

RESEARCH REPORT

Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence

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Abstract

Gamma-hydroxybutyrate (GHB) is a compound found in mammalian brain which meets many criteria of a neurotransmitter. GHB has been investigated as a tool for inducing absence (petit mal) seizures, for use as an anesthetic, and for treatment of narcolepsy, alcohol dependence and opiate dependence. Since 1990 GHB has been abused in the United States for euphoric, sedative and anabolic effects. Coma and seizures have been reported following abuse of GHB, but dependence liability has received little attention. The neuropharmacology, potential therapeutic uses and acute adverse effects of GHB are reviewed, followed by a case series of eight people using GHB. Adverse effects of GHB may include prolonged abuse, seizure activity and a withdrawal syndrome. This withdrawal syndrome includes insomnia, anxiety and tremor; withdrawal symptoms resolve in 3–12 days. GHB has the potential to cause a significant incidence of abuse and adverse effects. Prolonged use of high doses may lead to a withdrawal syndrome, which resolves without sequelae. Educational efforts should address the narrow therapeutic index, possible physical dependence and dangers of combining GHB with other drugs of abuse.

Introduction

Gamma-hydroxybutyrate (GHB) is a putative neurotransmitter, structurally related to gamma-aminobutyric acid (GABA) and glutamic acid, which has been the subject of investigation since 1960. GHB was first studied for its ability to induce short-term coma and possible surgical anaesthesia. Subsequent work focused on its ability to create absence (petit mal) seizures and thus to facilitate evaluation of anti-absence medications.

Neuropharmacology of GHB

Roth & Giarmann showed that GHB is a naturally occurring substance in mammalian brain and proposed its role as a neurotransmitter.¹ The structural similarity of GHB to GABA and the demonstration of pathways that can convert GHB to GABA led to speculation that GHB might be a GABA agonist. However, GHB does not appear to exert direct actions on the GABA_A receptor and, while GHB has partial agonist activity at GABA_B receptors, this effect has only

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been demonstrated at supraphysiologic concentrations.²⁻⁴

Several lines of evidence support the hypothesis that GHB is a neurotransmitter. Specific high-affinity binding sites for GHB have been found in rat brain.⁵ GHB has a specific enzyme for its biosynthesis and a high affinity uptake system.^{6,7} Moreover, it is located primarily in the synaptosomal compartment and is released from brain tissue by membrane depolarizing concentrations of potassium in a calcium dependent process.⁸ High affinity binding sites appear to be co-localized with dopaminergic structures.⁹ GHB administration transiently suppresses dopamine release, followed by a marked increase in dopamine release, particularly along the neurons of the nigrostriatal pathway.¹⁰ This increase in dopamine release is accompanied by increased release of endogenous opioids.¹¹

GHB pharmacokinetics

GHB is rapidly absorbed, with peak plasma concentrations occurring 20–60 minutes after oral administration. At a dose of 12.5 mg/kg, clearance is 14.0 ml min⁻¹kg⁻¹, and half-life is 20 minutes. GHB is almost completely oxidized to carbon dioxide.¹² Only 2–5% was eliminated in the urine.¹³ Pharmacokinetics are similar in alcoholics.¹⁴

Potential therapeutic indications for GHB

GHB was first synthesized in 1960 as an orally active GABA analog capable of crossing the blood–brain barrier. Because of its ability to induce both sleep and reversible coma, GHB was investigated for its potential as a surgical anesthetic. However, it was found to have little analgesic effect, and onset of coma was often associated with seizure activity including tonic-clonic jerking movements of the limbs or face.¹² GHB alters sleep cycles, increasing slow-wave sleep at the expense of sleep stages 1 and 2.¹⁵ This observation led to several small trials that have demonstrated the efficacy of GHB for the treatment of narcolepsy.¹⁶⁻¹⁹

GHB suppresses alcohol withdrawal tremors and seizures in rats.²⁰ Gallimberti and colleagues have followed-up on this observation with a series of clinical trials which suggest that GHB may have utility in the treatment of alcohol dependence. In a placebo-controlled trial in 23

subjects in alcohol withdrawal GHB, 50 mg/kg, markedly suppressed withdrawal for the 7-hour observation period and was well tolerated.²¹ The long-term efficacy of GHB in alcohol dependence was tested in a 3-month randomized trial. Subjects were administered placebo or GHB, 50 mg/kg/day, in three divided doses. Subjects were told at study intake that they should abstain from drinking, but further psychosocial intervention was not noted. Of the 82 subjects who entered the study, results were reported for the 71 who completed it. Subjects in the GHB group had three times as many abstinent days and half as many drinks per day during the study period. No data were presented on outcomes after GHB was discontinued.²²

