

FOOD & DRUG ADMINISTRATION
CENTER for DRUG EVALUATION and RESEARCH
CONTROLLED SUBSTANCE STAFF
BACKGROUND MATERIALS
ON
GAMMA-HYDROXYBUTYRATE (GHB; sodium oxybate)
FOR
PERIPHERAL and CENTRAL NERVOUS SYSTEM ADVISORY COMMITTEE
MARCH 15, 2001

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**GAMMA-HYDROXYBUTYRIC ACID (GHB)
SUMMARY OF PHARMACOLOGY, ABUSE AND DEPENDENCE**

**FDA/CDER OFFICE OF THE CENTER DIRECTOR
CONTROLLED SUBSTANCE STAFF**

FEBRUARY 20, 2001

BACKGROUND

By an Act of Congress, gamma-hydroxybutyric acid (GHB) was placed into Schedule I of the Controlled Substances Act (CSA) (per the Hillory Farias and Samantha Reid - Date-Rape Drug Prohibition Act of 1999 - HR 2130 - February 18, 2000). In addition, HR 2130 included a provision for control of any future GHB drug product in Schedule III, following approval by the Food and Drug Administration (FDA).

According to provisions of the CSA, the drug scheduling process requires that separate procedures be carried out by the two responsible agencies, the Drug Enforcement Administration (DEA) and the FDA. According to these requirements and prior to the Congressional action, DEA had requested the FDA to conduct a scientific and medical evaluation and recommendation to schedule GHB (1997). FDA responded by recommending control of GHB in Schedule I, because of increasing numbers of reports of GHB manufacture in clandestine laboratories, recreational abuse and misuse of GHB by young people, and numerous deaths and hospital emergency room cases.

At the same time that there was clear evidence in support of placement of GHB in Schedule I, FDA had authorized a treatment IND for the GHB drug product (Xyrem) for cataplexy associated with narcolepsy, in order to provide early availability for patients suffering from this condition, and to facilitate data collection in support of a new drug application (NDA). Importantly, the sponsor had obtained orphan designation for Xyrem from the FDA. The sponsor requested that Xyrem be controlled in Schedule III or IV, because there was no evidence that Xyrem was diverted or abused and the sponsor felt that the stringent CSA controls of Schedule I would hinder development of its product. GHB for the treatment of alcohol abuse as well as other indications is published in the European literature (Di Bello *et al.*, 1995). GHB has also been used in Europe as an anesthetic agent (Hunter *et al.*, 1971).

PHARMACOLOGY

GHB produces dose- and concentration-dependent CNS depression in humans and laboratory animals (the mouse, rat, rabbit, cat, dog and monkey). GHB abuse potential was evaluated in preclinical drug discrimination and self-administration studies, in which GHB produced sedative-like stimulus effects. GHB can function as a discriminative stimulus in rats. The GHB stimulus cue is complex, sharing some properties with CNS

depressants and, to a lesser extent, with some GABA-mimetic substances and morphine. GHB was not reinforcing in primates that were trained to self-administer PCP, cocaine and methohexital. Preference for GHB over placebo (water) was demonstrated in rodents.

GHB and alcohol have synergistic hypnotic effects. In rats, GHB produces a loss in righting reflex (sleep time) that is significantly potentiated by ethanol. There was a 4- to 5- fold increase in sleep time in rats administered GHB (0.41 nmole) in combination with 6.51 nmole ethanol.

Deaths from GHB in animals result with high doses. GHB has an LD₅₀ of 5100 mg/kg (in mice, p.o.), 3705 mg/kg (in rats p.o.), 4225 mg/kg (mice, i.p.), 2020 mg/kg (rats, i.p.), and 1855 mg/kg (mice i.v.). See **TABLE 1** for comparative safety of GHB to other hypnotics.

TABLE 1. COMPARATIVE SAFETY OF HYPNOTICS INCLUDING GHB.

DRUG	LD ₅₀ (mg/kg, rats, p.o.)	Maximum Recommended Hypnotic Dose in Humans (MRHD)	RATIO: MRHD/LD ₅₀
Triazolam	>5000 mg/kg (rats po)	1.0 mg p.o. (hypnosis)	2 x 10 ⁻⁴
Diazepam	710 mg/kg (rats p.o.)	10 mg p.o. (hypnosis)	1.4 x 10 ⁻²
Zolpidem	700-1000 mg/kg (rats po)	10 mg (for sleep)	1.0 x 10 ⁻² to 1.4 x 10 ⁻²
Pentobarbital	118 mg/kg (rats p.o.)	180 mg p.o. (hypnosis).	1.5
Secobarbital	125 mg/kg (rats p.o.)	100 mg p.o. (hypnosis).	8 x 10 ⁻¹
Phenobarbital	16214 mg/kg (rats po)	200 mg p.o.	1.2
Methaqualone	255 mg/kg (rats p.o.)	300 mg (hypnotic)	1.2
Chloral hydrate	479 mg/kg (rats p.o.)	1 gram	2.1
GHB	3705 mg/kg (rats p.o.)	4.5 grams/dose (Recommended dosage regimen of 9 grams/day in 2 divided doses separated by 3 to 4 hours in treatment of cataplexy).	1.2

GHB produces dose- and concentration-dependent changes in the level of consciousness. High doses produce effects ranging from sedation to profound CNS depression. In humans, GHB doses of 10 mg/kg produce amnesia and hypotonia. Oral or intravenous doses of 20 to 30 mg/kg promote the normal sequences of REM and nonREM sleep when given to normal subjects. Oral doses in this range produce high voltage slow wave activity and occasionally spindle sleep. Oral or intravenous doses of GHB greater than 50 mg/kg produce anesthesia in children and adults. In children, GHB 70 mg/kg, administered intravenously produces rapid onset of sleep. GHB is rapidly metabolized and the central effects of a 60-70 mg/kg dose last up to 3 hours.

