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Gamma hydroxybutyrate (GHB) intoxication

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INTRODUCTION

Gamma hydroxybutyrate (GHB) is a central nervous system (CNS) depressant that is abused recreationally as a "party drug" or "club drug" with a wide array of formulations, use patterns, and health risks.

Throughout this topic we use the term "GHB" to refer to GHB and its analogs, unless specifically noted.

The toxicology and management of acute GHB intoxication are reviewed here. GHB withdrawal, GHB in the treatment of narcolepsy, the toxicology of other drugs of abuse that may be co-ingested, and general management of the poisoned patient are all discussed separately:

- (See "Gamma hydroxybutyrate (GHB) withdrawal and dependence".)
- (See "MDMA (ecstasy) intoxication".)
- (See "General approach to drug poisoning in adults".)
- (See "Initial management of the critically ill adult with an unknown overdose".)
- (See "Treatment of narcolepsy in adults", section on 'Oxybates'.)

BACKGROUND

GHB was first synthesized in France as an analog of gamma aminobutyric acid (GABA) capable of crossing the blood-brain barrier. Initially used as an anesthetic in Europe, GHB was found to have inadequate analgesic effects and significant side effects, including myoclonus and emergence delirium, and did not receive approval in the United States [1]. In the 1980s, GHB was marketed as a bodybuilding and weight-loss drug and sold in health food stores. Recreational use of GHB subsequently became more widespread as it was abused at clubs, raves, and dance venues for euphoric, sexual, stimulant, and relaxant effects.

Following reports of adverse effects from and the enactment of government restrictions on GHB, gamma butyrolactone (GBL) and 1,4-butanediol (BD), two common industrial solvents, became popular as "dietary supplements" and were promoted for bodybuilding, weight loss, sleep, and in the treatment of depression, anxiety, and alcohol and drug dependence. Both GBL and BD are rapidly metabolized to GHB, with the same clinical effects. (See 'Pharmacology and cellular toxicology' below.)

Adverse events from and subsequent regulation of GBL and BD "supplements" led to the spurious sale of both compounds as "non-toxic" and "organic" solvents, "cleaning products," and "chemical samples" to avoid detection and prosecution [2]. These products were then replaced by industrial GBL and BD sold on the internet through unregulated companies in Asia and Europe. Analog products, sold as "nail polish remover," "massage emollient," "mood enhancers" promoted for sexual effects, or as “cleaners” and “chemicals,” have also been spuriously marketed in recent years. Illicit supplies of GHB and GBL have increased globally, account for a large proportion of seized psychoactive substances, and can be purchased from internet vendors [3].

GHB is also available in pharmaceutical formulations in the United States (Xyrem/sodium oxybate and Xywav/lower-sodium oxybate) and Europe (Xyrem/sodium oxybate, Alcover, and Somsanit). GHB toxicity resulting from therapeutic use and abuse of pharmaceutical formulations has been reported in the United States and Europe. (See 'Formulations and dosing' below.)

EPIDEMIOLOGY

The prevalence of GHB use among adults in the United States is low. Approximately 0.1 percent of adults have used GHB annually. Individuals who use GHB tend to be White males, gay, and 26 to 49 years old [4]. Reports of adverse events peaked in the early 2000s and then declined, remaining relatively stable through the mid-2000s. However, the United States National Poison Data System has reported increased exposure calls since 2017 [5]. As with many poisonings,

particularly those not detected on routine hospital toxicology screens, these figures likely underestimate the incidence of GHB toxicity and GHB-associated adverse events. The United States National Poison Data System documented 973 Xyrem exposure calls from 2002 to 2015 in individuals aged 8 months to 86 years, including 72 pediatric cases, with peak calls in 2014. Exposures included intentional abuse and misuse, suspected suicide, adverse drug reactions, and unintentional therapeutic errors [6].

The prevalence of annual GHB use in Europe and Australia among the general population tends to be less than 1 percent. GHB and gamma butyrolactone (GBL) intoxications are reported primarily in urban areas of the United Kingdom (UK), Norway, the Netherlands, Finland, and Spain, as well as in Australian cities. GHB was re-classified in the UK in 2022 to a higher category of controlled drugs [7]. Although occasionally used for bodybuilding and purported health benefits, GHB use appears concentrated among certain subgroups, including club and dance venue attendees and men who have sex with men (MSM) [4,7-13].

Despite the low prevalence of misuse, GHB continues to have significant adverse public health effects [3,7-9,14-32]. GHB poisoning accounts for a disproportionate number of severe drug ingestions, emergency transports, hospitalizations, and deaths [3,7,9,10,21,23-26,28-30,33,34]. In 2020, GHB was the fifth most common recreational drug reported by the EuroDEN Plus network (22 hospitals in 14 European countries), accounting for 11 percent of overdoses and 35 percent of critical care admissions [23]. Intoxication with severe depression of consciousness, often requiring tracheal intubation, was common. GBL use and poisonings have become increasingly common due to greater accessibility, cheaper cost, and the desirability of faster onset of effects compared with GHB [3,14,18,35].

Recreational use at social gatherings, clubs, bars, dance venues, and private homes now predominates even though misinformation about health benefits, particularly use for sleep, bodybuilding, depression, and anxiety, remain on internet drug forums, chat rooms, quasi-medical articles, and recreational drug information websites. Polydrug use is common, with GHB frequently co-ingested with MDMA (ecstasy), mephedrone, cocaine, methamphetamine, sildenafil, or ethanol [16,21,24,25,31,33,36-38]. Mass intoxications of recreational users at "raves" (dance parties) and clubs have been reported [3]. GHB use by MSM at clubs, sex parties, and in private homes to enhance sexual intercourse ("chemsex"), particularly in conjunction with crystal methamphetamine, mephedrone, MDMA, synthetic cathinones, cannabinoids, sildenafil, amyl nitrate, and ketamine, is widely reported and often results in complications including increased risk of sexually transmitted diseases, development of dependence, and death [8,10,18,37].

Individuals who are dependent on GHB often suffer chronic, repeat overdoses [22,26,32,39]. A study of 841 patients who presented with acute GHB intoxication in Sweden from 2010 to 2015 (nearly half presenting multiple times) found that 13 percent died within five years. Patients with psychiatric or affective disorders and with repeat presentations for overdose had increased mortality [32].

