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GHB Withdrawal Syndrome

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Karen Miotto, MD
UCLA Integrated
Substance Abuse Program
Kmiotto@mednet.ucla.edu

Brett Roth, MD, FACEP
UTSW Toxicology
Training Service
Brett.roth@email.swmed.edu



**Texas Commission on
Alcohol and Drug Abuse**
www.tcada.state.tx.us

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**Texas Commission on
Alcohol and Drug Abuse**

PO Box 80529 • Austin, Texas 78708-0529

9001 N. IH-35, Ste. 105 • Austin, Texas 78753-5233

(512) 349-6600 • (800) 832-9623

Web site: www.tcada.state.tx.us



Emerging trends in GHB withdrawal syndrome, detoxification

About this article

This article details the experience of two physicians in different metropolitan areas who have treated a number of patients who have gone through what appears to be withdrawal after the repeated use of GHB. They describe a syndrome that has similarities to both alcohol withdrawal and benzodiazepine (or other sedative hypnotic) withdrawal.

It is not intended as a set of specific recommendations for management of the described syndrome but rather as an alert that they have attended patients presenting with a specific and unique symptom complex related to the repeated ingestion of GHB.

They acknowledge the management of the syndrome has been arduous and invite others who have witnessed similar patients to contact them to more clearly define patient management and the pathophysiologic mechanisms underlying the proposed disorder.

— John P. Keppler, MD,
Clinical Director,
TCADA

Karen Miotto, MD
UCLA Integrated
Substance Abuse Program
Kmiotto@mednet.ucla.edu

Brett Roth, MD, FACEP
UTSW Toxicology
Training Service
Brett.roth@email.swmed.edu

Summary

- A GHB withdrawal syndrome that has aspects of alcohol withdrawal (delirium tremens) and benzodiazepine withdrawal (long duration of symptoms) is described.
- The syndrome appears to manifest itself in those patients who have self-administered GHB in an around-the-clock dosing schedule, i.e. users who take GHB every 2-3 hours are at increased risk for the emergence of severe symptoms. GHB withdrawal can occur after several months of around-the-clock use.
- Management of the withdrawal syndrome has necessitated the use of high dosages of sedative-hypnotic and physical restraints to control the confusion, delirium, psychosis, and resultant agitation. In the past five years there has been an increase in patients presenting in GHB withdrawal at emergency rooms and behavioral health providers. Stricter federal and state controls on the distribution of GHB have led to the use of a number of GHB analogs including GBL, which produce similar states of withdrawal.
- Recommendations —
 - Medical personnel who might come in contact with patients using dietary supplements and/or drugs of abuse should be aware of the possibility of GHB dependence and withdrawal in some of their patients.
 - Any patient who has been using this drug should be carefully questioned regarding the frequency of GHB use in addition to the amount and duration.
 - GHB withdrawal in its florid state needs to be treated in a hospital setting.

Overview

Many patients who use GHB are not dependent and can be educated about the risks of GHB and referred for outpatient therapy. Experience has shown that patients with a history of around-the-clock dosing may present with a disturbing and difficult-to-manage clinical picture.

This hallmark of severe dependence, i.e., the administration of GHB every two to four hours, 24 hours a day, begins with anxiety, insomnia, tremor, and episodes of tachycardia that develop with discontinuation. Symptoms may rapidly progress to a state of uncontrolled delirium and agitation. Once GHB dependence is recognized, aggressive efforts are generally necessary to ameliorate the patient's signs and symptoms of withdrawal. This is most effectively achieved by detoxifying the patient in an in-patient medical or psychiatric facility. In-patient therapy for GHB withdrawal helps to insure patient safety and dignity and may also decrease the risk of relapse.

Settings where GHB withdrawal may be recognized include the emergency department after treatment of an acute overdose; hospital wards during therapy for unrelated conditions, such as trauma or medical illnesses; physician offices; psychiatric facilities; and detoxification centers.

