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Review

Case series of 226 γ-hydroxybutyrate–associated deaths: lethal toxicity and trauma☆

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Abstract γ-Hydroxybutyrate (GHB) and its prodrugs are drugs of abuse that were also sold as "dietary supplements." Users present to emergency departments with overdose, impaired driving, withdrawal, and associated trauma. We compiled a series of GHB-associated deaths to elucidate lethal risks, GHB concentrations, cointoxicants, products, uses, and medical interventions. Death records were reviewed for toxicology, autopsy findings, and history. Inclusion cutoffs were as follows: 5/10 mg/L of GHB (antemortem blood/urine) and 50/20/7 mg/L of GHB (postmortem blood/urine/vitreous). Of 226 deaths included, 213 had cardiorespiratory arrest and 13 had fatal accidents. Seventy-eight deaths (35%) had no cointoxicants. Sixteen deaths involved "supplements" and 1 involved pharmaceutical GHB (Xyrem, Jazz Pharmaceuticals, Palo Alto, CA). Postmortem blood GHB was 18 to 4400 mg/L (median, 347 mg/L) in deaths negative for cointoxicants. Cardiorespiratory arrest occurred prehospital in 100% of 184 cases with available history. Of 72 cases with antemortem adverse effects reported, medical assistance was delayed or absent in 66; of these, acute GHB ingestion was known in 51, including 40 left to "sleep off" adverse effects. Thirty others were left "sleeping" and found dead. γ-Hydroxybutyrate is lethal even without cointoxicants, directly and through fatal accidents. Medical interventions were frequently delayed or absent despite known GHB ingestion, and witnessed adverse events and cardiorespiratory arrest occurred prehospital. Education is needed about the lethality of GHB and the necessity for prompt medical intervention.

1. Introduction

γ-Hydroxybutyrate (GHB) and its prodrugs, γ-butyrolactone (GBL) and 1,4-butanediol (BD), are drugs of abuse that were previously sold as "dietary supplements" for diverse purported health benefits [1,2]. γ-Hydroxybutyrate is also available in pharmaceutical form (Xyrem, Food and

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Drug Administration-approved for treatment of narcolepsy with cataplexy or excessive daytime sleepiness). Patients with GHB intoxication present to emergency departments (EDs) after intentional ingestion of supplements, illicit supplies, and Xyrem for recreational and therapeutic purposes and also after surreptitious dosing [1-3]. Accidental ingestions have been reported among children ingesting illicit supplies [4], GBL-containing solvents [5,6], and BD-coated toy beads [7]. Recreational and therapeutic users may also present to EDs with trauma from motor vehicle collisions (MVCs) and falls experienced while GHB-intoxicated [2,8,9]. GHB-dependent users, who dose multiple times daily, present to EDs repeatedly with acute intoxication, related trauma, impaired driving, and/or GHB withdrawal, any of which may be associated with death [2,10-15]. Furthermore, despite its lethal potential, GHB and its prodrugs have been promoted as "safe" and "nontoxic," particularly when taken without other drugs or alcohol. Web sites, product labels (see Fig. 1), and pamphlets instructed users to "sleep it off" in case of overdose with GHB as the sole intoxicant and explicitly advised against calling 911 [2,16,17]. (Note: Unless otherwise noted, we use the term "GHB" to include GHB, GBL, and BD).

Awareness of lethal risks of GHB is important for emergency physicians, who are uniquely placed to monitor and intervene in cases of acute GHB toxicity, related trauma, impaired driving, and withdrawal. However, although the lethality of other drugs of abuse has been documented in extensive case series [18-20], to date, there has been no detailed analysis of GHB lethality. The absence of systematic data on GHB mortality; the lack of routine hospital and forensic toxicologic testing for GHB; the absence of international disease classification coding for GHB as a cause of death (COD); and the lack of standardization in investigation, recording, and certification of drug-related deaths between and within jurisdictions [21] precludes epidemiologic assessments of GHB mortality. Discussion has, to date, been limited to isolated case reports and small series, most often involving cointoxicants, and focused on deaths due directly to acute toxicity.

Our aim was to compile a large, descriptive series of GHB-associated fatalities to elucidate the range of lethal risks of GHB and GHB concentrations, with and without cointoxicants, among deaths resulting indirectly through associated accidents as well as directly from acute intoxication. A secondary objective was to determine GHB use history, product types ("supplements," "solvents," pharmaceutical GHB), past medical encounters, and medical interventions before death, to identify areas for future research and targeting of patient education and interventions for injury prevention.

2. Methods

This study is a retrospective review of death records and was determined exempt from human subjects review. We compiled a convenience sample using several methods. We made written and telephone inquiries to medical examiners/coroners (ME/Cs) (n = 157) in all 50 US states and the District of Columbia to request autopsy, toxicology, and investigative reports for GHB-associated deaths from 1995 to 2005. In states with centralized death investigation reporting systems, we contacted chief MEs. In states lacking centralized systems, we targeted ME/Cs in 2 or more major cities with venues likely for use of GHB and other "club drugs" (night clubs, "raves," and others) and in jurisdictions where deaths had been reported. We also contacted 2 state health departments, 2 state toxicology laboratories, 6 law

Fig. 1 Front and back labels of "Zen," a "dietary supplement" containing BD. Label text reads as follows: Warnings!! Because of the potential deep sleeping effects of this product it should be used *ONLY* as a nighttime formula *WITHIN THE SAFETY OF YOUR HOME*. Advise those around you that you may be unarousable and that this is a *NORMAL* result of using ZEN. Excessive doses may result in sweating, muscle spasms, vomiting, bedwetting, and diarrhea. Unless drugs or alcohol have been taken with ZEN, the only treatment necessary is to *SLEEP IT OFF*! A call for help may result in uninformed emergency medical personnel using expensive, unnecessary, and potentially dangerous methods of arousal.

enforcement offices, 5 United Kingdom toxicologists, and coroners in 2 Canadian provinces to identify additional cases. Lastly, we systematically investigated media reports and GHB-associated fatalities reported to www.ProjectGHB.org (an informational Web site) for verification and inclusion.