GHB has been found to stimulate release of human growth hormone (HGH) from the anterior pituitary gland in humans. GHB (2.5 g iv) in six healthy male volunteers caused a rise in plasma levels of HGH at 30, 45, 60 and 90 minutes after injection. In addition, plasma prolactin levels increased at 45 and 60 minutes after GHB. Symptoms of acute toxicity with GHB reportedly include GI upset, CNS and respiratory depression,

confusion, inebriation, stupor, uncontrolled movements, myoclonus and seizures. There are also reports of GHB overdose and toxicity documenting GHB's effects on heart rate, blood pressure and respiration. This information was not collected from clinical trial experience, but rather from published reports of overdose following illicit use, which frequently includes polydrug abuse.

DEPENDENCE

Severe dependence has recently been reported in the published literature in a retrospective review of poison control center records. Case reports of GHB dose escalation by 8 patients were described. Craving was indicated by excessively high dose levels, increased frequency of use, and continued use despite adverse consequences (Dyer *et al.*, 2001). GHB at doses ranging from 43 to 144 grams/day was ingested every 1 to 3 hours around-the-clock. A stereotyped withdrawal syndrome consisting of symptoms of anxiety, insomnia, and tremor developed soon after GHB discontinuation, and progressed to severe delirium with autonomic instability in some patients.

Galloway *et al.* (1994, 1997) had previously published reports of individuals who abused GHB for its sedative, euphorogenic, or anabolic effects. Discontinuation of GHB produced a withdrawal syndrome characterized by insomnia, muscle cramps, tremor and anxiety. One individual abused GHB for 3.5 years. Tolerance developed to the euphoric and sedative effects. Abrupt cessation produced insomnia, anxiety, tremor, and sweating. (Frederick *et al.*, 1995).

ABUSE

In the 1980's, GHB was sold as a food supplement in health food stores or by mail order. GHB was marketed as a sleep and diet aid. GHB was used by bodybuilders as a growth hormone releaser, diet aid, antagonist to effects of CNS stimulants, and for sleep. Bodybuilders accounted for emergency room cases, cases of dependence, and deaths associated with GHB use. GHB and anabolic steroids were seized together. During the time that these GHB products were available, medical, law enforcement and poison control center reports appeared indicating that those who began using the drug as a sleep or diet aid continued to use it for its euphoric effects. In 1990, FDA issued a health alert and prohibited the sale of GHB as a supplement. Data from Poison Control Centers in California, Georgia, Florida, South Carolina, Minnesota, Arizona, Ohio, Texas and Virginia accounted for 57 case reports of GHB intoxication from June through November 1990. Seizures, bradycardia, hypotension, loss of consciousness, irregular tremors, myoclonus and depressed respiration have been reported. Severity and duration of symptoms depended upon the dose of GHB and the presence of other CNS depressants.

Although GHB has a history of abuse by bodybuilders, in recent years it has been used by young people and sold at nightclubs, rave parties, and bars (Chin *et al.*, 1992; MMWR, 1990). Kits for making GHB by the general public are sold through magazines and the

INTERNET. GHB has been made in small quantities using the kits on college campuses, and in larger scale clandestine laboratories. GHB abuse is for the purpose of getting high, producing a more profound effect from alcohol, countering the effects of stimulants, “regulating” the effects of hallucinogens, or alleviating withdrawal effects from alcohol. Users claim that GHB elicits effects common to alcohol and CNS depressants, marijuana, hallucinogens, and narcotics. GHB euphorogenic effects at low doses or in the early stages of intoxication have been compared to those produced by alcohol, barbiturates, marijuana, or MDMA. The INTERNET and underground literature include exchanges promoting GHB's aphrodisiac or sexually enhancing effects. There have been a number of high profile cases of GHB used in facilitating sexual assault (so-called “date rape”). These reports have originated from Florida, Texas, Maryland, Louisiana, California, Michigan, Wisconsin, and Massachusetts.

Poison Control Center databases show that there were over 600 GHB cases in 1996 and over 900 cases in 1997. The typical single doses of GHB needed to produce intoxication or euphoria range from 1 to 5 grams taken orally. Powdered GHB is usually dissolved in a liquid such as alcoholic beverages or fruit-flavored drink prior to ingestion. In some locales, liquid GHB is distributed and dispensed from medicine droppers.

DEA has documented 32 deaths in association with GHB use between 1990 and 1998. Twenty-two (69%) were male and 10 (31%) were female. GHB-associated deaths are reported by age in **TABLE 2** below.

TABLE 2. GHB Associated Deaths by Age

AGES OF DECEASED	NUMBER	PERCENT
10-19 years	3	9%
20-29 years	17	53%
30-39 years	7	22%
40-49 years	3	9%
50-59 years	1	3%
70-79 years	1	3%

Source: DEA

Drug Abuse Warning Network (DAWN) System.

DAWN provides information on health consequences of drug use in the United States as manifested by drug-related visits to emergency departments (ED). DAWN captures the non-medical use of a substance either for psychic effects, dependence, or suicide attempt. ED data come from a representative sample of hospital EDs, which are weighted to produce national estimates. Many factors can influence the estimates of ED visits, including trends in use of the ED in general. Some drug users may visit the EDs for a variety of reasons. Some may have been life-threatening, whereas others may have been for drug detoxification before entering a methadone treatment program. It is important to note that the variable “Motive” applies to the entire episode and since more than one drug may be mentioned per episode, the "Motive" may not apply to the specific drug for which the tables were created. DAWN reported 5,921 GHB-related ED episodes from 1992 to 1999, which increased from 20 to 2,981, respectively (**TABLE 3**).