Assessing GHB Withdrawal Symptoms

Due to the drug's short duration of action and rapid elimination,¹ the signs and symptoms of GHB abstinence syndrome appear rapidly, generally within 1-6 hours after the last dose. Table 1 describes the symptoms commonly encountered during GHB withdrawal and the temporal pattern of their occurrence.² Note that the course of GHB withdrawal symptoms may be prolonged, persisting for up to two weeks or more. After acute detoxification, many patients report persistent symptoms of anxiety, depression, insomnia, and cognitive deficits which often continue for many months.³ Concurrent alcohol and sedative-hypnotic use, the daily dose of GHB consumed, and the existence of concurrent psychiatric illness appear to be

important factors in determining the severity of GHB withdrawal.³

Alcohol vs. GHB Withdrawal

It appears that GHB withdrawal shares features of both alcohol withdrawal and benzodiazepine withdrawal (i.e., prolonged duration of symptoms).

Agitation can be ameliorated by pharmacological therapy but the delirium is highly resistant.

Unlike alcohol or sedative-hypnotic withdrawal, the initial symptoms of GHB withdrawal appear early, often within an hour, and delirium evolves more rapidly.³ Peak manifestations of the withdrawal syndrome may occur within 24 hours, and like delirium tremens, may last up to 14 days.^{2,3} Neuropsychiatric symptoms including confusion, psychosis, and delirium are similar to those seen with delirium tremens⁴ and appear to be the prominent features of GHB withdrawal.

Unlike delirium tremens from alcohol, autonomic instability (diaphoresis, tremor, hypertension, and temperature dysregulation) appears to be slightly less severe. Brief episodes of significant tachycardia begin (heart rate 160 or more) early in GHB withdrawal.

Treatment Guidelines for GHB Withdrawal

The following information is based on a review of the limited medical literature and clinical experience, and is not intended for the use of GHB-dependent individuals without the supervision of a medical doctor. To date, there is no medical literature establishing the safety and efficacy of any particular GHB detoxification protocol. Controlled trials are needed.

These treatment guidelines should be considered as a starting point for the treatment of more severe cases of GHB withdrawal syndrome. Less tolerant individuals may require a less aggressive approach.

TABLE 1: TEMPORAL PATTERN OF THE SYMPTOMS OF GHB WITHDRAWAL²

(Symptoms do not always progress from mild to severe in a predictable fashion.)

SYMPTOMS:	Early (1-24 hours)	Progressive (1-6 days)	Episodic when waning (7-14 days)
Anxiety/Restlessness	++	+++	++
Insomnia	+++	+++	++
Tremor	+	++	+
Confusion	++	+++	++
Delirium	++	+++	+++
Auditory, tactile, and visual hallucinations	+	+++	++
Intermittent Tachycardia	+++	+++	++
Hypertension	+	++	+
Nausea	++	+	+
Vomiting	++	+	0
Diaphoresis	+	++	+

Key: Mild = +, Moderate = ++, Severe = +++**Other signs and symptoms of acute GHB abstinence syndrome may include^{2,5}**

- Anorexia, abdominal cramps
- Nightmares
- Impaired concentration, memory, and judgment
- Increased sensitivity to sounds and tactile sensations
- Delusions
- Tonic-clonic activity (it is unclear if actual seizures occur during GHB withdrawal)
- Elevated temperature
- Dehydration

Recommendations for In-patient Therapy

While successful attempts at self-tapering doses of GHB have been reported among abusers, most GHB-dependent individuals are unable to tolerate the symptoms of withdrawal. Physicians should be aware that patients disabled by lack of sleep, and other disturbing symptoms, may attempt to self-detoxify by taking large doses of alcohol or medications, including benzodiazepines. Use of multiple substances in an unsupervised setting may place the patient in danger of drug overdose and can contribute to withdrawal severity. For the above reasons, an aggressive 7-14 day inpatient strategy with close follow-up care is recommended.

Benzodiazepines

Benzodiazepines such as lorazepam (Ativan), chlordiazepoxide (Librium), and diazepam (Valium), are useful in ameliorating some of the signs and symptoms of GHB withdrawal. Loading doses of oral or intravenous benzodiazepines do not decrease the likelihood of withdrawal delirium, but are important for controlling psychotic agitation.³ Most patients in GHB withdrawal have an extremely high tolerance to the sedating effects of benzodiazepines and require large frequent doses similar to those required for the treatment of severe alcohol withdrawal. In one case treated in an intensive care unit, one author (BR) described a patient who required 129 mg of lorazepam and 40 mg of diazepam during the first day of hospitalization.² Other case reports of severe withdrawal describe using 507 mg of lorazepam and 120 mg of diazepam over 90 hours to control agitation.⁶ Such large benzodiazepine

doses necessitate close medical attention and the application of continuous pulse oximetry to monitor for oxygen desaturation. A larger sample of patients in GHB withdrawal is necessary before general dosing for benzodiazepine administration can be established.