Inclusion criteria were voluntary collaboration of ME/Cs and toxicologic confirmation using gas chromatography/mass spectrometry (GC/MS) of GHB above cutoffs in one or more samples. γ-Hydroxybutyrate occurs endogenously antemortem at trace concentrations and may increase due to postmortem production and sample storage conditions. Although high endogenous concentrations have been documented [22,23], most postmortem blood samples in these and other studies are less than 50 mg/L [24-27]. Endogenous GHB in vitreous [25], postmortem urine [24], and antemortem blood and urine [28,29] have been documented at significantly lower concentrations than that of postmortem blood GHB. Accordingly, we used the following cutoffs: 5/10 mg/L or greater for antemortem blood/urine and 50/20/7 mg/L or greater for postmortem blood/urine/vitreous GHB. 1,4-Butanediol has also been documented endogenously at trace concentrations in human brain tissue [30]; the inclusion cutoff for postmortem blood BD was 1 mg/L or greater.

We reviewed death records and historical data for toxicology, pathology, medical history, history of GHB use, death investigation classification of and rationale for COD, and manner and circumstances of death including medical interventions. Cases were considered positive for cointoxicants if a parent drug or active metabolite was quantified in blood using standard blood toxicology analysis used within jurisdictional ME/C protocols. Based on review of death investigation reports, cases ruling in with qualifying exogenous concentrations were classified using previously defined categories [19] as follows: "drug-caused deaths" were those in which direct toxic effects of GHB caused or contributed to the death. "Drug-related deaths" were cases in which GHB intoxication was associated with accidents that directly caused death. "Indeterminate deaths" were cases with GHB detected above inclusion cutoffs, but its role in COD was unclear. Classification was made based upon GHB concentrations and death investigation classifications and rationale for COD; several cases in which study determinations vary from ME/C designations are discussed in Results.

Excel (Microsoft, Redmond WA) spreadsheets were used for data entry and analysis using descriptive statistics.

3. Results

A total of 288 cases were reviewed. Sixty-two cases were excluded, including 51 deaths with postmortem GHB concentrations below inclusion cutoffs and no reported history of acute GHB ingestion; 5 below exogenous cutoffs but with a history of GHB abuse (trace, 7, 12, 14, 49 mg/L); 4 with histories of acute GHB ingestion but lacking GHB quantitation (2 untested, 2 positive for GHB); and 2 with extended postmortem intervals.

Two hundred twenty-six deaths with GHB concentrations above inclusion cutoffs were included (Table 1). Primary data obtained for 18 deaths that have previously been briefly reported in abstracts, conference proceedings, and case reports [2,25,31-37] were included to enable detailed analyses of additional pathologic, toxicologic, and historic findings.

3.1. Drug-caused deaths

Two hundred seven deaths were classified as drug caused, with GHB determined causal or contributory to death (Fig. 2). Of these, 193 death reports specifically noted GHB toxicity in COD classification/rationale or disease diagnoses and 7 attributed COD more generally (ie, polypharmacy; polydrug overdose; multidrug toxicity) but specified concentrations of GHB and other drugs in toxicology findings. Seven cases had ME/C attributions of

Table 1 Case identification and demographic information

Total deaths included	226
ME/Cs	94
Case data	
Toxicology	226 (100%)
Autopsy report	202 (89%)
External examination only	2 (1%)
Case history [a]	193 (85%)
US/Canada/UK cases	209 US (36 states)/4 Canada (Quebec)/13 UK
US cases by state	Fla, 52; Calif, 36; Tex, 14; Ga, 14; NC, 14; Ill, 8; Mich, 7; Ohio, 6; Ala, 6; Nev, 6; Ind, 4; NJ, 4; Utah, 4; Minn, 3; Tenn, 3; Va, 3; Kent, 2; La, 2; NY, 2; Okla, 2; Pa, 2; Alaska, 1; Colo, 1; Conn, 1; Wash, DC, 1; Hawaii 1; Mass, 1; Md, 1; Mo, 1; Neb, 1; NH, 1; NM, 1; SC, 1; SD, 1; Wash, 1; Wis, 1
Deaths by year	1995—4; 1996—7; 1997—4; 1998—12; 1999—34; 2000—37; 2001—53; 2002—41; 2003—7; 2004—19; 2005—8
Sex	155 male (69%), 71 female (31%)
Age	Range, 15-53 y; mean, 28 ± 7.7 y (SD); median, 27 y
Race	199 white (88%), 5 Hispanic (2%), 4 African American (1.5%), 3 other (1%), 15 unknown (6.5%)
Manner of death	Accidental (156), unknown or unspecified (61), suicide (7, one with a suicide note), natural (2)

[a] Nature and detail of case histories varied dramatically, due to nonstandardization of investigative and reporting protocols.

COD to other drugs or pathologic causes (ie, aspiration of vomitus, valvular heart disease, and others). However, review of these 7 cases revealed factors supportive of exogenous source and contributory effects of GHB: 1 had a history of acute ingestion and nightly use of Xyrem (postmortem [PM] blood level, 141 mg/L); 1 had a history of GHB use and multiple blackouts (PM blood level, 220 mg/L); 1 had a history of acute GHB ingestion, observed adverse effects, and multiple exogenous levels (antemortem [AM] blood level, 730 mg/L; PM blood level, 612 mg/L); 1 had multiple exogenous levels (PM blood level, 166 mg/L; vitreous, 112 mg/L; urine, 26 mg/L); and 3 had high GHB concentrations, unlikely to be endogenous (AM urine, 17 mg/L; PM blood level, 540 mg/L; PM blood, 696 mg/L).

Blood toxicology identified no cointoxicants in 71 deaths (34%), detected depressant cointoxicant(s) in 76 (37%), stimulant cointoxicant(s) in 23 (11%), and both depressant and stimulant cointoxicant(s) in 34 (16.5%); blood toxicology for cointoxicants was unknown in 3 cases (1.5%). Alcohol (n = 84; 41%) and MDMA (n = 22; 11%) were the most common cointoxicants. Blood GHB concentrations documented in 187 cases are listed in Table 2; GHB concentrations documented in other biologic specimens for the remaining 20 deaths will be discussed elsewhere.

Historical data were available in 193 cases; however, due to variable death investigation reporting, case history detail varied greatly. All historical findings reported in this and the following paragraphs must, therefore, be interpreted as minimum estimates.

