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Trends in γ -Hydroxybutyrate (GHB) and Related Drug Intoxication: 1999 to 2003

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Abstract

Study objective—To analyze changes in γ -hydroxybutyrate (GHB) case reporting, we review GHB or congener drug cases reported to the California Poison Control System, comparing these to other data sets.

Methods—We identified cases from the California Poison Control System computerized database using standardized codes and key terms for GHB and congener drugs (“gamma butyrolactone,” “1,4-butanediol,” “gamma valerolactone”). We noted California Poison Control System date, caller and exposure site, patient age and sex, reported coingestions, and outcomes. We compared California Poison Control System data to case incidence from American Association of Poison Control Centers and Drug Abuse Warning Network data and drug use prevalence from National Institute for Drug Abuse survey data.

Results—A total of 1,331 patients were included over the 5-year period (1999–2003). California Poison Control System–reported GHB exposures decreased by 76% from baseline ($n=426$) to the final study year ($n=101$). The absolute decrease was present across all case types, although there was a significant proportional decrease in routine drug abuse cases and an increase in malicious events, including GHB-facilitated sexual assault ($P=.002$). American Association of Poison Control Centers data showed a similar decrease from 2001 to 2003. Drug Abuse Warning Network incidence flattened from 2001 to 2002 and decreased sharply in 2003. National Institute for Drug Abuse survey time trends were inconsistent across age groups.

Conclusion—Based on the precipitous decrease in California Poison Control System case incidence for GHB during 5 years, the parallel trend in American Association of Poison Control Centers data, and a more recent decrease in Drug Abuse Warning Network cases, a true decrease in case incidence is likely. This could be due to decreased abuse rates or because fewer abusers seek emergency medical care. Case reporting may account for part of the decrease in the incidence of poison center contacts involving GHB.

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INTRODUCTION

Background

Since the first reports of γ -hydroxybutyrate (GHB) abuse appeared in the early 1990s, this illicit drug has manifested changing use patterns marked by differing at-risk populations, forms of administration (including substitution of chemical congener precursors and analogs), and types of associated adverse effects. GHB was initially marketed as a dietary supplement in health food stores and later was promoted on the Internet as a safe agent for use by bodybuilders. It has also been touted for treating a variety of medical disorders, including insomnia, obesity, depression, alcohol addiction, and sexual dysfunction.¹ GHB use in the general population broadened greatly as it became known as a party drug.² It also gained a reputation as a date rape drug and has been implicated in a number of criminal drug-facilitated sexual assault cases.³

Editor's Capsule Summary

What is already known on this topic

Initially marketed as a dietary supplement, γ -hydroxybutyrate (GHB) is a popular party drug. It is also available under strict controls as a US Food and Drug Administration–approved treatment for narcolepsy.

What question this study addressed

A rapid and marked decrease in the number of cases involving GHB managed by the California Poison Control System was noted. The cause of this decrease was sought by analyzing national poisoning data, as well as other sources about the use of GHB.

What this study adds to our knowledge

The incidence of GHB use as reflected by these signal detection systems suggests that the misuse and abuse of GHB may be decreasing. Although the number of cases reported by these mechanisms has decreased dramatically, the proportion of cases involving malicious intent (attempted rape) increased.

How this might change clinical practice

When GHB intoxication occurs, specifically soliciting information about malicious events may be prudent. Involvement of law enforcement and maintenance of chain of custody may be prudent.

Importance

The heterogeneous acute and chronic effects (including drug withdrawal) associated with GHB and its principal congeners, γ -butyrolactone and 1,4-butanediol, are well described in the literature.^{4,5} Fewer data are available concerning a more recently introduced GHB congener, γ -valerolactone. We noted empirically a steep decrease in GHB-related calls to the California Poison Control System. Systematically confirming this potential change is important for the purposes of emergency medical care planning and delivery. In addition, the patterns of incidence among specific subgroups of GHB users could be relevant for targeting prevention and treatment interventions (eg, GHB-dependent users presenting to the emergency department [ED] in need of drug withdrawal management).

