

GHB acid: A rage or reprove

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ABSTRACT

Gamma-hydroxybutyric acid (GHB) is a naturally occurring analog of gamma-aminobutyric acid (GABA) that has been used in research and clinical medicine for many years. GHB was used clinically as an anesthetic in the 1960s but was withdrawn due to side effects that included seizures and coma. GHB has been implicated in a number of crime types; most notably in drug-facilitated sexual assault. GHB is abused by three main groups of users: Body builders who use the substance believing that it stimulated the release of growth hormone; sexual predators who covertly administer the drug for its sedative and amnesic effects and club-goers (rave parties) who take the drug for its euphoric effects. The short-lived hypnotic effects, relative safety and widespread availability of the drug have made it particularly well suited to this role. The drug has an addictive potential if used for long term. The primary effects of GHB use are those of a CNS depressant and therefore range from relaxation, to euphoria, confusion, amnesia, hallucinations, and coma. Despite the increased regulation, GHB remains widely available through the Internet where one can easily purchase the necessary reagents as well as recipes for home production. There are reports of patients being unresponsive to painful stimuli and cases of oral self-mutilations linked to the abuse of GHB, though quiet rare. Such cases should remind odontologists that intra-oral lesions may be the result of self-mutilation either due to mental illness or altered states caused by the use of prescription or non-prescription drugs.

Key words: Abuse, ecstasy, euphoria, gamma-hydroxybutyric acid, gamma-butyrolactone, hallucinations, odontologists

INTRODUCTION

Woman 'Pulled Own Teeth Out'. A woman who lost 18 of her teeth while she and her boyfriend were high on drugs has told a court she pulled them out herself. Samantha Court said she carried out the act which left her covered in blood because she was hallucinating after taking the drug GHB.

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Her boyfriend, Jason Morns, has denied grievous bodily harm after the accident in Bolton, Greater Manchester, in April 2002. Mr. Morris told Bolton Crown Court he has no recollection of the incident because he had "total memory loss" for a week after taking a large quantity of GHB.

Miss Court told the court she pulled her own teeth out with a pair of pliers, while hallucinating on GHB. She told the court: "I turned to face my bedroom wall and an illuminous green and pink fly flew out of the wall and down my throat.

'No pain' "That's when it started choking me."

Miss Court said that, to stop the choking, she removed her teeth. She said it was difficult to remove the first one, but after that "the rest just seemed to fall out", during which she felt no pain.

She denied she was making up her story to save her boyfriend.^[1]

It is well documented in the dental literature that certain cultures practice deliberate mutilation and non-therapeutic

extractions of the dentition to satisfy a variety of social, religious and cultural imperatives. Reasons for such activities include esthetic adornment, class identification and a means of facilitating oral sex. In Western cultures, deliberate mutilation however is considered pathologic.

Oral self-mutilation may be classified as either organic or functional. In organic self-mutilation, the person injures himself unknowingly and compulsively. The occurrence of oral self-mutilation resulting from a functional cause may be motivated by secondary gains, factitious or neurotic self-excoriations and self-mutilation during a psychotic episode.^[2-5]

The purpose of this article is to highlight the fact that though, oral self-mutilation, particularly auto-extraction, is rare, such cases should remind odontologists that intra-oral lesions, such as extraction sockets, may be the result of self-mutilation either due to mental illness or altered states caused by the use of prescription or non-prescription drugs.

History of GHB

Occurring naturally in many parts of our body from the brain to heart, to most muscles, kidneys and brown fat, gamma-hydroxybutyric acid or GHB for short was first synthesized in 1960s by Laborit in an attempt to study the effects of GHB and GABA, producing a compound that would interfere with beta oxidation and cross blood-brain barrier. Bessman and Fishbein later discovered that GHB was an endogenous compound and an endogenous metabolite of GABA.^[6] GHB was thus discovered in search for therapeutic GABA analogs.^[7]

Since its discovery, GHB has played many roles in the laboratory. It was used to create an absence seizure model.^[8,9] GHB was also shown to have tissue-protective effects in the setting of myocardial infarction, stroke, sepsis, small bowel ischemia, hypovolemic shock, ionizing radiation and oxygen free radicals.^[10,11] Despite promising beneficial effects, GHB has not found widespread clinical use. In the 1960, GHB was used as a general anesthetic agent but fell out of favor due to an association with abnormal electroencephalographic (EEG) patterns in animals.^[12,13]

In the year 1980, GHB could be bought in health food stores and the use began to rise amongst body builders as it was believed that taking this drug could improve muscle mass or improve exercise performance. While GHB has been present in laboratories and therapeutic trials for years, it has recently become a public health issue as a drug of abuse. Hence in the year 1990, FDA imposed ban over the counter sale of the drug throughout the United States. Simultaneously from 1997 to 1999, several states and countries passed laws to control the sale and consumption of GHB and finally designated it as a Schedule 1 substance in the United States in the year 2000.