Gallimberti *et al.* also evaluated the utility of GHB in suppressing the signs and symptoms of opiate withdrawal. GHB, 25 mg/kg, or placebo was administered in double-blind fashion to 22 heroin-dependent subjects and 19 methadone-dependent subjects. Withdrawal signs and symptoms were markedly suppressed for the 3-hour period of observation and the GHB was well tolerated. Subjects in the GHB group were given additional open-label doses every 2–6 hours for the following 8 days, which continued to suppress withdrawal.²³ Two other methadone-maintained patients were detoxified with GHB, 50/mg/kg every 4–6 hours and 30 mg/kg every 4 hours, respectively. GHB treatment was suspended after 9 and 8 days, respectively, and both subjects were given naloxone 0.4 mg IV; no withdrawal symptoms were noted.²⁴ Hajra *et al.*, in a double blind trial, failed to find any difference between GHB 0 mg/kg, 15 mg/kg, and 30 mg/kg in suppressing naloxone-precipitated withdrawal in an unspecified number of levorphanol dependent subjects.²⁵ While reports of the utility of GHB in the treatment of addictions are intriguing, confirmation by a second group of investigators is needed.

Current use

Although in limited use in Europe as a surgical anesthetic, GHB is not approved in the United States. It has, however, been marketed as a health food product in the United States for its hypnotic effects and also to promote weight loss and muscular development. The latter claim presumably stems from the fact that GHB acutely facilitates slow-wave sleep, during which growth

hormone release takes place. Luby, Jones & Zaleski have reported that several gymnasiums surveyed in South Carolina were selling GHB for this purpose, although the actual efficacy of GHB in promoting muscle development is not documented.²⁶ In addition to the above putative effects of GHB, subjective reports suggest that a significant proportion of users also experience a euphoric 'high' from the drug, and some users take more than the recommended dose (approximately 2.5 g or 36 mg/kg for a 70 kg person) to enhance this effect.^{13,26} GHB is sold as 'GHB', 'liquid ecstasy,' and occasionally as 'GBH' or 'grievous bodily harm'. GHB has gained limited popularity in the United Kingdom, where it has been sold at raves as 'liquid ecstasy'.²⁷ Illicit use has only been reported by the oral route.

Adverse effects

The dose-response curve for GHB is steep and exceeding the recommended or intoxicating dose can result in severe adverse effects. Effects of GHB in humans include somnolence leading to arousable sleep at 40–50 mg/kg and, at 60–70 mg/kg, coma for 1–2 hours (generally without depression of the reticular activating system). The LD₅₀ has been estimated at 5–15 times that inducing coma.¹² GHB and alcohol have synergistic hypnotic effects.²⁸

Introduction of GHB into the United States over-the-counter market in the spring of 1990 was rapidly followed by reports of adverse effects at doses from 1 tsp. (approximately 2.5 g) to 4 tbs. (approximately 30 g).^{13,29,30} Widespread reports of poisonings led to a US Food and Drug Administration ban on distribution for human use outside approved clinical trials in November of 1990. Consistent with known psychopharmacology, adverse effects reported include dizziness, nausea, vomiting, weakness, tonic-clonic seizure-like activity, loss of peripheral vision, confusion, agitation, hallucinations, bradycardia, decreased respiratory effort, unconsciousness and coma.^{13,26,30} These effects can appear within 15 minutes of oral ingestion of the drug and acute symptoms appear to remit after 7 hours, although some cases have reported lingering dizziness for up to 2 weeks.^{13,30} Respiratory arrest occurred in one healthy 24-year old male who reportedly ingested 'several' beers and a 'small' amount of GHB; he was intubated, mechanically ventilated, and recovered without sequelae.³¹

Given these reports and evidence that GHB produces relaxation and euphoria, it is clearly important to understand the abuse potential of this drug. Other authors have to date identified only acute adverse effects, not prolonged abuse or physical dependence. We report here on a series of eight cases of ingestion of GHB illustrating varied motivations for initial use, drug interactions, adverse reactions and evidence of a withdrawal syndrome.

Case series

Ms A, a 67 kg 30-year-old white female, presented at the Haight Ashbury Free Clinics with a 2-year history of GHB use.³² Prior attempts to discontinue GHB had resulted in 'feelings of doom', tremor and insomnia. She sought treatment because of decreased availability of GHB and because she was concerned that prolonged abstinence might result in more severe symptoms. Ms. A denied any adverse effects of the drug itself.

