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Inpatient Gamma-Hydroxybutyrate Detoxification: A Case Report Describing Day-to-day Therapeutic Management

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Background: Gamma-hydroxybutyrate (GHB) is a synthetic drug increasingly used by consumers of psychoactive substances. The sought after psychoactive effects of GHB have resulted in an increase in recreational use in Europe. GHB is considered to have a high dependence potential, and abrupt discontinuation after long-term use can result in a severe withdrawal syndrome. Despite a large number of publications related to GHB withdrawal and detoxification, to date, no evidence-based protocol or consensual international therapeutic guidelines are available (over and above the administration of benzodiazepines). We hereby present a day-to-day description of inpatient GHB detoxification management, from admission to discharge.

Case Summary: This case report pertains to a 47-year-old patient hospitalized for a severe GHB use disorder. The patient had independently made several unsuccessful attempts to stop GHB use. Following to these failures, the patient was oriented to our addiction department for inpatient detoxification. Withdrawal symptoms appeared 4 hours after the last dose of GHB, and consisted of diaphoresis, coenesthetic hallucinations, tremors, motor instability,

tachycardia, and a hypertensive peak. Symptoms were successfully managed with diazepam titration and nonpharmacological treatment. The duration of hospitalization was 13 days. At discharge, detoxification was complete and the patient was engaged in relapse prevention therapy. Three months after discharge, the patient had maintained abstinence.

Conclusions: GHB withdrawal, which can be severe, is better prevented or attenuated by daily medical monitoring and adjustment of treatment dosage. Failure of outpatient detoxification should be included in the indication criteria in the guidelines for inpatient detoxification.

Key Words: case report, gamma-hydroxybutyrate, substance use disorder, therapeutic management, withdrawal

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Gamma-hydroxybutyrate (GHB) is an endogenous compound both precursor to and metabolite of gamma aminobutyric acid (GABA). GHB is found in the hippocampus, cortex, thalamus, and amygdala where it binds to GHB receptors (White, 2017). Exogenous GHB is absorbed through the digestive system and easily crosses the blood-brain barrier. Exogenous administration of GHB results in the activation of the GABA-B receptor. GHB has a high affinity to GABA-B receptors and to a lesser extent to subtypes of GABA-A receptors (Kamal et al., 2015). In addition to interacting with GABA and GHB receptors, GHB has been shown to produce effects linked to other neurotransmitters, in particular dopamine, serotonin, acetylcholine, and norepinephrine (Wong et al., 2004). The effects of GHB on the central nervous system are 2-fold; GHB initially acts as an inhibitor of dopamine release, before secondly increasing dopamine concentrations. Furthermore, small increases in central nervous system serotonin and norepinephrine concentrations also occur. GHB produces a mix of stimulant-sedative subjective effects (Busardo and Jones, 2015). The dose-effect curve for GHB is steep, this means that small increases in dosage result in disproportionately large increases in effects and toxicity. Lower doses are sufficient to induce euphoria and well-being, whereas larger doses result in drowsiness and effects on both speech and motor coordination (Wood et al., 2011). GHB is approved as a treatment option for cataplexy in narcolepsy (the exact mechanism has not been elucidated, although a mechanism via the stimulation of inhibitory extrasynaptic GABA receptors has recently been proposed [White, 2017]). GHB is also used illicitly. Recreational users

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Written consent for the publication in medical literature was obtained from the patient.

LVT, JC, and HB were involved in the care and the treatment of the patient. CVV, DB, MR, and MGB participated in the interpretation of data. LVT wrote the first draft of the manuscript. MR, MGB, and CVV revised the manuscript. All authors approved the final version of the article to be published.

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seek GHB-induced euphoria, anxiolysis, and positive effect on libido. These effects explain the increase of the recreational use of GHB, during the last decades, in Europe (Corkery et al., 2015). Moreover, GHB has been incriminated in sexual assaults. Cases of sexual assault may be underreported as victims may be, due to the administration of GHB, heavily sedated or comatose. GHB-induced amnesia can also add further difficulty in the recollection of facts. This leads to a delay before care. When finally admitted for care, a victims' plasma or urine GHB concentrations may be too low to detect. Due to the potent depressant effect on the central nervous system, high GHB concentrations in plasma might cause death from cardiorespiratory depression (Busardo and Jones, 2015). Furthermore, GHB is considered to have a high dependence potential, and abrupt discontinuation after long-term use can result in a severe withdrawal syndrome (Kamal et al., 2016c). Despite a large number of publications related to GHB withdrawal and detoxification (eg, de Jong et al., 2012; Ghio et al., 2014; Kamal et al., 2014; Kamal et al., 2016a, 2016b, 2016c), to date, no evidence-based protocol or consensual international guidelines are available—over and above the administration of benzodiazepines (de Jong et al., 2013; McDonough et al., 2004; Busardo and Jones, 2015; Kamal et al., 2016c).

In the following sections, we discuss the clinical presentation and therapeutic implications relative to a 47-year-old patient hospitalized for GHB detoxification. To our knowledge, this is among the first detailed day-to-day descriptions of the management of inpatient GHB detoxification, from admission to discharge.

