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Gamma-Hydroxybutyric Acid: Patterns of Use, Effects and Withdrawal

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Gamma-hydroxybutyric acid (GHB) is gaining popularity as a drug of abuse. Reports of toxicity and lethality associated with GHB use have increased. This survey study was designed to identify patterns of GHB use, its effects, and withdrawal syndrome. A survey inquiring about the effects of GHB was administered to 42 users. The results showed that GHB was used to increased feelings of euphoria, relaxation, and sexuality. Adverse effects occurred more frequently in daily users and polydrug users than in occasional GHB users. Loss of consciousness was reported by 66%, overdose by 28%, and amnesia by 13% of participants during GHB use and by 45% after GHB use. Three daily users developed a withdrawal syndrome that presented with anxiety, agitation, tremor, and delirium. Participants described GHB intoxication as having similarities to sedative-hypnotic or alcohol intoxication. Regular use has been shown to produce tolerance and dependence. Participants dependent on GHB reported using multiple daily doses around the clock. High frequency users appeared at the greatest risk for developing withdrawal delirium and psychosis after abrupt discontinuation of GHB use. (Am J Addict 2001;10:232-241)

Gamma-hydroxybutyric acid (GHB) is a drug of abuse with hypnotic, anxiolytic, myorelaxant, and nonanalgesic anesthetic properties.[1] Users describe its effects similar to those of alcohol; however, as loss-of-consciousness episodes are more frequent and unpredictable after GHB use. Amnesic effects have contributed to its use as a "date rape drug." The Drug Enforcement Administration (DEA) has documented over 9,600 overdoses and law enforcement encounters between 1990 and March 2000.[2] The DEA has also documented 68 GHB-related deaths with additional cases under investigation.[2] Current case finding methods do not indicate the extent of GHB morbidity and mortality, as routine screens for drugs of abuse do not detect GHB. The Drug Abuse Warning Network (DAWN) ident-

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ified 629 GHB-related emergency visits in 1996, with the majority of these episodes occurring in Caucasian (94%) males (79%).[3] GHB-related emergency room visits across the United States have increased sharply to 1,343 in 1998.[2]

Patients who have overdosed on GHB generally present to the emergency room with nausea, bradycardia, and a marked decreased level of consciousness.[3-7] Alcohol, opiates, barbiturates, and benzodiazepines potentiate GHB toxicity.[8,9] In a review by Chin et al, 13% of 88 GHB overdose patients required intubation; however, recovery of consciousness typically occurred within 5 hours after GHB ingestion.[5] Opiate or benzodiazepine antagonists did not reverse GHB coma. Two case reports suggest the use of physostigmine or neostigmine for GHB overdose; however, the larger series by Chin et al recommends supportive treatment and monitoring due to the high rate of spontaneous recovery.[5,10,11] Further research is warranted before the use of physostigmine or neostigmine can be recommended as a reversal agent.[11]

GHB was developed as a general anesthetic agent; however, regular use was discontinued due to difficulties in dosing and side effects.[12] Ten mg/kg of GHB is an anxiolytic and myorelaxant dose, although amnesia has also been reported at this dose.[13] A dose of 20-30 mg/kg induces sleep, and 50 mg/kg produces anesthetic effects.[13] Coma has been reported in patients receiving doses greater than 50 mg.[14] GHB is often sold on the street or via the Internet as a clear liquid and is taken in capfuls or teaspoons. The capful or teaspoon concentration of a street dose has been reported to vary from 500 mg-5 g/dose (J. Dyer, Pharm.D., San Francisco Poison Control, oral communication, March 1998). GHB users who develop tolerance and dependence can take multiple doses around the clock in the range of >25 g per day.[15] This greatly exceeds an anesthetic 60 mg/kg dose (4.2 g/day for a typical 70 kg man).