Documented circumstances just before death included recreational drug use in bars/clubs/homes (n = 114), bodybuilding/workout sessions (n = 2), and use for sleep (n = 6). Accidental ingestions were reported in 4 individuals who mistook GHB for water and suspected in 7 others with circumstances suspicious for surreptitious dosing (6 in recreational contexts). Suicide was recorded as manner of death in 7 cases; only 1 documented a suicide note.

Specific compounds and products used before death were most often unknown or unreported. However, 16 deaths documented specific GBL and BD "supplements" and "cleaners," and 2 others reported unspecified "supplements" (Fig. 2). Xyrem was documented in one death.

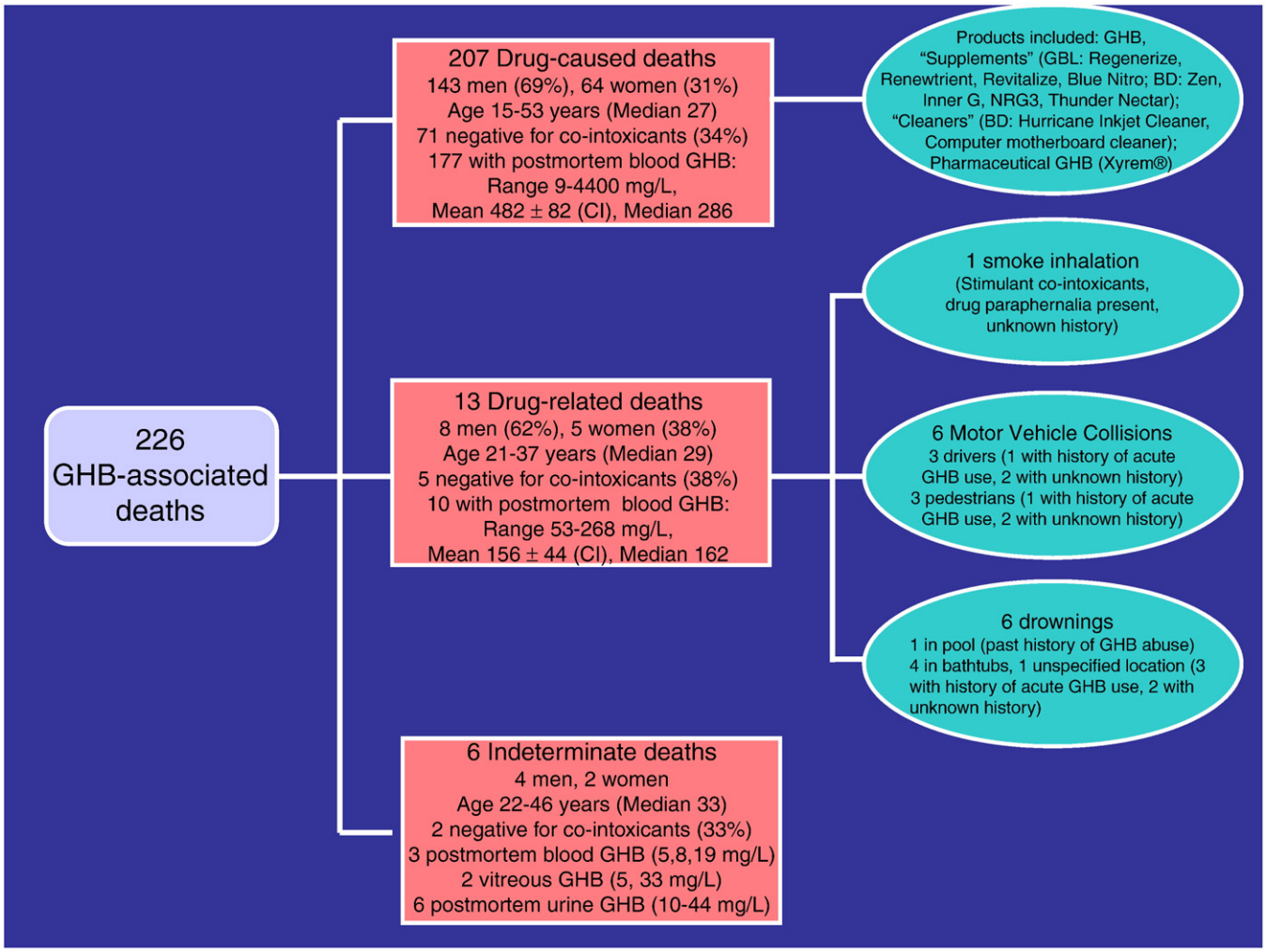

Fig. 2 226 GHB-associated fatalities: drug-caused deaths, drug-related deaths, and indeterminate deaths.

Eight decedents had reportedly presented to EDs before the date of death a combined total of 12 or more times with overdose (6 GHB/6 drugs unspecified). Two others had previously presented to EDs in GHB withdrawal and one had presented for impaired driving. Six decedents were identified as GHB dependent (history of treatment of GHB dependence and/or withdrawal reported), another 6 as regular users with multiple adverse events (medical and/or law enforcement encounters) reported, and another 4 as regular users for bodybuilding or sleep, with no prior adverse events reported.

Of 184 deaths with available history regarding medical interventions, 100% arrested prehospital. These included 174 deaths pronounced at the scene or in the ED after limited resuscitative efforts. Ten deaths occurred subsequent to life support, which ranged from 7 hours on a ventilator in the intensive care unit to 3.5 years comatose in a nursing home.

Of 102 cases with known symptoms before death, 30 were victims left "sleeping" or "snoring" by witnesses and later found in arrest or dead. Seventy-two others had witnessed adverse effects (agitation, vomiting, seizures, loss of consciousness); for 66 of these, activation of emergency medical services (EMS) was delayed until the victim was found in arrest or dead. Acute GHB ingestion was reportedly known to witnesses of short-term effects in 72 cases, of which 51 had witnessed adverse effects and another 21 were "sleeping"; all 72 were reportedly unaided.

3.2. Drug-related deaths

Thirteen deaths were classified as drug related, with death resulting from fatal accidents (Fig. 2). These included 6 MVCs (3 drivers/3 pedestrians), 6 drownings, and 1 death due to smoke inhalation/thermal injury. Five (38%) were negative for cointoxicants. Available historical data documented 4 deaths after recreational drug use. One deceased driver had a history of "supplement" use and a previous stop for erratic driving, with negative toxicology. One drowning victim was a long-term GHB abuser with a history of ED presentations with overdose and multiple near-drowning episodes.