Ms A had regularly consumed 25 g (370 mg/kg) of GHB p.o. per day in five divided doses for 2 years. Three months prior to admission she abruptly decreased her dose to 10 g p.o. (150 mg/kg) per day, in five divided doses. Other drug abuse history included: binge drinking on weekends at age 16 years, with subsequent intake limited to two glasses of wine per month; three doses of heroin at age 28; monthly marijuana use (the effects of which were markedly blunted by GHB); occasional MDMA use ending at age 28; and methamphetamine use every weekend from age 20–28 followed by semi-annual use for the last 2 years.

Ms A described GHB as producing feelings of relaxation, increased libido and marked euphoria. When she abruptly decreased her dose from 25 g to 10 g per day, she experienced anxiety that persisted for 1 week. On six subsequent occasions when she discontinued use of GHB she experienced tremor, insomnia and anxiety, which she described as 'feelings of doom'. These symptoms started 12 hours after the last dose of GHB, persisted until she resumed GHB use, and were relieved when she ingested two alcoholic beverages. The anxiety was moderate in intensity and not accompanied by diaphoresis, palpitations or chest pain. The tremor was described as being of moderate amplitude, present both with intention and at rest,

and was not accompanied by incontinence or loss of consciousness. She denied family history of psychiatric illness or familial tremor.

Ms A presented 7 hours after her last 2 g dose. At admission she had normal vital signs, normal complete blood count and normal 24-item blood chemistry panel, with the exception of a 12% transferrin saturation (normal 15–50%). Her physical examination was unremarkable. Based on the lack of physical findings and absence of life-threatening symptoms in the past, we advised Ms. A to avoid further ingestion of GHB and return to the clinic in 24 hours for further observation. Although she did not return to the clinic, Ms A reported by telephone that she had been abstinent from GHB for 30 days after her last visit. For the initial 12 days she again experienced insomnia, tremor and feelings of doom. The intensity of these symptoms diminished after the first 7 days of abstinence. She was requested to return to the clinic with a 2.5 g sample of GHB. She presented a sample that weighed 3.1 g. Infrared analysis was positive for GHB in the presence of water; no other compounds were detected.

Mr B, a 36-year-old, 70 kg, white male presented to the Haight-Ashbury Free Clinics and was diagnosed as dependent on methamphetamine and abusing multiple benzodiazepines. He also admitted near daily use of 2.5–5 g (36–72 mg/kg) of GHB p.o. q.d.-b.i.d. for the prior 2 years for euphoria and amelioration of the after-effects of methamphetamine. On one occasion he ingested 15 g as a single dose, vomited, was unarousable for approximately 3 hours, and was incontinent of bowel and bladder. He denied any adverse effects from GHB discontinuation.

Mr C, a 28-year-old, 66 kg, white male consumed 1 tsp. (approximately 2.5 g, 38 mg/kg) of GHB orally on 5–10 separate occasions in 1990. He secured his supply of GHB from the health food store where he was employed. His initial reason for consuming GHB was for anabolic effect, but this was rapidly superseded by a euphoric effect. He noted that GHB made him talkative, induced sleep and was heroin-like, although of lesser magnitude than heroin. Mr C noted that after taking GHB in the evening he would awaken, feeling refreshed, at 3 a.m. He considered this sufficiently unpleasant that he limited his use of GHB to a total of 5–10 doses. Mr C had been using 0.25 g methamphetamine

on an almost daily basis, drinking not more than five alcoholic beverages per month, and heroin on an occasional basis. He denied using of any of these substances concurrently with GHB.

Mr D, a 40-year-old, 107 kg, white male resident of San Francisco with a history of untreated hypertension, contacted the Haight Ashbury Free Clinics to describe his positive impressions of GHB. He reported a 3-year history of GHB use, initially consuming 2.5 g (23 mg/kg) of powder at bedtime, for hypnotic and anabolic effects. He described the effects as analgesic, euphoric, sedative, hypnotic and of 3 hours' duration. When he experienced a hypnotic effect he felt exceptionally well rested upon awakening. He noted variable subjective effects after GHB was removed from the over-the-counter market. Mr D gradually increased his dose over a 2-year period until he reached his current dose of 20 g (187 mg/kg) per day in six divided doses. He occasionally used higher doses, including one single dose of 50 g (467 mg/kg) that was not associated with adverse effects. He stated that he increased his dose both to maintain the euphoric effects to which he became tolerant and because tolerance to the hypnotic effect enabled him to ingest larger quantities while remaining conscious.