Properties

GHB occurs naturally in the human body primarily in the central nervous system. It is a metabolite of brain neurotransmitter GABA. Chemically, GHB is called gamma-hydroxybutyric acid,^[6] 4-hydroxybutyric acid, or gamma-hydroxybutyrate. GHB's structure consists of a chain of four carbon atoms, with an alcohol group (-C-OH) at one end and a carboxylic acid group (-C-OOH) at the other end. GHB usually exists either as a free acid, or as a sodium salt. The sodium salt is called Sodium Oxybate and is soluble in water and methanol. It is available as tablet, light-colored powder; colorless liquid, odorless, tasteless in small vials. It was first developed for its calming actions and was found out to have the ability to induce sleep. This made it to be used as an anesthetic in 1960s but was withdrawn due to its side effects like seizures and coma. Due to its euphoric effects, it is nowadays used as 'recreational drugs'. The vials contain as much as 10 hits and are often slipped into an unknowing victim's drink when they aren't noticing [Figure 1].^[14]

GHB is most commonly available in liquid form and is taken orally. It is also available in powder, putty, capsule and gel forms. Street names are Liquid ecstasy, Fantasy, GBH, Georgia Homeboy, Great hormones at bedtime, Liq. E, Liq. X, salty water, Soap, Everclear,^[8] Sodium Oxybate, Scoop,^[6] Poor man heroine. Trade names include Alcover (Italy), GammaOH (France), Somsanit (Germany) and Xyrem (US, Canada).^[14]

Metabolism and Neuromodulatory Properties

The most important synthetic pathway for GHB involves conversion of GABA to succinic semialdehyde by the molecule GABA aminotransferase, followed by reduction of succinic semialdehyde to GHB by cytosolic succinic semialdehyde reductase. Mitochondrial succinic semialdehyde dehydrogenase converts succinic semialdehyde to succinate. A minor pathway for GHB production involves partial oxidation of 1, 4 butanediol. Systemically administered gamma-butyrolactone (GBL) is converted by a circulating lactonase to GHB. The lactonase is not present in brain tissue.

- **NAME:** Gamma Hydroxy butyric acid
- **IUPAC:** γ -hydroxy butyrate
- **Molecular Formula:** C₄H₈O₃
- **Molecular weight:** 104.11
- **Average dose:** 1-5 grams.⁸
- **Trade names:** Liquid ecstasy, Fantasy, GBH, Liq.E, Liq.X.
- **Chemical structure:**

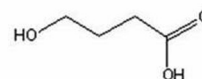


Figure 1: Properties of GHB

The most significant catabolic pathway for GHB degradation is the oxidation of GHB to succinic semialdehyde by NADP⁺-linked succinic semialdehyde reductase. The resultant succinic semialdehyde undergoes further metabolism to either GABA or succinate. There is disagreement as to whether there is significant metabolism of GHB through a beta oxidation scheme^[15] [Figure 2].

GHB exerts ubiquitous pharmacologic and physiological effects when it is administered systemically to animals.^[16] However, GHB also has many of the vital properties of a neurotransmitter or neuromodulator^[17] and neurodepressant. This neurodepressant effect may be mediated by a specific GHB receptor, binding to GABA receptors, modulation of GABA levels, or interactions with other neurotransmitters. There is compelling evidence that a novel GHB receptor exists in the CNS. These receptors are saturated at the levels of GHB achieved after exogenous administration.^[18,19] In addition to its own receptor; GHB is known to bind to the GABA_B receptor, although with a much lesser affinity.^[20,21] Physiologic levels of GHB would not bind this receptor sufficiently to cause pharmacologic effect. However, supraphysiologic levels achieved after exogenous administration could cause considerable binding of the GABA_B receptor leading to membrane hyper polarization and depression of the CNS.^[20-22]

Thus, experimental evidence to date suggests that the high concentrations of GHB in brain tissue that would be predicted to mount up from exogenous administration of this compound as occurs in the clinical scenarios of GHB intoxication, addiction and abuse may wield their protean pharmacologic, toxicologic and behavioral effects chiefly through mechanisms mediated by the GABA_B receptor.