Other Medications

Barbiturates: Barbiturates in combination with benzodiazepines have been used successfully to lower benzodiazepine requirements and improve withdrawal symptoms. Pentobarbital, a short acting parenteral barbiturate, can be titrated intravenously in 100-200 mg increments to symptoms. Phenobarbital also may be used and has the advantage of providing a longer duration of action due to its longer half life ($T_{1/2}$ ~90 hours). Depending on the dose of benzodiazepine already received, phenobarbital may be titrated in 250 mg increments intravenously to achieve a serum phenobarbital level of 5-15 micrograms per milliliter with most patients requiring approximately 500 mg for immediate control of symptoms. Tapering oral doses of both benzodiazepines and barbiturates can then be used over the course of several weeks when the patient's condition has stabilized.

Sedating Agents: Propofol is an anesthetic agent used for sedation in the ICU that has been reported to provide relief for the psychotic agitation in patients in severe GHB withdrawal.

Other Anticonvulsants: Patients in GHB withdrawal often demonstrate twitching, grimacing, and tonic-clonic movements. The concern of withdrawal seizure activity has not been adequately evaluated by current studies and even though some believe these movements represent myoclonus, rather than true seizures, the addition of anticonvulsants to the treatment regimen of patients with twitching or tonic-clonic activity seems wise.

Gabapentin has been used anecdotally (300 mg three times a day on day one, increasing the dose to 2-3 grams over the course of a week) with the goal of decreasing excitotoxicity and agitation.

Sodium Divalproate increases endogenous GHB levels and has been considered in the treatment of GHB withdrawal. While Sodium Divalproate can transiently elevate transaminase levels, elevated transaminase levels have been reported in patients during GHB withdrawal that were not treated with Sodium Divalproate. The significance of elevated liver function tests during GHB withdrawal has not been determined.

Antihypertensive Medications: Patients may request medications such as beta-blockers for the treatment of minor autonomic hyperactivity such as elevated heart rate, elevation of blood pressure, sweating, tremor, or panic attacks. Although blocking beta-adrenergic receptors is effective in decreasing autonomic symptoms, it is not effective in preventing delirium or psychosis, and thus should not be prescribed. However, clonidine has been used to provide relief of the intermittent episodes of tachycardia, which are described by patients as their heart "pounding" or "racing."

Animal models of agitated delirium suggest that beta-blockers used to control vital sign abnormalities via peripheral beta-blockade, without central nervous system sedation, may be detrimental.⁷ In the setting of catecholamine excess, beta-blockade may cause unopposed alpha-1 receptor stimulation and paradoxical vasospasm leading to worsening hypertension and even coronary ischemia.⁸ For these reasons, the use of beta-blockers in the setting of severe withdrawal is not recommended.

Haloperidol and Other Antipsychotic Medications: Clinicians have reported using large doses of antipsychotic medication in an attempt to control GHB withdrawal psychosis.⁹ In the authors' experience, antipsychotic medication, such as haloperidol in large doses, provided limited control of symptoms. Benzodiazepines and phenobarbital have been shown to provide better control of psychotic symptoms.⁹ Beware of dystonic reactions and temperature dysregulation if haloperidol or other neuroleptics are used with agitated, hyperthermic patients. Neuroleptics may also increase the risk of neuroleptic malignant syndrome and malignant hyperthermia.

Vitamins: Concerns are raised that GHB-dependent patients may have vitamin deficiencies due to poor nutritional habits. One case of thiamine deficiency has been reported.¹⁰ High-potency multivitamins and thiamine may be beneficial. The role of thiamine in delirium tremens and associated neurological syndromes is well known in cases of alcoholism and remains to be determined in GHB.

