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INPATIENT MANAGEMENT OF GHB/GBL WITHDRAWAL

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SUMMARY

Background: *Gamma-hydroxybutyrate (GHB) and its precursor gamma-butyrolactone (GBL) are popular drugs of abuse used for their euphoric, (potential) anabolic, sedative, and amnestic properties. Daily use of GHB/GBL can lead to addiction and the possibility of withdrawal syndrome on cessation which results in tremor, tachycardia, insomnia, anxiety, hypertension, delirium, coma.*

Aim: *To describe the baseline characteristics, treatment and retention in patients admitted for GHB/GBL withdrawal management.*

Methods: *A retrospective review of 4 consecutive cases of patients reporting GHB/GBL addiction who were admitted for inpatient management of withdrawal syndrome.*

Results: *All patients were using GHB/GBL daily, 1-1.5 ml per hour. One of them was using cannabis additionally, others were using alcohol, cocaine and amphetamine type stimulants. Psychiatric comorbidities as personality disorders, depression, anxiety and bigorexia were recognized. Patients were treated with benzodiazepines and/or clomethiazole, atypical and typical antipsychotics and beta-blockers. Delirium was developed in two patients. One patient completed detoxification and finished the treatment program. One patient completed detoxification but stopped his treatment earlier, two patients did not completed detoxification and left the program.*

Conclusion: *GHB/GBL withdrawal can be severe and retention in program is poor. Polysubstance use, psychiatric comorbidities and heavier GHB/GBL use as possible predictors of poor treatment outcome need consideration in treatment planning.*

Key words: *GHB/GBL - addiction - inpatient - treatment - withdrawal*

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INTRODUCTION

Gamma-hydroxybutyrate (GHB) is a synthetic drug which was initially developed as an anaesthetic agent but later found to be a naturally occurring compound in mammalian brain and tissue, existing as a by-product of GABA metabolism and putative neurotransmitter. Major chemical and metabolic precursors include gamma-butyrolactone (GBL) and 1,4-butanediol which are both rapidly converted to GHB in the body (EMCDDA 2002). Acts primarily as a central nervous system depressant but at low doses can also produce euphoric effects and effects that appear to be like those of stimulants (Abdulrahim & Bowden-Jones 2015). GBL is absorbed more rapidly than GHB and potentially has a faster onset of action (EMCDDA 2002). GHB and GBL have a high affinity to GABA-B receptors and to a lesser extent to subtypes of GABA-A receptors. There are effects on glutamate, dopamine, serotonin, norepinephrine and cholinergic systems (Kamal et al. 2016). GHB is considered to have a high dependence potential, and abrupt discontinuation after long-term use can result in a severe withdrawal syndrome with the quick onset (Kamal et al. 2016). It can happen 30 minutes after the last dose, but more typically it is a few hours. GHB/GBL withdrawal symptoms have been reported to last from 3 to 21 days (mean 9 days) (Abdulrahim & Bowden-Jones 2015). Often seen withdrawal symptoms are tremor, tachycardia, insomnia, anxiety, hypertension, delirium, coma (Wojtowicz et al. 2008). The recreational use of GHB (including its precursor GBL) has been reported among subgroups of drug users in Europe for the last two decades. Although national estimates, where they exist, of the prevalence of GHB use in adult and school populations remain low, there is a big clinical question what is the best treatment option for GHB/GBL addiction (EMCDDA 2019). The international evidence on the management of the acute and chronic harms related to the use of GHB and GBL mainly consists of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records (Abdulrahim & Bowden-Jones 2015).

In the following sections, we discuss the clinical presentation of 4 patients hospitalized for GHB/GBL detoxification. All patients were admitted to the detoxification ward at the Center for Treatment of Drug Addiction Ljubljana at University Psychiatric Clinic Ljubljana and planned to complete the treatment program which lasts 16 weeks and provide a multidisciplinary approach.

Case 1

33-year-old male patient with a university degree, employed, began using cocaine and benzodiazepines when he was 28 years old. After 5 years he was admitted for the inpatient treatment of addiction to the detoxification ward but left the program earlier and abstained 14 days. He relapsed with cocaine and benzodiazepines and started to use GBL. Before his second admission to the detoxification ward (6 months after first admission) he used 30 ml of GBL a day, split into doses taken every 1.5 hours and 0.5 to 1 g of cocaine a day. Withdrawal symptoms appeared 2 hours after the last dose of GBL, and consisted of diaphoresis, tremor, tachycardia, hypertension and later delirium with disorientation to time, place and person, poor attention

and agitation. First-line treatment with diazepam (30 to 60 mg a day) and quetiapine (75 mg a day) was unsuccessful. Symptoms were successfully managed with clomethiazole (up to 1920 mg a day), propranolol (20 to 60 mg a day) and risperidone (up to 2 mg a day). After 3 days symptoms of delirium disappeared, other withdrawal symptoms gradually subsiding on day 10 allowing for the rapid reduction in clomethiazole dosage. No adverse effects were observed during treatment. His complete blood cell count and biochemistry profile were within normal limits. He continues his inpatient treatment, bigorexia was recognised as co-occurring disorders but he did not want to change his diet and workout regimen.

