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GHB

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Among the substances termed *club drugs* by the National Institute on Drug Abuse (NIDA) is γ-hydroxybutyrate (GHB). A sedative-hypnotic, it is a simple, four-carbon molecule synthesized in the early 1960s in a search for an orally active γ-aminobutyric acid (GABA) analog. It has been used as a general anesthetic and to induce absence seizures in animal models of epilepsy. More recently, it has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy in narcolepsy (marketed as Xyrem) and is used for treating alcohol and opiate dependence primarily in Italy and Sweden, where it is marketed as Alcover.

GHB abuse reports date to the early 1990s. Initially available as a dietary supplement in the United States, it was attractive to bodybuilders via reports that GHB raised levels of growth hormone. The substance is taken orally, with misusers reporting a euphoric "high" from the drug; the effects have been described anecdotally as comparable to both alcohol intoxication (with disinhibition, drowsiness, and loss of motor control) and MDMA/ecstasy use (enhanced sensuality, empathogenesis) (1). In the United States, GHB is a Schedule 1 controlled substance, except that the FDA-approved formulation (for narcolepsy) is classified as Schedule 3. Other countries maintain similar regulatory classifications.

GHB is inexpensive and readily available at some social events (notably "raves") or via kits and recipes for home manufacture found on the Internet. Other names for GHB include "G," "liquid ecstasy," "fantasy," "Grievous Bodily Harm," "cherry meth," "soap," "salty water," and "Georgia Home Boy" (2). GHB is usually sold in a salty-tasting, aqueous solution that may have a variable concentration, undoubtedly contributing to the high incidence of adverse effects. It is also sold as a white powder ready for dissolution. Legal restrictions on the purchase of GHB have led to increased abuse of two substances that convert to GHB in the body: γ-butyrolactone (GBL), whose street names include "lactone," "Renewtrient," "Blue Nitro," and "Verve," and 1,4-butanediol (BD), also known as "Pro-G," "Thunder," "Weight Belt Cleaner," and "Pine Needle Extract." Both substances are available as industrial solvents. GBL is a Drug Enforcement Administration (DEA) List 1 chemical in the United States, requiring justification for sales, and the FDA classifies BD as a Class I Health Hazard (i.e., a potentially life-threatening drug).

PHYSIOLOGY AND PHARMACOKINETICS

Found endogenously at very low concentrations in the brain, GHB is both a precursor and degradation product of GABA and is structurally similar to GABA. GHB interacts in a complex way with endogenous GABA (the primary inhibitory neurotransmitter in the brain) and with GABA receptors (3). Oral doses are rapidly absorbed, with maximum plasma concentrations reached in 30 to 50 minutes. Plasma elimination half-life is in the range of 20 to 30 minutes (4,5). GHB is metabolized to succinate and then to CO2 and water via the citric acid cycle. GHB binds to and activates two receptors: the GABAb receptor, and a distinct GHB receptor. Human GHB receptors have recently been cloned and are pharmacologically distinct from GABA receptors; they are G-protein-coupled and do not bind GABA (6). GHB affects dopamine release biphasically: Low GHB concentrations stimulate dopamine release (which may increase addiction liability by activating reward pathways), whereas higher concentrations inhibit dopamine release. GHB also influences serotonin turnover, and affects neurosteroid, acetylcholine, and growth hormone levels (3).

The pharmacologic profile of BD is similar to that of GHB (7), whereas GBL is more rapidly absorbed and has greater lipid solubility than GHB (8). GHB can be detected for approximately 5 hours in blood and oral fluid, and <12 hours in urine (9).

EPIDEMIOLOGY

Estimates vary on the frequency of GHB use. Overall, 0.05% of U.S. youths aged 16 to 23 in a 2002 survey reported lifetime use of GHB (10). Some researchers found a recent decline in GHB use among U.S. youth (11,12). Sizable minorities in some populations report higher use rates. 7% of young adults and adolescents in treatment for substance abuse reported lifetime use of GHB (13). A study of 450 "club" drug-using gay and bisexual men in New York City found that 29% recounted GHB use in the previous 4 months (14). There have been occasional reports of increased use in specific locales (15).