The source of the drug is illicit. GHB is clandestinely manufactured and is therefore of unknown purity. Most of the reports involved Caucasian males, followed by 'other' or 'unknown' ethnicity. The majority of episodes involved individuals 18 to 34 years of age. The motivation for taking GHB was primarily for recreational use followed by other psychic effects, unknown causes, dependence and suicide. DAWN defines "recreational use" as a conscious action to use a drug for experimentation or to enhance a social situation (e.g., to get high, have fun, to party, or take it "for kicks"). Use of a drug to improve or enhance any mental, emotional, or physical state is reported under the "other psychic effects" term. Examples include anxiety, staying awake, helping to study, for weight control, reducing pain and inducing sleep. GHB was usually taken in combination with alcohol or other drugs, including stimulants and MDMA.

The DAWN Medical Examiner (ME) component provides information on the consequences of drug use in selected areas of the United States as manifested by drug-induced or drug-related deaths reported by participating medical examiners and coroners. It is important to note that the Medical Examiner's data do not come from a representative sample of medical examiner offices and cannot be used to produce national estimates of the number of drug-related deaths. Because some ME's stop sending data and others are continuously being recruited into the system, the number of ME's changes from year to year. To produce trends, DAWN formed a consistent panel of ME's who have been reporting consistently (at least 10 months of each year in question) over the time period of interest.

A medical examiner report to DAWN may have multiple drug mentions. Up to six different substances, in addition to alcohol, can be recorded for each reportable case. As a result, although the cause and manner of death is associated with each drug reported to DAWN, not every reported substance is by itself, the cause of death. To be reported to DAWN the death should have been drug-induced or drug-related; involved an illegal drug or non-medical use of a legal drug; and the reason for taking the substance should have been for psychic effect, dependence, or suicide. For the 1995-1999 period, 36 deaths related to GHB were reported in DAWN. GHB-related medical examiner's episodes increased from 1 in 1995 to 25 in 1999. In 1999, GHB was the only drug mentioned in 5 out of the 25 medical examiner's episodes. The majority of the deaths were attributable to overdose and usually involved alcohol in combination.

TABLE 3. Estimated number of emergency department (ED) drug episodes and GHB-related ED mentions by selected demographic characteristics for 1994-1999.¹

DAWN TOTALS	1992	1993	1994	1995	1996	1997	1998	1999
ALL EPISODES	433,493	460,910	518,521	513,633	514,347	527,058	542,544	554,932
GHB MENTIONS	20	38	55	145	638	762	1,282	2,981
Age								
6-17	-	-	1	1	14	27	74	267
18-25	-	13	26	80	427	475	838	1,506
26-34	-	-	25	60	163	201	303	905
35 +	-	-	4	3	30	58	65	299
Unknown	-	-	-	-	-	-	-	4
Sex								
Male	-	-	29	94	506	530	873	1,884
Female	12	13	20	51	125	228	409	1,040
Unknown	-	-	6	-	6	5	-	57
Race/Ethnicity								
White	18	25	46	104	336	370	921	2,305
Black	-	-	-	8	6	8	24	76
Hispanic	-	-	3	16	15	16	37	52
Other/Unk.	-	-	5	17	280	368	300	548
MOTIVE FOR TAKING DRUG²								
Dependence	-	-	6	13	25	129	94	209
Suicide	-	-	3	6	13	68	82	144
Recreational Use	14	31	25	85	421	436	481	2,136
Other Psychic Effects	-	-	4	6	17	11	395	102
Unknown	-	-	17	36	161	117	230	391
REASON FOR VISIT²								
Unexpected Reaction	-	-	15	49	172	229	434	839
Overdose	11	34	38	89	312	376	680	1,544
Withdrawal	-	-	-	-	2	1	4	27
Chronic Effects	-	-	-	-	1	2	11	19
Seeking Detox.	-	-	-	-	5	17	13	38
Accident	-	-	1	2	1	1	6	13
Other/Unknown	-	-	3	5	145	136	134	501
Drug Concomitance								
Single Drug	-	10	19	47	261	290	625	859
Multiple Drugs	16	16	36	98	376	472	657	2,114

“-“ Estimated quantity zero. ¹ Estimates are produced annually based on the application of analytical weights. The DAWN sample was designed to be able to produce estimates for the coterminous U.S. overall and for 21 metropolitan areas, with a specified level of precision. Each sample hospital has a base weight, the inverse of its probability of selection, which is adjusted to account for mergers/de-mergers and the like, non-response, and finally, a benchmark factor

² Motive and Reason refers to the entire drug episode, not the particular drugs mentioned. Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network.

SUMMARY

GHB is a psychoactive drug that produces a wide range of pharmacological effects. Administered intravenously or orally, it is a sedative-hypnotic agent that produces dose- and concentration-dependent CNS effects in humans. The dose-response curve for the sedative and hypnotic effects of GHB is steep. The onset of effect is rapid, making it an effective hypnotic and an effective drug of abuse in some settings. Its onset of sedative action occurs within 30 minutes of oral ingestion and lasts up to 3 hours. GHB in low doses has been associated with amnesia and hypotonia. As doses increase, effects range from mild sedation to profound coma and, if respiratory function is not supported, death.

The pharmacology of GHB as a sedative/hypnotic and potentiation of effects with alcohol make it a substance capable of physically and mentally incapacitating individuals, without their knowledge, when targeted for sexual assault and "date rape." GHB and alcohol have synergistic hypnotic effects. GHB is water soluble and therefore miscible in alcoholic beverages. The rapid onset of sedation, coupled with the amnestic features of this agent, particularly when combined with alcohol, which potentiate it, has proven to be dangerous for the voluntary and involuntary (assault victim) user.