GHB-intoxicated driving has been widely documented, particularly among dependent individuals and those that misuse chronically, sometimes resulting in fatal motor vehicle collisions [22,27,40-47]. "Sleep driving" has been reported in patients taking Xyrem [48]. Falls and injuries related to GHB overdose and sudden loss of consciousness are also common [27,33,49].

Fatal and non-fatal accidental ingestion has been reported in adults [13,40,50] and children (who may ingest GBL solvents or GHB left in water bottles in homes and health clubs) [51]. Children can be exposed to Xyrem through accidental ingestion and intentional administration. Seventy-two pediatric exposures (ages 8 months to 17 years) were reported to United States poison control centers from 2002 to 2015, all prior to Food and Drug Administration (FDA) approval in 2018 of Xyrem for use in children. Reported major adverse effects included respiratory depression and coma [6].

Fatal and non-fatal surreptitious drugging with GHB, GBL, and Xyrem to facilitate sexual assault has been reported [7,20,52-58]. Surreptitious drugging to facilitate robberies has also been reported [7,20,57]. Detection of GHB in surreptitious drugging cases is hampered by the lack of a rapid toxicology screen, the short half-life of GHB, amnestic effects, and delays in presentation. (See 'GHB-facilitated sexual assault' below.)

To date, there are reports of more than 800 deaths in the United States, Europe, New Zealand, and Australia associated with GHB, GBL, and 1,4-butanediol (BD) ingested intentionally, accidentally, or resulting from surreptitious administration [10,18,33,40,44,52,59-64]. Fatalities have increased in the UK [7,64]. Deaths have shifted from public spaces (clubs, dance venues) to private spaces (homes, private parties), possibly from an association with chemsex [8,10]. In two large series (375 total deaths), approximately 35 percent of deaths did not involve co-intoxicants [18,40]. GHB-associated deaths are likely under-detected and under-reported [18,40]. The detection of Xyrem-related fatalities is equally difficult [61,65]. (See 'Lethality' below.)

Internet websites, chat rooms, and forums have figured prominently in the provision of information, misinformation, and access to GHB, GBL, and BD [2,14,66]. Online access to Xyrem, illicit GHB, and other recreational drugs through cyber drug markets has increased dramatically in recent years with the advent of the "Deep Web" or "Darknet," which provides anonymous

access to "cryptomarkets" such as Silk Road, Alphabay, and their many successors, where drugs like GHB and GBL can be purchased with cryptocurrencies like Bitcoin [67]. Social media platforms such as Reddit provide specific interest forums called "subreddits," which provide information on and access to drugs like GHB and GBL through the Darknet [68]. GHB and other drugs also remain readily available through "clear web" or "surface web" sites for chemical companies, online pharmacies, phone apps, and peer-to-peer marketplaces such as eBay, Craigslist, and others [37,69]. Users report that GHB overdose and coma are perceived as common, harmless, or simply unavoidable [19,22,39,41] and recreational drug websites have advised bystanders to leave victims to “sleep it off,” which has resulted in deaths [18,33,40].

PHARMACOLOGY AND CELLULAR TOXICOLOGY

GHB is a short-chain fatty acid that exists endogenously in mammalian tissue. It is a metabolite and precursor of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. GHB interacts with GHB-specific receptors and also acts as a direct agonist of GABA-B receptors. In high doses, it may exert additional GABA-like effects through conversion to GABA. GHB affects multiple neurotransmitter systems, including those of opioids, dopamine, serotonin, glutamate, and acetylcholine [17].

Gamma butyrolactone (GBL) and 1,4-butanediol (BD) are GHB analogs that are rapidly metabolized to GHB after ingestion, with the same toxic and recreational effects. GBL is an endogenous lactone that is converted to GHB via a peripheral lactonase. Animal studies demonstrate that GBL has more rapid absorption, greater lipid solubility, higher serum concentrations, and more prolonged hypnotic effects than GHB [14].

BD is an aliphatic alcohol that is converted to gamma-hydroxybutyraldehyde and subsequently to GHB by alcohol dehydrogenase and aldehyde dehydrogenase, respectively. As with GBL, effects are mediated through GABA-B and GHB receptors. Unlike GBL, co-ingestion with ethanol may alter the pharmacokinetics of BD by inhibiting alcohol dehydrogenase and aldehyde dehydrogenase [18]. Interactions with co-ingested alcohol may cause a delayed and/or prolonged clinical course, possibly including prolonged unconsciousness and features mimicking toxic alcohol exposure [70].

FORMULATIONS AND DOSING

Currently available formulations of GHB and related substances include industrial gamma butyrolactone (GBL) and 1,4 butanediol (BD), illicit "supplement" and "solvent" products, street

supplies, home-synthesized GHB (made from recipes available on the internet), and pharmaceutical formulations. Current use of illicit GHB and analogs is primarily limited to liquid GHB and GBL. BD is also available in liquid form but has been less commonly reported since the early 2000s. Liquid GHB is odorless and clear, with a salty or soapy taste. GBL and BD supplements and solvents reportedly have a chemical taste and may also have colorants, scents, and flavorings added. GHB has also been sold in powder form, and GBL and BD have been sold in capsule form [1,2]. There have been rare reports of nasal insufflation, intravenous (IV) use, and vaginal and rectal administration [7,18,52]. Lists of GHB, GBL, and BD-containing products and slang terms are available (table 1).

Product concentrations vary widely, from undiluted GHB and industrial grade GBL and BD to dilute GBL and BD supplements and solvent products; street doses are reported to vary from 500 mg to 5 g per teaspoon or capful dose. Recreational doses of GHB (ie, for euphoric effects) are approximately 1 to 2.5 g (equal to a 50 mg/kg dose in a 50 kg individual) but may vary widely, from approximately 2 to 6 g (40 to 120 mg/kg dose in a 50 kg person), based on interindividual variability in effects, physical tolerance, dependence, and co-ingestion with other substances [7,18,71].

GHB toxicity may be compounded by toxic contaminants or additives in GBL- or BD-containing solvents, paint removers, and cleaners, as well as undissolved sodium hydroxide and other contaminants used in home-synthesized GHB.

