and are also associated with cardiovascular risks [77,78]. Petersson et al. reported that GHB was detected in two individuals who were also positive for AAS, although sex, age circumstances, and cause of death were not specified and no interaction emerged from the literature [79]. It has been demonstrated that, after a single administration, AAS allosterically modulate the $GABA_A$ receptor function, while they alter the physiological GABAergic transmission in neural circuits after chronic exposure [80].

The recreational use of phosphodiesterase type 5 (PDE5) inhibitors as 'club drugs' is growing among MSM, who misuse mainly sildenafil and tadalafil to facilitate the sexual performance during 'chemsex' sessions [81]. PDE5 inhibitors seem to not show any interactions with GHB, but they are sometimes added by pushers as adulterants for marketing purpose with buyers susceptible of unexpected adverse events [49] (Table 1).

4. Conclusion

Although several laboratories producing GHB from GBL have been dismantled across Netherland, Germany, Belgium, and Estonia, their non-medical use remained unchanged in this period of pandemic and still represents a social and public health threat. GHB and analogs are, along with opioids, cocaine, cannabis, amphetamine, MDMA, and tranquilizers, the most frequently reported substances in drug-related ED admissions marked by a polydrug use pattern [82,83]. Polydrug and polypharmacy are harmful conditions due to the unpredictable interactions of simultaneously consumed substances. PD, mainly CNS depressants, significantly contribute to the severity of GHB poisoning because of their additive effect on the CNS. Clinicians should be aware of the multidrug use scenario and physicians have to be careful while prescribing drugs with a potential for recreational use. A strict prescription policy has to be adopted to reduce the availability of drugs for diversion to the illicit market. The general advice is not to use both medical and recreational GHB in combination with other CNS depressants and not to administer GHB to those individuals with substances use disorders or other mental illnesses.

5. Expert opinion

Currently, the clinical treatment of GHB and its precursors in acute intoxications in involved individuals represents a medical challenge, since the signs and symptoms of intoxications are nonspecific. Without any rapid screening test, which has not been available up to now, confusion with intoxication or intake of other sedative-hypnotic drugs, such as alcohol or benzodiazepines can happen. No established guidelines for acute intoxications exist to be applied at Emergency Departments. The only suggested measure to treat intoxicated individuals admitted to hospital emergency departments is essentially supportive monitoring vital signs and ensuring the airways patency since emesis is a common symptom. The empirical use of benzodiazepines, naloxone and physostigmine has been suggested [84]. Furthermore, if individuals are unconscious then intubation should be taken

into consideration until recovery. This is particularly true when polyabuse with other psychotropic drugs might be occurred.

Although infrequent, long-term abuse of GHB and its precursors, especially when consumed for chemsex [36], causes physical dependence, addiction, tolerance, and ultimately withdrawal following regular use of increasing doses [84]. Also, in this case, no guidelines or established protocols exist. Similarly to acute intoxication treatments, high-doses of benzodiazepines such as diazepam and lorazepam are recommended up to disappearance of withdrawal symptoms. In the event that benzodiazepines administration is not effective, anticonvulsants such as barbiturates, or GABA-B receptor agonist baclofen or even an antipsychotic, (e.g.) olanzapine might be indicated. If resistance to the above reported treatments is observed, titration and tapering of pharmaceutical GHB can be tried [85].

Concerning the challenges encountered in the analytical disclosure of exogenous active and passive exposure to GHB and its precursors/analogues (GBL and 1,4-BD), it is fundamental to take into consideration the dual nature of this molecule, endogenous as neurotransmitter and exogenous as DOA or medication [20,86].

Negligible concentrations of GHB (<0.5–5 µg/mL) are therefore detectable in body fluids without any previous active or passive exposure to this compound [87]. One of the major challenges in forensic toxicology is represented not only in distinguishing between endogenous and exogenous GHB presence in human body, but also in demonstrating a recent exposure taking into consideration the quite short detection window of GHB in conventional biological matrices that is, 4–5 hours in blood compared with 8–10 hours in urine [20]. Especially in cases of GHB-FSA and other criminal cases a rapid and expeditious blood and urine collection is therefore crucial to increase the chance of detecting an eventual exogenous GHB intake [84]. If more than 10–12 hours have elapsed after the suspected exposure to GHB there is little hope of verifying this occurrence and other investigation approach may be taken into consideration. One the most reliable is represented by GHB hair testing, to document a single GHB exposure. For this purpose, it is necessary to wait a reasonable length of time for collecting hair (from a minimum of 7 days up to 1 month or more), considering the mean hair growth of 1 cm/month. The interval of 1 month from the possible exposure has been suggested before hair collection and this is the interval of time that we also highly recommend to disclose a single past exposure to GHB. The segmental analysis of hair into 5 mm segments and the calculation of a ratio between the targeted segment (characterizing the time of exposure) and the others represent a reliable method to detect single GHB intake [88]. To this purpose it is fundamental to define the value of this ratio. According to the Guidelines for the Forensic Analysis of DFSA and Other Criminal Acts of the UNODC [89], the ratio should be at least 10, meaning that the 'targeted segment' should present a GHB concentration at least 10 times higher than that in the other segment, to demonstrate a GHB exogenous intake. More recently Bertol et al proposed lower ratios than UNODC: 4.45:1 (95% CI 3.52–5.63) and 3.35:1 (95% CI 2.14–5.18) to detect a single GHB exposure after one and two months respectively [90]. Differently from other biological matrices such as blood and urine where cutoffs have been proposed both for ante-mortem and postmortem samples [91], in case of hair it has been suggested to use 'each subject as its own control,' taking into consideration a very broad concentration range of endogenous GHB: 0–12 ng/mg [90,92,93].

The situation is even more complicated in postmortem cases, not only for the presence of endogenous GHB, but also for its postmortem production, due to autolysis and bacterial action. Cutoffs in higher than those in ante-mortem samples have been proposed for postmortem cases: 10 µg/mL for urine samples and 30 µg/mL for whole blood, when no signs of advanced putrefaction are detectable. However, 50 µg/mL has also been suggested to distinguish endogenous production from active consumption for postmortem central blood. When applying these cutoff values, it is fundamental to carefully evaluate the postmortem interval (PMI) as suggested by Busardò et al [91], which strongly influences postmortem production of GHB both in blood and urine specimens.

Despite the broad number of analytical strategies and cut-off values to discriminate between endogenous and exogenous GHB, this differentiation remains a very difficult task for forensic toxicologists. It requires an integrated approach, for example, by analyzing multiple biological matrices, when available, for a correct interpretation of each case.

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