Goals of This Investigation

Patterns of GHB abuse have not been systematically analyzed. This study of GHB and related drug cases reported to the California Poison Control System was conducted in order to test the

hypothesis that the incidence of GHB was changing over the study period. Specifically, we hypothesized that key demographic and clinical characteristics of the cases would demonstrate a systematic (nonrandom) pattern of decreasing incidence that might affect certain subgroups more than others (for example, by sex, by case severity, or by calls originating from health care centers compared to the general public). We further hypothesized that specific subsets of GHB California Poison Control System reports (such as those experiencing a GHB withdrawal syndrome or patients maliciously poisoned) would have differing characteristics potentially related to changing case incidence.

MATERIALS AND METHODS

Study Design and Setting

We retrospectively reviewed case records reported to the California Poison Control System involving suspected exposures to GHB or its congeners (precursors and analogs), principally γ -butyrolactone, 1,4-butanediol, and γ -valerolactone. Throughout this paper, the term GHB will refer to gamma hydroxybutyrate as well as these congeners, because in clinical practice it is not typically possible to identify with precision the specific compound that has been ingested. We also separately enumerated and reviewed California Poison Control System calls related to GHB classified as “information only” (no reported exposure took place). The review covered a 5-year period from January 1, 1999, through December 31, 2003. The University of California, San Francisco, Committee on Human Research approved this study.

The California Poison Control System is a 24-hour emergency telephone consultation service. All data in the case records are collected by the California Poison Control System staff in accordance with the criteria of the American Association of Poison Control Centers.⁶

Selection of Participants

GHB-related cases were identified by searching the California Poison Control System computerized database for 160 American Association of Poison Control Centers generic and product codes for known chemical, commercial, and slang names for GHB and its congeners. In addition to the numeric generic and product codes, the database contains a verbatim substance field. To capture ambiguously coded cases, we searched for all cases with substance name fields containing the words GHB or its congeners or the descriptive words “rape” or “assault.” These ambiguously coded cases were subjected to the same exclusion criteria as all other case records.

Before manual review, all duplicate records were eliminated using the poison center case record number. On initial manual review, misidentified case records were designated ineligible, for example, cases containing the 3-character sequence “ghb” appearing in unrelated words such as “neighbor.”

Cases were divided among 6 investigators for detailed review and data extraction. If there was no clear history of GHB/P involvement *and* the patient did not exhibit symptoms consistent with GHB/P intoxication, the case was reviewed by a second investigator and then excluded if this reviewer concurred.

Data Collection and Processing

Ten percent of the case records, as well as all case records coded as “unrelated” or “death” outcomes, were independently reviewed by a second investigator. For all death cases, California Poison Control System death summaries were reviewed in addition to the case record. Data were formatted for analysis using a computerized statistical package (SAS 8.02,

Cary, NC). For comparisons testing our a priori hypotheses about changing patterns of incidence with time, we used the χ^2 , χ^2 test for trend, or Fisher's exact test.

Methods of Measurement

In addition to the standard format items in the California Poison Control System case record related to demographics and case presentation, we extracted information from coded fields or narrative text relevant to GHB intoxication, especially neurologic and cardiopulmonary status (specifically, the use of mechanical ventilatory support) and any toxicologic test results. We analyzed duration of hospitalization only for the subgroup of dependent or withdrawal cases for which this information was collected most systematically.

The American Association of Poison Control Centers case report form includes a standard "Reason for Exposure" field that categorizes exposures as unintentional accidental, intentional abuse, intentional suicide, or malicious. Given their relevance to GHB, we included 3 additional mutually exclusive categories: bodybuilding, insomnia, and sexual enhancement. We also recorded manually whether the location of exposure was noted to be a motor vehicle or whether driving under the influence of GHB was noted.

We designated cases as "GHB-dependent" (including a subset of withdrawal) when clinical evidence of withdrawal was recorded (for example, cessation of GHB use followed by agitation and disorientation) or when a history was recorded of frequency of use (with or without escalation of dosing) indicative of drug tolerance or in cases with any mention of "dependence" or of the patient seeking detoxification.

We designated cases as "malicious" (including a subset of drug-facilitated sexual assault) if noted in the standard American Association of Poison Control Centers "Reason for Exposure" field or in case records that described the patient as being drugged surreptitiously, followed by effects consistent with GHB. Thus, these cases could be classified as malicious if "GHB" was found in the verbatim substance field or in the history, along with an open text field reference to surreptitious drugging, or the word "rape" or "assault" was found in the verbatim substance field, even without mention of GHB. In these latter cases, however, clinical symptoms consistent with GHB were required with no other clearly identifiable intoxication (eg, alcohol).