3.3. Indeterminate deaths

Six deaths were classified as indeterminate (Fig. 2). Victims were found dead, with limited history and, although GHB concentrations exceeded inclusion cutoffs, its role was unclear.

4. Discussion

4.1. Background

γ-Hydroxybutyrate is a short-chain fatty acid that occurs naturally as a metabolite and precursor of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter. γ-Hydroxybutyrate interacts with GHB-specific receptors and GABA B receptors; high doses may exert additional GABA-like effects through conversion to GABA. γ-Hydroxybutyrate also affects dopamine, opioid, serotonin, acetylcholine, and glutamate neurotransmitter systems [38]. Initial use as an anesthetic declined due to inadequate analgesia, emergence delirium, and seizure-like effects. However, popular use by

Table 2 Blood GHB levels in 187 drug-caused deaths

Categories	Antemortem blood GHB level (mg/L)				Postmortem blood GHB level [a] (mg/L)			
	n	Range	Mean (±CI)	Med	n	Range	Mean (±CI)	Med
GHB with no cointoxicants	2	510-1300	NA	NA	64	18 [b]-4400	544 (±161)	347
GHB with one or more depressant cointoxicants [c]	5	15 [b]-700	349 (±245)	230	62	9 [b]-2300	404 (±112)	240
GHB with one or more stimulant cointoxicants [c]	2	190, 444	NA	NA	20	23 [b]-2900	525 (±277)	279
GHB with one or more stimulant and depressant cointoxicant	1	730	NA	NA	29	67-1680	451 (±167)	230
Unknown cointoxicants; blood levels unquantified	0	NA	NA	NA	2	270, 1575	NA	NA
Total	10	15-1300	492 (±228)	477	177	9-4400	482 (±82)	286

Med indicates median; CI, confidence interval; NA, not applicable.

[a] In cases with multiple postmortem blood samples, one sample was used for analysis, selected in the following order of preference, to minimize effect of postmortem redistribution: femoral, iliac, subclavian, unspecified site, or central.

[b] Cases with postmortem blood GHB levels less than 50 mg/L have elevated levels in one or more additional matrices (postmortem urine, gastric, vitreous, and/or brain GHB, postmortem blood BD).

[c] Depressants include (in order of frequency): ethanol, diazepam, morphine, alprazolam, ketamine, hydrocodone, oxycodone, diphenhydramine, methadone, trazodone, meperidine, temazepam, zolpidem, fentanyl, phenobarbitol, chlordiazepoxide, cyclobenzaprine, propoxyphene, carisoprodol, meprobamate, amitriptyline, mirtazepine, paroxetine, phencyclidine, and dextromethorphan.

[d] Stimulants include (in order of frequency): MDMA, cocaine, methamphetamine, amphetamine, pseudoephedrine, methylphenidate, methylphenidate, and phentermine.

bodybuilders in the late 1980s for purported anabolic effects and sleep was followed by recreational abuse for euphoric, relaxant, stimulant, and sexual effects [1]. Abuse extended to GBL and BD, 2 common industrial chemicals, which, when ingested, are rapidly metabolized to GHB, exerting the same clinical effects. γ-Hydroxybutyrate, GBL, and BD were marketed as "dietary supplements" for sleep benefits, weight loss, antiaging, antidepressant, and anxiolytic effects (Fig. 1, "Zen") [1,2]. Reports of adverse events resulted in regulation and shifts from sale of "supplements" to "all-natural solvents" and "nontoxic cleaners" in efforts to escape detection [2]. Multiple formulations remain available, including home-synthesized GHB, Xyrem, GBL and BD "solvents" and "cleaners," and industrial GBL and BD.

γ-Hydroxybutyrate is rapidly absorbed and metabolized. Pharmacokinetics are nonlinear and dose-dependent, with capacity-limited absorption and elimination [39]. Onset of effects is typically within 10 to 20 minutes and is often abrupt. Peak plasma concentrations have been documented 30 to 90 minutes postingestion; presence of food in the stomach has been shown to significantly decrease mean peak plasma concentration and increase median time to peak concentration. Mean elimination half-life is 30 to 50 minutes and is dose dependent [40-43]. Effects may be biphasic, with initial stimulant-like effects followed by sedation as blood concentrations rise [43]. Clinical effects include somnolence, confusion, anterograde amnesia, agitation, combativeness, vomiting, myoclonus, bradycardia, respiratory depression, coma, and death [1,2,13,44]. Risk of adverse events may be heightened by the variability, and therefore, unpredictability, of clinical effects and steep dose-response curve of GHB, resulting to a narrow therapeutic index [1,41,45-48]. Although recreational doses are estimated at approximately 2 to 3 g (28-43 mg/kg in a 70-kg person), confusion, sedation, and dizziness have been shown to result from oral doses as low as 25 mg/kg [45]. Oral doses of 50 to 63 mg/kg resulted in loss of consciousness and profound coma [47]. Respiratory depression has been documented at low oral doses in clinical studies and Xyrem trials [8,41,49]. Chronic use results in tolerance and physical dependence, typically involving multiple daily doses that escalate in size and/or frequency to achieve desired effects or to control rapid onset of withdrawal symptoms [14].

Literature suggests that the steep dose response, variable effects, and abuse liability of GHB may result in substantial morbidity and mortality [46,50-52]. Calculations of safety ratios based on estimated lethal dose and customary recreational dose rate GHB as more physiologically toxic than ketamine, MDMA, and flunitrazepam [53].

Systematic data on use prevalence are lacking. Monitoring indicates a decline from a peak of 4969 GHB-related ED mentions in the United States in 2000 [54], but 2007 Poison Center data reveal that use persists, with a 7% increase in case mentions over 2006 data and an increase of more than 400% of exposures in children younger than 6 years [55,56]. Data from the 2008 "Monitoring the Future" survey indicate low levels of annual use among 8th, 10th, and 12th graders surveyed but documents that, despite earlier periods of decline, use levels have stabilized or increased [57]. Furthermore, reports of abuse have continued in Europe [12,58,59] and Australia [60], primarily among club, rave, and partygoers. Reports of GHB addiction and withdrawal have also continued abroad, with cases documented in Canada [61], Britain [62], Ireland [63], and Switzerland [12]. ProjectGHB, an informational Web site, reports continuing cases of abuse and requests for help with GHB addiction in the United States, Europe, and Australia [64]. The number of GHB-impaired drivers documented in Sweden has increased yearly since 2002, with a 63% increase in 2006 over 2005 [59]. Finally, recent data suggest increased use of GBL, accessible through legitimate and illicit suppliers of industrial chemicals [51,65].