In early 1990, under claims of low toxicity, GHB was distributed over-the-counter as a dietary supplement, sleep aid, and muscle builder. The observation that GHB increases slow-wave sleep and stimulates growth hormone release contributed to its use with body builders and health food advocates.[16,17] However, by November 1990, the FDA removed GHB from the market due to reports of GHB-related coma and seizures. In March 2000, GHB became a Federal Schedule I Controlled Substance, and it is a felony under FDA regulations to manufacture or transport it across state lines for distribution or sale.[3,18] As regulations have increased, multiple GHB analogs or precursors, such as gamma-butyrolactone (GBL), with similar abuse potential have emerged and are illicitly sold on the street and Internet under various names.[19] Street names include "liquid ecstasy," "G," "scoop," and "easy lay." Internet names include "renewtrient," "gamma g," and "revivarant."

The therapeutic potential of GHB is currently being investigated in experimental animal and human studies. In animal studies, GHB has been shown to induce a rodent model of absence epilepsy.[20] In humans, it is currently being developed for the treatment of sleep disorders[21] and studied for the treatment of alcohol and drug dependence.[22] Studies by Gallimberti et al suggest that GHB reduces alcohol consumption and suppresses withdrawal symptoms.[23, 24] This same group of investigators also proposed GHB use for the treatment of opiate withdrawal.[25] In addition, preclinical studies have suggested the use of GHB as a pharmacologic agent in the treatment of cocaine addiction.[26] Clearly, the role of the GHB receptor system in the neurobiology of addiction merits further study.

GHB, a metabolite of the major inhibitory neurotransmitter, gamma-amino-

butyric acid (GABA), has been identified as an inhibitory endogenous neurotransmitter with agonist effects at the $GABA_B$ receptor.[1] Despite its sedative and hypnotic effects, GHB does not appear to directly affect the $GABA_A$ receptor. Baclofen is another example of an agonist at the $GABA_B$ receptor. It is an active spasmolytic and has been shown to induce withdrawal after abrupt discontinuation, with symptoms including psychosis, hallucinations, and seizures.[27] Unlike GHB, no addiction liability has been reported for badofen, suggesting that GHB receptors play an important role in tolerance and dependence. GHB receptors have been identified in several structures of the human and rodent brain, including the hippocampus, cortex, and dopaminergic structures.[28] In addition, GHB interacts with multiple neurotransmitter systems including GABA, opioid, serotonin, cholinergic, and dopamine.[29-31]

GHB exhibits dose-dependent absorption and non-linear elimination kinetics, as indicated by an increase in GHB half-life with dose. Dose-dependent saturation of the GHB metabolic pathway is presumably responsible for the non-linear kinetics, as GHB is not excreted by the kidney and only 2-5% is eliminated in the urine of humans.[32] GHB is a water-soluble, four-carbon molecule that freely crosses the blood brain barrier.[1] The half-life of an oral dose of 12.5 mg/kg is 20 minutes. A large dose of 75 mg/kg has been reported to clear from the plasma in 8 hours and from the urine in 12 hours in nondependent users.[33] This makes the window of opportunity to test for GHB narrow.

This survey report is the first systematic study of the effects of illicit GHB use. This study examines patterns of GHB use, tolerance, dependence, and withdrawal. Awareness of the medical and behavioral effects of GHB is important for primary and consulting psychiatrists.

METHODS

Thirty-three males and nine females were included in the study. All participants were recruited by advertisements for "regular GHB users" in two local English language newspapers. Participants were compensated with $20 in vouchers for either groceries or movie tickets. One hundred and twenty GHB users or their families responded to the ads; however, only 42 participants came in for an interview. Either a master's degree counselor or an addiction psychiatrist conducted the interviews. One participant, who did not have transportation, was interviewed over the telephone. Data from one subject was discarded due to concerns that responses were falsified. This pilot study did not include funding for GHB assays; therefore, plasma or urine assays to confirm GHB use were not done. The Human Subject Protection Committee of the University of California-Los Angeles reviewed the protocol of the study, and all subjects provided written informed consent.