GHB is used as a therapeutic agent in the United States and Europe. In the United States, pharmaceutical GHB is available as Xyrem (sodium oxybate) and Xywav (lower-sodium oxybate) for the treatment of cataplexy and excessive daytime sleepiness. The approval of Xyrem gave GHB a bifurcated Drug Enforcement Administration (DEA) scheduling status: GHB used for illicit purposes is a Schedule I Controlled Substance, while pharmaceutical GHB used for therapeutic purposes is a Schedule III drug. Xyrem and Xywav are distributed in the United States through a single central pharmacy with a risk management program. While postmarketing safety surveillance conducted by the manufacturer, Jazz Pharmaceuticals, reports a low incidence of abuse or misuse of Xyrem [59], cases of Xyrem/sodium oxybate toxicity, dependence, and withdrawal have been documented, as well as abuse, diversion, Xyrem-associated sexual assault, impaired driving, and fatalities [59-61,72,73]. The National Poison Data System documented 973 Xyrem exposure calls from 2002 to 2015 in individuals aged 8 months to 86 years, including cases of intentional abuse, suspected suicide, and unintentional therapeutic errors. Seventy-two pediatric cases (ages 8 months to 17 years) were included, all prior to Food and Drug Administration (FDA) approval in 2018 of Xyrem for use in children age 7 to 17 years

[6]. Xyrem is also available through websites posing as online pharmacies [18] and through cryptomarkets on the Darknet. (See "Treatment of narcolepsy in adults", section on 'Oxybates'.)

KINETICS

- **Absorption and elimination** – GHB is rapidly absorbed and eliminated following oral ingestion. Oral doses of 25 mg/kg to 72 mg/kg administered to healthy volunteers resulted in mean peak plasma concentrations from 40 mg/L to 167 mg/L, time to mean peak plasma concentrations from 20 to 57 minutes, and mean elimination half-lives of 30 to 52 minutes [71,74-77].

  Studies indicate first-order kinetics at low therapeutic doses and zero-order kinetics with rate-limited elimination at higher doses (>50 to 60 mg/kg), due to saturation of metabolic enzymes, which is relevant for high recreational abuse doses, particularly when ethanol is co-ingested [47,77-79].

  1,4-butanediol (BD) is rapidly and extensively metabolized to GHB, with measurable plasma GHB detectable in a majority of subjects within five minutes of ingestion [80]. Animal studies suggest that GBL is more rapidly absorbed, demonstrates higher serum concentrations, and has more prolonged hypnotic effects than GHB [14].

- **Variability of pharmacokinetic parameters** – Significant intersubject variability exists in the pharmacokinetic parameters of GHB and BD [74,75,81,82]. Variability may result from differences in bioavailability, absorption rate, drug-metabolizing enzyme activities, or tolerance resulting from chronic use.

- **Metabolism** – GHB is metabolized via several intracellular pathways, the most important of which produces succinic acid, which in turn enters the tricarboxylic acid (ie, Krebs) cycle. GHB recovery in urine ranges from 1.2 to 5 percent [75,76].

- **Factors affecting pharmacokinetics** – Food has been shown to reduce peak plasma concentrations and systemic absorption of GHB [83]. Coadministration of ethanol with GHB resulted in statistically insignificant elevations in maximum plasma concentrations and the elimination half-life of GHB. At higher recreational doses, however, such elevations could result in greater clinical toxicity [76,79]. Gender does not affect kinetics.

EFFECTS NOTED DURING CLINICAL STUDIES

Observational and therapeutic trials of GHB describe clinical effects found with low to moderate doses and no co-ingestants. Below, we summarize the effects noted during clinical studies.

Onset of clinical effects of oral doses of GHB is rapid, typically 15 to 20 minutes, with peak clinical effects 30 to 60 minutes postingestion, and a steep dose response curve [83,84]. Intravenous (IV) dosing produces onset of cognitive effects within five minutes.

GHB primarily affects the central nervous system (CNS). Although dose-related CNS depression is most commonly described, stimulant effects are also observed. A mixed stimulant-sedative pattern of effects was documented following oral doses of 20 mg/kg to 72 mg/kg [71,74,77,82,85]. Stimulant effects peaked at 45 to 60 minutes, and sedative effects peaked at 60 to 120 minutes. Effects were generally dose-dependent and lasted up to two to three hours [71,74,82].

Confusion, dizziness, and drowsiness occur following low oral doses of GHB (25 mg/kg) [75] and 1,4-butanediol (BD) (25 mg/kg) [80]. Higher doses (40 to 72 mg/kg) result in psychomotor impairment, dizziness, impaired memory, and variable levels of sedation. Effects were dose-dependent, with peak effects at 30 minutes with lower doses and 90 minutes for higher doses, and duration of approximately two hours [76,82,86-88]. Studies of simulated driving following a 50 mg/kg dose report significantly impaired psychomotor function, with an increase in collisions and decrease in performance (eg, slower reaction time, weaving, erratic driving with deviations in speed and lane position, and lower self-rating of driving ability) [89,90]. Memory impairment is reported in controlled studies [84,87,88].

Depression, psychosis, suicidal ideation, suicide attempts, and completed suicides have been reported in clinical trials of Xyrem for patients with narcolepsy [91].

Cardiorespiratory symptoms include minor increases in blood pressure and, at higher doses, a significant decrease in heart rate. Decreased respiratory rates and lower oxygen saturation levels may occur with low oral doses of GHB and BD [76,80]. Coadministration of ethanol can potentiate these effects [76,92]. Cheyne-Stokes breathing has been reported [83]. Profound respiratory depression has been documented during clinical trials of Xyrem [91,93,94].

Coadministration of ethanol with moderate doses of GHB consistent with therapeutic dosing resulted in hypotension and vomiting [76], respiratory depression, and impaired cognitive function [87].

Myoclonus was reported during surgical induction with GHB [95] and during clinical trials of Xyrem [91]. Disconjugate gaze (exophoria) [74], nausea, vomiting, and urinary and fecal incontinence have been reported at therapeutic doses [76,84,85,91]. Confusion and

"sleepwalking" (6 percent) were documented in clinical trials of Xyrem and associated significant injury in several cases [91].