We analyzed data from 3 additional sources reporting on nationwide drug use. The first was composed by the reports of the American Association of Poison Control Centers for 2001, 2002, and 2003 (the American Association of Poison Control Centers did not separately identify GHB exposures before 2001).

Second, we analyzed data from the Substance Abuse and Mental Health Services Administration program, the Drug Abuse Warning Network for GHB abuse as reported by the ED component during 1999 to 2003. For 2003, Drug Abuse Warning Network ED-derived data are available only for the 6-month period from July to December because of changes in its data collection methodology that broadened case reporting eligibility. To estimate annual incidence for 2003, therefore, we multiplied these data by a factor of 2.⁷

The third source was the National Institute for Drug Abuse annual survey "Monitoring the Future." This survey tracks illicit drug use and attitudes toward drugs among eighth, 10th, and 12th graders. In addition, annual follow-up questionnaires are mailed to a sample of each graduating class for a number of years after their initial participation, providing a sample of college students and younger adults aged 19 to 28 years.⁸ Data for reported GHB use among eighth, 10th, and 12th graders was available for 2000 through 2003; for college students and other young adults, these data were limited to 2002 and 2003 only. For each year with available data, we generated weighted combined prevalence estimates for the eighth- through 12th-grade

group (3 substrata) and the college and other young adults group (2 substrata) based on the proportion of each substratum within the overall sample, as reported by National Institute for Drug Abuse.

Outcome Measures

We coded outcome according to the standard American Association of Poison Control Centers definitions.⁶ Of subjects treated in a health care facility, ED treatment after patient discharge was identified separately from patients receiving hospital admission.

RESULTS

Characteristics of Study Subjects

Table 1 summarizes case record identification, ineligible cases, and exclusions. In total, 589 cases were excluded. Of these exclusions, 484 (82%) were case records that involved no apparent exposure (information requests only; analyzed separately). In total, 1,331 exposure case records were ultimately included in the analysis of exposure-related cases (Table 1). Only 6 (0.45%) case records included were identified using an assault history and narrative descriptive alone, rather than from the substance field. Total California Poison Control System human exposure calls during the 5-year study period were 1,113,811 (mean annual incidence of $222,809 \pm 8,894$).

Main Results

There was an overall decrease of 76% in total case reporting of GHB California Poison Control System exposure cases from 1999 to 2003 (Figure). Moreover, the decrease accelerated (18%, 21%, 33%, and 45% relative to each preceding year, throughout the study period). In contrast, there was an increase in total cases reported to the California Poison Control System of 5.3% from 1999 to 2003, with a maximum year-to-year variation for total California Poison Control System case reporting $\pm 5.0\%$ between any 2 sequential years. Information calls related to GHB from the public, as well as health care facilities, also decreased during the study period, from 206 inquiries in 1999 to 24 in 2003, an 88% decrease during this period.

The Figure compares California Poison Control System to national GHB data sources. Summary reports from the American Association of Poison Control Centers for national poison center data for 2001 through 2003 demonstrate a linear decrease nationally.⁹⁻¹¹ It should be noted that California Poison Control System reports based *only* on standard coding of cause would have contributed to these American Association of Poison Control Centers totals, whereas the case-finding strategy that we used for the California Poison Control System data yielded more cases.

In contrast to both the California Poison Control System and American Association of Poison Control Centers data, GHB cases reported through Drug Abuse Warning Network ED surveillance demonstrated a more complex pattern (Figure). Drug Abuse Warning Network reporting for GHB increased 64% from 1999 to 2000, decreased 33% from 2000 to 2001, remained stable from 2001 through 2002, and then decreased steeply in 2003.⁷ The Drug Abuse Warning Network incidence is based on data extrapolated from the last 6 months of 2003. We therefore examined 2002 in 6-month increments. We found a decrease from the first 6 months of that year ($n=2134$) compared to the second half ($n=1196$), a 44% decrease in that year).

Data from the National Institute for Drug Abuse Monitoring the Future survey indicate a different trend for college students and other young adults compared to eighth to 12th graders. Among the former group (Figure), the estimated prevalence of GHB usage decreased from 760

per 100,000 to 540 per 100,000 (a 29% decrease).⁸ The prevalence of GHB use among the younger age stratum was stable.