A survey consisting of a 45-minute semi-structured interview was given to participants in two parts. The first part reviewed demographic and psychiatric treatment history, and the second part addressed GHB use. The questions asked in the second part were based on the clinical literature describing the effects of GHB and on interviews with users or inpatients treated for GHB abuse or withdrawal. On a scale from 0 to 4, they were asked to rate the severity of effects experienced during GHB intoxication and adverse effects after GHB use. (0 = "not at all"; 1 = "slightly"; 2 = "moderately"; 3 = "very much"; and 4 = "extremely.") To try and avoid confounding the effects of polydrug use, participants were asked to answer the questions exclusively in reference to GHB intoxication if possible. Participants were

also asked questions about patterns of GHB use, concomitant drug and alcohol use, and diagnostic criteria for GHB dependence.

Descriptive statistics were used to examine demographic, drug use data and GHB effects. All analyses were exploratory; no hypotheses were tested.

RESULTS

Table 1 lists the characteristics of the study participants. Thirty-one percent of participants endorsed a history of treatment for psychiatric problems, either for depression or anxiety. At the time of the study interviews, participants did not demonstrate any significant psychiatric problems, such as confusion, delirium, or psychosis.

Table 2 lists the subjective effects associated with GHB use and adverse effects following use. They are grouped by the percentages of participants who reported the various effects as being present or absent, and within these groupings, they are rank- ordered in severity based on a 0 to 4 scale. Although participants were asked to identify the isolated effects of GHB, it is important to note that participants who used GHB with other drugs reported more severe adverse events than those who used GHB alone. During GHB use, positive effects, such as euphoria, increased sexuality and well being, and tranquility, were commonly reported. Adverse effects after GHB use were reported more frequently by high-dose users.

Table 3 describes the participants' GHB use pattern, including frequency, route of administration, source of GHB, and desired effects. Ninety-one percent estimated the duration of effects of one dose (generally one capful) to be less than 4 hours. Twenty-one percent of participants reported being physically dependent on GHB. Three of the high-dose users reported taking GHB every two hours around the clock to avoid withdrawal symptoms, namely anxiety, insomnia, and confusion.

Nine participants in this study were daily GHB users. Seven of these daily users had a history of drug problems. Only the daily GHB users were aware that GHB could produce a withdrawal reaction. Two participants reported unsuccessful attempts of at-home detoxification using benzodiazepines, where after 24 hours of abstinence,

TABLE 1. **Characteristics of Study Participants**

Number of Interviews	N = 42	Percentage
Mean age, years ± SD	26.3 ± 9.8	
Gender		
Male	32	76.2%
Ethnicity		
Caucasian	31	73.8%
Hispanic	3	7.1%
Asian/Pacific Islander	3	7.1%
Other	5	11.9%
Sexual Orientation		
Heterosexual	29	70.7%
Employed	29	39%
Psychiatric Status		
Current psychiatric problem	4	9.5%
Past outpatient psychiatric treatment	13	31%
History of psychiatric hospitalization	8	19%

TABLE 2. **Subjective Effects Percentage of Participants Reported During and After GHB Use***

During GHB Use	Adverse Effects After GHB Use
Reported by 100% to 75%	Reported by 60% to 30%
Euphoria	Exhaustion
Happiness	Sluggishness
Increased sexuality	Amnesia
Increased well being	Confusion
Heightened sense of touch	Clumsiness
Relaxation	Reported by 29% to 15%
Increased tendency to talk	Anxiety
Tranquility	Insomnia
Disinhibition	Mumbling
Pleasant drowsiness	Weakness
Optimism	Agitation
Reported by 74% to 50%	Stiff muscles
Increased intensity of orgasm	Babbling
Increased energy	Craziness
Giddiness	Depression
Increased sensitivity to sound	The shakes
Silliness	Overdose
Sweatiness	Pessimism
Loss of consciousness	Sadness
Reported by 49% to 25%	Dizziness
Craziness	Giddiness
Nausea	Reported by 14% to 1%
Auditory hallucinations	Visual hallucinations
Visual hallucinations	Auditory hallucinations
Headache	Emergency room evaluation
Frequent bathroom visits	Loss of peripheral vision
Vomiting	Loss of consciousness
Reported by 24% to 1%	Anger
Stiff muscles	Difficulty reaching orgasm
Amnesia	Rage
Chills	
Reduced appetite	
Diarrhea	
Seizures	
Loss of bladder control	

*Listed in order of most severely to least severely endorsed.

withdrawal delirium and agitation developed. This withdrawal delirium lasted two weeks or longer. As a result, they were hospitalized and treated by one of the authors (KM) in a monitored bed with 4-point restraints for safety reasons. Prominent symptoms at presentation to the hospital included tachycardia, tremor, and anxiety. High dose benzodiazepines and a mood stabilizer helped to decrease agitation but did not shorten the course of delirium.