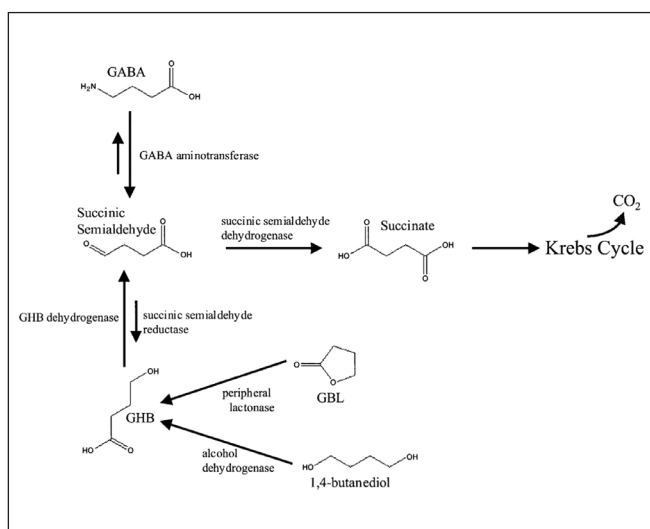


Figure 2: Primary pathway for gamma-hydroxybutyric acid synthesis and elimination. GABA = Gamma-aminobutyric acid, GBL = Gamma-butyrolactone

Specific Effects of the Drug

GHB is generally taken orally and is rapidly absorbed from the gastrointestinal tract. The onset of GHB's effects is delayed and systemic effects occur generally within 15 min.

Positive Aspect of GHB

Cardiovascular and respiratory effects

Laborit observed a constant but short drop in blood pressure in rabbits after administration of GHB, but in dogs there was either no effect or a slight progressive increase in blood pressure. In all animals, a constant bradycardia was observed. Laborit and Leterrier also observed a strong hepatic and renal vasodilating action, particularly during hemorrhagic shock in animals, indicating that GHB has "antishock activity". In man, there appeared to be no effect on blood pressure.^[23] Laborit also observed that at low hypnotic doses of GHB, a decrease in ventilatory rate was reported with an increase in amplitude. At high (sleep-inducing) doses of GHB, a Cheyne-Stokes rhythm appeared.

Central nervous system effects

Based on behavioral and electroencephalographic criteria, GHB-induced sleep has been described as being indistinguishable from natural sleep, i.e. unlike coma, the natural stages of sleep 1-2-3-4-REM (rapid eye movement) all occur in their normal sequence. The effect of GHB-enhanced sleep appears to wear off after 3-4 hours at "normal" doses.^[24] Tables 1 and 2 show the reported blood concentration and its pharmacological effects on CNS.

GHB in obstetrics

GHB had a spectacular action on the dilation of the cervix and furthermore was beneficial in obstetric surgery due to the absence of respiratory depression in the infant and its antishock property against possible cardiac anoxia.^[23]

Sexual enhancing effects of GHB

GHB is "aphrodisiac" in man. It has four sexual-enhancing effects; disinhibition (e.g. relaxation), heightened sense of

Table 1: Reported blood concentration of GHB

Dose	Route	Symptoms	Level
25 mg/kg (1.75 g/70 kg)	Orally	Dizziness, drowsiness	80 mg/L at 0.5 h
75 mg/kg (5.25 g/70 kg)	Orally	Dizziness, drowsiness	90 mg/L at 2 h 9 mg/l by 6 Hrs.
50 mg/kg (3.5 g/70 kg)	IV	Dizziness, drowsiness	170 mg/L

Table 2: Pharmacological symptoms associated with GHB^[6]

GHB >260 mg/L	Deep sleep
GHB 156-260 mg/L	Moderate sleep
GHB 52-156 mg/L	Light sleep
GHB <52 mg/L	Wakefulness

touch, enhancement of male erectile capacity and increased power of orgasm.^[25] These drugs also appear to promote high-risk sexual behaviors that have been associated with increased HIV infection.^[26]

Use of GHB in the treatment of narcolepsy and associated cataplexy

GHB is used as a potential treatment for narcolepsy due to its sleep-inducing properties. It was thought that in narcoleptic patients, GHB would act to “normalize” sleep patterns and reduce the problems associated with the disorder such as cataplexy, sleep paralysis, daytime-drowsiness and hypnagogic events. Many of the patients reportedly felt more alert during the day and there was a reduction in hallucinations, cataplexy and sleep paralysis. A degree of weight loss was also reported in some obese patients.

