Letter to the Editor DOI: 10.2478/aiht-2019-70-3295

Gamma-hydroxybutyric acid, gamma-butyrolactone, and 1,4-butanediol addiction: a serious health threat

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Gamma-hydroxybutyric acid (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) pose a serious threat to the health of (ab)users, and the aim of this letter is to start a discussion in order to increase awareness of their large abuse potential, especially in *chemsex* practices and sexual assaults. In addition, we would like to open a discussion about detection and control options.

GHB is a naturally occurring precursor to gamma-aminobutyric acid (GABA) and a neurotransmitter that can affect serotonin (5-HT, hydroxitryptamine), noradrenaline (NA, norepinephrine), dopamine (DA), and acetylcholine (ACh) production. It has its own presynaptic G protein-coupled receptor in the brain. In its natural form, GHB is present in the brain and body fluids at low concentrations.

As recreational or party drug of abuse it is known under the street name of *liquid ecstasy* and has a biphasic action: at low concentrations it produces euphoria and removes personal or social inhibition, whereas at higher concentrations it causes visual impairment, dizziness, lower body control, sleepiness/drowsiness, short-term memory impairment, and unconsciousness. Recreational doses are relatively high in view of most sedatives and range between 1.8 and 2.7 g, but most people are completely sedated by higher doses (>4 g) (1). It can also produce empathy (empathogenic/entactogenic effects) and cause hallucinations, agitation, or aggression (2, 3).

Early effects of GHB resemble those of alcohol intoxication, and are often confused with drunkenness. Hence its reputation of a rape drug (4, 5). Regular use may lead to physical dependence and substance use disorder (6) and create tolerance, which means that users need to up the dosage to achieve the same effect.

Although GHB has been approved for the treatment of narcolepsy with catalepsy by the United States Food and Drug Administration (FDA) (7) and is currently controlled, its abuse continues through unlawful production in clandestine laboratories and illegal sales on the internet (6). As of late, its recreational use is being replaced by that of its prodrug GBL, which is cheaper and easier to obtain due to several legal industrial applications. Its use, however, entails a higher risk of overdosing because of higher liposolubility and density. The first is responsible for GBL reaching higher plasma peak levels faster than an equimolar dose of GHB, whereas higher density means that smaller doses are needed, which are more difficult to measure. This narrows the safety margin between causing the desired effects and coma. Fortunately, however, these are also the reasons why GBL is seldom used undiluted. In addition, the effects of GBL depend on user's genetic setup, that is, lactonase activity, as it can slow down the onset of its effects (8). The toll is high, however, as GHB and its precursors (GBL and 1,4 BD) have been involved in reports of poisoning, overdose, rape, seizures, coma, and even death (6).

GHB, GBL, and 1,4-BD are often used in combination with designer drugs such as synthetic cathinones (9–12). GHB is at times mixed with other substances to offset any unwanted effects or maximise the perceived benefits. There have been reports of intoxication in homosexual men who consumed GHB combined with sildenafil to enhance sexual effects, as part of *chemsex* practices (5, 13). Such practices, however, are not meant to dilute or *cut* a given drug with another substance (e.g. the way in which cutting agents and adulterants such as benzocaine, lidocaine, or levamisole are used by cocaine dealers to increase their profits by diluting the drug with cheaper substances) (14), but rather to maximise and prolong the effects.

GHB has a rapid elimination – four to six hours after ingestion regardless of the dose – and a narrow detection window (less than 12 hours in urine). Petersen et al. (15) have therefore proposed a new biomarker with a longer detection window – GHB-glucuronide. This GHB metabolite has successfully been spotted in several biological matrices (plasma, urine, hair, nails, cerebrospinal fluid, and whole blood) (16–18) through the use of hyphenated techniques, but its levels were minimal in virtually useless in all these studies irrespective of whether the parent drug had been administered as a medication or abused as recreational drug (15–21).

The development of hyphenated analytical techniques (17, 18) such as ultra-high performance liquid chromatography

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tandem mass spectrometry (UHPLC-MS/MS) and gas chromatography tandem mass spectrometry (GC-MS/MS) is therefore crucial if we want to be able to identify GHB and its precursors in conventional and unconventional biological matrices, bearing in mind the current proposed cut-offs to distinguish between endogenous and exogenous GHB (22). In samples taken from living subjects these are 5 mg/L for blood and 10 mg/L for urine, whereas in post-mortem specimens they are 30 mg/L and 50 mg/L for peripheral and central blood, respectively and 10 mg/L for urine (22).

In conclusion, we urge the scientific community investigating GHB to focus on new alternative metabolites, such as the carboxylic glucuronated metabolite, that may provide a longer detection window than the current ones.

Conflicts of interest

None to declare.

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