Case 2

30-year-old patient with a primary school education, unemployed and without permanent housing reported chronic use of different drugs (amphetamines, cannabis, cocaine...) from his adolescence. He was treated by psychiatrist after several suicide attempts and diagnosed with borderline personality disorder. Daily use of GHB/GBL started when he was 26 years old. After several unsuccessful detoxification attempts without any medical support he was admitted to the detoxification ward for the first time. At intake, he used 1.2 to 1.5 ml of GHB/GBL per hour in combination with different doses of methamphetamines. Withdrawal symptoms appeared 4 hours after the last dose of GHB/GBL and consisted of tremor, anxiety, hypertension, tachycardia, insomnia. To reduce withdrawal symptoms, we treated patient with clonazepam up to 6 mg, propranolol up to 80 mg and quetiapine up to 75 mg. Dosages were adjusted daily. Next day he began describing paranoid delusions that patients are against him and he was afraid. After introducing haloperidol up to 4 mg a day paranoid delusions subsided after 3 days, other symptoms gradually subsided on day 7 when he left the inpatient treatment program. No adverse effects were observed during treatment. His complete blood cell count and biochemistry profile were within normal limits.

Case 3

20-year-old female patient with a primary school education, unemployed, began using alcohol and drugs (cannabis, amphetamines, methamphetamines, psilocybin mushrooms...) when she was 15 years old after the death of both parents in less than 6 months. Patient began using GBL when she was 19 years old. Before admission at the ward she used up to 25 ml a day of GBL, split into doses taken every 1.5 to 2 hours, 3 to 4 cigarettes of cannabis a day, alprazolam up to 0.5 mg a day and irregularly 3-methylmethcathinone (3-MMC). She had one accidental GBL overdose and several withdrawal seizures in last months. Also, she had a car accident under the influence of GBL. Two hours after the last dose of GBL she became inattentive, unable to maintain reasonable conversation. We started therapy with diazepam, but later in the same day she became agitated and responding to visual and auditory hallucinations. The patient had to be physically restrained. She was administered up to 60 mg of diazepam, up to 1152 mg of clomethiazole and up to 50 mg of quetiapine. No adverse effects were observed during treatment. A complete blood cell count showed leucocytosis 13,900/mm^3, C-reactive protein 7, creatine kinase was 12.91 μkat/L, no hydroelectrolytic disorders were found. Symptoms of delirium persisted for 5 days, after that we began gradually reducing dosage of prescribed therapy. On day 12 she left the inpatient treatment program prematurely.

Case 4

34-year-old patient with a university degree, unemployed, with a psychiatric history of anxiety disorder and depression began using GHB/GBL when he was 32 years old. The substance helped him to decrease his anxiety. He started during the weekends but gradually his use became daily (a total of 30 ml of GBL a day, split into doses every 1.5 to 3 hours). At admission, he unreliably reported lower dosage of GBL (10 to 30 ml a day) and use of alcohol in the evening (4 units of 40% spirit). Occasionally he used amphetamines and cocaine. He had 3 unintentionally amphetamine and GBL overdoses and was treated at the emergency unit. Two hours after the last dose of GBL he began reporting increased anxiety and craving. He was administered diazepam (a total of 60 mg, split into 6 doses), quetiapine 100 mg and pregabaline (a total of 200 mg, split into 2 doses, prescribed by his psychiatrist for anxiety), but the next day left the ward. He did not allow us to take a blood sample for laboratory tests.

DISCUSSION

These case reports describe inpatient GHB/GBL detoxification of patients who planned to complete the whole treatment program but most of them left the program earlier. According to studies uncompleted detoxification, the early relapse and the reduced time spent in treatment have been found to be associated with poorer outcomes at follow-up. A major challenge in addiction treatment is to identify wich treatment modality or other factors motivate patients to stay in treatment (Brorson et al. 2013). We noticed the rapid onset of symptoms (2 to 4 hours from the last dose of GHB/GBL) similar to those of GABAergic withdrawal (diaphoresis, tremor, tachycardia, hypertension, anxiety, insomnia…) (Abdulrahim & Bowden-Jones 2015, Miotto et al. 2001). To reduce withdrawal symptoms patients were treated with long half-life benzodiazepines and/or clomethiazole (McDonough et al. 2004). Antipsychotics (typical and atypical) have been necessary for the treatment of psychotic symptoms. We also use atypical antipsychotics for their anxiolytic properties (McDonough

et al. 2004). Withdrawal symptoms can be self- limiting in some patients, but others can present with more severe withdrawal that can progress to delirium (Gonzalez & Nutt 2005). There are indications that heavy, frequent users are most likely to progress to severe delirium (Gonzalez & Nutt 2005). All our patients can be described as heavy, frequent users but just two of them progress to delirium. It has been proposed that withdrawal in cases of co-dependence on GHB/GBL and another CNS depressant (opiates or other sedatives) or a stimulant is likely to be more severe (McDonough et al. 2004). Patients were supervised with the daily therapy adjustments. All patients had more than one unsuccessful attempt of detoxification independently of any medical support what was already suggested to be a criterion for the indication of inpatient detoxification (von Theobald et al. 2017). All of them reported poly-substance use and had co-occuring psychiatric disorder what have been consider in treatment planning.

CONCLUSION

The symptomatic treatment is indicated for GHB/ GBL withdrawal syndrome. Recommended therapy with benzodiazepines as a first line medication in combination with propranolol and antipsychotics was effective for reducing withdrawal symptoms. We also have a good experience with clomethiazole. We recognized patient's poor compliance as a main problem. Polysubstance use, psychiatric co-morbidities and heavier GHB/GBL use as a possible predictors of poor treatment outcome need consideration in treatment planning.

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Conflict of interest: *None to declare.*

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