Medical Complications of GHB Withdrawal

Fluid and Electrolyte Imbalance: Clinical management of GHB withdrawal requires maintaining the patient's fluid and electrolyte balance during detoxification. Many patients lose their appetite and ignore food and water. Patients who become dehydrated should receive intravenous fluids, electrolytes, dextrose, and thiamine.

Fever: Elevation of temperature has been reported in severe cases of GHB withdrawal.⁹ Patients often become extremely agitated and require the application of four-point restraints for safety. Evaluation of potential sources of infection, such as meningitis or aspiration pneumonia, is essential. This is particularly true in patients who receive high doses of medications to control withdrawal.

Rhabdomyolysis: Severe agitation may lead to rhabdomyolysis requiring fluid therapy to establish a brisk urine output and the need for aggressive sedation to decrease muscular activity.

Death: One case of GHB withdrawal resulted in an unexpected death on hospital day 12.² Whether or not this patient's death was directly related to the GHB withdrawal syndrome is speculative. Autopsy results failed to implicate other medical causes for the patient's death. Further research is needed to determine if other GHB fatalities have occurred during withdrawal.

Hypothesis for the Mechanism of GHB Tolerance and Withdrawal

Specific detoxification protocols for GHB withdrawal await a better understanding of the neurobiology of GHB addiction. Clinical observations suggest that GHB abuse leads to tolerance and increased frequency of dosing. In Figure 1, it is postulated that GHB tolerance is associated with dysregulation of inhibitory neurotransmitter systems including GABA and GHB. Decreased GHB consumption and the withdrawal state may be associated with excitotoxicity involving neurotransmitter systems such as glutamate, norepinephrine, and dopamine.

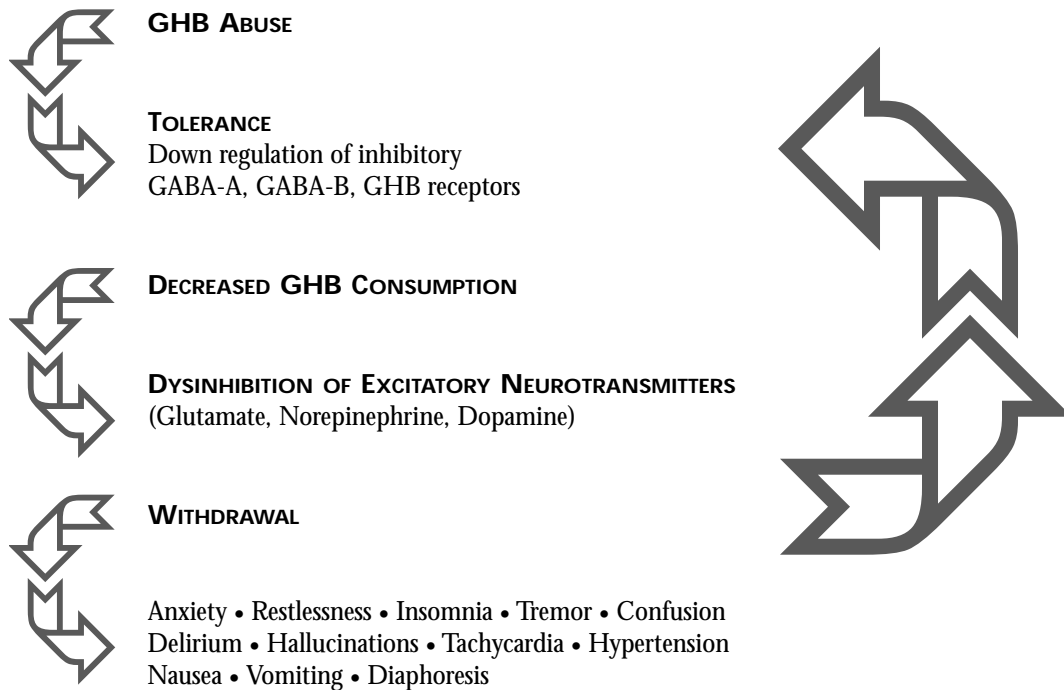
Pathophysiology

Pathophysiologic mechanisms of withdrawal are complex and vary according to the substance abused (see Table 2).