On three occasions Mr D discontinued his GHB use for up to 30 days. On each of these occasions he experienced insomnia which resolved in three days. Mr D noted approximately 20 times when, while consuming his usual GHB regimen, he ingested 100 or more mg of methamphetamine. On each of these occasions he experienced loss of consciousness, and was observed to be 'spasming'. He denied any incontinence during, or soreness after, these episodes, stating rather that he awoke feeling refreshed. Mr D possesses a considerable amount of primary literature concerning GHB and, based on his reading, does not feel that his seizure-like activity was of concern. Nonetheless, on six subsequent occasions, Mr D ingested two tablets (of unknown strength) of phenobarbital before combining methamphetamine with GHB; he remained conscious and without involuntary motion during these occasions. On multiple occasions Mr D consumed various psychedelics, including LSD, while using GHB; he considered this combination quite pleasant due to the anxiolytic properties of GHB, although no dramatic interactive effects were noted. Mr D regularly

consumed caffeinated beverages during the day for the purpose of antagonizing the sedating and hypnotic effects of GHB. Beyond the above drugs, Mr D also admitted using heroin twice, diazepam abuse ending 2 years prior to his first dose of GHB, and daily consumption of 6–10 alcoholic drinks per night in the 2 years preceding his GHB use. After Mr D began using GHB, he found the taste of alcohol aversive and the hypnotic effects superfluous and decreased his use to two drinks per year; he did not increase his use of alcohol when his supply of GHB was interrupted. Mr D considers his GHB use to be beneficial and has no intention of discontinuing it.

Mr E, a 25-year-old, racially mixed 73 kg male, presented to the Haight Ashbury Free Clinics seeking information to distribute to warn others of the hazards of GHB. He had ingested approximately one tablespoonful of a GHB solution in a Los Angeles area nightclub in May of 1993. He was told that GHB was natural, euphorogenic and an amino acid. He had consumed approximately 10 alcoholic beverages in the 3 hours preceding his ingestion of GHB. Within 15 minutes he began vomiting and experienced dysarthria and dis-co-ordination; he was escorted home and put to bed. Mr E suffered no sequelae of his GHB ingestion, but considered the experience quite unpleasant.

Mr F, a 39-year-old white, employed male had entered into recovery because of the disabling effects that alcohol had on his family functioning. He was abstinent from alcohol, regularly attending Alcoholics Anonymous and participating in an exercise program at a local gymnasium. At the gymnasium he was advised that nutritional supplements might complement his exercise program. Mr F began taking amino acids and was introduced to GHB. He found that GHB had profound alcohol-like effects and began to rapidly escalate the dosage, although he remained abstinent from alcohol and other drugs. At his peak dosage, he averaged one bottle (size unknown, although units for retail sale ranged from 30 g to 250 g) per day of GHB and found that it produced many adverse effects including blacking-out and loss of consciousness. In addition, it produced impairment in his ability to drive. He was stopped for drunk driving while under the influence of GHB. Since he had not been using alcohol or any other measurable drug, he was not charged.

Mr F's GHB intoxication produced a situation in which he lost consciousness while minding his children. This event made him stop using GHB. Upon ceasing GHB use, he described a profound withdrawal syndrome with muscle cramps, anxiety and insomnia. These symptoms peaked in 3 days, and resolved in 1 week, except for an additional week of feeling 'drained'. He went back to the health food store and found that GHB was no longer available so he began to buy it from the underground, escalating to his prior peak dosage. He also began mixing the GHB with alcohol and, as a result of severe relapse, re-entered inpatient treatment. Since detoxification he has been abstinent from alcohol, GHB and all mood-altering drugs. He has not suffered from any long-term sequelae as a result of his GHB addiction.

Ms G, a 22-year-old white female, was a regular participant in rave clubs where she took 3, 4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). She describes no adverse effects with MDMA, but one evening took GHB in combination with her usual dose of MDMA. She became agitated and delusional, requiring hospitalization where she received 2 mg of haloperidol and 2 mg of lorazepam. After 2 days of hospitalization and medication, she stabilized and suffered no long-term sequelae. The dosage of GHB in combination with MDMA appears to have produced intoxication psychosis.