CASE PRESENTATION

Mr X is a 47-year-old patient with a medical history characterized by Peyronie disease, treated with several surgical interventions. He also reported chronic use of cocaine.

Mr X began using GHB in a social context, at a swingers' party when he was 37 years old. The substance allowed him to improve his sexual ability and to decrease his performance anxiety, with entactogenic and anxiolytic effects persisting for a few hours. Progressively (for several years), these effects became shorter and less potent, indicating a pronounced phenomenon of tolerance. Mr X's use of GHB gradually became daily, and then increased to multiple uses per day (a total of 15–20 g of GHB a day, split into doses taken every 3 hours). Mr X described strong craving with a loss of control over his use, leading to a reduction of his social and recreational activities. Seven years after his first encounter with the drug, Mr X began to synthesize GHB at home. The precursors gamma butyrolactone and sodium hydroxide were ordered over the Internet. The chronic use of GHB resulted in a psychomotor retardation, an attention deficit disorder and alexithymia. Although, he was aware of the negative consequences of his consumption, Mr X was unable to stop. Indeed, he had made several attempts at detoxification, independently of any medical support. Each attempt was marked by the following symptoms: sweating, shaking, palpitations, motor instability, increased anxiety, and increased craving.

Following to these failures, the patient was referred to our addiction center by his general practitioner. A severe GHB

use disorder according to the *Diagnostic and Statistical Manual of Mental Health Disorders 5th edition* (American Psychiatric Association, 2013) was diagnosed, and medical detoxification was programmed in our inpatient detoxification unit. A multidisciplinary approach is provided, combining physical, psychological and social interventions, and a medication protocol. The GHB inpatient detoxification time line is presented in Figure 1.

Following the admission, withdrawal symptoms appeared 4 hours after the last dose of GHB with diaphoresis, tremors, motor instability, tachycardia, and hypertensive peaks (systolic blood pressure 190 mm Hg). The patient also reported coenesthetic hallucinations of the trunk and limbs, accompanied by a painful feeling of “sweating flames” and “burning skin.” Mr X recognized the hallucinatory nature of these sensations and was able to critically analyze them. A chromatographic assay found a urinary level of GHB of 3160 mg/L. Screening of urine sample for other substances (cocaine, opiates, methadone, buprenorphine, and tetrahydrocannabinol) was also done by immuno-fixation. Only benzodiazepines were prescribed by the patient's general practitioner for anxiety were detected. A complete blood cell count showed hyperleukocytosis 12,900/mm³ with normal C-reactive protein, liver function tests indicated minimal cytolysis of 1.5N. No hydroelectrolytic disorders or rhabdomyolysis was found.

To reduce withdrawal symptoms, Mr X was treated with diazepam. Dosage, of up to 60 mg/d, was adjusted daily. No adverse effects were observed during treatment. Nondrug measures included the development of outdoor activities (walking alone or with a nurse) and cold showers aimed at soothing the coenesthetic sensations. Symptoms persisted for 48 hours in paroxysmal fashion before gradually subsiding on day 8, allowing for the rapid reduction in diazepam dosage (as shown in Fig. 1). The Cushman score (Cushman et al., 1985) was recorded during day 1 through day 4 to assess the severity of the GHB withdrawal symptoms. The Cushman score, usually used for alcohol withdrawal management, is calculated from the clinical data of blood pressure, heart rate, breathing rate as well as the presence of tremors, sweating, agitation, and sensory symptoms. In the absence of a specific GHB withdrawal management tool, we decided to use the Cushman score as GHB withdrawal presents symptomatic similarities with alcohol withdrawal. GHB urine concentration was zero on day 4 and withdrawal symptoms present at admission completely regressed after day 8. After discharge, relapse prevention therapy was continued. Three months after discharge Mr X was still abstinent.

DISCUSSION

This case report pertains to a patient who successfully completed inpatient GHB detoxification, after several unsuccessful detoxification attempts without any medical support. We are reminded of the existence of severe GHB use disorders and this case also confirms existing data on withdrawal modes: the rapid onset of symptoms (Wojtowicz et al., 2008), clinical symptoms similar to those of GABAergic withdrawal (Miotto et al., 2001), the frequency of hallucinatory symptoms (Hernandez et al., 1998), and the effectiveness of long half-life benzodiazepine therapy—including

