

REVIEW ARTICLE

DRUG THERAPY

 γ -Hydroxybutyric Acid

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THE SHORT-CHAIN FATTY ACID γ -HYDROXYBUTYRIC ACID (GHB) WAS SYNTHESIZED in 1960 in an attempt to create an analogue of the ubiquitous inhibitory brain neurotransmitter γ -aminobutyric acid (GABA) that would cross the blood–brain barrier.¹ GHB turned out to have sedative properties similar to those that had been reported for γ -butyrolactone 13 years earlier.² In fact, γ -butyrolactone has since been shown to be biologically inactive,^{3,4} since all its biologic and behavioral effects are due to its rapid conversion to GHB by an active lactonase.⁵ Although GHB has found limited clinical use as an anesthetic agent^{6–8} and in the treatment of narcolepsy⁹ and alcoholism,¹⁰ widespread interest has developed during the past 5 to 10 years because GHB has emerged as a major recreational drug and public health problem in the United States. GHB has diverse neuropharmacologic and neurobiologic properties and appears to have dual neuronal mechanisms of action that include activation of both the γ -aminobutyric acid type B (GABA_B) receptor and a separate, GHB-specific receptor (Table 1). This complex interaction between GHB and the GHB and GABA_B receptors within mesocorticolimbic dopamine pathways is probably responsible for the addictive nature of GHB and for symptoms of withdrawal from it.

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N Engl J Med 2005;352:2721-32.

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NEUROPHARMACOLOGIC FEATURES

METABOLISM AND NEUROMODULATORY PROPERTIES

GHB occurs naturally in mammalian brain tissue,³¹ where it is derived from the conversion of its parent neurotransmitter, GABA,³² to succinic semialdehyde through mitochondrial GABA transaminase (Fig. 1). Succinic semialdehyde is then reduced to GHB by cytosolic succinic semialdehyde reductase.¹⁴ GHB may be metabolized through the action of GHB dehydrogenase to succinic semialdehyde, which may be further metabolized either to GABA by GABA transaminase or to succinate through the action of mitochondrial succinic semialdehyde dehydrogenase.³³

GHB exerts ubiquitous pharmacologic and physiological effects when it is administered systemically to animals (Table 1).³⁴ However, GHB also has many of the requisite properties of a neurotransmitter or neuromodulator,³⁵ including a discrete, subcellular anatomical distribution in neuronal presynaptic terminals, along with its synthesizing enzyme. GHB is released by neuronal depolarization in a calcium-dependent fashion.³⁶ A sodium-dependent GHB-uptake system in the brain has also been described,³⁷ and an active vesicular uptake system that is most likely driven by a vesicular inhibitory amino acid transporter has been reported.³⁸

GHB RECEPTORS

The existence of a specific GHB receptor is suggested by specific, high-affinity GHB-binding sites that are observed in the brains of rats and humans. The kinetics of the GHB receptor are related to the 1-to-4- μ M concentration of GHB that is typically found in mammalian brain tissue.^{14,31} Although there are contradictory data,³⁹ evidence suggests that the GHB receptor is presynaptic and G-protein-coupled¹⁵ and that it may

Table 1. Molecular Mechanisms and Physiological Consequences of Ingestion of GHB.*

Variable	References
Molecular mechanisms	
Altered dopamine release (mediated by GABA _B receptors)	Howard and Banerjee ¹¹
Increased serotonin turnover	Gobaille et al. ¹²
Increased level of acetylcholine	Sethy et al. ¹³
Increased level of dynorphin A	Maitre ¹⁴
Increased level of 3'-5' cyclic guanosine monophosphate in brain	Maitre ¹⁴
Altered activity of adenylyl cyclase (mediated by GHB receptors)	Snead ¹⁵
G-protein activation (mediated by GHB receptors)	Snead ¹⁵
Decreased glucose use in brain	Kuschinsky et al. ¹⁶
Reduced mitogen-activated phosphorylation of protein kinase in brain (mediated by GABA _B receptors)	Ren and Mody ¹⁷
Altered presynaptic release of GABA and glutamate (mediated by GHB receptors and GABA _B receptors)	Hu et al., ¹⁸ Ferraro et al. ¹⁹
Decreased binding to NMDA receptors	Sircar and Basak ²⁰
Increased plasma concentration of neurosteroids (mediated by GABA _B receptors)	Barbaccia et al. ²¹
Physiological consequences	
Hypothermia (mediated by GABA _B receptors)	Quéva et al. ²²
Hypertension (mediated by GABA _B receptors)	Hicks et al. ²³
Tachycardia (mediated by GHB receptors and GABA _B receptors)	Hicks et al. ²³
Increased activity of renal sympathetic nerves (mediated by GABA _B receptors)	Hicks et al. ²³
Decreased minute ventilation	Hedner et al. ²⁴
Decreased intestinal motility (mediated by GABA _B receptors)	Carai et al. ²⁵
EEG and behavioral changes, including absence-like seizures and slow-wave sleep, depending on the dose (mediated by GHB receptors and GABA _B receptors)	Snead, ²⁶ Van Cauter et al. ²⁷
Impaired spatial learning	Sircar and Basak ²⁰
Increased protection against neurotoxicity	Ottani et al., ²⁸ Yosunkaya et al., ²⁹ Guney et al. ³⁰

* Parenthetical data regarding mediation indicate whether the effects cited are due to an effect of GHB on GHB receptors or GABA_B receptors. When no mechanism is indicated, there are no data regarding mediation. GHB denotes γ -hydroxybutyric acid, GABA_B receptor, γ -aminobutyric acid type B receptor, GABA γ -aminobutyric acid, NMDA *N*-methyl-D-aspartate, and EEG electroencephalography.

function to inhibit the release of GABA.¹⁸ Despite data showing that GHB may be biologically active in its own right, compelling evidence suggests that most of the physiologic and pharmacologic effects of systemically administered GHB are mediated by the GABA_B receptor (Table 1).

GABA RECEPTORS

GABA is ubiquitous in the brain and can activate ligand-gated ion channels — GABA type A (GABA_A) and GABA type C (GABA_C) receptors — as well as GABA_B receptors. Activation of the GABA_A receptor results in the influx of chloride ions and the generation of a fast inhibitory postsynaptic potential (Fig. 2).⁴¹ There is little evidence to support the hypothesis that GHB interacts with the ionotropic GABA_A receptor.⁴²

The GABA_B receptor mediates a slow inhibitory postsynaptic potential. Effector mechanisms associated with the GABA_B receptor include signaling through the action of the adenylyl cyclase system

and activation of calcium channels and G-protein-coupled, inwardly rectifying potassium channels. The GABA_B receptor is a heterodimer composed of receptor 1 and receptor 2 subunits. The GABA_B receptor is transported from the interior of the cell to the cell surface by the receptor 2 subunit. Postsynaptic GABA_B receptors are coupled to G-protein-coupled, inwardly rectifying potassium channels. Presynaptic GABA_B receptors are subdivided into those that control the release of GABA (autoreceptors) and those that inhibit the release of all other neurotransmitters (heteroreceptors). GABA_B receptors mediate their presynaptic effects through voltage-dependent inhibition of high-voltage-activated calcium channels (Fig. 2).⁴³