Intoxication Reasons given for GHB use include "to be sociable," to enhance sex, and to explore altered states of consciousness. Subjective effects of GHB include slurred speech, ease in socializing, feelings of increased sexual intimacy, drowsiness, and feelings of depression after the GHB "high" is past (16). GHB administered under controlled laboratory conditions produces sleepiness, sedation, fatigue, and feelings of being "easy going" or "mellow." Effects noted by observers of intoxicated subjects include decreased psychomotor performance and level of alertness

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and increased ratings of muscle relaxation and abnormal posture (17). In overdose, clinical characteristics include those expected from a CNS depressant—bradycardia, vomiting, somnolence, obtundation, stupor, and coma—but a literature review also identified agitation, combativeness, and self-injurious behavior as relatively common in persons using GHB alone and with cointoxicants (18). The frequent use of alcohol with GHB is thought to worsen GHB-induced sedation and may increase episodes of vomiting, hypotension, and respiratory depression (7).

Abuse Liability, Dependence, and Withdrawal Physical dependence and addiction have been reported with GHB, GBL, and BD (19,20), though knowledge of dependence on these drugs comes from a relatively small number of studies. One estimate places the likelihood for GHB abuse intermediate to triazolam and pentobarbital (17). Dependence may develop rapidly, usually with frequent (four or more times a day) dosing. Time course estimates for the development of physical dependence and severe withdrawal range from 7 days (21) to use over 2 months or more (20,22,23).

Though the withdrawal syndrome may be mild, with insomnia, agitation, anxiety, and limited sympathetic arousal, an analysis of reports of GHB withdrawal found that severe, potentially life-threatening withdrawal states may develop requiring vigorous inpatient clinical management. Signs and symptoms are similar to those seen in alcohol withdrawal: tremor, tachycardia, restlessness, and delirium, including hallucinations (24).

Adverse Effects Because the dose-response curve for GHB is steep and concentrations of GHB in illicitly purchased or homemade solutions are notoriously hard to predict, overdose is a hazard. Symptoms of CNS depression are dose-related, with reports of somnolence within 15 minutes at a dose of 30 mg/kg, and loss of consciousness and coma at doses exceeding 50 mg/kg (25). Overdose may lead to intubation and management in an ICU, although in one study the majority of overdose patients were discharged within 6 hours of presentation (26). Long-term sequelae of using GHB and congeners are not presently known.

GHB-associated deaths, both with and without cointoxicants, have been identified in the United States, Europe, and Australasia (27). GHB use is associated with risky behaviors such as coingestion of ethanol, driving under the influence of GHB (28), and risky sexual behaviors (29). GHB has been associated with drug-facilitated sexual assaults (30,31). Such use may be facilitated by GHB's properties of being colorless, odorless, sedating, purportedly causing amnesia, and detected poorly in urine after 12 hours.

TREATMENT

Treatment for GHB intoxication is largely supportive. McDonough, Kennedy, et al. conducted a retrospective analysis of treatment for GHB withdrawal and give recommendations for management. In their review, a tapering regimen of benzodiazepines was used in 91% of 38 cases, with a mean dose in diazepam equivalents of 335 mg (range 20 to 2,655 mg). Mean duration of withdrawal was 9 days. In 82% of the 38 cases, other drugs were used in combination with benzodiazepines: antipsychotics for psychosis and delirium and anticonvulsants and non-benzodiazepine sedatives such as pentobarbital. They note that withdrawal delirium developed in more than one-half the cases wherein GHB use occurred every 8 hours or less, or with use of >30 g of GHB a day. They recommend inpatient management of withdrawal in these cases and note that though antipsychotics have been used for delirium and psychosis, they do not appear sufficient or necessary. Pentobarbital was effective where symptoms of withdrawal persisted despite high doses of benzodiazepines. They conclude by noting that management of GHB withdrawal requires more study (24).

REFERENCES

1. Galloway GP, Frederick-Osborne SL, Seymour R, et al. Abuse and therapeutic potential of gamma-hydroxybutyric acid. *Alcohol* 2000;20(3):263–269.
2. Maxwell JC. Party drugs: Properties, prevalence, patterns, and problems. *Subst Use Misuse* 2005;40(9–10):1203–1240.
3. Drasbek KR, Christensen J, Jensen K. Gamma-hydroxybutyrate—a drug of abuse. *Acta Neurol Scand* 2006;114(3):145–156.
4. 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(4):353–356.
5. Brenneisen R, Elsohly MA, Murphy TP, et al. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol* 2004;28(8):625–630.
6. Andriamampandry C, Taleb O, Kemmel V, et al. Cloning and functional characterization of a gamma-hydroxybutyrate receptor identified in the human brain. *FASEB J* 2007;21(3):885–895.
7. Thai D, Dyer JE, Jacob P, et al. Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrate after oral 1,4-butanediol administration to healthy volunteers. *Clin Pharmacol Ther* 2007;81(2):178–184.
8. Kohrs FP, Porter WH. Gamma-hydroxybutyrate intoxication and overdose. *Ann Emerg Med* 1999;33(4):475–476.
9. Verstraete AG. Detection times of drugs of abuse in blood, urine, and oral fluid. *Ther Drug Monitor* 2004;26(2):200–205.
10. U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2002 National Survey on Drug Use and Health: National Findings, 2003. *DHHS Publication No. SMA 03-2836. NSDUH Series H-22.* Accessed February 2008 at http://www.oas.samhsa.gov/nhsda/2k2nsduh/Results/2k2Results.htm.