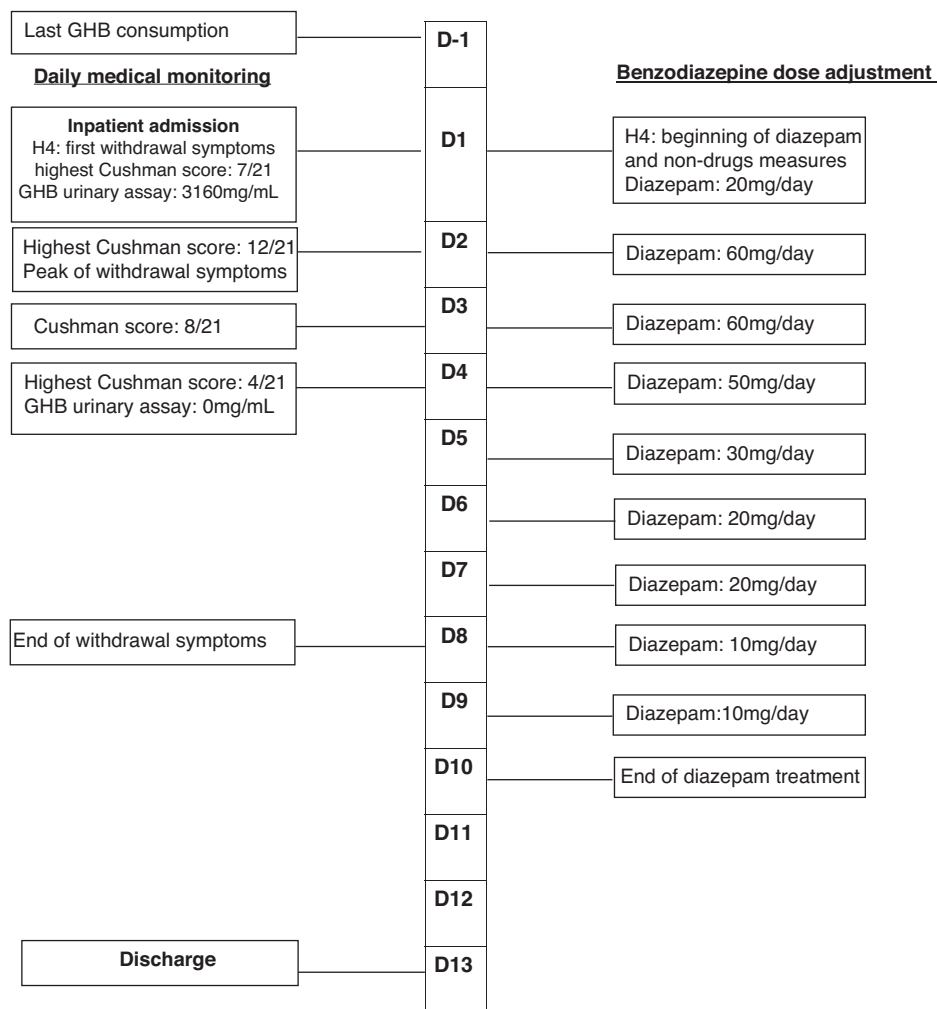


FIGURE 1. Time line of the reported GHB inpatient detoxification and benzodiazepine protocol. D, days; GHB, gamma hydroxy butyrate; H, hours.

diazepam as a first intention therapeutic option to endure withdrawal symptoms (McDonough et al., 2004). In this case report, withdrawal symptoms lasted 8 days, which can be considered as a long time in light of the period of elimination of GHB. Withdrawal symptoms beginning within 1 to 12 hours after the last dose (4 hours for our patient) and which may continue for 3 to 21 days were reported in literature (Wojtowicz et al., 2008). Although it is known that GHB increases the intracellular level of dopamine in both the mesolimbic system and the nigrostriatal pathway, the translation to the clinical symptoms observed during withdrawal is unclear. The sustained modifications within the central nervous system (Nicholson and Balster, 2001), persisting even after stopping GHB, could explain the kinetics and the complex forms of the withdrawal syndrome (agitation, anxiety, hallucinations). Treatment with typical or atypical antipsychotics has been necessary in some cases (McDonough et al., 2004), although not for the patient in this case report. This suggests that scheduled inpatient detoxification, with daily supervision and medication dosage adjustments, could help patients cope with the severity of withdrawal syndrome and

prevent complications. Recently, Kamal et al. (2014) have developed decision guidelines to determine whether an outpatient or inpatient setting should be chosen. Surprisingly, they do not consider a history of unsuccessful outpatient detoxification as a criterion for the indication of inpatient detoxification. In this context, it is important to establish consensual international guidelines. Furthermore, using an established tool for the management of GHB withdrawal syndrome symptoms could provide a basis for improved adaptation of medication dosage to the specific needs of patients.

One must also keep in mind that the best treatment remains prevention. To achieve this, 2 barriers must be prioritized. First, medical use of GHB should be limited, because of its potential for misuse, to a few indications under strict medical supervision. Caution is particularly required when a history of substance use disorder (Caputo et al., 2009) or borderline personality disorder (Keating, 2014) is reported. Secondly, prohibiting the selling of GHB precursors (gamma butyrolactone and 1,4-butanediol) to the public, as decided by some governments (eg, the French Ministry of Health's

decision on September 2, 2011). These measures aim to minimize the availability GHB and the associated risks of intoxication and dependence.

CONCLUSIONS

The example of Mr X highlights the value of case reports and the insight that they can provide in establishing specific consensus on the management of GHB use disorder. Indeed, GHB withdrawal, which can be severe, is better prevented or attenuated by daily medical monitoring and adjustment of treatment dosage. Failure of outpatient detoxification should be included in the indication criteria in the guidelines for inpatient detoxification.

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