GHB AND GABA_B RECEPTORS

Because of the structural similarity of GHB to GABA and the pharmacologic GABA_B-like effects of GHB, the question of whether the GHB receptor and the GABA_B receptor are the same has been raised, and

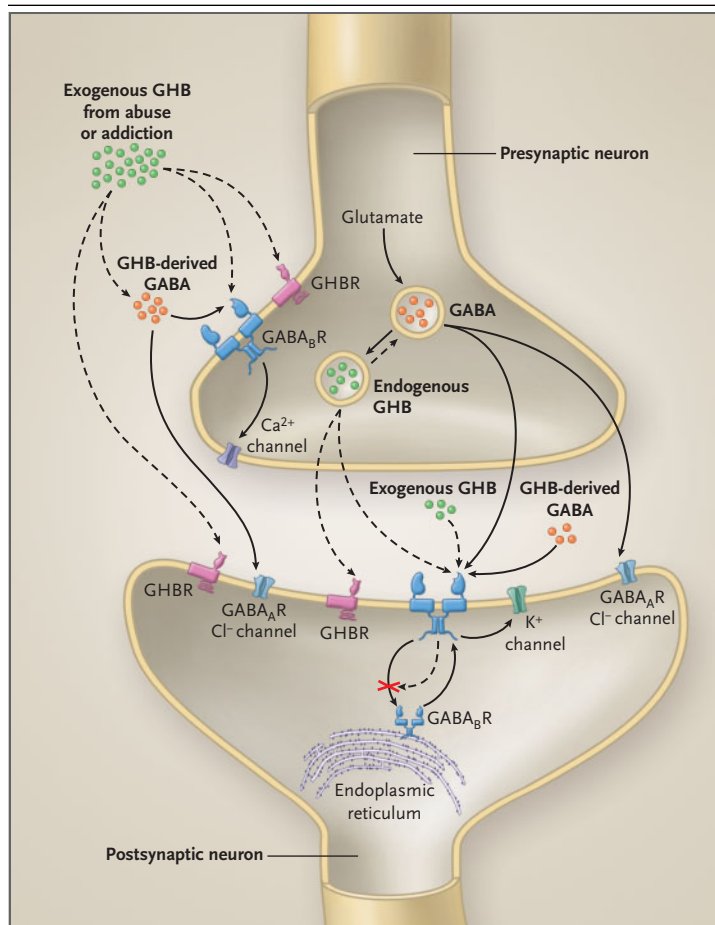


Figure 2. Synthesis and Release of GHB and GABA at Synapses.

The diagram shows the presynaptic and postsynaptic effects of endogenously released γ -hydroxybutyric acid (GHB) (as indicated by dashed arrows) and γ -aminobutyric acid (GABA) (as indicated by solid arrows) and the effects of the exogenously administered GHB, as in abuse and addiction. GABA is synthesized from glutamate in inhibitory neurons and in turn gives rise to GHB. Both GHB and GABA are released on depolarization of the GABA-releasing (GABAergic) neuron. GABA, in forms that are either endogenous or derived from exogenously administered GHB, acts on GABA_A and GABA_B receptors (GABA_AR and GABA_BR, respectively). GABA_A receptors are ionotropic and, when activated by GABA, cause fast postsynaptic inhibition by the efflux of chloride ions (Cl⁻). GABA_B receptors are metabotropic and, when activated by either GABA or high concentrations of GHB, induce slow postsynaptic inhibition by activating potassium (K⁺) currents. Presynaptic GABA_B autoreceptors — when activated by GHB, GABA, or both — reduce the release of GABA by suppressing the influx of calcium (Ca²⁺). Both endogenous and exogenous forms of GHB have a dual action on the GHB receptor (GHBR) and the GABA_B receptor. GHB that binds with high affinity to the presynaptic GHB receptor decreases the release of GABA; GHB that binds to a low-affinity site on the GABA_B receptor increases activation of cell-surface receptors by inhibiting constitutive and agonist-induced endocytosis. The result is enhancement of GHB function mediated by GABA_B receptors, with a greater effect on presynaptic inhibition than on postsynaptic inhibition. Adapted from Owens and Kreigstein.⁴⁰

In addition to being a weak partial agonist of the GABA_B receptor, GHB may also activate the GABA_B receptor indirectly, through its conversion to GABA (Fig. 2). This hypothesis could explain the inordinately high concentration of GHB required to produce GABA_B-receptor-mediated effects, since high micromolar to low millimolar concentrations of GHB are required to produce enough GHB-derived GABA to activate GABA_B receptors.⁴⁷ Furthermore, recent data suggest that GHB-derived GABA activates the GABA_B receptor and induces endocytosis of the GABA_B receptor, whereas GHB itself opposes this process and, acting at the GABA_B receptor, causes the GABA_B receptor to be retained on the cell surface, thus prolonging the functionality of the receptor.⁵¹

Thus, experimental evidence to date suggests that the high concentrations of GHB in brain tissue that would be predicted to accrue from exogenous administration of this compound⁴ — as occurs in the clinical scenarios of GHB intoxication, addiction, and abuse — may exert their protean pharmacologic, toxicologic, and behavioral effects primarily through mechanisms mediated by the GABA_B receptor (Fig. 2).

TOXICITY, ABUSE, ADDICTION, AND WITHDRAWAL

GHB TOXICITY

GHB has a half-life of 20 to 30 minutes, plasma levels peak about 40 minutes after oral ingestion, and the compound can be detected in urine for up to 12 hours.⁵² GHB has a narrow margin of safety. Doses of 20 to 30 mg per kilogram of body weight lead to euphoria and memory loss, as well as to drowsiness and sleep. However, coma may result when twice this dose (or more) is administered.⁵³ In some series, GHB was the second most common drug detected in the serum of young people presenting with drug-induced coma, just behind cocaine.⁵⁴

The clinical hallmark of GHB overdose is rapid onset of profound coma, myoclonus, respiratory depression, hypoventilation, and bradycardia. These signs persist for an unusually short time, given the depth of the coma.⁵³ The usual rapid and uneventful recovery from GHB intoxication can create a false sense of security in the GHB user.⁵⁵ The level of consciousness in patients with GHB-induced coma does not correlate with the serum level of GHB.⁵⁶ GHB intoxication should be considered in any pa-

tient, particularly any young man, who presents with rapid onset of coma of unknown cause when head trauma, metabolic disorders, central nervous system infection, and increased intracranial pressure have been ruled out.

Death from an overdose of GHB may occur as a result of respiratory compromise, aspiration, positional asphyxia, or pulmonary edema,^{53,57,58} as well as traumatic injury or accident, possibly due to the abrupt loss of consciousness induced by GHB.^{53,59} Well over half of all patients who present with GHB intoxication have abused other drugs as well.^{60,61} Chief among these drugs is ethanol, which is synergistic with GHB in the induction of respiratory depression and hypotension⁶² and thus increases the risk of an adverse outcome with an overdose of GHB.

