

Part 2 of the GHB review article series

## GAMMA-HYDROXYBUTYRATE (GHB) WITHDRAWAL

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### Case

A 35-year-old man with no significant medical history presented to a university ED complaining of anxiety, tremors and insomnia. The patient denied use of common street drugs or tobacco. He admitted to social weekend alcohol consumption, but had not been drinking during the preceding 2 weeks. His vital signs were: temperature 37.2°C, pulse 105/min, respirations 16/min, blood pressure 148/88 mmHg. Physical examination revealed a muscular young man with a resting tremor and obvious anxiety, but was otherwise unremarkable. The patient's girlfriend took the physician aside and revealed the actual reason for seeking ED treatment was that he was trying to quit using GHB. She also confirmed he had not been drinking alcohol and was not a habitual alcohol user. The patient subsequently admitted to using increasing amounts of GHB for the previous 2.5 years, and was consuming 1 to 2 "capfuls" of liquid GHB 4 to 6 times daily (exact dose unknown). His last dose was 20 hours prior to presentation. The patient first started using GHB at the urging of weight-lifting friends. He had attempted to quit multiple times without success. A presumptive diagnosis of GHB withdrawal was made. The patient was treated with 20 mg of oral diazepam in the ED, which relieved the tremors. After a 3-hour observation period, he was discharged with a 3-day prescription for lorazepam, referred to a local primary care clinic and given substance abuse counseling information.

Although laboratory confirmation of GHB use was not obtained, this case illustrates the features of GHB withdrawal that will be discussed in this article: the clinical manifestations of the GHB withdrawal syndrome, the similarities to withdrawal from other sedative-hypnotic agents, and the treatment options. Recognizing and treating GHB withdrawal will be of increasing importance to emergency physicians as its popularity continues to grow.

### Clinical Manifestations

GHB is a naturally occurring substance, found in highest concentrations in the basal ganglia and hypothalamus of brain tissue.<sup>1</sup> Although commercial sale of GHB is illegal in the United States, it is still easy to obtain, as evidenced by its abundance at rave parties. GHB recipes and various precursor formulations containing gamma-butyrolactone, 1,4-butanediol, dihydro-2(3H)-furanone and 4-butanolide are also available via the internet.<sup>2</sup> The precursors are converted *in vivo* to GHB after ingestion. GHB is popular among rave crowds and body-builders, and has been implicated as a "date-rape" drug. Investigational narcolepsy treatment is the only FDA approved use for GHB in the United States.

As GHB use has increased because of its sedative, eu-

phoric and purported anabolic effects, a clinical GHB withdrawal syndrome has emerged among habitual users. The habit-forming nature of GHB and a description of clinical features associated with abruptly stopping or decreasing use was first noted in 1994.<sup>3</sup> A withdrawal syndrome is characterized by various expectant psychological and/or physical signs and symptoms caused by the abrupt cessation of a drug that is used habitually. Given the multiple independent descriptions of similar signs and symptoms associated with the cessation of chronic GHB use, GHB is now considered to possess a true withdrawal syndrome.<sup>4,11</sup> Based on these case series and reports, the signs and symptoms of GHB withdrawal include varying degrees of anxiety, agitation, and insomnia. Ophthalmoplegia with sixth cranial nerve palsies has been reported in association with GHB withdrawal, although this may represent concomitant thiamine deficiency. Autonomic hyperactivity manifesting as diaphoresis, tremors, tachycardia or elevated blood pressure is commonly reported. Behavioral and psychiatric features include paranoia, hallucinations (auditory and/or visual) and delirium. Symptoms may manifest as soon as 12 hours after last use and may last up to 12 days. It is believed that more severe symptoms occur in individuals with longer habits and in those taking larger amounts of GHB. Many patients will also have a history of prior GHB cessation failures.<sup>9</sup>

The largest report of cases implicating a physical dependence to GHB came from Italian researchers using GHB for treatment of alcohol dependence.<sup>5</sup> Eleven patients (10% of subjects completing a 24 week protocol of t.i.d. dosing of 50mg/kg GHB) developed "cravings" for the drug and voluntarily increased their doses to achieve anxiolytic and hypnotic effects. The authors noted that anxiety and insomnia were reported after decreasing the GHB doses, which likely represented mild GHB withdrawal.

### Similarity to Other Withdrawal Syndromes

GHB withdrawal appears to be very similar to ethanol, benzodiazepine (BZD) and barbiturate withdrawal. This similarity is likely related to GHB's chemical structural similarity with GABA, the principle inhibitory CNS neurotransmitter. GHB exhibits a marked affinity for the GABA<sub>B</sub> receptor, compared to the GABA<sub>A</sub> receptor, as well as an affinity for a recently discovered GHB-specific receptor. An extensive review of the neuropharmacology of GHB by Tunnicliff<sup>12</sup> reveals that low doses of GHB tend to inhibit CNS dopamine release, whereas in higher and sustained doses, analogous to a habitual user, CNS dopamine levels increase. A decrease or total cessation of the dependent drug is all that is needed to precipitate the clinical withdrawal, a feature common to many sedative-hypnotic agents.

Table 1 shows the time course of symptoms for the withdrawal syndromes from GHB and some other substances of abuse. Autonomic hyperactivity is common in CNS depressant withdrawals, with symptoms ranging from mild tachycardia and tremor to extreme diaphoresis and elevated blood pressure. Seizures have not been reported to occur in GHB withdrawal, however, the number of case reports is relatively small. Aside from seizures, no other clinical feature reliably distinguishes GHB withdrawal from the other sedative-hypnotic withdrawal syndromes. Thus, obtaining a truthful history from the patient, a close friend or relatives is crucial.