The drug is abused in social settings primarily by young people. Case reports of severe dependence and craving on GHB are noted by the use of increasingly large doses, increased frequency of use, and continued use despite adverse consequences. DAWN ED mentions increased 100-fold from 1992 to 1999. Sixty percent of the ED mentions involved individuals 25 years and younger. Numerous deaths have been reported, including five in the DAWN system in which GHB was the only drug mentioned.

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Gamma-Hydroxybutyrate Withdrawal Syndrome

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Received for publication December 3, 1999. Revisions received September 6, 2000, and November 9, 2000. Accepted for publication November 18, 2000.

Presented at the North American Congress of Clinical Toxicology annual scientific meeting, San Diego, CA, October 1999.

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0196-0644/2001/\$35.00 + 0

47/1/112985

doi:10.1067/em.2001.112985

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Study objective: Gamma-hydroxybutyrate (GHB) withdrawal syndrome is increasingly encountered in emergency departments among patients presenting for health care after discontinuing frequent GHB use. This report describes the characteristics, course, and symptoms of this syndrome.

Methods: A retrospective review of poison center records identified 7 consecutive cases in which patients reporting excessive GHB use were admitted for symptoms consistent with a sedative withdrawal syndrome. One additional case identified by a medical examiner was brought to our attention. These medical records were reviewed extracting demographic information, reason for presentation and use, concurrent drug use, toxicology screenings, and the onset and duration of clinical signs and symptoms.

Results: Eight patients had a prolonged withdrawal course after discontinuing chronic use of GHB. All patients in this series were psychotic and severely agitated, requiring physical restraint and sedation. Cardiovascular effects included mild tachycardia and hypertension. Neurologic effects of prolonged delirium with auditory and visual hallucinations became episodic as the syndrome waned. Diaphoresis, nausea, and vomiting occurred less frequently. The onset of withdrawal symptoms in these patients was rapid (1 to 6 hours after the last dose) and symptoms were prolonged (5 to 15 days). One death occurred on hospital day 13 as withdrawal symptoms were resolving.

Conclusion: In our patients, severe GHB dependence followed frequent ingestion every 1 to 3 hours around-the-clock. The withdrawal syndrome was accompanied initially by symptoms of anxiety, insomnia, and tremor that developed soon after GHB discontinuation. These initial symptoms may progress to severe delirium with autonomic instability.

[Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med.* February 2001;37:147-153.]

INTRODUCTION

Gamma-hydroxybutyrate (GHB) was introduced as an anesthetic agent in 1960. In recent years, GHB has been abused as a nutritional supplement for bodybuilding,¹ a drug of abuse for euphoria,² a sexual enhancer, and as an incapacitator for assault. It is also being investigated for the treatment of narcolepsy³ and the management of alcohol⁴ and opiate⁵ withdrawal. GHB is illegal to prescribe or sell in the United States; however, it is easily available over the Internet and through precursors sold as dietary supplements. The precursors are rapidly converted systemically into GHB: γ -butyrolactone is hydrolyzed by a peripheral lactonase, and 1,4-butanediol is oxidized by alcohol dehydrogenase to γ -hydroxybutyraldehyde, then by aldehyde dehydrogenase to GHB.

The acute effects of GHB include coma, myoclonus, and bradycardia, which resolve rapidly in the absence of complications. Many patients can be discharged within a few hours of reaching medical care.⁶ Recently, we observed a prolonged illness after the discontinuation of compulsive GHB use. We describe 8 patients whose symptoms and signs of central nervous stimulation and autonomic instability followed discontinuation of GHB abuse.

MATERIALS AND METHODS

Seven patients exhibiting features of sedative withdrawal among individuals discontinuing excessive GHB use were identified in a retrospective review of California Poison Control System records from the San Francisco Division. An eighth case was brought to our attention by the Miami-Dade County Florida medical examiner.

We reviewed poison center records (except case 3) and medical records (except cases 5 and 6). Information was extracted using a standardized form including demographics, medical history, concurrent drug use, reason for presentation, level of GHB use, toxicology screenings, onset and duration of clinical signs and symptoms, and the recorded results of laboratory tests, electrolytes, blood cell counts, and liver function studies, which yielded no remarkable abnormalities. Evidence of GHB use was confirmed in cases 1, 2, and 3 by laboratory analysis of the product ingested or urine toxicology.

RESULTS

Case 1

A 24-year-old salesman with attention deficit disorder who was taking no other medications used GHB for body-

building and "to help him focus." He denied current alcohol abuse but admitted intense and frequent GHB use. The patient presented to the emergency department 6 hours after his last dose of GHB complaining of intermittent anxiety, tremor, nausea, and vomiting. The patient was initially treated with diazepam, 10 mg orally, to be taken as needed, but returned the next morning with worsening symptoms. He was oriented but reported agitation, tremor, and fearful hallucinations. Within 24 hours of admission he developed tachycardia, confusion, and extreme agitation, necessitating the use of 4-point restraints, a lorazepam drip infusion, and admission to the ICU. He was treated with large doses of sedative-hypnotic and antipsychotic medications. His course continued with intermittent episodes of tachycardia, confusion, and agitation requiring restraints until hospital day 7, when he was lucid with occasional agitation. On hospital day 10, his mentation continued to improve and the lorazepam drip infusion was tapered. On day 12, he was discharged to his family while receiving tapering doses of diazepam. During hospitalization, the patient's family brought in 2 unlabeled, 8-oz translucent plastic bottles containing clear solutions of sodium GHB at 675 mg/mL and 255 mg/mL. Analysis was performed with modification of a gas chromatography-mass spectrometry method.⁷ The estimated daily dose using the higher concentration of GHB ranged from 70 to 105 g.