The management of GHB intoxication in a patient who is spontaneously breathing is primarily supportive and includes stabilization of the airway, establishment of intravenous access, oxygen supplementation, and administration of atropine for persistent bradycardia.^{53,63,64} Intubation is rarely indicated but should be performed in the presence of marked hypoventilation, hypoxemia, or mucosal ulcerations or in the absence of the gag response.⁵³ Mucosal ulcerations are of concern because illicit forms of GHB are often made from γ -butyrolactone and sodium hydroxide, an extremely basic mixture that causes mucosal burns. Aspiration of this mixture into the lungs can lead to serious pulmonary complications.⁵⁷

There are no specific antidotes to GHB, nor is there a role for naloxone or flumazenil in the reversal of GHB-induced coma.⁶⁵ Activated charcoal is not indicated because of the very short half-life of GHB and the risk of aspiration.⁵³ Although physostigmine has been used to reverse the clinical signs of GHB intoxication, there is insufficient evidence to recommend its use in the treatment of GHB toxicity.⁶⁶ A patient who has recovered within six hours after the onset of symptoms can be discharged, because GHB has a relatively short half-life, and patients usually have a rapid and uneventful recovery from an overdose of GHB. Before discharge, the cause of the GHB toxicity should be determined — in other words, did the overdose occur accidentally during a one-time recreational use, or did it occur in the context of repeated GHB abuse? Discharge plans should be made accordingly, to provide the patient with assistance in dealing with the issues that led to the GHB overdose. This strategy is particular-

ly important in the avoidance of GHB withdrawal if chronic GHB abuse led to the overdose. Any patient with a recovery time that is longer than six hours should be admitted to the hospital.

GHB ABUSE

Since the early 1990s, GHB and its prodrugs, γ -butyrolactone and 1,4-butanediol, have been used and abused by bodybuilders⁶⁷ because these compounds were reported to stimulate the production of growth hormone (Table 2).²⁷ Like γ -butyrolactone, 1,4-butanediol has behavioral and toxic effects caused primarily by its metabolism to GHB by an alcohol dehydrogenase.^{72,73} However, the diol itself carries inherent toxicity and is particularly dangerous when used in conjunction with ethanol, which enhances its toxicity, probably because of competition of the two compounds for alcohol dehydrogenase.⁷⁴

By the late 1990s, GHB had become a popular club drug and had gained substantial notoriety both as a major recreational drug of abuse^{55,62,68} and as a “date rape” drug.⁷⁵ Subsequently, data on the addictive properties of these compounds began to emerge.⁵⁹ In 1990, the Food and Drug Administration had banned the sale of nonprescription GHB; in 2000, the agency classified it as a Schedule I substance.⁷⁶ However, illicit forms of GHB remain available under a number of names, such as G, liquid ecstasy, grievous bodily harm, Georgia home boy, liquid X, soap, easy lay, salty water, scoop, cherry meth, and nitro.^{53,69} In addition, γ -butyrolactone and 1,4-butanediol are still available for purchase on the Internet, where they are advertised for mood enhancement, sleep induction, and bodybuilding.⁷⁷

The abuse of GHB and its congeners, γ -butyrolactone and 1,4-butanediol, probably stems from the euphoria, disinhibition, and heightened sexual awareness said to be experienced after administration of the drug.⁶⁹ The psychic effects of GHB have been likened to those of ethanol in combination with reduced anxiety, feelings of euphoria, enhanced sensuality, and emotional warmth.⁵³ The resultant dreamy, altered sensorium accompanying the use of GHB has made it popular among attendees of so-called circuit parties⁷⁷ or “raves”.⁶⁰ Raves, all-night dance parties attended by large numbers of young people, are characterized by clandestine venues, hypnotic electronic music, and the liberal use of drugs, among them GHB.⁷⁸ Circuit parties differ from raves in that they are usually attended by men who are either bisexual or homosexual.⁷⁷ When

Table 2. Clinical Aspects of GHB Overdose, Abuse, Addiction, and Withdrawal.*

Feature	Comments	References
Overdose		Couper et al., ⁵⁶ Chin et al., ⁶³ Mokhlesi et al. ⁶⁵
Clinical characteristics	Men with history of drug overdose, substance abuse, or psychiatric illness Profound coma of rapid onset associated with myoclonus, hypoventilation, bradycardia, and miosis Clinical symptoms indistinguishable from overdose of benzodiazepine or ethanol Respiratory depression worse when ingested with ethanol Usually rapid and uneventful recovery Difficult to diagnose because of nonspecific nature of symptoms, rapid disappearance of GHB from urine and blood, and failure of routine screens to detect GHB	
Treatment	Supportive treatment with stabilization of the airway, intravenous access, oxygen supplementation, and atropine for persistent bradycardia No specific antidote No indication for activated charcoal, naloxone, or flumazenil Little evidence for efficacy of physostigmine Intubate for serious hypoventilation, absence of the gag reflex, hypoxemia, or presence of mucosal ulcerations	
Abuse		Van Sassenbroeck et al., ⁶⁰ Kam and Yoong, ⁶⁸ McDonough et al. ⁶⁹
Clinical characteristics	Increased prevalence in young men Club drug used at raves and circuit parties Abused in conjunction with ethanol, cocaine, and "ecstasy" Taken for euphoria, disinhibition, and heightened sexual awareness	
Treatment	None	
Addiction		Teter and Guthrie, ⁵⁵ Freese et al. ⁵⁹
Clinical characteristics	Rarely occurs in occasional users Occurs in bodybuilders and those using GHB for anxiety and insomnia Frequent and increased dosing prompted by rebound insomnia Use of drug every 2 to 4 hr around the clock	
Treatment	None	
Withdrawal		McDonough et al., ⁶⁹ Tarabar and Nelson, ⁷⁰ Anderson and Dyer ⁷¹
Clinical characteristics	Increased prevalence in men History of bodybuilding, anxiety, or insomnia Use of drug every 2 to 4 hr around the clock Onset of symptoms 1 to 6 hr after last dose Tremor, autonomic dysfunction, anxiety, delirium Symptoms lasting up to 2 wk, possibly recurring in episodic fashion	
Treatment	Supportive care; correction of imbalance in fluids, glucose level, and electrolytes Physical restraint possibly required Sedation with high-dose benzodiazepines No indication for antipsychotic or anticonvulsant drugs	

* GHB denotes γ -hydroxybutyric acid.

used at raves and circuit parties, GHB frequently is ingested along with other illicit drugs, most commonly ethanol, methylenedioxymethamphetamine (MDMA, or "ecstasy"), or cocaine.⁶⁰ The abuse of GHB at raves and other party settings appears to be far more prevalent among men than among women.^{61,69,79}