The majority of the California Poison Control System GHB cases (55%) were men (Table 2). Although the proportion of women among cases increased from 38% in 1999 to 60% in 2003, there was no statistically significant trend in the sex mix. The mean age of subjects was 27±9 years and was stable during the study period. Based on standard American Association of Poison Control Centers definitions, the outcome of most cases (59%) was “moderate” in severity. The cases with major outcomes or deaths accounted for 11% of case records during the study period. There was no statistically significant trend with time in case severity. There were 48 case records with inadequate documentation or follow-up to determine an outcome (4% of all records).

The majority of consultations originated from health care facilities (Table 2). This proportion of such calls, however, decreased significantly year by year during the study period (χ^2 test for trend, $P<.001$).

Of the 968 cases from health care facilities, 909 (94%) originated from the ED (data not shown). Hospital admission was documented in 299 case records (22%). Overall, a total of 216 patients (16%) received documented mechanical ventilatory support by endotracheal tube. Although the majority of cases overall (844; 63%) were categorized as drug abuse-related, this proportion decreased significantly with time, with a concomitant proportional increase (not in absolute numbers) among “malicious” events (χ^2 test for trend, $P=.002$).

Polysubstance use was common. Self-reported ethanol coingestion was noted among 280 (21%) of all subjects. Ethanol involvement was confirmed by laboratory testing in only 14 cases. Other coingestants confirmed by laboratory testing were documented among 152 (11.4%) cases, most commonly methylene dioxymethamphetamine (“ecstasy”) (n=44), other amphetamines (n=37), cocaine (n=19), marijuana (n=18), and benzodiazepines (n=15). We identified 39 reports of GHB use either in persons driving under the influence or found in a car while intoxicated by GHB. Ten case records reported laboratory testing for GHB. Of these, 2 cases had pending levels at last follow-up, and 2 had negative blood/urine test results. Six cases reported positive laboratory values for GHB, of which 2 were fatalities (detailed below) and 4 were overdoses. The 4 overdose cases met criteria for moderate or major outcomes. The reported urine levels ranged from 98.4 to 1340 $\mu\text{g/mL}$, the serum levels ranged from 58.1 to 118 $\mu\text{g/mL}$ and 1 plasma level of 92.6 $\mu\text{g/mL}$.

Of the 262 cases characterized as malicious intent, 49 (19%) reported sexual assault. The majority (87%) were female cases. Ages ranged from 12 to 58 years (mean 26±SD 8). Self-reported ethanol coingestion was noted in 113 (43%) of the malicious cases, and 126 (47%) incidents were reported to have occurred at an entertainment venue (eg, bar, club, or party). In only 72 cases (27%) was the contact with the California Poison Control System made within 12 hours of exposure, a time during which GHB could reasonably be detected for forensic purposes. Memory impairment was reported in 102 (38%) cases of malicious intent compared with 148 (11%) of all other subjects.

Of 167 cases of GHB dependence, 11 people reported GHB use for bodybuilding purposes; among all the nondependent cases, only 19 people used GHB for bodybuilding. Similarly, 10 people of the dependence cases reported using GHB for insomnia compared with only 16 of all others. Only 2 case records (none with physical dependence) specifically mentioned the use of GHB for sexual enhancement. Among the 167 patients with dependence, 135 (81%) patients had a clinical presentation consistent with drug withdrawal, and 80 (48%) patients were admitted to a hospital overnight or longer compared to all others ($P<.01$). The median hospital stay among this group was 3 days, with 27 of 80 (34%) patients admitted for 5 days or longer.

Four deaths were reported. One death was of a GBL-dependent 52-year-old man. To self-treat withdrawal symptoms, the patient drank “very large” amounts of water for 4 days. A witnessed seizure occurred 4 days after his last GBL dose. The patient became unresponsive, with a serum sodium level of 107 mEq/L, and died despite sodium replacement and aggressive supportive care. The second fatal case was of a 29-year-old man found dead after polysubstance use, including mirtazapine, risperidone, ketamine, and GHB. The postmortem GHB level in serum was 72 $\mu\text{g/mL}$ and 30 $\mu\text{g/mL}$ in urine. The third death was of a 20-year-old man found in a river. Postmortem levels included an ethanol level of 420 mg/dL and GHB tissue level of 130 $\mu\text{g/g}$ of tissue (tissue sampling sites were not specified by the autopsy report). The fourth case was of an 18-year-old woman who drank a salty liquid presumed to be GHB. She was later found unresponsive, with evidence of aspiration, and was asystolic and apneic on arrival of the paramedics. The patient died as a result of anoxic brain injury. GHB toxicology screening was not performed. Urine toxicology testing results were negative, except for a serum ethanol level of 10 mg/dL.