Case 2

A healthy 23-year-old female college student and bodybuilder used GHB daily for 1 year for alleged anabolic effects. Six weeks before admission, she increased her dosing frequency to every 3 hours around-the-clock to prevent the anxiety and tremors she experienced without it. All symptoms were relieved by another dose of GHB. She presented to her private physician's office with anxiety, insomnia, and tremor. On admission, she exhibited tachycardia and reported increasing paranoid feelings, visual and auditory hallucinations, and agitation requiring restraint. Sedation was managed with intravenous benzodiazepine administration; the patient showed little additional improvement with other sedative-hypnotic or antipsychotic drugs. A dystonic reaction to antipsychotic drugs developed on hospital day 2 prompting an ICU admission. On hospital day 7, she began rapid improvement, no further hallucinations occurred, and she was discharged on day 9. Six months later, she remained asymptomatic without medication and finished her semester with a perfect grade point average. The GHB solution she used contained 721 mg/mL GHB. The estimated daily dose ranged from 43 to 144 g.

Case 3

A 24-year-old male claims adjuster presented to a crisis center complaining of auditory and visual hallucinations. He admitted heavy GHB use over 10 months and increased his use to prevent GHB withdrawal hallucinations. His last dose was just before evaluation. He exhibited no evidence of hallucinations and was released with instructions to follow up in drug rehabilitation.

Two months later, the patient presented to a detoxification unit complaining of nausea, vomiting, and diarrhea for 2 months. In addition to feeling "weak and swollen," the patient complained of diplopia, blurred vision, short-

ness of breath, frequency of urination, thirst, blackout spells, and loss of appetite. He had been using GHB every 30 minutes with the last dose 20 minutes before his arrival. He denied concurrent drug use. His pupils were dilated, and he was tremulous and anxious. The ECG showed normal sinus rhythm with left ventricular hypertrophy and questionable inferior wall ischemia. He was admitted and treated with lorazepam for agitation. Over the next 24 hours, he developed tachycardia, combativeness, visual hallucinations, and persistent tremors. The hospital course was complicated by right lower lobe pneumonia requiring endotracheal intubation and mechanical venti-

Table 1.
Characteristics of patients experiencing GHB withdrawal.

Patient	Past Medical History	Reason for Presentation	GHB Source/Reason for Use	Dose/Interval/Duration of GHB Use
1 24-year-old male salesman	Attention deficit disorder, prior history of amphetamine abuse; denied current alcohol abuse	Brought in by mother due to confusion, emotional lability	Unknown source*/bodybuilding and "to help focus"	1 capful every hour for 2 mo
2 25-year-old female college student	Anabolic steroid use >2 y prior	Self-presented to private physician's office; anxiety and tremors	Biochemist friend†/bodybuilding	1–5 capsful every 3 h for 6 wk; less daily for a year
3 24-year-old male claims adjuster	Prior history alcohol, cocaine, and marijuana abuse; denied recent abuse	Nausea, vomiting, blurred vision; "blackout spells"	Unknown source/euphoric agent	1.5 tsp every 30 min–1 h for 10–12 mo; consumed approximately a gallon every 2 wk
4 30-year-old male roofer	Prior history of amphetamine abuse; denied alcohol abuse	Fell off a ladder; presented to the hospital with an open, right ankle fracture	Unknown source/initially used for bodybuilding; later to avoid withdrawal	1 tsp every 1–2 h for 7 mo; daily use for 3 y
5 26-year-old woman, unemployed	History of cocaine and alcohol abuse; denied alcohol in past year	Day 8 after last GHB dose, referred from drug rehabilitation center after admission for GHB and cocaine abuse	Unknown source/used as an alcohol substitute	Used daily for >10 mo
6 22-year-old male personal trainer	Prior history anabolic steroid use	Self-presentation 7 d after last GHB dose with severe insomnia for 6 d; paranoia and mumbling	Unknown source/bodybuilding	Ingested every 1–2 h for approximately a year
7 24-year-old male computer salesman	Depression, occasional marijuana use; denied alcohol abuse; paroxetine (40 mg/d), lorazepam (1–3 mg/d)	Found comatose by roommate (probably GHB overdose)	Synthesized per instructions on Internet/ depression, mood control	1–2 g every 1–2 h for 6 mo, to 40 g/d; less often for 1 y
8 38-year-old male sheet metal worker	Prior history of cocaine, heroin, and alcohol abuse; denied current drug abuse; stopped alcohol 6 wk before admission (increased GHB at that time)	Self-presented to ED for detoxification	Gamma sorption from Bricker Labs/bodybuilding, alcohol substitute	1 tsp every hour for 6 mo

*Patient 1 analysis of GHB solutions 675 mg/mL and 255 mg/mL.

†Patient 2 analysis of GHB solution 721 mg/mL.

lation for 6 days with propofol sedation. After extubation, he continued to require benzodiazepines and antipsychotic drugs. Despite sedation he was persistently confused and hallucinating, requiring the use of leather restraints. On

hospital day 12, his symptoms were improving and lorazepam was being tapered. On day 13, he was delirious but arousable. That evening, he died after an episode of spontaneous, generalized, spastic, muscular contractions

Table 2.
Manifestations of GHB withdrawal.