GHB poses a serious risk for persons who are in-

fectured with the human immunodeficiency virus who are taking protease inhibitors, since these compounds alter the metabolism of GHB through their interaction with the cytochrome P-450 system. The result is that even small doses of GHB in the presence of these compounds may lead to the classic signs of GHB overdose (i.e., coma and respiratory compromise).^{80,81}

GHB ADDICTION

GHB is highly addictive.⁷⁶ Occasional users of the drug may be at risk for rape, overdose, or death, given the settings in which occasional use occurs, but occasional users are unlikely to become addicted. Frequent users who take GHB as an antidepressant or for sleep, weight loss, or the enhancement of bodybuilding are far more likely to become addicted.⁵⁹ Some GHB users describe rebound insomnia or alertness occurring after two or three hours of sleep, an effect that often leads them to take additional doses to return to sleep. Thus, such users may ultimately escalate the dosage to one dose every two to four hours, around the clock.⁸² GHB users typically do not see GHB as a drug because of assurances they find in publications and on the Internet that it is a “safe” and “natural” product.⁸³ Therefore, the GHB user may ignore warnings from friends and family who may comment about increasingly bizarre behavior; users also generally fail to recognize their incipient addiction until withdrawal ensues.⁸⁴

Protocols for the treatment of GHB addiction and systematic detoxification have not been published, to our knowledge. However, it would make sense to consider the use of baclofen, a GABA_B receptor agonist, for such therapy, since this compound appears to be effective in reducing the need for addictive drugs in animal models of GHB addiction as well as cocaine, heroin, and ethanol addiction.^{85,86}

GHB WITHDRAWAL

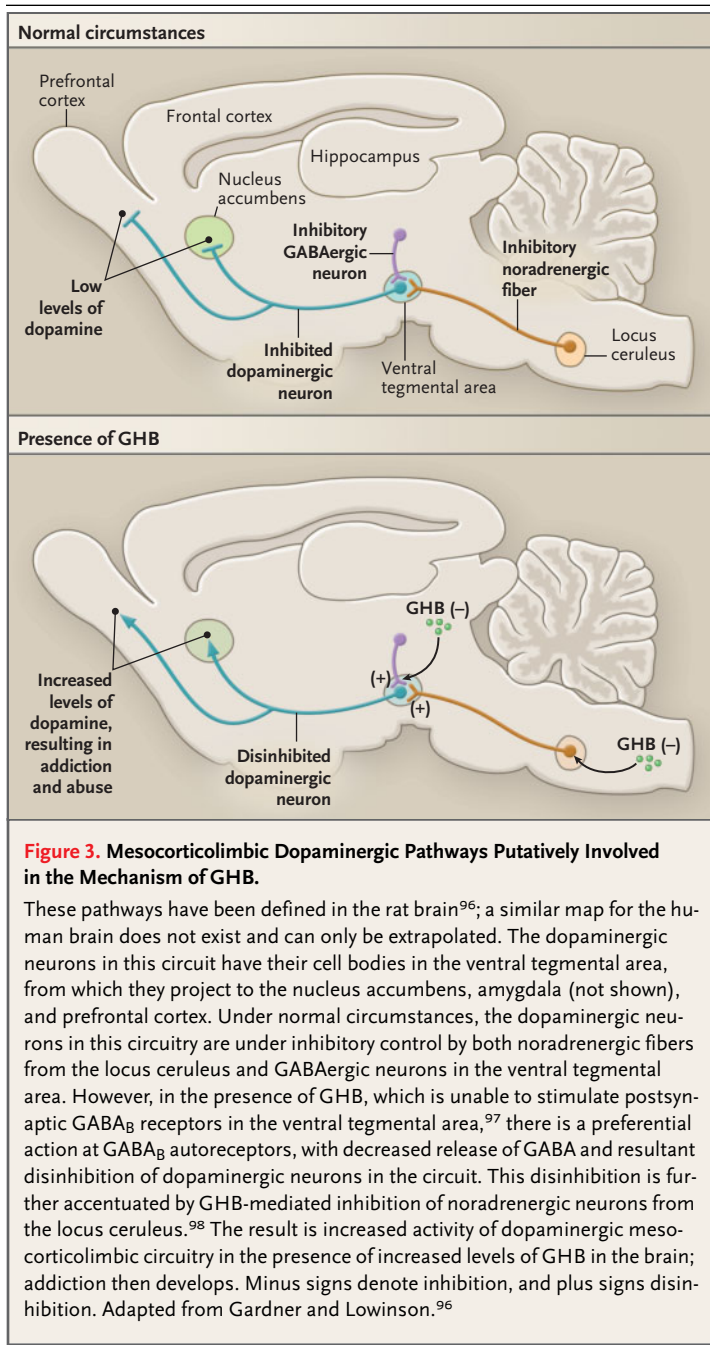
Frequent ingestion of GHB can be associated with severe, potentially life-threatening withdrawal symptoms, necessitating vigorous clinical management, preferably in an inpatient setting.^{62,69,82} Although occasional users of GHB may have a mild withdrawal syndrome when the drug is discontinued, those who have been taking GHB every one to three hours can have severe symptoms similar to those of withdrawal from ethanol or benzodiazepine.⁷⁰ In dependent persons, withdrawal symptoms may start within one to six hours after cessation of the drug.⁶⁹ Although most withdrawal symptoms occur in those who have taken the drug every one to three hours, such symptoms have also been noted in persons who have used the drug every eight hours. In contrast, cessation of GHB prescribed in the context of once-daily dosing for narcolepsy usually does not lead to withdrawal symptoms.⁷⁰

The minimum daily dose of GHB that is associated with withdrawal is reported to be 18 g; for γ -butyrolactone, it is 10 g.⁵⁴ However, the major caveat concerning these data is the lack of quality and quantity controls with respect to the ingestion of GHB. Since most patients who present with GHB toxicity or withdrawal have purchased the drug illegally, the purity and size of the described “capful” or “teaspoon” doses are quite variable, ranging from 500 mg to 5 g per dose.⁵⁹ As in other forms of addiction and abuse, most patients who present in GHB withdrawal are male.⁶⁹ Most of them have been taking GHB for less than two years, and about 75 percent have been using GHB, rather than precursors such as γ -butyrolactone.⁵⁴

GHB withdrawal symptoms may be mild on presentation, but they may increase in intensity and severity over hours or days and culminate in delirium or frank psychosis. The most common features of withdrawal are tremor, tachycardia, restlessness, insomnia, anxiety, nausea, and vomiting. Delirium, often with diaphoresis and hypertension, occurs in people with severe dependence.^{59,69} Death from GHB withdrawal caused by pulmonary edema has been reported.⁶⁹

Symptoms of withdrawal from GHB may last up to two weeks. In addition to the acute GHB withdrawal syndrome, a prolonged withdrawal state lasting from three to six months and characterized by dysphoria, anxiety, memory problems, and insomnia has been reported.⁸⁷ A person with protracted or untreated symptoms of GHB withdrawal may abuse either alcohol or benzodiazepines in an attempt to relieve anxiety and insomnia.