Systematic data on GHB mortality are also lacking. Variable familiarity of ME/Cs with GHB as a lethal drug, the lack of routine hospital or ME/C toxicologic testing for GHB, costly GC/MS analysis necessary for detection, the absence of GHB as a code for COD in international disease classifications, and variable death investigation procedures and recording between and within jurisdictions preclude epidemiologic assessments of GHB mortality. Furthermore, endogenous postmortem production of GHB complicates interpretations of postmortem concentrations, particularly in cases lacking detailed histories. The largest case series of GHB-associated fatalities to date documents 10 deaths in Australia and New Zealand [66]. The GHB-associated fatalities reported in western Sweden in 2004 (n = 7) roughly equaled deaths associated with heroin (n = 6) and cocaine (n = 6) and included first-time and experienced users [52]. Thirty-three GHB-associated deaths were reported in Sweden, but data beyond postmortem GHB concentrations are lacking [59]. Similarly, case data on 47 deaths with GHB implicated or detected postmortem in the United Kingdom from 1993 to 2005 are limited to GHB concentrations, cointoxicants, and COD [67]. We present the first extensive case series of deaths associated with GHB taken singly or with cointoxicants and discuss key findings.

4.2. Drug-caused deaths

4.2.1. Clinical effects

Although the exact mechanism of GHB lethality in humans cannot be determined with certainty, respiratory depression documented in clinical studies [41,49] and trials [8], as well as use of GHB as an anesthetic, support respiratory depression/arrest as the most likely mechanism. Cardiac arrhythmias have been rarely reported in cases of GHB toxicity [68], so primary cardiac arrest, although unlikely, cannot be definitively excluded. Aspiration or asphyxiation (included in cause-of-death in only 7 deaths in our series) may be contributory.

Our series demonstrates that, despite Internet and product label portrayals as safe when ingested singly, GHB may be

lethal even without cointoxicants; blood toxicology was negative for cointoxicants in 34% of drug-caused deaths, in which GHB was determined to be causal or contributory to death. Blood samples were typically screened (drugs of abuse screens, autopsy panels, and others) and quantitated using GC and/or GC/MS and frequently augmented with urine toxicology screens and/or confirmatory testing of other biologic samples such as liver, gastric contents, brain, and others, as has been described for postmortem toxicology investigations [69]. Toxicologic analysis was performed according to jurisdictional ME/C death investigation protocols and likely fairly represents the true proportion of deaths with and without cointoxicants. Our series also supports extensive polydrug use previously documented among GHB-intoxicated patients [12,58,70]. Hospitalization of GHB users has previously found an association with alcohol ingestion [71]; 41% of fatalities in our series had alcohol as a cointoxicant. These findings point to the need for educational interventions with users regarding the lethal risks of GHB with and without cointoxicants.

The range of postmortem blood GHB concentrations in 63 deaths without cointoxicants (18-4400 mg/L; mean, 544 mg/L; median, 347 mg/L) encompasses blood GHB concentrations previously reported for postmortem endogenous production, pharmacokinetic studies, Xyrem clinical studies, anesthesia research, nonfatal GHB toxicity, and GHB-associated fatalities (Table 3). Interpretation of postmortem concentrations is complicated by diverse variables, including time from ingestion to death, potential postmortem production and redistribution, postmortem interval to sample collection and testing, and means of sample storage and analysis. However, this widely disparate range of postmortem blood GHB concentrations raises several important points for clinicians. First, the variability of clinical effects of GHB noted earlier extends to lethality, and as with other drugs [18,19], there is no clearly definable "lethal" concentration. This variability underscores the need for education regarding the importance of prompt medical assistance in overdose. Second, therapeutic use may present risk, especially with cointoxicants. Our series contains one death that occurred subsequent to use of Xyrem as treatment of cataplexy; this and 3 other Xyrem-associated fatalities are reported in detail elsewhere [82,83]. Clinical study of Xyrem documented a mean peak serum GHB concentration of 142 mg/L after administration of two 4.5-g doses [74]. Postmortem blood GHB in the death in our series was 141 mg/L, with stimulant and depressant coingestants also detected. Two other Xyrem-associated deaths document postmortem GHB concentrations consistent with therapeutic concentrations (165.6 mg/L [83] and 110 mg/L [82]); both also occurred with cointoxicants. Furthermore, one death also documented postmortem urine GHB at a concentration consistent with therapeutic dosing (90.7 mg/L) [83]. Decedents also had conditions that could compromise respiratory function (sleep apnea [82,83], obesity [82], sarcoidosis [83]). Xyrem informational materials specifically warn against use with sedative hypnotics and urge caution for use by patients with conditions that may potentially compromise respiratory function. Lastly, death may occur with GHB at low blood concentrations, in a delayed fashion after loss of consciousness and progressive hypoventilation and hypoxia, as GHB and other drugs are metabolized; this has previously been reported in alcohol- [84] and methadone-associated fatalities [18]. Five deaths in our series had postmortem blood GHB concentrations within endogenous range (<50 mg/L); however, exogenous source is supported in all 5 by exogenous GHB concentrations detected in one or more other samples (eg, vitreous, urine, gastric) and, in 3 cases, also by histories of acute GHB ingestion or GHB found at the scene [85]. The occurrence of delayed deaths at low GHB concentrations further supports the need for user education regarding the potential lethality of GHB with and without cointoxicants and the importance of prompt intervention in cases of overdose.

