

# Severe Gamma-Hydroxy-Butyric Acid (GHB) Dependence with Repeated Withdrawal Syndrome and Induced Delirium

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## Abstract

Gamma-Hydroxy-Butyric acid (GHB) and its liquid precursor Gamma-Butyrolactone (GBL) have become increasingly popular beyond the clubbing culture and daily consumption as well as dependence has become a more common problem. This case report illustrates the presentation and management of severe GHB-dependence and its sequelae, which are increasingly encountered in the addiction and general hospital setting.

**Keywords:** Gamma-Hydroxy-Butyric acid (GHB); Gamma-Butyrolactone (GBL); Dependence; Withdrawal; Delirium

## Case Report

Mrs. M is a 36-year old Caucasian female with documented severe GBL-dependence, in addition to alcohol, cocaine, amphetamine and cannabis abuse and chronic kidney disease stage V on hemodialysis. She was wandering aimlessly through Zurich searching for the hemodialysis practice. Her mental status was altered with hypervigilance and severely reduced awareness, disorientation, severe cognitive impairment, and psychomotor restlessness to agitation. She was brought to the University Hospital Zurich and admitted to the nephrology floor as she was not able to attend to hemodialysis by herself.

Upon presentation, blood pressure, heart rate and temperature were normal, the patient was afebrile. Initial laboratory findings revealed an elevated Potassium (6.1 mmol/l), blood urea nitrogen and creatinine (BUN 19.3 mmol/l, Crea 1185  $\mu$ mol/l); the alkaline phosphatase was mildly elevated (127 U/l), both creatinine kinase and myoglobin were elevated (CK 295 U/l, myoglobin 782  $\mu$ g/l). The patient was anemic, hemoglobin was 88 g/l, hematocrit 0.263, the mean corpuscular volume and mean concentration of hemoglobin were elevated (MCV 101.9 fl, MCH 34.1 pg). The urine toxicology tested only positive for GHB. The EKG revealed an unspecific S-T elevation.

Mrs. M was known to the hospital from previous admissions in GBL-withdrawal and associated delirium. On the floor, the patient developed an even more severe hyperactive delirium. Her consciousness continued to be severely altered and she was disoriented to all qualities and severely cognitively impaired. The thought process was incoherent, visual hallucinations occurred. The mood was irritable, the affect labile and severe psychomotor agitation present. Judgment and insight were severely impaired, word-finding difficulties and dysarthria present.

According to the working diagnosis, GBL-dependence, GBL-withdrawal and GBL-induced delirium, Mrs. M was administered increasing doses - up to 5 mg every hour - of lorazepam in order to achieve symptom control. Haloperidol was administered for the management of the visual hallucinations. Over the next days, the mental status improved at a very slow pace, the patient repeatedly requested to be discharged against medical advice, which was not granted due to the lack of decisional capacity, and she posed a difficult management challenge for all the staff involved. At the end a total amount of more than 200 mg of lorazepam was administered - the patient stabilized and eventually was transferred to addiction psychiatry for further management of her dependence on GBL.

On previous admissions, the patient had to be managed in the intensive care setting with continuous, intravenous administration of midazolam. She has been GBL-dependent since 2008 and consumed on average 100 ml of GBL daily. Her alcohol, benzodiazepine, cocaine and cannabis use varied. Prior to 2008, she consumed alcohol and benzodiazepines regularly, however had never been in treatment, nor suffered from withdrawal, seizures or delirium tremens. The cannabis use was more sporadic and supplemented alcohol and benzodiazepine use. She was previously admitted several times to somatic and psychiatric hospitals. To date, no intervention has been successful in altering Mrs. M's consumption of GBL.

## Literature Review of GHB-pharmacology, -dependence, -withdrawal and -management

GHB has formerly been used as an anesthetic and developed into a popular psychoactive drug [1]. GBL is primarily used as a solvent in the pharmaceutical industry, a precursor of GHB and converted to GHB following hydrolysis by 1-4 Lactonase. The plasma half-life of GBL is less than one minute. GHB has at least two distinct binding sites: As an agonist at the GHB-receptor, which is excitatory and as a weak antagonist at the GABA<sub>B</sub>-receptor. Activation of both GHB- and GABA<sub>B</sub>-receptors is responsible for the addictive properties of GHB. In defined areas of the brain, activation of the GHB-receptor results in the release of glutamate. The dopamine release of GHB is biphasic. Low doses stimulate dopamine release via the GHB-receptor, higher concentrations then inhibit dopamine release via the GABA<sub>B</sub>-receptor, and eventually, after an initial phase of inhibition, dopamine release is again increased via the GHB-receptor. The time to peak serum levels ranges from 36-57 minutes, the elimination half-life between 30-52 minutes. Addiction occurs when prolonged, repeated GHB use disrupts the balance of brain transmitters and circuits controlling reward, memory and cognition leading to compulsive use. The

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duration of clinical effects are dose-dependent and range from 2.5-4 hrs. The early GHB-withdrawal syndrome resembles the alcohol withdrawal syndrome which is associated with autonomic instability, tremor, anxiety, restlessness, and insomnia. GHB withdrawal usually lasts 3 to 21 days [2]. However, severe withdrawal syndromes can produce acute delirium requiring hospitalization, even leading to intensive care management and fatal outcome. Important differential diagnoses for GHB withdrawal syndrome include alcohol or benzodiazepine withdrawal, delirium caused by somatic conditions, neuroleptic malignant syndrome and serotonin syndrome [3,4]. The mainstay of management of the GHB-withdrawal syndrome remains the administration of benzodiazepines and high doses are generally required. In contrast to GHB acting on the GABA<sub>B</sub>-receptor, benzodiazepines are indirect GABA<sub>A</sub>-agonists explaining the requirement for high doses of benzodiazepines [5]. Another approach managing GHB-withdrawal is the administration, titration and tapering of GHB [6].

## Discussion

The case of Mrs. M. illustrates the requirement for a heightened awareness of the growing prevalence of daily GHB/GBL use causing dependence, the subsequent severe withdrawal syndrome inducing delirium, requiring the administration of high doses of benzodiazepines, and triggering potentially life-threatening complications such as rhabdomyolysis, seizures, bradycardia, and cardiac arrest.

In the absence of current alcohol, benzodiazepine or other drug

use, the GHB withdrawal syndrome was confirmed. Gamma-hydroxybutyrate detoxification by titration and tapering. Eur Addict Res 18: 40-45.

syndrome or serotonin syndrome were excluded by the absence of antipsychotic or serotonergic medication and laboratory evidence. Her chronic kidney disease very likely worsened the delirium, however, based on her attending hemodialysis regularly and hemodialysis on admission without mental status improvement, ruled the kidney disease as sole etiology for her delirium out.

Both, management with enteral and intravenous benzodiazepines, were successful in achieving symptom control. Nonetheless, all attempts at rehabilitation and achieving abstinences were futile and the prognosis for the patient remains doubtful as she has not been able to control her addictive behavior.

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