The mainstay of therapy for GHB withdrawal is supportive care and sedation to prevent injury, hyperthermia, and rhabdomyolysis. Physical restraint may be required in about one third of patients.⁶⁹ Benzodiazepines (either lorazepam or diazepam), often in very high doses, are the primary agents used to treat GHB withdrawal^{53,69-71,82} because they have a broad therapeutic range, a high threshold for respiratory depression, and are relatively free of cardiovascular complications. Antipsychotic agents are not indicated in the management of GHB withdrawal and have the added disadvantage of lowering the seizure threshold.⁷⁰ However, there is no evidence that anticonvulsant drugs are effective in the treatment of GHB withdrawal.⁷⁰ In withdrawal that is refractory to benzodiazepines, pentobarbital administered in the intensive care setting is said to be effective.^{69-71,88} Multiple relapses after GHB detox-



ification in patients who have gone through addiction and withdrawal are common, as are insomnia, depression, and abuse of other drugs.⁸⁴

GHB-FACILITATED SEXUAL ASSAULT

GHB has received substantial notoriety during the past several years as a date-rape drug — in other

words, a compound used to facilitate sexual assault. Low doses of GHB (10 to 20 mg per kilogram) induce short-term anterograde amnesia, increased libido, euphoria, suggestibility, and passivity, all of which contribute to the use of GHB in sexual assaults.^{75,89-91} Populations that are at high risk for drug-facilitated sexual assault include single women or men in unfamiliar social settings. The sodium salt of GHB is generally available as a liquid that is colorless, odorless, and water-soluble and tastes slightly salty; this liquid can be easily and surreptitiously added to a drink without detection by the intended victim. Drug administration may occur in a bar or club, when the recipient is inattentive or accepts a drink or an already opened bottle.⁹²

Most of the published evidence of GHB in this role is anecdotal; ethanol and benzodiazepines appear to be more commonly used in drug-facilitated assault.^{93,94} However, GHB should be considered in cases of sexual assault that occur after drinking and a social encounter, particularly when the patient has a gap in memory. In making a diagnosis of GHB-facilitated sexual assault, it is important to collect samples of blood and urine as soon as possible after the alleged assault and to measure GHB levels with the proper analytic techniques. Since GHB is undetectable by the usual toxicologic screens, laboratory diagnosis of GHB-facilitated assault is challenging. GHB levels may be determined in plasma and urine samples by gas chromatography–mass spectrometry with selected-ion monitoring.⁹⁵ Although this analytic technique for the detection of GHB is not readily available, it may be performed by state and national reference laboratories.⁵⁶

PUTATIVE MECHANISMS OF ACTION

The dopamine neurons in the brain are involved in reward-dependent learning; therefore, neurons involved in abuse, addiction, and withdrawal have their cell bodies in the ventral tegmental area and project into the basal forebrain structures, such as the nucleus accumbens, amygdala, and frontal and limbic cortices (Fig. 3).^{96,99,100} Activation of these mesocorticolimbic dopaminergic neurons, with a resultant increase in the output of dopamine in innervated projection structures, has been reported with virtually all major drugs of abuse. Conversely, during abstinence there is a marked decrease in the activity of dopaminergic neurons in the ventral teg-

mental area.⁹⁹ Therefore, the mesocorticolimbic circuitry of the brain is a likely target for GHB in abuse, addiction, and withdrawal.

Although a variety of neurotransmitters interact with mesocorticolimbic dopamine pathways,⁹⁹ the mechanism of action that would explain the addictive properties of GHB appears to be related to the effects of dopamine mediated by GABA_B receptors¹⁰¹ in mesocorticolimbic circuitry. However, the reported finding that GHB decreases dopaminergic neuronal activity in the ventral tegmental area and thereby reduces the release of dopamine into the nucleus accumbens¹⁰² poses a conundrum, since drugs of abuse are classically associated with an increase in the neuronal activity of mesocorticolimbic dopamine.

A potential explanation for this paradox may lie in recently published experiments⁹⁷ showing that GHB is unable to activate potassium channels mediated by GABA_B receptors in dopamine neurons in the ventral tegmental area. However, GHB was able to activate GABA_B receptor-mediated potassium channels in GABA-releasing (GABAergic) neurons of the ventral tegmental area because of a difference in the expression of potassium-channel subunits between the dopaminergic and GABAergic neurons. GHB also is known to decrease the release of GABA by a presynaptic, GHB-specific action.^{15,18} Hence, in GHB abuse and addiction, which are accompanied by an increased concentration of GHB in the brain, GHB may inhibit GABAergic neurons preferentially and decrease the release of GABA through effects mediated by GABA_B receptors and GHB receptors, respectively. The result would be a disinhibition of dopaminergic neurons of the ventral tegmental area with increased dopaminergic activity within that circuitry (Fig. 3), which in turn would lead to the psychic symptoms that accompany GHB abuse and addiction. This hypothesis would also explain the difference between GHB, which is addictive, and the GABA_B receptor agonist baclofen, which is not. In fact, baclofen may be useful in decreasing the reinforcement effects of cocaine, heroin, nicotine, ethanol,⁸⁵ and GHB,⁸⁶ probably by reducing the release of dopamine in the ventral tegmental area. Finally, GHB has been recently shown to decrease the activity of neurons in the locus ceru-

leus,⁹⁸ providing yet another route by which GHB could disinhibit mesocorticolimbic dopaminergic circuitry (Fig. 3).

In summary, data indicate that the mechanism of GHB abuse, addiction, and withdrawal may be due to inhibition of GABAergic neurons by mechanisms mediated by GABA_B receptors and inhibition of presynaptic GABA release in mesocorticolimbic dopaminergic pathways by a mechanism mediated by GHB receptors, with a resultant disinhibition of dopamine neurons and increase in dopaminergic activity in the mesocorticolimbic circuitry (Fig. 3).

FUTURE DIRECTIONS

The pharmacologic properties of GHB and its GABA_B receptor-mediated effects are well known. However, the neurobiologic function of GHB remains elusive. This function will probably be delineated after the successful molecular cloning of the primary GHB receptor in brain tissue and the subsequent engineering of mice with mutant GHB receptors. These developments will lead to a more precise elucidation of the relationship between the GHB receptor and GABA_B receptor and will facilitate careful investigation of the relative contributions of GHB-induced GABA synthesis, GHB-induced alterations in GABA release, and the signaling pathways involved in GHB-induced alteration of intracellular movement of GABA_B receptors. In a similar fashion, a mutant mouse that is deficient in succinic semialdehyde dehydrogenase¹⁰³ may provide insight into the mechanisms of GHB addiction and withdrawal because it has inordinately high levels of GHB and GABA in brain tissue. Given the experimental evidence of the efficacy of the GABA_B receptor baclofen in GHB abuse,^{85,86} controlled, prospective clinical trials of this compound in the treatment of GHB addiction and withdrawal and of a GABA_B receptor antagonist¹⁰⁴ in the treatment of GHB overdose will be important.