GHB use in alcohol and opiate withdrawal

The use of GHB in alcohol withdrawal has been investigated by various researchers and was found to reduce tremors after consumption of alcohol. GHB has also been shown to inhibit voluntary ethanol consumption. The exact mechanism of GHB-enhanced alcohol and opiate withdrawal is unknown. However, a profound inhibition of dopamine output in the nucleus accumbens and ventral caudate nucleus has been associated with alcohol and opiate withdrawal syndromes, and increased dopamine output is known to be involved in the rewarding effects of morphine and alcohol.^[27] Therefore, it is possible that GHB suppresses these symptoms as it increases the dopamine levels in these regions of the brain and maintains the dopamine reward pathway.

Negative Aspect of GHB

GHB is an extremely dangerous drug as the dose range between safe and toxic is very narrow. After being swallowed the Ecstasy pill begins to disintegrate. It starts to enter the bloodstream through the lining of the small intestine. Once in the bloodstream the active ingredient of

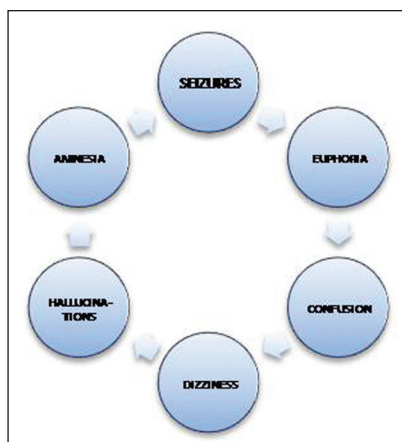


Figure 3: GHB toxicity

GHB will be pumped into the heart. After about 30 minutes, the GHB will be small enough to cross the capillaries into the brain and the ‘high’ will start to be felt. GHB makes nerves in the brain release serotonin. This serotonin then causes a gland in the brain to release Oxytocin also known as ‘the cuddle chemical’. Oxytocin creates the feeling of euphoria and the illusion of strong connection with others. The brain also releases dopamine which allows the user to focus hard on one thing, like beat of a song in a club. It also affects the hypothalamus which controls the body temperature. GHB users are a high risk for overheating.

GHB makes you high but it also drags you way down. The way the drug affects a person can be compared to the swinging pendulum. The “feel good” emotions for the abuser go far beyond their usual boundaries. But the person feels far worse than usual as the pendulum of emotions swings back in the other direction. The main adverse effects include respiratory depression, amnesia, apnea, hypotonia, aggressiveness, hallucinations, dizziness, euphoria, confusion and seizures [Figure 3]. Resolution of CNS depression occurs abruptly with patients going from unresponsive to agitated and combative over very short period of time.

GHB abuse

Due to the various effects of GHB and the various groups of people using the compound, it has a wide-ranging abuse potential.^[6]

Various myths have come up from time to time which has made the usage of GHB even more adverse. Many people use it for weight lifting. A few credit GHB for keeping them young. According to some it is the safest of all euphoric drugs, in terms of having zero negative side effects. However some are of opinion that it is good!!! Better than alcohol as you need not overload the liver with processing excess amounts of alcohol. A few even use it as a vitamin supplement.

Physical dependence has been observed at prolonged high dosage. Reports indicate that GHB is abused for various reasons and by various sections of society. Three main group of abusers include [Figure 4].