Patient	Vital Signs on Presentation (BP, P, T, RR)	Physical Findings	Toxicology Screen*	Medications During Withdrawal Period	Onset and Duration of Withdrawal
1 24-year-old male salesman	124/61, 93, 96.8°F, 18	Audio/visual hallucinations, tremulous, combative, incoherent; nausea and vomiting	Urine toxicology screen negative	Withdrawal day 1 Lorazepam: 129 mg Haloperidol: 12 mg Diazepam: 50 mg Diphenhydramine: 25 mg	Onset: 6 h Duration: 12 d
2 23-year-old female college student	138/98, 110, 98.5°F, 18	Audio/visual hallucinations, tremor, paranoia, disorientation, agitation	Urine toxicology screen negative	Withdrawal day 2 Lorazepam: 9 mg Diazepam: 30 mg Clonazepam: 0.5 mg	Onset: 3 h Duration: 9 d
3 24-year-old male claims adjuster	147/90, 93, 97.4°F, 18	Audio/visual hallucinations, nausea, vomiting, tremor, agitation, later developed pulmonary edema requiring endotracheal intubation	Urine toxicology screen and blood alcohol negative Admit urine: 1,760 mg/L GHB	Withdrawal day 2 Lorazepam: 12 mg Propofol sedation	Onset: <1 h Duration: 13 d*
4 30-year-old male roofer	133/85, 87–102, 100.0°F, 20	Admitted with normal mental status; developed delirium with "shaking"—lightning-like, small-amplitude, irregular myoclonic jerks throughout body Audio/visual hallucinations, garbled speech, and loss of short-term memory. Pupils mid-sized, diaphoretic	Urine toxicology screen positive for opiates, 2 acetaminophen/hydrocodone taken for pain	Withdrawal day 3 Lorazepam: 20 mg Haloperidol: 40 mg Diazepam: 30 mg	Onset: 6 h Duration: 15 d
5 26-year-old female, unemployed	130/74, 82, 97.9°F, 20	Confused, incoherent, tremulous throughout body, thrashing, audio/visual hallucinations; hypertonia. Pupils 3–5 mm, diaphoretic	Comprehensive urine and serum toxicology screens negative	Withdrawal day 8 Lorazepam: 12 mg Haloperidol: 15 mg Benzotropine: 8 mg	Onset: 6 h Duration: 12 d
6 22-year-old male personal trainer	120/60, 102, 98.5°F, 18	Confused, audio/visual hallucinations, delusions of "muscles deteriorating," mumbling, pupils 3–5 mm, diaphoretic	Urine toxicology screen negative	Withdrawal day 7 (12 h) Lorazepam: 2 mg Haloperidol: 3 mg Temazepam: 30 mg Chloral hydrate: 500 mg	Onset: 6 h Duration: 10 d
7 24-year-old male computer salesman	135/90, 100–123, 98.2°F, 20	Audio/visual hallucinations, delusions of being kidnapped, myoclonic tremor involving head and all extremities, 3+ reflexes, diaphoresis. Pupils midrange, mild cog wheeling	Urine toxicology screen positive for tetrahydrocannabinol and benzodiazepines	Withdrawal day 2–3 Lorazepam: 16 mg Haloperidol: 30 mg Trifluoperazine: 2 mg	Onset: <5 h Duration: 10 d
8 38-year-old male sheet metal worker	240/130, 103–132, 99.3°F, 18	Seen in ED with normal mental status, developed audio/visual hallucinations, agitation, hypertension, diaphoresis, nausea, vomiting, and myalgias	Serum and urine toxicology screens negative	Withdrawal day 2 Labetolol: 600 mg Lorazepam: 2 mg every 15 min as needed	Onset: 2 h Duration: 5 d

BP, Blood pressure (mm/Hg); P, pulse rate (in beats/min); T, temperature; RR, respiratory rate (breaths/min).

*Urine toxicology screen for cocaine, opiates, phencyclidine, tetrahydrocannabinol, benzodiazepines, barbiturates, amphetamines, and ethanol.

*Patient 3 died on day 13 after developing generalized spastic muscle contraction and severe bradycardia unresponsive to atropine.

with an upward gaze. Cardiac arrest followed severe bradycardia despite aggressive resuscitation attempts including atropine, epinephrine, and an external pacer. The autopsy showed pulmonary edema and an enlarged heart (490 g) with left ventricular hypertrophy, and focal severe stenosis (75%) of the left anterior descending coronary artery, without evidence of myocardial infarction. Analysis at 36 hours post mortem showed a lorazepam level consistent with therapeutic dosing at 0.02 mg/L (0.06 μ mol/L), and haloperidol was undetectable. The hospital admission urine sample contained a GHB concentration of 1,750 mg/L (17 mmol/L), consistent with unpublished spot urine levels after acute overdose (Dyer, unpublished data). Rapid clearance of GHB prevents detection beyond 12 hours after a therapeutic dose.⁸ The cause of death was reported as a complication of GHB withdrawal resulting from chronic substance abuse.

ADDITIONAL CASES

The 8 cases summarized in Tables 1 and 2 demonstrate a withdrawal syndrome that begins rapidly within 6 hours of the last dose. Early symptoms of insomnia, tremor, confusion, nausea, and vomiting are mild, and medical admission to a health care facility is often delayed until more severe symptoms of agitation and hallucinations are experienced. The withdrawal syndrome progresses over the initial 2 to 3 days with mild autonomic instability manifested by tachycardia, hypertension, tremor, and diaphoresis. Central nervous system symptoms include vivid hallucinations and anxiety. Confusion, disorientation, and delirium with agitation and combative behavior occur as the syndrome progresses, often requiring 4-point leather restraints and sedation. These symptoms become episodic in nature as the syndrome wanes (Table 3).