Supported in part by a grant (14329 MOP) from the Canadian Institutes of Health Research, a grant (NS40270) from the National Institutes of Health, members of the Partnership for Pediatric Epilepsy Research (including the American Epilepsy Society, the Epilepsy Foundation, Anna and Jim Fantaci, Fight against Childhood Epilepsy and Seizures, Neurotherapy Ventures Charitable Research Fund, and Parents Against Childhood Epilepsy), and an endowment from the Bloorview Children's Hospital Foundation.

REFERENCES

- Laborit H. Sodium 4-hydroxybutyrate. *Int J Neuropharmacol* 1964;32:433-51.
- Rubin BA, Giarmann NJ. The therapy of experimental influenza in mice with antibiotic lactones and related compounds. *Yale J Biol Med* 1947;19:1017-22.
- Roth RH, Delgado JMR, Giarmann NJ. γ -Butyrolactone and γ -hydroxybutyric acid. II. The pharmacologically active form. *Int J Neuropharmacol* 1966;5:421-8.
- Snead OC III. The γ -hydroxybutyrate model of absence seizures: correlation of regional brain levels of γ -hydroxybutyric acid and γ -butyrolactone with spike wave discharges. *Neuropharmacology* 1991;30:161-7.
- Roth RH, Levy R, Giarmann NJ. Dependence of rat serum lactonase upon calcium. *Biochem Pharmacol* 1967;16:596-8.
- Vickers MD. Gammahydroxybutyric acid. *Int Anesthesiol Clin* 1969;7:75-89.
- Hunter AS, Long WJ, Rylie CG. An evaluation of gamma-hydroxybutyric acid in paediatric practice. *Br J Anaesth* 1971;43:620-8.
- Meyer S, Gottschling S, Georg T, Lothschütz D, Graf N, Sitzmann FC. Gamma-hydroxybutyrate versus chlorprothixene/phenobarbital sedation in children undergoing MRI studies. *Klin Padiatr* 2003;215:69-73.
- Fuller DE, Hornfeldt CS. From club drug to orphan drug: sodium oxybate (Xyrem) for the treatment of cataplexy. *Pharmacotherapy* 2003;23:1205-9.
- Poldrugo F, Addolorato G. The role of γ -hydroxybutyric acid in the treatment of alcoholism: from animal to clinical studies. *Alcohol Alcohol* 1999;34:15-24.
- Howard SG, Banerjee PK. Regulation of central dopamine by γ -hydroxybutyrate. In: Tunnicliff G, Cash CD, eds. *Gamma-hydroxybutyrate: molecular, functional, and clinical aspects*. London: Taylor & Francis, 2002:111-9.
- Gobaille S, Schleef C, Hechler V, Viry S, Aunis D, Maitre M. Gamma-hydroxybutyrate increases tryptophan availability and potentiates serotonin turnover in rat brain. *Life Sci* 2002;70:2101-12.
- Sethy VH, Roth RH, Walters JR, Marini J, Van Woert MH. Effect of anesthetic doses of γ -hydroxybutyrate on the acetylcholine content of rat brain. *Naunyn-Schmiedeberg Arch Pharmacol* 1976;295:9-14.
- Maitre M. The γ -hydroxybutyrate signalling system in brain: organization and functional implications. *Prog Neurobiol* 1997;51:337-61.
- Snead OC III. Evidence for a G protein-coupled gamma-hydroxybutyric acid receptor. *J Neurochem* 2000;75:1986-96.
- Kuschinsky W, Suda S, Sokoloff L. Influence of γ -hydroxybutyrate on the relationship between local cerebral glucose utilization and local cerebral blood flow in the rat brain. *J Cereb Blood Flow Metab* 1985;5:58-64.
- Ren X, Mody I. γ -Hydroxybutyrate reduces mitogen-activated protein kinase phosphorylation via GABA_B receptor activation in mouse frontal cortex and hippocampus. *J Biol Chem* 2003;278:42006-11.
- Hu RQ, Banerjee PK, Snead OC III. Regulation of γ -aminobutyric acid (GABA) release in cerebral cortex in the γ -hydroxybutyric acid (GHB) model of absence seizures in rat. *Neuropharmacology* 2000;39:427-39.
- Ferraro L, Tanganelli S, O'Connor WT, et al. γ -Hydroxybutyrate modulation of glutamate levels in the hippocampus: an in vivo and in vitro study. *J Neurochem* 2001;78:929-39.
- Sircar R, Basak A. Adolescent gamma-hydroxybutyric acid exposure decreases cortical N-methyl-D-aspartate receptor and impairs spatial learning. *Pharmacol Biochem Behav* 2004;79:701-8.
- Barbaccia ML, Colombo G, Affricano D, et al. GABA_B receptor-mediated increase of neurosteroids by γ -hydroxybutyric acid. *Neuropharmacology* 2002;42:782-91.
- Quéva C, Bremner-Danielsen M, Edlund A, et al. Effects of GABA agonists on body temperature regulation in GABA(B1)-/- mice. *Br J Pharmacol* 2003;140:315-22.
- Hicks AR, Kapusta DR, Varner KJ. Mechanisms underlying the sympathomimetic cardiovascular responses elicited by gamma-hydroxybutyrate. *J Cardiovasc Pharmacol* 2004;44:631-8.
- Hedner J, Jonason J, Lundberg D. Respiratory effects of gamma-hydroxybutyric acid in anesthetized rats. *J Neural Transm* 1980;49:179-86.
- Carai MAM, Agabio R, Lobina C, et al. GABA_B-receptor mediation of the inhibitory effect of γ -hydroxybutyric acid on intestinal motility in mice. *Life Sci* 2002;70:3059-67.
- Snead OC. γ -Hydroxybutyrate and absence seizure activity. In: Tunnicliff G, Cash CD, eds. *Gamma-hydroxybutyrate: molecular, functional, and clinical aspects*. London: Taylor & Francis, 2002:132-49.
- Van Cauter E, Plat L, Scharf MB, et al. Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young men. *J Clin Invest* 1997;100:745-53.
- Ottani A, Vergoni AV, Saltini S, et al. Effect of late treatment with gamma-hydroxybutyrate on the histological and behavioral consequences of transient brain ischemia in the rat. *Eur J Pharmacol* 2004;485:183-91.
- Yosunkaya A, Ak A, Bariskaner H, Ustun ME, Tuncer S, Gurbilek M. Effect of gamma-hydroxybutyric acid on lipid peroxidation and tissue lactate level in experimental head trauma. *J Trauma* 2004;56:585-90.
- Guney O, Bengi Celik J, Arazi M, Erkan Ustun MJ. Effects of gamma-hydroxybutyrate on cerebrospinal fluid lactate and glucose levels after spinal cord trauma. *J Clin Neurosci* 2004;11:517-20.
- Doherty JD, Hattox SE, Snead OC, Roth RH. Identification of endogenous γ -hydroxybutyrate in human and bovine brain and its regional distribution in human, guinea pig, and rhesus monkey brain. *J Pharmacol Exp Ther* 1978;207:130-9.
- Snead OC III, Furner R, Liu CC. In vivo conversion of gamma-aminobutyric acid and 1,4-butanediol to gamma-hydroxybutyric acid in rat brain: studies using stable isotopes. *Biochem Pharmacol* 1989;38:4375-80.
- Chambliss KL, Gibson KM. Succinic semialdehyde dehydrogenase from mammalian brain: subunit analysis using polyclonal antiserum. *Int J Biochem* 1992;24:1493-9.
- Wong CGT, Chan KFY, Gibson KM, Snead OC. γ -Hydroxybutyric acid: neurobiology and toxicology of a recreational drug. *Toxicol Rev* 2004;23:3-20.
- Bernasconi R, Mathivet P, Bischoff S, Marescaux C. Gamma-hydroxybutyric acid: an endogenous neuromodulator with abuse potential? *Trends Pharmacol Sci* 1999;20:135-41.
- Maitre M, Cash C, Weissmann-Nanopoulos D, Mandel P. Depolarization-evoked release of γ -hydroxybutyrate from rat brain slices. *J Neurochem* 1983;41:287-90.
- Hechler V, Bourguignon JJ, Wermuth CG, Mandel P, Maitre M. γ -Hydroxybutyrate uptake by rat brain striatal slices. *Neurochem Res* 1985;10:387-96.
- Muller C, Viry S, Miehle M, Andriamampandry C, Aunis D, Maitre M. Evidence for a γ -hydroxybutyrate (GHB) uptake by rat brain synaptic vesicles. *J Neurochem* 2002;80:899-904.
- Castelli MP, Ferraro L, Mocchi I, et al. Selective γ -hydroxybutyric acid receptor ligands increase extracellular glutamate in the hippocampus, but fail to activate G protein and to produce the sedative/hypnotic effect of γ -hydroxybutyric acid. *J Neurochem* 2003;87:722-32.
- Owens DF, Kreigstein AR. Is there more to GABA than synaptic inhibition? *Nat Rev Neurosci* 2002;3:715-27.
- Whiting PJ. The GABA_A receptor gene family: new opportunities for drug development. *Curr Opin Drug Discov Devel* 2003;6:648-57.
- Snead OC III, Liu CC. GABA_A receptor function in the γ -hydroxybutyrate model of generalized absence seizures. *Neuropharmacology* 1993;32:401-9.
- Bettler B, Kaupmann K, Mosbacher J, Gassmann M. Molecular structure and physiological functions of GABA_B receptors. *Physiol Rev* 2004;84:835-67.
- Kaupmann K, Cryan JF, Wellendorph P, et al. Specific γ -hydroxybutyrate-binding sites but loss of pharmacological effects of γ -hydroxybutyrate in GABA_{B(1)}-deficient mice. *Eur J Neurosci* 2003;18:2722-30.
- Wu Y, Ali S, Ahmadian G, et al. γ -Hydroxybutyric acid (GHB) receptor and the γ -aminobutyric acid_B receptor