Hernandez et al[34] described a similar case of GHB withdrawal delirium treated in a psychiatric hospital. Jo Ellen Dyer also describes a case series of individuals with GHB withdrawal delirium, but these individuals were treated in an intensive care unit because of the large doses of benzodiazepines required for sedation.[35]

TABLE 3. **Patterns of GHB Use**

	Mean (Std)/Frequency n=42	Percentage
How often do you use GHB?		
Every day	9	21.4%
2-6 days per week	10	23.8%
1 day per week	5	11.9%
1 day per month	5	11.9%
Less than once per month	7	16.7%
Other	6	14.3%
How many times per day?		
Once per day/night	12	28.6%
2-3 times per day/night	18	42.9%
4 or more times per day/night	12	28.6%
How much use at a time?		
Less than 1 capful	4	9.5%
1-3 capfuls	21	73.8%
More than 3 capfuls	6	14.3%
Other	1	2.4%
How do you ingest GHB?		
Drink it in a water-like liquid	36	87.7%
Drink it in some other liquid	6	14.3%
Other	0	0.0%
How is GHB obtained?		
Purchase	21	50.0%
Free	13	31.0%
Both	8	19.0%
How likely are you to obtain GHB from: (0 = Not at all, 4 = Extremely)		
Dance Club	0.9 ± 1.4	
Gym	0.4 ± 1.0	
Make it myself	0.6 ± 1.1	
Friend	2.6 ± 1.6	
Dealer	1.1 ± 1.5	
Other	0.05 ± 0.3	
Where do you use it? (0 = Not at all, 4 = Extremely)		
When I am out with friends	2.4 ± 1.5	
On a date	0.6 ± 1.2	
When I'm alone	1.2 ± 1.6	
During school/work	0.4 ± 1.0	
When I'm working out	0.5 ± 1.2	
When I'm with family	0.2 ± 0.8	
Other	0.6 ± 1.3	
What do you want to achieve by taking GHB? (0 = Not at all, 4 = Extremely)		
Ease negative effect of other drugs	0.5 ± 1.1	
Increase sensuality/sexual arousal	2.0 ± 1.5	
Increase feelings of well-being	2.8 ± 1.3	
Increase sociability/reduce inhibitions	1.7 ± 1.5	
Induce sleep	1.3 ± 1.6	
Increase muscle mass	0.6 ± 1.1	
Lose weight	0.3 ± 0.7	
Extend the 'high' achieved from other drugs	1.4 ± 1.6	
Other	0.5 ± 1.1	
Have you ever felt physically dependent on GHB?		
Yes	9	21.4%
No	33	78.6%

Forty percent of participants reported using GHB intentionally to extend the "high" from other drugs, and 71% reported that they "usually use GHB with other drugs." The drugs most frequently used in combination with GHB were ecstasy (53%), followed by marijuana (50%), cocaine (43%), amphetamines (40%), and alcohol (37%). During the month preceding the interview, two-thirds of the sample reported using alcohol or marijuana, 36 percent reported taking ecstasy, and roughly a quarter of the sample used cocaine, amphetamines, benzodiazepines, and tobacco. Despite these reported drug use patterns, 60% of participants were aware of the increased risk of overdose associated with combining GHB with other drugs and alcohol.

In general, participants emphasized the positive effects of GHB and showed limited concern about the adverse experiences. However, multiple family members called the investigators during the course of this study with anecdotal complaints of a "change in personality," described as increased aggression, irritability, and memory problems associated with increased GHB use. In addition, 45% of daily users (n = 9) complained of frequent amnesic periods that were not associated with loss of consciousness. In contrast, unpredictable loss-of-consciousness episodes lasting minutes to hours were reported by 69% of participants in this survey. Participants were often uncertain if the loss of consciousness was the result of GHB alone or in a combination with other substances. Participants considered these episodes as "falling asleep," in contrast to an overdose or toxic state. Eighty-three percent of users did not drive after using GHB due to concern about decreased coordination and loss of consciousness. Twenty-six percent reported overdosing on GHB; however, only 9% had been treated in the emergency room. Three of the emergency-evaluated patients reported seizures.