CLINICAL FEATURES OF ACUTE TOXICITY

Risk factors for acute toxicity — The risk of acute GHB toxicity is heightened by several factors, many of which may be unknown to the user: the drug's steep dose-response curve (narrow safety margin), the abrupt onset of effects including loss of consciousness, the variability and unpredictability of effects, and the availability of a wide variety of forms with highly variable concentrations [1,40,84]. GHB users report difficulties titrating to a desired effect, and overdose is common [19,96]. Repeat recreational dosing (“stacking”) and the common perception that GHB overdose and coma are harmless increase the risk for acute toxicity [19,22,41].

The risk of acute toxicity is greater among GHB-dependent users who dose frequently to suppress withdrawal symptoms. Individuals with GHB dependence may present with acute toxicity and progress rapidly into withdrawal over the course of several hours [2]. (See "Gamma hydroxybutyrate (GHB) withdrawal and dependence".)

Use of co-intoxicants, including other illicit drugs and ethanol, is common among GHB users and presents a significant risk. Co-ingestion with ethanol is associated with a greater incidence of vomiting and agitation, greater depression of consciousness, a need for treatment, admission to the intensive care unit, and a longer hospital stay [25,36,97]. Co-ingestion with cocaine or MDMA is associated with a deeper and more prolonged coma [24,97]. Co-ingestion of illicit drugs and/or alcohol is associated with a greater incidence of adverse effects, including vomiting, anxiety, hypotension, and bradycardia, more profoundly reduced consciousness at emergency department (ED) arrival, and a longer time to complete recovery of consciousness. Patients with co-ingestants also more frequently require treatment, including sedation, intubation, and mechanical ventilation [16,31,98].

General presentation — Acute GHB toxicity manifests primarily as dose-related central nervous system (CNS) depression, although stimulant effects such as agitation are reported. Sudden onset of effects, as well as abrupt awakening and resolution of effects, frequently occur [99,100]. The signs and symptoms of acute GHB toxicity are described below.

Ingested doses for patients presenting with acute GHB toxicity are most often unknown but likely significantly exceed those described in GHB and 1,4-butanediol (BD) administration studies.

Onset and duration of effects — Symptoms of acute GHB toxicity typically develop within 15 to 45 minutes, often with an abrupt onset. The duration of clinical effects is dose-dependent. Effects typically last two to five hours, with complete recovery in three to eight hours [83]. Clearing of effects may also be abrupt [99,100]. Hospital stays are typically two to four hours for nonintubated patients. Symptom duration and hospital stays may be longer, particularly in the presence of co-intoxicants [36].

Vital signs

- **Blood pressure** – Hypotension (systolic blood pressure ≤90 mmHg) occurs at relatively low rates in large case series of GHB-intoxicated patients presenting with and without co-intoxicants (2 to 10 percent overall) [16,20,29,31,36,98]. The incidence of hypotension in patients without co-intoxicants is 1.5 to 3 percent [29,31,36,98].

- **Heart rate (HR)** – Bradycardia (HR <55 bpm) is commonly reported (up to 25 percent) in large case series of GHB-intoxicated patients presenting with and without co-intoxicants [16,31,98,101]. The incidence of bradycardia in patients without co-intoxicants is 23 percent [31,36,98]. Tachycardia is also reported but may be linked to agitation and co-ingestion of stimulants [29].

- **Respiratory rate** – Bradypnea (<10 breaths per minute), apnea, and hypoxemia (<95 percent arterial oxygen saturation) are reported in large case series of GHB-intoxicated patients presenting with and without co-intoxicants (3 to 5 percent overall) [16,20,31,36,98,101]. Respiratory arrest has been reported [102-104].

- **Temperature** – Hypothermia has been reported [31,36,98,105].

CNS effects

- **Decreased level of consciousness** – Decreased level of consciousness (Glasgow Coma Scale [GCS] <13) is a common and prominent effect of GHB toxicity, is frequently severe (<GCS 9), even in the absence of co-intoxicants, and may be compounded by co-ingestion of ethanol or other drugs [16,20,25,31,36,98,101].

- **Coma** – Coma is common with GHB intoxication [24,29,101]. Loss of consciousness may occur quickly (within 15 minutes). Coma (ie, GCS score of 3) has been recorded in cases without co-intoxicants [101,105-108].

- **Agitation** – Agitation is well-documented [2,29,31,36,98,105,109,110] and may occur in up to 38 percent of patients, even in the absence of co-intoxicants [29,31,36,98]. Agitation manifests in various forms, including emergence delirium, agitation in response to

interventions such as intubation, and spontaneous agitation, occurring before, after, or in abrupt alternation with somnolence, obtundation, or coma. Self-injurious behavior, such as striking the head on the floor or with fists, as well as bizarre behaviors, facial tics, and grimacing, have all been reported [2,109].

- **Amnesia** – Amnesia is reported by GHB users [96,101] in GHB-intoxicated drivers [43] even with no loss of consciousness [41], and by patients presenting with acute GHB intoxication [2,22,111-113]. Amnestic effects play an important role in cases of GHB-facilitated sexual assault. (See 'GHB-facilitated sexual assault' below.)

- **Seizures and seizure-like effects** – Myoclonus, seizure-like effects, and seizures have been reported in cases of acute GHB intoxication with and without co-intoxicants but are not common [1,18,29,36,114].

- **Other CNS effects** – Ataxia and sudden loss of muscle control have been reported, sometimes associated with falls and related trauma [2,27,33,49,115]. Disconjugate gaze, nystagmus (horizontal and vertical), and visual effects including blurred vision and loss of peripheral vision have been reported [105,113,116]. Although pupils may be miotic during deep coma, pupillary reactions are variable and may be affected by co-ingestants [16]. GHB comas may be neurotoxic, with potentially long-term cognitive effects [117].

Respiratory effects — Respiratory depression is common [16,20,29,31,36,98,102,105], and respiratory arrest and apnea have been reported [102-105,118].

Cardiovascular effects — GHB can cause bradycardia and hypotension. (See 'Vital signs' above.)

Other documented cardiovascular effects associated with GHB toxicity are limited to isolated reports of the following: atrial fibrillation [119]; paroxysmal sympathetic surge with one to two minute cyclical increases in pulse and blood pressure [120]; and cardiac arrhythmias, all transient except for one in which temporary pacing was used [121]. There is one reported case of cardiac arrest, from which the patient recovered [122]. There are no reports of consistent or significant electrocardiographic changes associated with GHB toxicity.