LIMITATIONS

The majority of cases lacked laboratory confirmation of GHB. GHB analysis is not routinely available at hospitals. Exogenous GHB administration undergoes rapid elimination, resulting in levels that cannot be differentiated from “background” blood and urine levels within 6 to 12 hours, respectively, severely limiting analysis in delayed presentation. Because of limitations in toxicologic confirmation, the cases tallied in this study may underestimate the true case incidence. The lag time before the American Association of Poison Control Centers introduced the standard identification codes for GHB and its congeners is a further potential source of underidentification of cases. The retrospective study design is another potential weakness, primarily because of incomplete documentation in some case records. Perhaps most important, poison center data collection is a passive surveillance source affected by reporting biases by both physicians and the general public.

DISCUSSION

We observed a precipitous decrease in GHB exposures reported to the California Poison Control System for 1999 through 2003, which parallels decreasing GHB exposures reported nationally through the American Association of Poison Control Centers during 2001 to 2003 and is consistent with the overall trend in Drug Abuse Warning Network data in 2002 to 2003, although not from earlier years. In contrast, National Institute for Drug Abuse survey data on GHB use among high school students did not indicate a temporal decrease during the same period, although reported use among college students and young adults did decrease in 2003 compared with 2002.

There could be multiple explanations for the apparent decrease in incidence evident in GHB poison center case reports. First, this may indeed reflect the true incidence in GHB toxicity and underlying abuse. Second, the decrease in events may reflect a decreased frequency of adverse events without a decrease in overall GHB usage. Finally, the apparent decrease could be spurious or due to random variability.

Considering the findings of all 3 case incidence surveillance systems (California Poison Control System, American Association of Poison Control Centers, and Drug Abuse Warning Network), the observed decrease in GHB-related reporting to the California Poison Control System is likely to represent a true decrease in adverse GHB-related events in patients presenting for ED care. Increased familiarity of ED staff with GHB overdoses may result in fewer consultations with poison centers and therefore explain a differential decrease comparing poison center to Drug Abuse Warning Network data (the latter directly samples ED records

without a physician reporting step). The observation that malicious event reporting decreased less sharply (proportionally increasing with time) may further support the presumption that although health care practitioners and even the lay public are more familiar with GHB adverse effects and thus may be less likely to report misadventures, they still contact a poison center for consultation in certain exposure situations.

In response to the growing abuse and danger of GHB, the Controlled Substances Act was amended in 2000 to add GHB. Illicit GHB is a Schedule I agent.¹² Nonetheless, in 2002 the US Food and Drug Administration approved GHB (Xyrem, Orphan Medical, Minnetonka, MN) as a Schedule III agent for the treatment of cataplexy, thus making it available by prescription. γ -Butyrolactone is a List 1 controlled “chemical” and not treated as a drug itself. List 1 chemicals are defined as “important to the manufacture of a controlled substance.” Thus, based on these 2 drug and chemical restrictions, with the exception of physicianprescribed Xyrem, it is now illegal to possess, manufacture, or sell GHB, gammabutyrolactone (GBL), gammavalerolactone (GVL), or 1,4 butendiol (BD) when the intent is for ingestion. These changes have limited substantially the availability of GHB. These restrictions may have had a chilling effect on the willingness of people to call the California Poison Control System to report use of an illegal substance through fear of possible legal sanction, lowering reporting but not actual numbers of adverse events. The use of GHB congeners may also be an explanation for the decreasing incidence of California Poison Control System reports. GHB restrictions, as described above, have a significant loophole that allows for the legal sale of GHB congeners as long as the use is “*not* intended for ingestion.” There are still Internet Web sites marketing GHB congeners masked as cleaning chemicals and other products. There is also anecdotal evidence that the GHB congener γ -valerolactone may have less potency than GHB, resulting in lower incidence of adverse events.¹³⁻¹⁵ Thus, changing patterns in congener use could alter adverse event frequencies, even with the relatively stable prevalence of use observed in the National Institute for Drug Abuse survey.