The patients ranged from 22 to 38 years of age, and most (88%) were employed. Bodybuilding was frequently (63%) the motivation for GHB use. Results of urine toxicology screenings were negative for common drugs of abuse except for 2 patients: No. 4 with a fractured leg had detectable opiates, and No. 7 had detectable tetrahydrocannabinol in addition to the benzodiazepines, which were prescribed therapeutically for early withdrawal symptoms. All patients reported frequent ingestion of GHB, every 1 to 3 hours around-the-clock with nighttime awakening to take doses. The duration of GHB use was 2 months to 3 years. Some patients had recently escalated their dosing frequency.

The patients exhibited a consistent abuse pattern of large frequent amounts of GHB documented by family

and friends. A similar withdrawal toxidrome rapidly followed the last dose of GHB. The denial of concurrent alcohol and drug abuse accompanied by the lack of social or laboratory evidence of alcoholism makes delirium tremens in the setting of alcohol withdrawal an unlikely explanation for this syndrome.

DISCUSSION

GHB overdose has become a significant cause of patients with drug-induced coma presenting to EDs⁶; however, reports of a withdrawal syndrome are rare.² The low incidence of dependence and the rapid onset of withdrawal symptoms are probably related to the rapid absorption and elimination kinetics of GHB. After ingestion, GHB effects can begin within 10 to 15 minutes. Absorption of GHB is capacity limited, resulting in increased time to peak levels with increased dose. A therapeutic dose (50 mg/kg) produced peak levels in 45 minutes. The elimination of GHB is rapid but saturable, culminating in a terminal half-life of 23 minutes after a 50-mg/kg dose.⁹ Consequently, frequent dosing is expected to be required to maintain levels sufficient for physiologic adaptation and dependence. Our patients reported physiologic adaptation with dosing every 3 hours around-the-clock.

After dependence develops, GHB use is maintained as withdrawal symptoms threaten whenever GHB is discontinued. The approximate daily dose estimated in cases 1 and 2, where the concentration of GHB was known, ranged

Table 3.
Manifestations of withdrawal from GHB.

Symptoms	Early (1-24 h)	Progressive (1-6 d)	Episodic When Waning (7-14 d)
Anxiety/restlessness	+++	+++	++
Insomnia	+++	+++	++
Tremor	+	++	+
Confusion		+++	++
Delirium		+++	
Auditory, tactile, and visual hallucinations		+++	++
Tachycardia	+	++	+
Hypertension	+	++	+
Nausea	++	+	
Vomiting	++	+	
Diaphoresis	+	++	+

+, Mild; ++, moderate; +++, severe.

Note: Symptoms did not always progress from mild to severe in a predictable fashion.

from 43 to 144 g/d. In contrast, evaluations of GHB for narcolepsy reported neither tolerance to GHB during experimental courses of 6 months to 9 years nor withdrawal symptoms at their completion (reference 3 and Mamelak M, Baycrest Hospital Toronto Canada; personal communication, July 1998). These narcolepsy studies used total daily doses of 4.5 to 9 g per night administered as two or three 30-mg/kg doses 3 hours apart, leaving a GHB-free period of more than 12 hours. The balance between dose and dosing interval necessary to produce GHB dependence is not known, but around-the-clock dosing is a feature of our cases.

GHB exerts a distinct effect at specific GHB receptors. The close structural and metabolic relationship of GHB and γ -aminobutyric acid (GABA) may also play an important role in the withdrawal syndrome. In vivo conversion of radioactive GHB into GABA has been described, and current research has proposed that GHB modulates both GABA_A and GABA_B receptors.^{10,11} The end result, acutely, is neuroinhibition with physiologic tolerance developing over time.

Clinical similarities between GHB withdrawal and other sedative hypnotic withdrawal syndromes suggest a common mechanism (Table 4). Ethanol increases endogenous levels of GHB and acts synergistically with GHB to produce central nervous system and respiratory depression.¹² Cross-tolerance has been demonstrated between ethanol and GHB in rats, and GHB has been used to suppress acute alcohol withdrawal symptoms.¹³ Chronic alcohol, benzodiazepine, and GHB administration down-regulate inhibitory GABA receptors.¹⁴⁻¹⁶ Diminished GABA synaptic activity releases excitatory neurotransmitters and pathways from inhibition and likely plays an

important role in the subsequent withdrawal syndrome.¹⁷ One may also speculate that an excess dopaminergic state, known to be associated with psychotic hallucinosis,¹⁸ may be part of the GHB withdrawal syndrome. Baclofen, a GABA_B receptor agonist, has been associated with severe psychological reactions during withdrawal.^{19,20}

The differential diagnosis for GHB withdrawal syndrome includes the other sedative, hypnotic, or alcohol withdrawal syndromes (Table 4). Conversely, GHB withdrawal can resemble acute drug intoxication by sympathomimetic agents, as well as serotonin syndrome and neuroleptic malignant syndrome. Altered mental status may result from metabolic causes such as thiamine deficiency caused by poor nutritional balance from dieting, weight training programs, or when GHB has been used as an ethanol substitute. Endocrine abnormalities including thyroid storm and pheochromocytoma should be considered. Bodybuilders who abuse GHB may also abuse injectable steroids, which increase their risk of infectious complications through needle sharing and steroid psychosis.

Management of GHB withdrawal is symptomatic and supportive, stressing sedation to prevent injury, hyperthermia, and rhabdomyolysis. Benzodiazepines effectively sedate, although extremely high doses may be required. Barbiturates have been shown to be effective in the treatment of refractory cases of GABA-minergic withdrawal. Propofol has also been used successfully. However, unpublished cases using valproic acid, which has been shown to raise endogenous GHB levels in rat brain,²¹ or baclofen, the GABA_B agonist, did not dramatically alter the withdrawal course. Animal studies are needed to analyze the cross-tolerance of GHB to other sedatives, the

Table 4.
Comparison of various sedative-hypnotic withdrawal syndromes.