Rhabdomyolysis — In European surveillance data, GHB was the third most common recreational drug identified in patients with rhabdomyolysis (72 cases involved GHB, following cannabis [74 cases] and cocaine [106 cases]) [123]. Rhabdomyolysis is also reported in a case of GHB toxicity in which the patient developed withdrawal that involved seizures [124] and in a case of gamma butyrolactone (GBL) ingestion followed by prolonged unconsciousness and immobility [125]. (See "Rhabdomyolysis: Clinical manifestations and diagnosis".)

Gastrointestinal effects — In large case series of GHB toxicity, vomiting is common, occurring in 11 to 25 percent of patients [16,20,31,36,98], but appears to occur more frequently with co-ingestants, particularly ethanol [16,29,31,36]. Aspiration may result. Urinary and fecal incontinence have been reported [2,105,112].

GHB-associated trauma — GHB toxicity may result in falls and associated trauma, such as extremity sprains, fractures, and head injuries [2,27,33,49,115]. Trauma may also result from motor vehicle collisions (MVC) caused by GHB-intoxicated drivers [22,27,40,41,43-48]. Clinical effects of GHB that may impair driving include cognitive effects, such as confusion, inattention, and loss of critical thinking; psychomotor effects, such as loss of coordination; and visual effects, such as loss of peripheral vision and visual distortion. In addition, the abrupt onset of vomiting and sudden loss of consciousness that can occur with GHB intoxication may lead to MVCs. The risk for trauma is higher in GHB-dependent users who dose frequently throughout the day to control or prevent withdrawal [42,49]. (See "Gamma hydroxybutyrate (GHB) withdrawal and dependence".)

Lethality — GHB toxicity may be lethal with or without co-intoxicants [10,15,33,40,44,59-61,63,64]. In-hospital deaths are rare but have been reported among patients who have been deeply comatose, anoxic, or who suffered a cardiac arrest prior to hospital arrival [10,15,33,101]. Respiratory arrest is the primary mechanism of death. Death may also occur from aspiration pneumonia, positional asphyxiation, or trauma sustained while intoxicated. Trauma-related fatalities have occurred from MVCs (involving both GHB-intoxicated pedestrians and GHB-impaired drivers), fires, falls, and drowning [33,40,44]. Due to the presence of endogenous GHB, which may increase following death, care must be taken to distinguish exogenous and endogenous GHB when performing postmortem analyses [78]. (See "Initial management of trauma in adults".)

Xyrem-associated deaths have been reported. In addition to cases of suicide and fatalities from acute overdose consistent with abuse [59,61], three case reports document deaths with postmortem GHB levels consistent with therapeutic dosing [60,61]. Sedative co-intoxicants were found in all three deaths, as well as conditions of potential respiratory compromise, such as sleep apnea, obesity, and sarcoidosis [60,61]. A protocol was subsequently developed for monitoring Xyrem-treated narcolepsy patients for the development of sleep-disordered breathing (ie, sleep apnea) [126].

The full extent of Xyrem-associated fatalities remains unclear due to limitations of voluntary reporting systems, incomplete fatality data provided by the drug manufacturer (Jazz Pharmaceuticals) [127,128], and ambiguous safety surveillance reporting. Although a "correction" of earlier data documented 227 total deaths among patients taking Xyrem from

2002 to 2011, including 82 previously unreported deaths, cause of death was reported as unknown in 45 percent of cases, and for 19 overdose deaths documented, no information is provided beyond a statement that the fatalities were intentional, unintentional, or suspected drug overdoses "with or without sodium oxybate" [128]. 2018 prescribing information mentions only one death in clinical trials [91]. The Food and Drug Administration (FDA) requires that the Xyrem drug label include a warning to health care professionals and the public of the risks of using Xyrem with CNS depressant drugs or alcohol [129].

DIAGNOSIS

GHB is not detected on routine hospital urine drug-of-abuse screens. The diagnosis of GHB toxicity as a cause of altered mental status is made clinically, based on history and exclusion of other potentially serious etiologies. Abrupt onset of coma (particularly in the absence of other intoxicants) that resolves spontaneously or abruptly within several hours raises suspicion for GHB toxicity.

Characteristic patterns of agitation prior to, following, or in abrupt alternation with coma are also suggestive. Such patterns include:

- Agitation in alternation with somnolence
- Agitation followed by somnolence
- Self-injurious or bizarre behaviors, particularly in the absence of stimulant co-intoxicants

Bottles found on site, particularly water bottles or containers for supplements or cleaning products, as well as eyedroppers or small containers of fluids or cleaners, may aid in diagnosis. Definitive diagnosis can be made by gas chromatography/mass spectrometry (GC/MS), but results are not available in time to assist clinicians managing acutely intoxicated patients.

DIFFERENTIAL DIAGNOSIS

Obtundation, stupor, and coma — GHB intoxication is difficult to distinguish from other causes of obtundation without a clear history of ingestion. Other etiologies of obtundation, stupor, and coma to consider include medications, opioids, ethanol, and sedative-hypnotic agents (table 2). Head injury, intracranial hemorrhage, increased intracranial pressure from stroke or other causes, hypoglycemia or hyperglycemia, shock, hypoxia, acidosis, postictal state, electrolyte disorders, central nervous system (CNS) infection, and renal or liver failure all may result in altered mental status. The approach to the patient with altered mental status is reviewed in detail separately. (See "Stupor and coma in adults".)

Clinicians should suspect GHB intoxication based upon a suggestive history (eg, witnessed ingestion, history of GHB abuse, presentation after a party), characteristic examination findings (eg, agitation followed by obtundation, bradypnea, bradycardia, hypothermia), and the absence of signs suggesting alternative diagnoses (eg, no evidence of trauma, no response to naloxone or dextrose). (See 'Clinical features of acute toxicity' above and 'Diagnosis' above.)

Psychomotor agitation — Psychomotor agitation may result from intoxication with ethanol or sympathomimetic drugs of abuse (eg, cocaine, phencyclidine, amphetamines, methamphetamine). Psychiatric disorders and withdrawal from sedative-hypnotic drugs or ethanol must be considered, as well as the causes of altered mental status listed immediately above. (See "Cocaine: Acute intoxication" and "Phencyclidine (PCP) intoxication in adults" and "Methamphetamine: Acute intoxication" and "Acute amphetamine and synthetic cathinone ("bath salt") intoxication" and "Management of moderate and severe alcohol withdrawal syndromes".)