Ms H is a 31-year-old white female carpenter and body-builder who started using GHB for hypnotic and anabolic purposes 3.5 years ago. Her drug use history consisted of: three periods of anabolic steroid abuse, each lasting 3 months; daily use of 2 g of cocaine at age 18; one alcoholic beverage per month; and rare use of marijuana. She noted marked antagonism of the effects of marijuana on the one occasion when she smoked it while under the influence of GHB.

Ms H began using 2.5 g (1 tsp.) of GHB powder once in the afternoon and once at bedtime. She admitted four episodes of somnambulism while under the influence of GHB, one with apnea. After 1.5 years she switched to GHB in liquid preparation taking 2 capfuls (approximately 1 teaspoonful each) in the afternoon and 3 at bedtime. She slept for 3 hours after the bedtime dose and took an additional 1–2 doses of 3 capfuls each evening. Prior attempts to taper GHB use resulted in insomnia. Over a 4-day holiday weekend, she increased her dose by 3

capfuls three times a day and reported feeling 'hyper', 'shaky', light-headed and unable to perform fine motor work due to tremor on Monday morning. At that time she took 2 capfuls and obtained complete symptom relief, a practice she continued until she presented for detoxification. She also took one 0.25 mg dose of alprazolam which relieved her 'shaky' and 'hyper' feelings for 1 hour. She presented at 9 a.m., having taken her last dose of 3 capfuls at 3:30 a.m. Ms H had a pulse of 92, blood pressure of 136/90, mild tremor, normal deep tendon reflexes, mydriasis and pallor. Her liver was palpable to 2 cm. She complained of feeling 'weird', 'shaky' and scared.

Phenobarbital 30 mg p.o. was administered at 9:30 a.m. At 11:00 a.m. her pulse was 84, blood pressure 124/84, she was mildly hyper-reflexic, her tremor was slightly greater, her mydriasis was decreased and she denied dysphoria. She was instructed to take 30 mg of phenobarbital every 8 hours and return in 2 days. She took 75 mg of phenobarbital over the next 16 hours, in divided doses. She described the effects of phenobarbital as aversive and had insomnia until the following evening, after which she resumed her normal sleeping pattern, abstained from GHB and had no further ill effects.

Discussion

GHB is a putative neurotransmitter that has a number of potential clinical roles, including treatment of alcohol and opiate dependence, and a recent history of abuse. These cases, and prior reports, indicate that GHB is abused for its euphorogenic, anabolic and sedative properties. GHB can cause a variety of adverse effects, including potentially fatal respiratory depression, seizure activity, vomiting and dis-co-ordination. Combining GHB with alcohol, methamphetamine or MDMA may increase the incidence of adverse effects. The antagonism of marijuana's effects is intriguing and may indicate a relationship between pathways involving GHB and THC receptors. Tolerance and physical dependence, as evidenced by a withdrawal syndrome that may include insomnia, muscular cramping, tremor and anxiety, can develop.

While physical dependence is only noted to develop after use of high doses, clinicians, both those treating patients abusing GHB and those using GHB therapeutically, need to be aware of

this phenomenon. Physical dependence on GHB may contribute to the continued use among those individuals who continue to abuse it despite adverse consequences. Evaluation of the effects of discontinuation of GHB at the end of clinical trials is essential, particularly in light of the suggestion that GHB be used as a maintenance medication in the treatment of alcoholism, analogous to use of methadone in opiate dependence.²² Prudent management of GHB dependence would appear to include observation, reassurance of the absence of dangerous withdrawal symptoms and drug abuse counseling. The role of sedative-hypnotic drugs in relieving symptoms of GHB withdrawal is unclear; their use should be limited to patients in whom withdrawal is severe or presents a significant risk for relapse.

As with any illicitly manufactured drug of abuse, purity and dose of GHB are uncertain, increasing the likelihood of adverse reactions. GHB may be misrepresented as a safe, natural and non-addictive hypnotic or anabolic. Patients in recovery are often troubled by insomnia and are generally advised to exercise; this may make them vulnerable to the claims made for GHB and makes it imperative for them to consult with a recovery-sensitive health professional before using any substance. The euphoric and physical dependence-inducing properties of GHB may lead to widespread and prolonged abuse. Several points will be important to emphasize in educational campaigns to reduce abuse of, and harm from, GHB. Psychostimulants, such as methamphetamine, may increase the risk of seizures from GHB; concurrent use with alcohol may increase the risk of vomiting and respiratory depression; the therapeutic index of this compound is low; accurate dosage estimates are difficult with illicit supplies, particularly when sold in solution; and physical dependence is a possibility.

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