Finally, patterns of illicit drug use for many substances are inherently variable with time, driven in part by a seemingly endless search by individuals for an altered state of consciousness. Sedative hypnotics were popular in the 1940s and 1950s, LSD was in vogue in the 1960s, cocaine seemed dominant in the 1980s,¹⁶ and the attractiveness of amphetamines in the 20th century has continued unabated as we enter the 21st century. Ultimately, the increase and decrease of GHB throughout the last decade may merely reflect the same pattern.

We identified a precipitous decrease in GHB-related calls to the California Poison Control System and decreases in national poison center and Drug Abuse Warning Network reporting as well. There was no time trend in the California Poison Control System case severity mix. Overall, the death cases were infrequent and were the result of out-of-hospital events. Although it is likely that true incidence has indeed decreased, surveillance estimates using multiple data sources should be used to confirm this trend and to link these observations to survey data on drug use patterns.

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Figure.

A comparison of total GHB and related congener Exposure and Drug Information cases reported to the California Poison Control System (1999-2003), the American Association of Poison Control Centers (2001-2003), the Drug Abuse Warning Network (DAWN; 1999-2003), and the National Institute for Drug Abuse Monitoring the Future Survey (2000-2003).

Table 1

California Poison Control System case record identification: GHB and related drug cases, 1999 to 2003.

Case Record by Type	N
Total exposure case records found during initial search	4,062
Ineligible cases	
Duplicate case records eliminated by case record number	1,097
Non-GHB case records eliminated during manual review	1,045
Total ineligible cases	2,142
Excluded cases	
Information calls only (no actual exposure occurred)*	484
Duplicate case records eliminated during manual review	14
Ocular exposure only (no systemic contact)	7
Dermal exposure only (no systemic contact)	1
Outcome unrelated to GHB	75
Sexual assault cases without GHB mentioned or symptoms	8
Total excluded cases	589
Total excluded and ineligible case records	2,731
Total eligible exposure case records*	1,331

* The 484 information-only calls were analyzed separately.

GHB and congener cases reported to the California Poison Control System, 1999 to 2003.

Table 2

Case Characteristic	Total Cases by Study Year					
	All Years N=1331 (%)	1999 n=426 (%)	2000 n=346 (%)	2001 n=276 (%)	2002 n=182 (%)	2003 n=101 (%)
Female, No.	595 (45)	161 (38)	156 (45)	136 (49)	81 (45)	61 (60)
Age, mean±SD	27 ± 9.0	26 ± 8.4	27 ± 9.3	26 ± 8.5	28 ± 9.1	26 ± 7.8
Outcome, No.						
No/minimal	348 (26)	93 (22)	103 (30)	71 (26)	47 (26)	34 (34)
Moderate	790 (59)	281 (66)	205 (59)	151 (55)	98 (54)	55 (54)
Major/death	145 (11)	46 (11)	21 (6)	39 (14)	31 (17)	8 (8)
Unknown	48 (4)	6 (1)	17 (5)	15 (5)	6 (3)	4 (4)
Caller site, No. *						
Health care facility	968 (73)	330 (78)	260 (75)	206 (75)	119 (66)	53 (53)
Home or other site	363 (27)	96 (22)	86 (25)	70 (25)	63 (34)	48 (47)
Case type, No. †						
Abuse	844 (63)	301 (71)	222 (64)	172 (62)	105 (28)	44 (44)
Malicious	262 (20)	60 (14)	56 (16)	61 (22)	43 (24)	42 (42)
Sexual assault	49 (4)	14 (4)	14 (4)	5 (2)	8 (8)	8 (8)
Dependence	167 (13)	50 (12)	53 (15)	27 (10)	27 (15)	10 (10)
Withdrawal	135 (10)	43 (10)	41 (12)	20 (7)	22 (12)	9 (9)
All others	58 (4)	15 (4)	15 (4)	16 (6)	7 (4)	5 (5)

* Caller site by location (health care facility vs home or other site), χ^2 test for trend $P<.001$. Sex was missing for 12 subjects; age was missing for 56 subjects. GHB information-only calls not included in the table: 1999, 206; 2000, 137; 2001, 53; 2002, 64; 2003, 24.

† Major case type by year (abuse, malicious, dependence, all other), χ^2 test for trend $P=.002$.