LABORATORY EVALUATION

Specific tests — GHB is not detected on a routine hospital toxicology screen. Definitive confirmation requires analysis using gas chromatography/mass spectrometry (GC/MS), which may require 7 to 14 days and therefore is not helpful in the diagnosis and management of acute toxicity. Specimen collection (especially first-catch urine, if possible) is recommended if there is suspicion of drug-facilitated sexual assault. (See 'GHB-facilitated sexual assault' below.)

In preparation for GC/MS testing, collect 100 mL of urine into a standard urine collection cup and refrigerate the specimen. Also collect 10 to 30 mL of blood into a gray-top tube (containing sodium fluoride and potassium oxalate) and refrigerate the specimen.

GHB occurs naturally in the body at low levels. Recommended cutoffs to differentiate endogenous and exogenous levels of GHB are 5 mg/L in blood and 15 mg/L in urine [78].

Although several rapid assays for GHB detection in urine and serum have been developed, targeted analysis using GC/MS remains the mainstay for detection. Methods for the detection of GHB in hair, saliva, and beverages are in development [58,78].

General testing — Routine laboratory evaluation of the poisoned patient should include the following:

- Fingerstick glucose, to rule out hypoglycemia as the cause of any alteration in mental status

- Acetaminophen and salicylate levels, to rule out these common co-ingestions
- Electrocardiogram, to rule out conduction system poisoning by drugs that effect the QRS or QTc intervals
- Pregnancy test in women of childbearing age

A negative toxicology screen, either comprehensive or specifically for drugs of abuse, in the presence of symptoms strongly suggestive of GHB toxicity may support the diagnosis of GHB intoxication. Similarly, typical GHB symptoms with a low or negative serum ethanol level may support the diagnosis, although ethanol is a common co-ingestant. Further testing varies according to clinical presentation. As an example, creatine kinase and urine myoglobin should be obtained in patients at risk for rhabdomyolysis. (See "Ethanol intoxication in adults".)

MANAGEMENT

Management of acute GHB toxicity consists of supportive care, including airway protection (which may involve tracheal intubation and mechanical ventilation), monitoring, sedation for agitation, and treatment of complications. Throughout this review, we use the term "GHB" to refer to GHB and its analogs, unless specifically noted.

Airway and breathing support — Clinicians must ensure airway patency with basic maneuvers (head-tilt, chin-lift, jaw-thrust) and assist ventilation with a bag-valve mask, supplemental oxygen, or tracheal intubation and mechanical ventilation, as necessary. (See "Basic airway management in adults".)

Intubation and mechanical ventilation — Agitation may occur in response to intubation attempts. We suggest rapid sequence intubation (RSI) using succinylcholine, unless contraindications exist. Induction agents for RSI may not be necessary in patients already heavily sedated from GHB. Although the potential for hypotension from GHB toxicity theoretically makes etomidate a better induction agent than midazolam or propofol, such hypotension is likely to be transient and clinically insignificant. (See "Rapid sequence intubation in adults for emergency medicine and critical care".)

Based on the frequency of cases with rapid, spontaneous recovery, some clinicians suggest a conservative approach to intubation [20,97,130,131]. Close monitoring of vital signs and respiratory status is critical in all cases; the infrequency of intubation-related complications and the potentially life-threatening risk of respiratory depression and arrest must guide treatment decisions. We believe end-tidal CO_2 monitoring can play an important and useful role in

monitoring the ventilatory status of these patients. (See "Carbon dioxide monitoring (capnography)".)

Monitoring — Cardiac and pulse oximetry monitoring should be performed in all patients. Capnography can be invaluable for monitoring the respiratory status of stuporous or sedated patients. Monitoring is no longer necessary once the patient is fully awake. (See "Carbon dioxide monitoring (capnography)".)

Agitation and seizures — Use of physical and chemical restraints may be necessary for the control of agitation. Chemical restraint is much preferred, and physical restraints should be removed as soon as sedation is achieved. Appropriate monitoring is crucial, particularly while physical restraints are in place. Benzodiazepines (eg, lorazepam) and antipsychotics (eg, droperidol or haloperidol) may be used for sedation. (See "Assessment and emergency management of the acutely agitated or violent adult".)

Although seizures have been reported in rare instances, causality is by no means established. Benzodiazepines should be effective for controlling seizures.

Complications — Clinicians should examine the patient carefully for injuries resulting from falls, motor vehicle collisions, or other accidents sustained while the patient was intoxicated. Aspiration has been noted in rare instances. (See "Initial management of trauma in adults" and "Trauma management: Approach to the unstable child".)

Decontamination — Due to the risk of abrupt loss of consciousness and a loss of airway-protective reflexes, the induction of vomiting has no role in management.

Gastric lavage and decontamination with activated charcoal are typically not performed because GHB is rapidly absorbed and the time of ingestion is frequently unknown. We suggest administering activated charcoal in cases when a potentially harmful co-ingestion is suspected. Charcoal should be withheld in patients who are sedated and may not be able to protect their airway unless tracheal intubation is performed first. However, tracheal intubation should not be performed solely for the purpose of giving charcoal. (See "Gastrointestinal decontamination of the poisoned patient".)

Antidotes and reversal agents — No clinically proven reversal agents or antidotes for GHB toxicity exist. Flumazenil and naloxone are not clinically effective [83]. Some clinicians report using physostigmine, but we do not recommend doing so because of the potential adverse effects and lack of proven efficacy [83,132,133]. (See "Anticholinergic poisoning", section on 'Antidotal therapy with physostigmine for severe toxicity'.)

Disposition — The vast majority of GHB toxicity cases resolve spontaneously without complications. In some cases, a severe coma necessitating intubation and mechanical intubation may require admission to the intensive care unit (ICU).

Most patients may be discharged from the emergency department (ED) following observation when they are clinically stable and mental status changes have fully resolved. Monitoring is no longer necessary once the patient is fully awake. Recovery may be rapid and abrupt. Discharge is appropriate as long as the patient shows no signs of withdrawal, is able to ambulate, and demonstrates a clear understanding of discharge instructions. (See "Gamma hydroxybutyrate (GHB) withdrawal and dependence".)