DISCUSSION

Most participants in the study reported taking GHB with friends in an attempt to achieve feelings of well-being, sociability, and sensuality or sexuality. Participants in our study demonstrated a range of severity of GHB abuse and dependence similar to that reported by Gallimberti et al.[36] They estimate that 14.9% of 195 patients treated with GHB for drug and alcohol addiction developed problematic GHB use. Three types of GHB misuse were observed: one third of these patients demonstrated dose escalation; one third exhibited GHB intoxication (from 1 to 10 times per year); and one third demonstrated GHB dependence. The description provided is notable: "Subjects appeared to be constantly engaged in searching for the euphoric, empathogenic, hypnoinducing, anxiolytic, and antidepressive effects of GHB. Life without GHB was described as unacceptable."[36]

Episodes of loss of recall were characteristic of GHB intoxication, overdose, and withdrawal. In some cases, these may have been due to concomitant drug use or treatment with benzodiazepines; however, amnesia appears to be a direct effect of GHB. Participants and their families described unpredictable behavioral arrests that increased the likelihood of accidents and injuries, such as "falling asleep standing up." Several investigators of human sleep studies observed GHB-treated participants displaying slow wave sleep EEG patterns though the participants were behaviorally awake.[14,37,38] The lack of recall described by GHB abusers appeared to reduce awareness of the consequences of GHB use and delay treatment efforts. The possibility of persistent problems with memory acquisition has not yet been studied in regular GHB users but is warranted.

Although young employed Caucasian males were the largest group of participants

in this study, as was found in DAWN's 1996 statistics, the sample may have been biased based on the readers of the local newspapers selected for recruitment. Another potential limitation of this study was the lack of urine screens, which would have served to verify participants' reported GHB use. Without the verification of urine tests, it could be argued that participants provided information without having taken GHB. However, most of the participants were enthusiastic to provide detailed information about their GHB experiences, and the similarities of their reports and clinical GHB literature make this unlikely.

Our findings suggest that GHB is often used with other drugs of abuse. In this sample, GHB was often obtained free from friends. Reported patterns of use among recreational users included during exercise, dancing, and in other social situations. In contrast, dependent individuals described using GHB alone, as did those who used GHB as a hypnotic. A history of drug abuse as well as escalating frequency of GHB appeared to be risk factors for developing GHB dependence. These, and other possible risk factors merit further study.

Dependent participants described a spectrum of mild to severe adverse events after abrupt discontinuation of GHB, including anxiety, tremor, insomnia, autonomic instability, psychosis, and delirium. Similar descriptions of GHB withdrawal have been reported in the literature. Friedman et al identified a single case of thiamine deficiency leading to Wernicke-Korsakoff Syndrome in a patient during GHB withdrawal.[39] Galloway et al and Addolorato et al describe mild GHB withdrawal symptoms including tremor, anxiety, and insomnia, that were treated on an outpatient basis with phenobarbital or diazepam.[8,40] A more severe GHB withdrawal reaction requiring hospitalization has been identified by several investigators.[34,39,41,42] In the case report by Craig et al, high doses of benzodiazepines were required to control psychotic agitation.[41] Similarly, in a paper by McDaniels and Miotto, severe psychosis and delirium developed early in the course of GHB withdrawal, and high dose benzodiazepines were required, with limited response to antipsychotic medications.[43] Propranolol was used to treat tachycardia associated with GHB withdrawal in combination with benzodiazepines and phenothiazines in a report by Dyer and Andrews.[42] Controlled studies investigating the role of benzodiazepines, mood stabilizers, and antihypertensives in the management of GHB withdrawal are needed. Early recognition of GHB addiction and withdrawal are important due to the ease of availability and lack of public awareness of the hazards of this drug.

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