4.2.2. Popular use: "supplements," party drugs, and GHB dependence

Our series demonstrates several risks associated with popular use of GHB. First, unique among drugs of abuse, GHB, GBL, and BD were marketed as "dietary supplements" for diverse purported health benefits. "Natural" and "nontoxic" "supplements" were marketed as safe, hangover-free, nonaddictive recreational alternatives to alcohol and other drugs [1,2,17]. However, 16 deaths in our series (including 9 negative for cointoxicants) were associated with GBL and BD "supplements," reportedly used for sleep, athletic training, sexual effects, and partying. One decedent reportedly took repeat doses of an unlabeled "supplement" that he had been told was "nontoxic." Another decedent, found dead in bed, reportedly used RenewTrient for sleep on recommendation of a chiropractor.

Second, features of uncontrolled recreational use, particularly in public places, may compound inherent risks resulting from the abrupt onset, steep dose response, and unpredictable effects of GHB. For example, GHB, GBL, and BD are used primarily in liquid form, dosing of which may be less controllable than pill form. Furthermore, formulations have ranged from dilute products of variable potency (ie, "supplements" identified in our series ranged from 6% GBL/Revivarant to 18% BD/NRG3) to 99.9% industrial GBL and BD and 100% GHB, and active ingredients and concentrations may be unlisted or unknown to users. Recreational users often purchase GHB by the "capful" (dose/concentration unknown), frequently use it with cointoxicants, and, according to interview data, report difficulties with dose titration and frequent overdoses [48,50]. Risk of accidental ingestion may be heightened by GHB's availability as a clear, odorless liquid, as well as efforts to disguise or transport it in unlabeled containers such as water bottles; deaths after ingestion of GHB "mistaken for water" have been reported in the United Kingdom [67] and Germany [86]. Surreptitious dosing to facilitate sexual assault presents additional risk due to

Table 3 Blood GHB levels reported in clinical studies, case reports, and case series

Study, enrollment	Dosage (oral route unless noted)	GHB level (mg/L) in plasma (unless noted)	Clinical effects
Endogenous postmortem GHB			
Kintz 2004 [22]	Deaths with no GHB ingestion		Not applicable
Cardiac blood (n = 71)		Range, 0.4-409; mean, 36.7; median, 17.5	
Femoral blood (n = 5)		Range, 16.8-44.1; mean, 30.4; median 34.3	
Elliott 2004 [24]	Deaths with no GHB ingestion		Not applicable
Femoral blood (n = 35)		Range, 2-29; mean, 12.6; median 12	
Moriya 2005 [72]	Deaths with no GHB ingestion		Not applicable
left cardiac chamber blood (n = 21)		Range, ND to 15.8; mean, 4.0; median, 3.1	
right cardiac chamber blood (n = 19)		Range, ND to 14.4; mean, 4.9; median, 4.3	
aortic blood (n = 20)		Range, ND to 23.7; mean, 4.0; median, 2.5	
femoral venous blood (n = 23)		Range, ND to 11.6; mean, 4.6; median, 4.7	
Pharmacokinetic studies			
Brenneisen 2004 [45] volunteers (n = 8)	25 mg/kg of GHB	Mean peak, 39.7 (SEM, 10.6) Range, 4.7-76.3	Confusion, sleepiness, dizziness
Thai 2007 [49] volunteers (n = 8)	25 mg/kg of BD	Mean peak, 45.6 (SD, 19.7) Range, 22.2-85.7	Respiratory depression, lightheadedness, headache, transient blood pressure increase
Thai 2006 [41] volunteers (n = 16)	50 mg/kg of GHB	Mean peak, 72.6 (SD, 16.2)	Sedation, vomiting, respiratory depression
Abanades 2006 [73] volunteers (n = 8)	40 mg/kg of GHB, n = 4 50 mg/kg of GHB, n = 5 60 mg/kg of GHB, n = 4 72 mg/kg of GHB, n = 2	Mean peak, 79.1 (SD, 26.4) Mean peak, 83.1 (SD, 28.8) Mean peak, 113.5 (SD, 20.1) Mean peak, 130.1 (SD, 10.7)	Mixed stimulant-sedative pattern of effects; euphoria, well-being; transient blood pressure increase; sedation, impaired psychomotor performance, ataxia, exophoria
Borgen 2000 [74], volunteers (n = 12), divided doses of Xyrem, administered 4 h apart	*Regimen 1 (4.5 g total)* Dose 1, 2.25 g of GHB Dose 2, 2.25 g of GHB *Regimen 2 (9 g total):* Dose 1, 4.5 g of GHB Dose 2, 4.5 g of GHB	Dose 1: Mean peak, 26.6 Dose 2: Mean peak, 60.1 Dose 1: Mean peak, 77.6 Dose 2: Mean peak, 141.9	Sleep; adverse events including nausea, headache, dizziness, and vomiting more frequent with regimen 2 (9 g total dose)
Anesthesia study			
Helrich 1964 [75], surgical patients (n = 14)	100 mg/kg of GHB, intravenous, no premedication or other drugs administered	Mean peak blood level, 307 Range, 234-520	Variable response at similar blood levels; light sleep to deep sleep [a]; periodic breathing; all intubated

Table 3 (*continued*)

Study, enrollment	Dosage (oral route unless noted)	GHB level (mg/L) in plasma (unless noted)	Clinical effects
Nonfatal GHB toxicity cases	*All cases negative for co-intoxicants*	*Blood GHB level (sample drawn while in the ED)*	*Symptoms while in ED*
Dargan 2008 [3]	600 mg/kg of Xyrem	569 (serum); 7 h post-ingestion 377; 8.5 h post-ingestion	GCS = 3; HR, 48 bpm, RR, 8/min, respiratory acidosis; nasopharyngeal airway and oxygen
Couper 2004 [76]	Unknown dose (BD)	490	Coma; intubated
Couper 2000 [77]	Unknown dose	130	Confusion, vomiting, ataxia, apnea; intubated
Dyer 1994 [78]	Unknown dose	101	Coma
Lenz 2008 [79]	Unknown dose (GBL)	161	Coma
Megarbane 2002 [80]	Unknown dose (BD)	222 [b]	GCS = 10, generalized seizures
Strickland 2005 [81]	Unknown dose (BD)	1200	Respiratory arrest; intubated 14 hrs
Zvosec 2001 [2]	Unknown dose (BD)	317 [c]	GCS = 11, labile level of consciousness
GHB-associated fatalities	*12 deaths negative for co-intoxicants*		
Caldicott 2004 [66]	Unknown dose in all cases	PM, 77; AM, 220; AM, 210	Death in all cases
Duer 2001 [33]		PM, 303	
Harty 2002 [34]		PM, 1270	
Lenz 2008		PM, 165	
ACMD 2007 [67], 6 deaths		AM, 430; PM, 42, 120, 159, 403, 1575	

ED indicates emergency department; ND, nondetectable at 0.5 mg/L; GCS, Glasgow Coma Scale; HR, heart rate; bpm, beats per minute; RR, respiratory rate; AM, antemortem; PM, postmortem.