- (GABA_BR) binding sites are distinctive from one another: molecular evidence. *Neuropharmacology* 2004;47:1146-56.
46. Gervasi N, Monnier Z, Vincent P, et al. Pathway-specific action of gamma-hydroxybutyric acid in sensory thalamus and its relevance to absence seizures. *J Neurosci* 2003; 23:11469-78.
47. Hechler V, Ratomponirina C, Maitre M. Gamma-hydroxybutyrate conversion into GABA induces displacement of GABA_B binding that is blocked by valproate and ethosuximide. *J Pharmacol Exp Ther* 2003; 281:753-60.
48. Mathivet P, Bernasconi R, DeBarry J, Marescaux C, Bittiger H. Binding characteristics of gamma-hydroxybutyric acid as a weak but selective GABA_B receptor agonist. *Eur J Pharmacol* 1997;321:67-75.
49. Lingenhoehl K, Brom R, Heid J, et al. Gamma-hydroxybutyrate is a weak agonist at recombinant GABA(B) receptors. *Neuropharmacology* 1999;38:1667-73.
50. Crunelli V, Leresche N. Action of γ -hydroxybutyrate on neuronal excitability and underlying membrane conductances. In: Tunnichliff G, Cash CD, eds. *Gamma-hydroxybutyrate: molecular, functional, and clinical aspects*. London: Taylor & Francis, 2002:75-110.
51. Wong CGT, Wu Y, Wang YT, Snead OC. GHB increases cell surface GABA_B receptors independent of agonist activation or conversion to GABA. Abstract viewer/itinerary planner program no. 159.6. Washington, D.C.: Society for Neuroscience, 2003. (Accessed June 6, 2005, at <http://apu.sfn.org/content/publications/annualmeeting/index.html>.)
52. Brenneisen R, Elshohly MA, Murphy TP, et al. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol* 2004;28:625-30.
53. Dyer JE, Haller CA. γ -Hydroxybutyrate, γ -butyrolactone, and 1,4-butanediol. In: Dart RC, ed. *Medical toxicology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004:1097-102.
54. Miró Ó, Nogué S, Espinosa G, To-Figueras J, Sánchez M. Trends in illicit drug emergencies: the emerging role of gamma-hydroxybutyrate. *J Toxicol Clin Toxicol* 2002;40:129-35.
55. Teter CJ, Guthrie SK. A comprehensive review of MDMA and GHB: two common club drugs. *Pharmacotherapy* 2003;21:1486-513.
56. Couper FJ, Thatcher JE, Logan BK. Suspected GHB overdoses in the emergency department. *J Anal Toxicol* 2004;28:481-4.
57. Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, Peacock EA. Adverse effects, including death, associated with the use of 1,4-butanediol. *N Engl J Med* 2001; 344:87-94.
58. Li J, Stokes SA, Woekener A. A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. *Ann Emerg Med* 1998;31:729-36.
59. Freese TE, Miotto K, Reback CJ. The effects and consequences of selected club drugs. *J Subst Abuse Treat* 2002;23:151-6.
60. Van Sassenbroeck DK, Calle PA, Rousseau FM, et al. Medical problems related to recreational drug use at nocturnal dance parties. *Eur J Emerg Med* 2003;10:302-8.
61. Sporer KA, Chin RL, Dyer JE, Lamb R. Gamma-hydroxybutyrate serum levels and clinical syndrome after severe overdose. *Ann Emerg Med* 2003;42:3-8.
62. Miotto K, Darakjian J, Basch J, Murray S, Zogg J, Rawson R. Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *Am J Addict* 2001;10:232-41.
63. Chin RL, Sporer KA, Cullison B, Dyer JE, Wu TD. Clinical course of γ -hydroxybutyrate overdose. *Ann Emerg Med* 1998;31: 716-22.
64. Okun MS, Boothby LA, Bartfield RB, Doering PL. GHB: an important pharmacologic and clinical update. *J Pharm Pharm Sci* 2001;4:167-75.
65. Mokhlesi B, Garimella PS, Joffe A, Velho V. Street drug abuse leading to critical illness. *Intensive Care Med* 2004;30:1526-36.
66. Traub SJ, Nelson LS, Hoffman RS. Physostigmine as a treatment for gamma-hydroxybutyrate toxicity: a review. *J Toxicol Clin Toxicol* 2002;40:781-7.
67. Tunnichliff G. Sites of action of gamma-hydroxybutyrate (GHB) — a neuroactive drug with abuse potential. *J Toxicol Clin Toxicol* 1997;35:581-90.
68. Kam PCA, Yoong FFY. Gamma-hydroxybutyric acid: an emerging recreational drug. *Anaesthesia* 1998;53:1195-8.
69. McDonough M, Kennedy N, Gasper A, Bearn J. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug Alcohol Depend* 2004;75:3-9.
70. Tarabar AF, Nelson LS. The γ -hydroxybutyrate withdrawal syndrome. *Toxicol Rev* 2004;23:45-9.
71. Anderson HB, Dyer JE. Withdrawal — central nervous system depressants. In: Dart RC, ed. *Medical toxicology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins, 2004: 135-41.
72. Poldrugo F, Snead OC III. 1,4-Butanediol and ethanol compete for degradation in rat brain and liver in vitro. *Alcohol* 1986;3: 367-70.
73. Carai MA, Colombo G, Reali R, et al. Central effects of 1,4-butanediol are mediated by GABA_B receptors via its conversion into γ -hydroxybutyric acid. *Eur J Pharmacol* 2002;441:157.
74. Poldrugo F, Barker S, Basa M, Mallardi F, Snead OC. Ethanol potentiates the toxic effects of 1,4-butanediol. *Alcohol Clin Exp Res* 1985;9:493-7.
75. Raess BU, Tunnichliff G. Abuse potential and toxicology of γ -hydroxybutyrate. In: Tunnichliff G, Cash CD, eds. *Gamma-hydroxybutyrate: molecular, functional, and clinical aspects*. London: Taylor & Francis, 2002: 188-96.
76. Smith KM, Larive LL, Romanelli F. Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate. *Am J Health Syst Pharm* 2002;59:1067-76.
77. Camacho A, Matthews SC, Dimsdale JE. Use of GHB compounds by HIV-positive individuals. *Am J Addict* 2004;13:120-7.
78. Weir E. Raves: a review of the culture, the drugs and the prevention of harm. *CMAJ* 2000;162:1843-8.
79. Elliott SP. Nonfatal instances of intoxication with gamma-hydroxybutyrate in the United Kingdom. *Ther Drug Monit* 2004; 26:432-40.
80. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. *Arch Intern Med* 1999;159:2221-4.
81. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002;36:1598-613.
82. Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med* 2001;37:147-53.
83. Dean W. GHB demonization proceeds in states: a call to action: stop criminalization of GHB now. (Accessed June 6, 2005, at http://www.erowid.org/chemicals/ghb/ghb_info2.shtml.)
84. Project GHB home page. (Accessed June 6, 2005, at <http://www.projectghb.org>.)
85. Cousins MS, Roberts DCS, deWit H. GABA_B receptor agonists for the treatment of drug addiction: a review of recent findings. *Drug Alcohol Depend* 2002;65:209-20.
86. Fattore L, Cossu G, Martellotta MC, Deiana S, Fratta W. Baclofen antagonises intravenous self-administration of γ -hydroxybutyric acid in mice. *Neuroreport* 2001;12: 2243-6.
87. McDaniel CH, Miotto KA. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five case studies. *J Psychoactive Drugs* 2001;33:143-9.
88. Sivilotti ML, Burns MJ, Aaron CK, Greenberg MJ. Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann Emerg Med* 2001;38:660-5.
89. Bismuth C, Dally S, Borron SW. Chemical submission: GHB, benzodiazepines, and other knock out drops. *J Toxicol Clin Toxicol* 1997;35:595-8.
90. Schwartz RH, Milteer R, LeBeau MA. Drug-facilitated sexual assault ('date rape'). *South Med J* 2000;93:558-61.
91. Varela M, Nogue S, Oros M, Miro O. Gamma hydroxybutyrate use for sexual assault. *Emerg Med J* 2004;21:255-6.
92. Dyer JE. Special considerations in the evaluation of drug-facilitated assault. In: Olsson KR, ed. *Poisoning & drug overdose*. 4th ed. New York: McGraw-Hill, 2004:63-5.
93. ElSohly MA, Salamone SJ. Prevalence of