Body builders who believe that by taking this drug could improve muscle mass or improve exercise performance

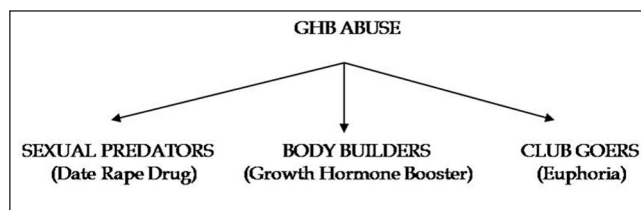


Figure 4: Agents of GHB abuse

but there is no evidence of such effects. Therefore it is illicitly sold/distributed in gymnasiums. Some people erroneously refer to GHB as an anabolic steroid, which is not the case, as its chemical structure does not resemble a steroid. Conversely, other people sometimes use GHB as an apparent appetite suppressant or weight loss product, although there is very little definite scientific data to support these claims. Second group includes the sexual predators who covertly administer drug for its sedative and amnesic effects and lastly club goers who take the drug for its euphoric effects. GHB use is very often in night clubs and is an alternative to ecstasy. Most patients are transported from night clubs with 84% of cases presenting between midnight and 0600 hours. There have also been reports of GHB being used to facilitate sexual assault.

Epidemiology of GHB Abuse

At present, GHB appears to be mainly used and abused in the United States and Europe, where it was reported by the United Kingdom, Italy, The Netherlands, Belgium, Sweden, Finland, Ukraine, France, Spain, Switzerland, Czech and Denmark. Australia reported minimal abuse [Figure 5].

GHB Dependence and Withdrawal

GHB can be easily manufactured at home with very little knowledge of chemistry, as it only involves the mixing of its two precursors, GBL and an alkali hydroxide (such as sodium hydroxide) to form the resulting GHB salt. Due to the ease of manufacture, it can even be produced in private homes by low level producers. It can be purchased overseas via Internet and then shipped to the purchaser.

GHB withdrawal is similar to withdrawal from other sedative/hypnotic agents such as ethanol. GHB's significant "likelihood of abuse" is evident with its sixth place ranking out of 19 hypnotic drugs compared. It is ranked second only to pentobarbital with respect to toxicity taking into account withdrawal severity.



Figure 5: Epidemiology of GHB abuse

Onset of withdrawal symptoms typically occurs within a few hours after cessation of GHB or its prodrugs. The withdrawal symptoms include: insomnia, anxiety, tremor, delirium, seizures and in extreme cases even, death. Wernicke-Korsakoff syndrome has also been associated with GHB withdrawal.^[28]

In the majority of GHB-related deaths, the concentration in post mortem blood has been found to be high. Furthermore, in living persons, similar concentrations have been detected in unconscious patients who awake a few hours later with no obvious side effects. Due to the rapid absorption and metabolism of GHB, however, it is difficult to predict how much of the original dose such post mortem concentrations represent. Hence more research and thorough analysis of GHB in fatalities and poisonings are still required before the true involvement of GHB can be established and accurate mortality and morbidity figures produced.^[6]

GHB Detection

GHB can be detected in hair even months after GHB ingestion. To detect GHB in urine, the sample must be taken within 8-12 hours of GHB ingestion. In some cases, however, extensive drug screening is performed and presence of GHB has been confirmed by gas chromatography and mass spectrometry.

Management: A Dilemma

GHB consumption is like a double-edged sword. Due to rapid absorption from GIT, gastric lavage and activated charcoal is of limited use. Mainly supportive treatment with intubation is needed. To reduce the risk of aspiration pneumonia and positional asphyxia, the patient is laid down in recovery position. Convulsions from GHB can be treated with diazepam or lorazepam. NCS-382-GHB antagonist is used in basic science research. However to the best of our knowledge, this agent has not been used in clinical setting, and thus can be a ray of hope for future.

FINAL POINT

Everything you do carries some element of risk, be it your health, liberty or even your life. Always try and reduce that risk to as small a possibility as you can by being as informed and as careful as you can.

GHB, GBL and congeners are popular at rave parties. CNS and respiratory depression are the major toxicities which may even be fatal. Auto or self-extraction is rare but should always be considered when examining oral lesions of unknown cause. The mode of abuse of GHB frequently involves the use of other drugs whether it is alcohol or heroine which further exacerbates its toxicity. In comparison to other forms of self-mutilation, tooth extraction is rare. Practitioners should include oral self-mutilation in the differential diagnosis for patients with

histories of unexplainable oral lesions. Abrupt cessation in habituated patients may produce withdrawal. Supportive care by and large suffices for treatment.

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