For patients who openly admit to habitual GHB use,

the diagnosis is straightforward. However, for patients with the myriad of symptoms which by themselves are not diagnostic or pathognomonic, making the diagnosis and initiating treatment can be challenging. Negative urine or serum toxicology screens for other common drugs of abuse can be useful in making the diagnosis. GHB, however, is not detected by routine drug tests. Specific serum or urine testing for GHB is not generally indicated and is not widely available, except at regional specialty labs. There appears to be cross-reactivity of GHB with ethanol, BZDs and opiates, which may explain why many patients coingest these other substances, perhaps in an attempt to offset the withdrawal symptoms.<sup>6,7,9,13</sup> GHB has been used successfully for over a decade in Europe to treat opioid and alcohol dependence,<sup>13,14</sup> lending further support to the notion of pharmacological cross-tolerance among these CNS depressants.

*Treatment Options*

Clinically, patients respond well to BZD treatment and supportive measures while other diagnoses are worked up and excluded. Table 2 summarizes the various medications that have been reported as useful for GHB withdrawal. Case reports indicate that the best results are achieved using a benzodiazepine, alone or in combination with an antipsychotic agent. Intermediate- to long-acting BZDs are emerging as the first-line treatment of choice: 20mg oral diazepam or 4mg oral lorazepam is a suggested starting dose. Massive amounts of sedatives (507mg lorazepam and 120mg diazepam in one patient over 90h) have been reported in one case series.<sup>9</sup> Behavioral and psychotic features of GHB withdrawal respond to antipsychotic medications. Referral to outpatient substance abuse and support groups is recommended. Patients with severe withdrawal features, hemodynamic instability, florid psychosis or those requiring large doses of medication to control symptoms should be admitted to an appropriate monitored unit for continuous cardiopulmonary and neurologic monitoring.

**TABLE 1**

*Common Withdrawal Syndromes*

<u>Dependent Substance</u>	<u>Onset of Symptoms</u>
<u>Duration</u>	
GHB	12 h-12 days
1-7 days	
Sedative-hypnotics	2-7 days
1-2 weeks	
(BZD, Barbiturates)	
Ethanol	6-24 h
2-5 days	
Opioids	4-36 h
3-14 days	

*Summary*

Habitual ingestion of GHB has been associated with a withdrawal syndrome consisting of autonomic hyperactivity and various behavioral and psychotic features when the drug is stopped or the dose is decreased. The description of a GHB withdrawal syndrome is based on multiple, independent descriptions of similar clinical presentations in patients with admitted or confirmed GHB habitual use. GHB withdrawal is similar to other sedative-hypnotic withdrawal syndromes. The popularity of GHB with the rave crowd and body-builders is increasing. Emergency physicians need to be aware of the signs and symptoms associated both with GHB intoxication and with GHB withdrawal. Benzodiazepines are first-line treatment for mild GHB withdrawal; severe cases with unstable vital signs or florid psychosis should be treated in an inpatient setting.

**TABLE 2**  
Medications Used in GHB Withdrawal

<u>Benzodiazepines</u>
lorazepam <sup>4,6,7,9</sup>
diazepam <sup>8,9,11</sup>
<u>Antipsychotics</u>
haldoperidol <sup>6,7</sup>
chlorpromazine <sup>4</sup>
Phenobarbital <sup>6</sup>
Propranolol <sup>15</sup>
(reference 15 also used unspecified BZDs and antipsychotics)

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*EMERGING INFECTIONS in 2001*

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Emerging infections continues to be a hot topic in the infectious disease literature. Articles continue to be published revealing more insights into new diseases and disease processes. PCR and molecular techniques have made this detective work much reliable and accurate. Some of the more recent articles include the following:

**Transmission of Lyme disease. How long must a tick bite?**

Ticks can remain attached to humans for long periods of time feeding on blood. It has been debated how long a tick must remain attached for the Lyme spirochete *Borrelia burgdorferi* to actually migrate through the tick and flow into the human host. In this study, (Vignes, *JID* 2001, 183:773-8), infected ticks were allowed to attach to mice and were removed at 24 hour intervals up to 96 hours. Infectivity of both ticks and mice for *Borrelia burgdorferi* was tested using PCR techniques. No mice became infected if ticks were removed before 24 hours. Between 24 and 48 hours only 8% of mice became infected. Ticks allowed to feed 72 hours transmitted Lyme disease to 66% of host mice. Ticks allowed to feed 96 hours transmitted disease to 92% of host mice. If this can be correlated to humans, it would mean that the chances of acquiring Lyme disease for a tick that had been attached for less than 48 hours would be minimal

**What are the complications associated with La Crosse Encephalitis?**

La Crosse Encephalitis is one of the more virulent forms of California Encephalitis, a *bunyivirus* wide-spread throughout the United States. The disease has an animal reservoir and is transmitted to humans via mosquitoes primarily in rural areas. Some states have aggressive mosquito abatement control, in part for the control of potentially serious diseases like La Crosse Encephalitis. Many children may present with only flu-like symptoms such as headache, fever, and discharge from an emergency room with a diagnosis of "viral syndrome." However, a recent article by McJunkin suggests that some children who develop La Crosse Encephalitis may not fair so well (McJunkin, *N Engl J Med*, 344[11]:801-7). In an analysis of 127 patients, most were found to present with symptoms of headache, fever, vomiting, seizures, and disorientation during the summer months. Ten percent of children developed a complicated course including intubation and ICU care. Although all children survived, 12% overall had significant permanent neurologic problems including decreased IQ, paralysis, memory loss and behavioral changes or cerebral dysfunction