- drugs used in cases of alleged sexual assault. *J Anal Toxicol* 1999;23:141-6.
- 94.** Slaughter L. Involvement of drugs in sexual assault. *J Reprod Med* 2000;45:425-30.
- 95.** Morris-Kukoski CL. γ -Hydroxybutyrate: bridging the clinical-analytical gap. *Toxicol Rev* 2004;23:33-43.
- 96.** Gardner EL, Lowinson JH. Drug craving and positive/negative hedonic brain substrates activated by addicting drugs. *Semin Neurosci* 1993;5:359-68.
- 97.** Cruz HG, Ivanova T, Lunn ML, Stoffel M, Slesinger PA, Luscher C. Bi-directional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. *Nat Neurosci* 2004;7:153-9.
- 98.** Szabo ST, Gold MS, Goldberger BA, Blier P. Effects of sustained gamma-hydroxybutyrate treatments on spontaneous and evoked firing activity of locus coeruleus norepinephrine neurons. *Biol Psychiatry* 2004;55:934-9.
- 99.** Maldonado R. The neurobiology of addiction. *J Neural Transm Suppl* 2003;66:1-14.
- 100.** Camí J, Farré M. Drug addiction. *N Engl J Med* 2003;349:975-86.
- 101.** Erhardt S, Andersson B, Nissbrandt H, Engberg G. Inhibition of firing rate and changes in the firing pattern of nigral dopamine neurons by γ -hydroxybutyric acid (GHBA) are specifically induced by activation of GABA_B receptors. *Naunyn Schmiedebergs Arch Pharmacol* 1998;357:611-9.
- 102.** Madden TE, Johnson SW. Gamma-hydroxybutyrate is a GABA_B receptor agonist that increases a potassium conductance in rat ventral tegmental dopamine neurons. *J Pharmacol Exp Ther* 1998;287:261-5.
- 103.** Hogema BM, Gupta M, Senephansiri H, et al. Pharmacologic rescue of lethal seizures in mice deficient in succinate semialdehyde dehydrogenase. *Nat Genet* 2001;29:212-6.
- 104.** Froestl W, Gallagher M, Jenkins H, et al. SGS742: the first GABA(B) receptor antagonist in clinical trials. *Biochem Pharmacol* 2004;68:1479-87.

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CORRECTION

γ -Hydroxybutyric Acid

γ -Hydroxybutyric Acid . On page 2724, lines 8 through 11 under the subhead GHB Toxicity should have read, "In some series, GHB was the second most common drug detected in the urine of young people presenting with drug-induced coma, just behind cocaine," rather than "detected in the serum," as printed.