Assessment for problematic use and a brief intervention may be helpful for patients presenting with GHB toxicity [134]. Clinicians should educate the patient about the potentially lethal risks of GHB abuse and dependence and, if possible, arrange substance abuse counseling. Consultation with social services may be helpful.

GHB withdrawal typically begins within one to six hours of the last dose and may occur in dependent patients presenting with acute toxicity, trauma, or other conditions resulting in the abrupt cessation of dosing [2,9].

The following may be helpful in preventing acute withdrawal or determining which patients are at risk:

- Question the patient and family members about past GHB (or supplement) use to identify chronic and dependent users.
- Review records for prior presentations with toxicity, withdrawal, or injuries of unexplained mechanism that may be related to GHB intoxication.
- Monitor the patient for the onset of withdrawal symptoms, including anxiety, tremor, diaphoresis, and agitation. Patients who manifest signs of withdrawal require immediate admission for treatment.

Pitfalls in diagnosis and management — GHB toxicity may be confused with or masked by the effects of co-intoxicants. Presentations suggestive of GHB intoxication may be misinterpreted. They include the following:

- Coma with rapid and abrupt onset
- Coma or altered mental status that clears suddenly
- Coma in the absence of depressant intoxicants
- Agitation in alternation with somnolence

- Agitation followed by somnolence
- Self-injurious or bizarre behaviors, particularly in the absence of stimulant co-intoxicants

GHB-FACILITATED SEXUAL ASSAULT

GHB is used to facilitate sexual assault due to its rapid onset, disinhibitory and amnestic effects, and rapid clearance from blood and urine, which makes the drug difficult to detect [7,52-58]. Voluntary and involuntary intoxication with GHB puts individuals at risk for sexual assault and risky sexual behaviors. Findings suggestive of sexual assault include complaints of unexplained lapses in memory, a sudden onset of intoxication out of proportion to reported ethanol consumption or blood ethanol level, and missing or disheveled clothing. Symptoms consistent with GHB intoxication (eg, agitation, sedation, coma) may be present. The evaluation and management of sexual assault victims are reviewed separately. (See "Evaluation and management of adult and adolescent sexual assault victims in the emergency department".)

Targeted analysis with gas chromatography/mass spectrometry (GC/MS) is necessary for detection of GHB and must be specifically requested. GHB is detectable in blood for 4 to 6 hours and in urine for 6 to 12 hours. Urine is the specimen of choice for toxicological testing in potential assault cases; a first-catch urine specimen is optimal. Collect 100 mL of urine in a standard urine collection cup and refrigerate. Collect 10 to 30 mL of blood in a gray-top tube (containing sodium fluoride and potassium oxalate) and refrigerate. Maintain specimens in compliance with chain of custody rules. Hair analysis for detection of acute drug exposure may be considered at a later date [57,58,62].

ADDITIONAL RESOURCES

Regional poison control centers — Regional poison control centers in the United States are available at all times for consultation on patients with known or suspected poisoning, and who may be critically ill, require admission, or have clinical pictures that are unclear (1-800-222-1222). In addition, some hospitals have medical toxicologists available for bedside consultation. Whenever available, these are invaluable resources to help in the diagnosis and management of ingestions or overdoses. Contact information for poison centers around the world is provided separately. (See "Society guideline links: Regional poison control centers".)

Society guideline links — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links:

General measures for acute poisoning treatment" and "Society guideline links: Treatment of acute poisoning caused by recreational drug or alcohol use".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Care after sexual assault (The Basics)")
- Beyond the Basics topic (see "Patient education: Care after sexual assault (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Sources** – Gamma hydroxybutyrate (GHB) and its analogs (gamma butyrolactone [GBL] and 1,4-butanediol [BD]) have been used recreationally for intoxicant effects, surreptitiously to facilitate sexual assault, and as "dietary supplements" for purported health benefits. (See 'Background' above and 'Epidemiology' above.)
- **Pharmacology** – GHB is a metabolite and precursor of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. GHB interacts with GHB-specific receptors and also acts as a direct agonist of GABA-B receptors. GBL and BD are GHB analogs that are rapidly metabolized to GHB after ingestion, with the same toxic and recreational effects. (See 'Pharmacology and cellular toxicology' above.)
- **Clinical features** – GHB may be lethal in overdose, with or without co-intoxicants. Acute GHB toxicity manifests primarily as dose-related central nervous system (CNS) depression.

Coma is common. Stimulant effects such as psychomotor agitation may occur. Abrupt onset of effects and sudden awakening with resolution of effects frequently occur. Co-intoxicants are common. (See 'Clinical features of acute toxicity' above.)

- **Diagnosis** – The diagnosis of GHB toxicity should be suspected in a patient with an abrupt onset of coma (particularly in the absence of other intoxicants) that resolves spontaneously or abruptly within several hours or in a patient with agitation alternating with somnolence. The diagnosis of GHB toxicity is made clinically based on history, clinical findings, and exclusion of other potentially serious etiologies. GHB intoxication is difficult to distinguish from other causes of obtundation without a clear history. (See 'Diagnosis' above and 'Differential diagnosis' above.)

- **Laboratory evaluation** – GHB is not detectable on routine hospital toxicology screens, and definitive confirmation, which typically may require days to result, is not helpful in the diagnosis and management of acute toxicity. Testing should focus on exclusion of other etiologies of altered mental status and can include fingerstick glucose, acetaminophen and salicylate levels, electrocardiogram, and pregnancy test. (See 'Laboratory evaluation' above.)

- **Management** – Acute GHB intoxication is managed with supportive care. The primary goals are airway protection, control of agitation with sedative medications, and treatment of any complications. Intubation and mechanical ventilation may be necessary. Close monitoring of vital signs and respiratory status (including end-tidal CO_2 if available) is critical in all cases. (See 'Management' above.)

- **GHB-facilitated sexual assault** – GHB is used to facilitate sexual assault due to its rapid onset, disinhibitory and amnestic effects, and rapid clearance from blood and urine, which makes the drug difficult to detect. If testing is needed for forensic purposes, specifically request targeted analysis with gas chromatography/mass spectrometry (GC/MS) for GHB, which is detectable in blood for 4 to 6 hours and in urine for 6 to 12 hours after use. (See 'GHB-facilitated sexual assault' above.)