Perhaps the most important activity GHB possesses with regard to its withdrawal syndrome is a close metabolic relationship with GABA. An *in vivo* conversion of radioactive GHB into GABA has been described and it appears that, along with exerting a distinct effect at special GHB receptors, GHB possesses "GABAminergic" properties as well.¹¹ Current research has proposed that GHB modulates both GABA A receptors and GABA B receptors.¹² The end result, acutely, is neuroinhibition with physiologic tolerance developing with frequent dosing.

Clinical similarities between GHB withdrawal and other sedative hypnotic withdrawal syndromes suggest that shared common mechanisms of central action may exist. Ethanol increases endogenous levels of GHB and acts synergistically with GHB to produce central nervous system and respiratory depression.¹³ Cross-tolerance has been demonstrated between ethanol and GHB in rats, and GHB has been used to suppress withdrawal symptoms in patients presenting in

FIGURE 1. CYCLE OF ABUSE, PHYSIOLOGIC TOLERANCE AND GHB WITHDRAWAL PATHOPHYSIOLOGY



acute alcohol withdrawal.^{14,15} Chronic alcohol, benzodiazepine, and GHB administration have been shown to cause down-regulation of inhibitory GABA receptors.^{16,17} During benzodiazepine withdrawal, GABA synaptic activity becomes so diminished that inhibitory control of excitatory neurotransmitters and pathways is also lost, and the subsequent withdrawal syndrome ensues.¹⁸ A similar type of situation may be occurring with GHB withdrawal. One also may speculate that an excess dopaminergic state, shown to be associated with psychotic hallucinosis,¹⁹ may be part of the GHB withdrawal syndrome. Baclofen, a GABA B receptor agonist has also been associated with severe psychological reactions during withdrawal states.^{20,21}

Undoubtedly, several mechanisms are responsible for the GHB withdrawal state and future studies are necessary to clarify these mechanisms.

Contribute Your Clinical Case Experiences

The authors welcome any feedback regarding the success or failure of any treatment regimens being used in your area. Your feedback will allow these guidelines to be refined and more closely tailored to the severity of withdrawal experienced by each patient. Your communication of the successes and failures of different treatment approaches will help achieve the goal of improved care for patients with GHB withdrawal.

The authors are particularly interested in knowing about successful pharmacologic therapies and doses, tapering regimens, behavioral therapies, as well as how, or if, successful detoxification has been achieved without patient hospitalization.

TABLE 2. COMPARISON BETWEEN VARIOUS WITHDRAWAL SYNDROMES²

Substance	Onset/ Duration	Autonomic Instability	Neuropsychiatric Symptoms	Mortality	Possible Mechanism inducing W/D State
GHB	1-3 hrs/ 6-12 days	Mild	Severe	?	Loss GHB, GABA A, and GABA B mediated inhibition
Benzodiazepine	1-3 days/ 5-9 days	Moderate	Moderate	1%	Loss of GABA A mediated inhibition
Ethanol	Usually >6 hrs/ 10-14 days	Severe	Moderate to Severe	5-15%	Loss of GABA A mediated inhibition, disinhibition of NMDA receptors

Conclusion

Gamma-hydroxybutyrate (GHB) is an emerging drug of abuse with anesthetic and sedative-hypnotic effects. GHB is easily made and sold under multiple names such as Renutrient and Revitalize Plus. In addition, GHB analogs such as Gamma-butyrolactone (GBL) continue to surface, often disguised as health food supplements, and can be readily found on the Internet. These frequent name changes and analog preparations have contributed to the lack of awareness of the risks and dangers associated with GHB use. This has also resulted in confusion for medical care providers who provide care for patients in GHB withdrawal.

Emerging medical information has recently provided new insights about GHB dependence and withdrawal. However, research on treatment is an important area that remains to be developed. This manuscript was created to alert medical care providers to some of the risks and dangers associated with GHB withdrawal. It is the authors' experience that many clinicians are unaware of the signs of GHB withdrawal and similarly do not know how to provide symptomatic relief for GHB withdrawal symptoms. This has deterred patients from seeking the proper medical care. This manuscript was created to inform and provide health care providers with a framework for treatment, and is not intended that users of GHB use this information as a guide to self-medicate.

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