Substance	Onset/ Duration*	Autonomic Instability†	Neurologic/ Psychiatric Symptoms	Mortality	Major Mechanism Inducing Withdrawal State‡
GHB	Hours/5-12 d	Mild	Severe	Case 3	Loss of GHB, GABA _A , and GABA _B -mediated inhibition
Benzodiazepine	1-3 d/5-9 d	Moderate	Moderate	1%	Loss of GABA _A -mediated inhibition
Baclofen	12-96 h/8 d	Moderate	Severe	None reported	Loss of GABA _B -mediated inhibition
Ethanol	Hours/10-14 d	Severe	Moderate to severe	5%-15%	Loss of GABA _A -mediated inhibition; dysinhibition of NMDA receptors.

NMDA, *N*-methyl-D-aspartate.

*Duration of severe symptoms.

†Tachycardia, fever, hypertension, diaphoresis.

‡All withdrawal states involve multifactorial processes.

usefulness of directed therapy with GABA_B agonists, and the benefits of early aggressive sedation for the management of GHB withdrawal syndrome.

The GHB withdrawal syndrome is increasingly reported²² and also occurs after dependence on the precursors, γ -butyrolactone and 1,4-butanediol. Among the 232 exposures to GHB that were recorded by the California Poison Control System during 1998, 17 cases of GHB withdrawal were identified. The following year, 30 of the 356 GHB exposure reports included withdrawal symptoms. An Internet help site offering information on the GHB dependence and withdrawal syndrome has recorded 184 cases over 6 months from 33 states.²³ GHB dependence is a new and emerging challenge for emergency physicians. Severe GHB dependence developed after frequent ingestion every 1 to 3 hours around-the-clock and was manifested by anxiety, insomnia, and tremor that occurred whenever GHB was discontinued. The withdrawal syndrome may progress to severe delirium with autonomic instability. Early recognition of these signs can identify those patients who would benefit from inpatient medical detoxification.

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Controlled Substances Act-Regulatory Requirements

	Schedule I (Heroin, LSD, Methaqualone, etc.)	Schedule II (Barbiturates, PCP, Methylphenidate, etc.)	Schedule III (Barbiturates, anabolic steroids, etc.)	Schedule IV (Benzodiazepines, Methohexital, etc.)	Schedule V (Codeine cough preparations)
Registration	Required	Required	Required	Required	Required
Recordkeeping	Separate	Separate	Readily Retrievable	Readily Retrievable	Readily Retrievable
Distribution Restrictions	Order Forms	Order Forms	Records Required	Records Required	Records Required
Dispensing Limits	Research use only	Rx: written No Refills	Rx: written or oral Refills with MD's authorization	Rx: written or oral Refills with MD's authorization	OTC (Rx drugs limited to MD's order
Manufacturing Security	Vault/Safe	Vault/Safe	Secure Storage	Secure Storage	Secure Storage
Manufacturing Quotas	Yes	Yes	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)
Import/Export Non-Narcotic	Permit	Permit	Permit	Permit	Permit to import, declaration to export
Reports to DEA Manufacturer and Distributor	Yes	Yes	Mfr. reports required for specific drugs	Mfr. reports required for specific drugs	No

Scheduling Criteria. Section 202 (b) of the CSA, [21 U.S.C. 812 (b)].

Schedule I

- The drug or other substance has a high potential for abuse.
- The drug or other substance has no currently accepted medical use in treatment in the United States.
- There is a lack of accepted safety for use of the drug or other substance under medical supervision.
- Some Schedule I substances are heroin, LSD, marijuana, and methaqualone.

Schedule II

- The drug or other substance has a high potential for abuse.
- The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
- Abuse of the drug or other substance may lead to severe psychological or physical dependence.
- Schedule II substances include morphine, PCP, cocaine, methadone, and methamphetamine.

Schedule III

- The drug or other substance has a potential for abuse less than the drugs or other substances in Schedules I and II.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
- Anabolic steroids, codeine and hydrocodone with aspirin or acetaminophen, and some barbiturates are Schedule III substances.

Schedule IV

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.
- Included in Schedule IV are dextropropoxyphene, barbital, alprazolam, diazepam.

Schedule V

- The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.
- The drug or other substance has a currently accepted medical use in treatment in the United States.
- Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule IV.
- Over-the-counter cough medicines with codeine are classified in Schedule V.

RISK MANAGEMENT PLANS FOR RECENTLY APPROVED DRUGS*

Goal: To ensure safe use of the drug as labeled

COMPONENTS OF RISK MANAGEMENT PLANS	DRUG NAME
Restricted Prescribing: Physician Agreement Physician Registry Restricted Specialty/Certification Physician Education	Actiq, Fentanyl Oralet, Mifeprex, Thalomid Accutane, Actiq, Thalomid
Restricted Distribution: Central Pharmacy Pharmacy Registration Hospital Pharmacy Limited Supply/Refills	Clozaril, Fentanyl Oralet, Mifeprex, Thalomid Actiq (C II), Thalomid
Patient Agreement/Registry Patient Education/Medication Guide	Accutane, Mifeprex, Thalomid Accutane, Actiq, Mifeprex, Thalomid
Family Members & Caregivers Education/Emergency Numbers Safe Storage, Proper Handling and Disposal	Actiq Actiq
Restricted Advertisement Special Reporting Agreement	Actiq, Fentanyl Oralet, Thalomid Actiq, Thalomid

*Approved Drugs: **

Accutane = isotretinoin

Actiq = Oral Transmucosal Fentanyl Citrate

Clozaril = clozapine

Fentanyl Oralet = Oral Transmucosal Fentanyl Citrate

Mifeprex = mifepristone

Thalomid = thalidomide