

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/mem.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 23-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 capsul 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	Gammasorption 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.

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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 Benztropine: 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 pacemaker. 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 μmol/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.

14. Gianutsos G, Suzdak PD. Evidence for down-regulation of GABA receptors following long-term gamma-butyrolactone. *Naunyn-Schmiedeberg Arch Pharmacol.* 1984;328:62-68.
15. Little HJ. The benzodiazepines: anxiolytic and withdrawal effects. *Neuropeptides.* 1991;19(Suppl):11-14.
16. Livingston MG. Benzodiazepine dependence. *Br J Hosp Med.* 1994;51:281-286.
17. Fifkova E, Eason H, Buelmann K, et al. Changes in GABAergic and non-GABAergic synapses during chronic ethanol exposure and withdrawal in the dentate fascia of LS and SS mice. *Alcohol Clin Exp Res.* 1994;18:989-997.
18. Diamond I, Messing RO. Neurologic effects of alcoholism. *West J Med.* 1994; 161:279-287.
19. Pauker SL, Brown R. Baclofen-induced catatonia [letter]. *J Clin Psychopharmacol.* 1986;6:387-388.
20. Rivas DA, Chancellor MB, Hill K, et al. Neurological manifestations of baclofen withdrawal. *J Urol.* 1993;150:1903-1905.
21. Vayer P, Cash CD, Maitre M. Is the anticonvulsant mechanism of valproate linked to its interaction with the cerebral gamma-hydroxybutyrate system. *Trends Pharmacol Sci.* 1988;9:127-129.
22. Craig K, Gomez HF, McManus JL, et al. Severe gamma-hydroxybutyrate withdrawal: a case report and literature review. *J Emerg Med.* 2000;18:65-70.
23. GHB: the stone cold truth. Available at: www.ashesonthesea.com/ghb.

REFERENCES

1. Dyer JE. Gamma-hydroxybutyrate: a health-food product producing coma and seizure-like activity. *Am J Emerg Med.* 1991;9:321-324.
2. Galloway GP, Frederick SL, Stagers FE, et al. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction.* 1997;92:89-96.
3. Mamelak M, Scharf MB, Woods M. Treatment of narcolepsy with γ -hydroxybutyrate. A review of clinical sleep lab findings. *Sleep.* 1986;9:285-289.
4. Addolorato G, Castelli E, Stefanini G, et al. An open multicentric study evaluating 4-hydroxybutyric acid sodium salt in the medium-term treatment of 179 alcohol dependent subjects. *Alcohol Alcohol.* 1996;31:341-345.
5. Gallimberti L, Cibir M, Pagnin P, et al. Gamma hydroxybutyric acid in the treatment of opiate withdrawal syndrome. *Neuropsychopharmacology.* 1993;9:77-81.
6. Chin RL, Sporer KA, Cullison B, et al. Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med.* 1998;31:716-722.
7. Ferrara SD, Tedeschi L, Frison G, et al. Therapeutic gamma-hydroxybutyric acid monitoring in plasma and urine by gas chromatography-mass spectrometry. *J Pharm Biomed Anal.* 1993;11:483-487.
8. Hoes MJ, Vree TB, Guelen PJ. Gamma hydroxybutyric acid as a hypnotic. *Encephale.* 1980;6:93-99.
9. Palatini P, Tedeschi L, Frison G, et al. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol.* 1993;45:353-356.
10. Snead OC, Nichols AC. Gamma-hydroxybutyric acid binding sites: evidence for coupling to a chloride anion channel. *Neuropharmacology.* 1987;26:1519-1523.
11. 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.* 1997;281:753-760.
12. Mamelak M. Gamma-hydroxybutyrate: an endogenous regulator of energy metabolism. *Neurosci Biobehav Rev.* 1989;13:187-98.
13. Colombo G, Agabio R, Lobina C, et al. Cross-tolerance to ethanol and gamma-hydroxybutyric acid. *Eur J Pharmacol.* 1995;273:235-238.