[a] Light sleep indicates spontaneous movements, occasional eye opening. Moderate sleep indicates spontaneous blinking, response to deep pressure. Deep sleep indicates no response to touch, pin-prick, or deep pressure; no blinking; pupils small, eyes central and fixed; abolition of pharyngeal and laryngeal responses.

[b] This patient was known to be a regular GHB user.

[c] This patient was known to be GHB dependent.

unpredictable effects, uncertain dose, and disguising in alcoholic drinks [2]. Our series demonstrates the previously described risks; 114 deaths occurred in recreational drug use contexts, including 5 decedents who reportedly "gulped" too much GHB and 4 others who mistook GHB for water. Furthermore, 7 deaths in our series potentially involved surreptitious dosing, including one woman found being raped while unconscious.

Third, habitual GHB users, particularly dependent users, may be at increased risk of lethal overdose, due to escalation of dose size and frequency. Contrary to explicit promotions as nonaddictive, long-term use of GHB and its prodrugs may result in tolerance and physical dependence, with potentially lethal withdrawal upon dosing cessation [14,15]. GHB-dependent users report dosing up to every 15 minutes, often around-the-clock, to prevent or control withdrawal symptoms, resulting in repeated ED presentations with overdose [10]. Swedish investigation documents lethal overdoses among novice and experienced users, noting there to be "no indication that one can learn how to deal with this drug safely" [52]. Sixteen decedents in our series were identified as regular or dependent users, including 4 who had previously presented a total of 6 or more times to EDs for treatment of overdose or withdrawal.

4.2.3. Potentially preventable deaths

A review of MDMA (ecstasy)-associated fatalities describes public perceptions of MDMA as a "safe" drug and documents significant delays in 911 activation [20]. Similarly, available histories for our series document 72 decedents with acute GHB use known to witnesses who reportedly left them unassisted, 51 with reported adverse effects and 21 reportedly "sleeping." Decedents were left or moved to a couch/bed/floor; one was placed in the "recovery position." In marked contrast with frequent and diverse intervention efforts reported by witnesses of heroin overdoses [87], only one case in our series documented witnesses' attempts to revive a known GHB overdose victim, using a water hose. Although additional undocumented interventions may have occurred, several factors unique to GHB may shed light on documented failures to assist. First, as noted above, unlike other drugs of abuse,

GHB, GBL, and BD were marketed as safe nontoxic "supplements." Second, product labels (Fig. 1) and Web sites explicitly discouraged 911 activation in cases of GHB overdose with no cointoxicants. The GHB effects were described as ranging from drowsiness to "short-term harmless 'coma,'" and users were advised to simply "sleep it off" [2,16]. Interview data with GHB users suggest that such misinformation has affected perceptions and behaviors; users reported beliefs that overdose was harmless and cited the Internet as a significant source of information [48,50]. Misinformation persists on the Internet; for example, one drug forum currently posts, "GHB and GBL are TOTALLY SAFE to use—but you have to be scientific and adult about it. The idiots who end up in hospital deserve to be there….you simply cannot jump in and swig down capfuls of the stuff hoping that you will be OK—you will not. Actually though, the usual effects of an OD are just a few hours' unrousable sleep—often mistaken for proper coma by dumb cops and ER staff. The problem with G is this: the dose, which makes you feel good, is only a little lower than the dose, which knocks you out for a few hours. GHB/GBL does NOT suppress breathing so you'll be OK as long as your airway is clear. The dose, which will KILL you, though, is MUCH larger. You need to drink a huge amount of GBL to actually kill yourself. You'd be sick and throw it up first" [88]. A recent report documents a regular user in Germany who mistook his concentrated GBL for water and gulped it; realizing his error, he logged onto an Internet drug forum to solicit advice and information on lethal dose, rather than call for medical assistance. He apparently rapidly lost consciousness and was found later by roommates, unarousable on the floor in front of his computer, and subsequently died [86].

Our series documents that 100% of decedents with known location of death arrested prehospital. Conversely, a previous review of 18 acute GHB toxicity case series (total n = 642 patients) found no deaths, 100% recovery rates, and virtually no complications in patients for whom medical assistance was accessed [89]. In deaths negative for cointoxicants in the current series, 92% of postmortem blood GHB concentrations were less than 1200 mg/L, a concentration previously reported in a BD overdose patient who received timely medical care and survived with no sequelae [81]. This suggests that, with timely EMS activation, many deaths in our series may have been preventable and that public education is critical regarding the lethality of GHB and the need for prompt medical intervention.

4.3. Drug-related deaths

Although fatal trauma associated with alcohol and drug intoxication has been well described [18,19,90], our series is the first to document diverse fatal accidents associated with GHB intoxication, including MVCs involving impaired drivers and pedestrians, drownings, and fire. Previous reports of GHB involvement in fatal accidents include a drowning and a fatal bicycle collision with a bus (United Kingdom) [67], a fatal fall from a height (Australasia) [66], and unspecified fatal trauma (Sweden) [52]. GHB effects that may increase accident risk include confusion, dizziness, vomiting, agitation, altered vision, impaired coordination and judgment, and loss of consciousness, which may be abrupt [9]. Although absolute certainty regarding the role of GHB in fatal accidents in our series is impossible, our findings are consistent with previously reported nonfatal accidents associated with GHB use. Xyrem trials documented a 9% rate of accidental injury, including falls and setting clothes on fire [91]. Nonfatal fires; falls; impaired driving; MVCs [2,9,59,83]; head trauma; and "walking, running, or 'jumping' in traffic" [13] have been reported among users of illicit GHB, "supplements," and Xyrem. GHB driving simulations document significantly increased collisions and off-road accidents, poorer response times, and more speed and position deviations among subjects receiving GHB (50 mg/kg dose) compared with placebo [92]. GHB users report abrupt loss of consciousness ("G-napping") as a hazard of driving while GHB-intoxicated, express limited concern regarding police stops due to the absence of a rapid GHB detection test, and report repeated traffic stops for driving while GHB-intoxicated, with no legal consequences [93]; if consistent with findings among alcohol-intoxicated drivers, this avoidance of legal sanction may facilitate recidivism and continued risk [94]. Risk of associated trauma is increased among habitual and dependent users among whom maintenance dosing for control/prevention of withdrawal requires frequent use, encompassing daily activities such as driving and cooking, which present accidental risk [10,11].