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11. Johnston LD, O'Malley PM, Bachman JG, et al. Monitoring the future: National results on adolescent drug use. National Institute on Drug Abuse, 2005. Accessed February 2008 at http://www.nida.nih.gov/PDF/overview2005.pdf.
12. Anderson IB, Kim SY, Dyer JE, et al. Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. *Ann Emerg Med* 2006;47(2):177–183.
13. Hopfer C, Mendelson B, Van Leeuwen JM, et al. Club drug use among youths in treatment for substance abuse. *Am J Addict* 2006;15(1):94–99.
14. Halkitis PN, Palamar JJ. GHB use among gay and bisexual men. *Addict Behav* 2006;31(11):2135–2139.
15. Knudsen K, Greter J, Verdicchio M, et al. A severe outburst of GHB poisonings (gamma-hydroxybutyrate, gamma-hydroxybutyric acid) on the West Coast of Sweden. Mortality numbers ahead of heroin. *Clin Toxicol* 2006;44(5):637–638.
16. Sumnall HR, Woolfall K, Edwards S, et al. Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). *Drug Alcohol Depend* 2008;92:286–290.
17. Carter LP, Richards BD, Mintzer MZ, et al. Relative abuse liability of GHB in humans: A comparison of psychomotor, subjective, and cognitive effects of supratherapeutic doses of triazolam, pentobarbital, and GHB. *Neuropsychopharmacology* 2006;31(11):2537–2551.
18. Zvosec DL, Smith SW. Agitation is common in gamma-hydroxybutyrate toxicity. *Am J Emerg Med* 2005;23(3):316–320.
19. Galloway GP, Frederick SL, Staggers F Jr. Physical dependence on sodium oxybate. *Lancet* 1994;343(8888):57.
20. McDaniel CH, Miotto KA. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: Five case studies. *J Psychoactive Drugs* 2001;33(2):143–149.
21. Perez E, Chu J, Bania T. Seven days of gamma-hydroxybutyrate (GHB) use produces severe withdrawal. *Ann Emerg Med* 2006;48(2):219–220.
22. Dyer J, Roth B, Hyma B. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med* 2001;37(2):147–153.
23. Miotto K, Darakjian J, Basch J, et al. Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *Am J Addict* 2001;10(3):232–241.
24. McDonough M, Kennedy N, Glasper A, et al. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: A review. *Drug Alcohol Depend* 2004;75(1):3–9.
25. Okun MS, Boothby LA, Bartfield RB, et al. GHB: An important pharmacologic and clinical update. *J Pharm Sci* 2001;4(2):167–175.
26. Couper FJ, Thatcher JE, Logan BK. Suspected GHB overdoses in the emergency department. *J Anal Toxicol* 2004;28(6):481–484.
27. World Health Organization (WHO) 34th Expert Committee on Drug Dependence. Pre-review of gamma-hydroxybutyric acid (GHB). 2006. Accessed February 2008 at http://www.who.int/-medicines/areas/quality_safety/5GHBPreReview.pdf.
28. Kim SY, Anderson IB, Dyer JE, et al. High-risk behaviors and hospitalizations among gamma hydroxybutyrate (GHB) users. Am J Drug Alcohol Abuse 2007;33(3):429–438.
29. Romanelli F, Smith KM, Pomeroy C. Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Topics HIV Med* 2003;11(1):25–32.
30. Scott-Ham M, Burton FC. Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. *J Clin Forensic Med* 2005;12(4):175–186.
31. Stillwell ME. Drug-facilitated sexual assault involving gamma-hydroxybutyric acid. *J Forensic Sci* 2002;47(5):1133–1134.