- **Disposition** – Most patients may be discharged from the emergency department (ED) following observation when they are clinically stable and mental status changes have fully resolved. Recovery may be rapid and abrupt. In some cases, severe coma necessitating intubation and mechanical intubation may require admission. GHB-dependent patients may present with acute toxicity and progress directly into GHB withdrawal; symptoms of withdrawal (eg, anxiety, tremor, diaphoresis, and agitation) generally appear within one to

six hours of cessation. (See 'Disposition' above and "Gamma hydroxybutyrate (GHB) withdrawal and dependence".)

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GRAPHICS

Products containing GHB and related compounds

	Gamma hydroxybutyrate (GHB)	Gamma butyrolactone (GBL)	1,4 Butanediol (BD)
Chemical synonyms	Gamma hydroxybutyric acid, sodium oxybate	2,3(H) furnanone dihydro, dihydro-2(3H) furanone dihydro	Tetramethylene glycol, Sucol B, 1,4 butylene glycol
Street names	G, Gina, Liquid Ecstasy, Liquid E, Liquid X, Georgia Home Boy, Grievous Bodily Harm, Fantasy (Australia, New Zealand), Gamma OH, Salty water, Soap, Swirl Names referring to sexual effects and/or use for sexual assault: Great Hormones at Bedtime, Easy Lay, Scoop	GBL, Lactone, Furanone	BD, One4B, Fantasy (Australia, New Zealand
Pharmaceutical preparations	Xyrem® (US, sodium oxybate) Xyway® (US, oxybate) Alcover®, Somsanit® (Europe)	None	None
"Dietary Supplements" (NOTE: supplements have largely been removed from the market)	Oxy-sleep, Gamma OH, Genetika, Alcover	Blast, Blue Nitro, Blue Nitro Vitality, Eclipse 4.0, Firewater, Furan, Furanone, Furamax, G3, Gamma G, Gamma Ram, GenX, GH Gold, GH Revitalizer, Insom-X, Invigorate, Jolt, Nu-Life, ReActive, Regenerize, Remforce, Renewsolvent, RenewTrient, Rest-Eze, Revivarant, Thunder, V3,	Amino Flex, Biocopia PM, BlueRaine®, Cellu-plex, Dormir, Enliven, InnerG, Liquid Gold, N-Force, NRG3, Potion 9, Rejuv@Nite, Rest-Q, Serenity, Soma Solution SomatoPro, Thunder Nectar, Ultradiol, Zen, and others

		Verve, Verve 5.0, and others	
Cleaners and solvents	None	Beta Tech, Bravo Ink Cleaner, Contact Cement Remover, Miracle Cleaning Cloth, Once Removed nail polish remover, Paton's (non acetone) nail polish remover pads, Tonercleen, Verve 5.0, and others	BlueRaine®, European Cosmetics, Miracle Cleaning Cloth, Organic Hurricane, Phantasy, Puritech, Rejoov, Thunder, Weight Belt Cleaner and others; also Flower Power "plant hormones"
Other products	GHB recipes available on the Internet for easy home synthesis of GHB using GBL and NaOH or KOH	Industrial grade GBL, diverted from chemical supply companies	Industrial grade BD, diverted from chemical supply companies

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Causes of coma

I. Symmetrical, nonstructural
Toxins
Lead
Thallium
Mushrooms
Cyanide
Methanol
Ethylene glycol
Carbon monoxide
Drugs
Sedatives
Barbiturates*
Other hypnotics
Tranquilizers
Bromides
Alcohol
Opiates
Paraldehyde
Salicylate
Psychotropics
Anticholinergics
Amphetamines
Lithium
Phencyclidine
Monoamine oxidase inhibitors
Metabolic
Hypoxia
Hypercapnia
Hypernatremia*

II. Symmetrical, structural
Supratentorial
Bilateral internal carotid occlusion
Bilateral anterior cerebral artery occlusion
Sagittal sinus thrombosis
Subarachnoid hemorrhage
Thalamic hemorrhage*
Trauma-contusion, concussion*
Hydrocephalus
Infratentorial
Basilar occlusion*
Midline brainstem tumor
Pontine hemorrhage*
Central pontine myelinolysis
III. Asymmetrical, structural
Supratentorial
Thrombotic thrombocytopenic purpura¶
Disseminated intravascular coagulation
Nonbacterial thrombotic endocarditis (marantic endocarditis)
Subacute bacterial endocarditis
Fat emboli
Unilateral hemispheric mass (tumor, abscess, bleed) with herniation
Subdural hemorrhage bilateral
Intracerebral bleed
Pituitary apoplexy¶
Massive or bilateral supratentorial infarction
Multifocal leukoencephalopathy
Creutzfeldt-Jakob disease

Hypoglycemia*
Hyperglycemic nonketotic coma
Diabetic ketoacidosis
Lactic acidosis
Hypercalcemia
Hypocalcemia
Hypermagnesemia
Hyperthermia
Hypothermia
Reye syndrome
Aminoacidemia
Wernicke encephalopathy
Porphyria
Hepatic encephalopathy*
Uremia
Dialysis encephalopathy
Addisonian crisis
Hypothyroidism
Infections
Bacterial meningitis
Viral encephalitis
Postinfectious encephalomyelitis
Syphilis
Sepsis
Typhoid fever
Malaria
Waterhouse-Friderichsen syndrome
Psychiatric
Catatonia
Other
Postictal seizure*

Adrenal leukodystrophy
Cerebral vasculitis
Cerebral abscess
Subdural empyema
Thrombophlebitis¶
Multiple sclerosis
Leukoencephalopathy associated with chemotherapy
Acute disseminated encephalomyelitis
Infratentorial
Brainstem infarction
Brainstem hemorrhage
Brainstem thrombencephalitis

Diffuse ischemia (myocardial infarction, heart failure, arrhythmia)
Hypotension
Fat embolism*
Hypertensive encephalopathy
Hypothyroidism
Nonconvulsive status epilepticus
Heat stroke

* Relatively common asymmetrical presentation.

¶ Relatively symmetrical presentation.

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