4.4. Potential interventions and areas for future research

Our series demonstrates lethal consequences of 3 previously identified high-risk behaviors associated with increased risk of hospitalization among GHB users: (1) GHB use with alcohol, (2) GHB use and driving, and (3) GHB use to prevent withdrawal [71]. Consistent with previous reports of repeat ED presentations among GHB users [12,13], 11 decedents in our series reportedly had a total of 15 or more prior ED presentations with overdose, impaired driving, and withdrawal. Furthermore, witnesses commonly failed to access medical care in cases of observed overdose with known GHB ingestion. Emergency physicians should be alert to potential GHB involvement in cases of overdose, impaired driving, and accidents with unexplained mechanism, particularly in cases with negative toxicology. Finally, as has been recommended for ED physician interventions with alcohol abuse [95,96] and alcohol-impaired driving [94], each GHB-related ED visit presents opportunities for substance abuse intervention, including careful questioning about GHB use, high-risk behaviors, and adverse effects, and for appropriate referrals

for chemical-dependency treatment. Emergency physicians may be in a position to similarly educate users regarding the range of lethal risks of GHB use and the need for prompt medical intervention in case of overdose.

Prospective research is also needed to identify predictors of morbidity and mortality among GHB users. Research is ongoing regarding optimal form, appropriate targeting, and efficacy of brief ED interventions for alcohol abuse [97]. Research efforts should be extended to include brief ED interventions regarding use of other potentially lethal drugs of abuse, including GHB.

4.5. Limitations

Our study has the limitations of convenience sampling, thereby precluding insights into the incidence of GHB-associated mortality. Furthermore, there are doubtless numerous cases that were not identified for review as follows: identification of new cases and acquisition of previously reported cases were limited to jurisdictions with publicly available death information, searchable databases or ME/C's with recall of GHB-associated deaths, and adequate resources for searches and/or retrieval. However, systematic data on GHB mortality are unavailable, and our purpose was to collect a descriptive case series of size sufficient to elucidate the range of lethal risks, toxicology, and historical data, and our findings represent a significant advance over the largest case series reported to date (n = 10).

Second, our series may have included false-positives. The likelihood of inclusion of false-positives is minimized, however, by requirement of GC/MS quantitation of GHB above inclusion cutoffs in one or more samples, as opposed to reliance simply upon ME/C designation of GHB as causal or contributory to death, with or without a history of acute GHB ingestion. For example, 13 cases with GHB specified in COD were excluded due to blood GHB concentrations less than 50 mg/L and no confirmatory exogenous concentrations in other samples (9) or lack of GHB quantitation. Although false-positives are also possible due to endogenous GHB and high concentrations of endogenous GHB in postmortem blood have been documented [22,23], most samples in these and other studies are less than our cutoff of 50 mg/L [22-27], which exceeds that used in several other studies (ie, 30 mg/L) [24,59,72]. To minimize effects of postmortem redistribution, peripheral blood concentrations were used for data analysis whenever possible. Furthermore, 84% of deaths categorized as drug caused had a history of acute ingestion, presence of GHB at the scene, and/or multiple exogenous concentrations detected. Of 24 cases that ruled in based on a single postmortem blood GHB sample, concentrations typically substantially exceeded inclusion cutoffs (range, 59-5324 mg/L; mean, 749 mg/L; median, 335 mg/L). Last, our series is consistent with postmortem blood GHB ranges previously reported [59,66,67] and provides previously unavailable detail.

Third, our methods may have excluded additional GHB-associated deaths (false-negatives), due to adherence to GC/MS cutoffs of GHB blood concentrations higher than 50 mg/L when there were no other confirmatory samples. As our series demonstrates, however, death may occur with blood GHB concentrations within the endogenous range. For example, one case with a history of GHB use, concurrent MDMA intoxication, and an ME/C attribution of death as "combined drug toxicity" was excluded due to a postmortem blood GHB concentration of 49 mg/L (cutoff, 50 mg/L). Four other cases with postmortem blood GHB concentrations of 45 to 48 mg/L were also excluded: 3 with depressant cointoxicants and 1 with depressant and stimulant cointoxicants. Four additional deaths were excluded due to lack of GC/MS quantitation of GHB, although all had histories of acute GHB ingestion and 2 tested positive for GHB; ME/Cs cited GHB as causal or contributory to death in all 4 cases. Although these deaths may have been GHB associated, our purpose was not simply to amass the greatest number of cases but rather to describe GHB-associated deaths with regard to toxicologic, pathologic, and historic variables.

Fourth, analytic methods and drugs included on toxicology testing varied between jurisdictions, and analytic findings may be erroneous. However, analytic methods were assumed to conform to professional standards [69], and screening was performed in accordance with jurisdictional protocols; detailed analysis of toxicologic methods is beyond the scope of this article.

Last, the amount and quality of historical data varied among cases, resulting in different denominators in various groups analyzed, and historical information may be biased or false. However, such variation was unavoidable due to nonstandardized reporting requirements, and potentially false or biased information are inherent limitations of historical data. Exclusion of such data would preclude valuable insights into products, use contexts, medical encounters, and potential points of intervention.

5. Conclusions

We present the first extensive series of GHB-associated fatalities. γ-Hydroxybutyrate is lethal, even without cointoxicants, and death may result directly from intoxication and indirectly from accidents. Lethal ingestions may result from intentional recreational or therapeutic use and from unintentional ingestions. Postmortem blood concentrations vary widely, with no clearly definable lethal concentration. All documented cardiorespiratory arrests occurred prehospital, and EMS activation was often delayed or absent despite known GHB ingestion and witnessed adverse effects. Education of emergency physicians and GHB users about lethal risks of GHB, with and without cointoxicants, and the need for prompt medical intervention is needed.

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