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Case report

AMISULPRIDE REDUCES CRAVING IN PATIENTS WITH GBL ADDICTION - CASE SERIES AND REVIEW OF THE LITERATURE

Tom Sugnet[1], Suzana Jonovska[1,2] & Vesna Šendula-Jengić[2,3]
[1]Department of Addictions and Psychotrauma, Psychiatric Hospital Rab, Rab, Croatia
[2]Faculty of Health Studies, Rijeka, Croatia
[3]Research Department, Psychiatric Hospital Rab, Rab, Croatia

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INTRODUCTION

γ-hydroxybutyric acid (GHB) or 4-hydroxybutanoic acid, is a naturally occurring neurotransmitter and a psychotropic drug. It acts as a strong agonist at the GHB receptor and is a weak agonist at the $GABA_B$ receptor. It is used, in the form of a salt (sodium γ-hydroxybutyrate or sodium oxybate) in the treatment of narcolepsy and has seen limited use in the treatment of alcohol use disorder, in countries like Italy and Austria (Caputo et al. 2015). More often than not, GHB is used illegally as an intoxicant (Kam & Yoong 1998) or as a date rape drug, especially in the form of a prodrug γ-butyrolactone (GBL). Central nervous system depressant effects, more prominent at higher doses, when GHB's $GABA_B$ agonism prevails, have been compared to those of barbiturates and alcohol, and can lead to depressed breathing, amnesia, unconsciousness and death, especially when combined with other psychoactive substances, like alcohol or benzodiazepines (Schepp et al. 2015). At lower doses, its effects have been likened to those of MDMA, with increased euphoria, sociability and entactogenic effects, that is why it has been called ´liquid ecstasy´ by the users. With chronic administration, tolerance to euphoric and stimulating effects can develop. Consequently, users feel compelled to up the dose, which can lead to life-threatening side effects, due to the narrow therapeutic interval of the drug. Chronic use has been found to impair learning and memory (especially working memory and spatial memory) similar to other GABAergics like benzodiazepines and alcohol. Physical dependence develops with continuous chronic use of higher doses of GBL/GHB, and withdrawal syndrome occurs, associated with tremor, insomnia and rebound anxiety, although severe withdrawal symptoms such as delayed-onset or protracted delirium can occasionally be seen (Busardò & Jones 2015). $GABA_B$ agonist baclofen has been found effective in alleviating withdrawal symptoms of GBL/GHB (LeTourneau et al. 2008), but its role in the management of psychological GBL/GHB dependence has not been documented. Benzamide antipsychotics were found to upregulate GHB receptors (Ratomponirina et al. 1998). We report a case of two GBL/GHB-addicted patients who were successfully treated with low doses of amisulpride, reporting no craving for GBL/GHB and abstaining from it for twelve months.

CASE SERIES

We describe two patients, one male, one female, who were admitted to our drug rehabilitation ward because of their long-term GBL abuse, which started years ago, in the context of poly-drug use. Both of them had been hospitalized multiple times in acute care facilities due to GBL overdose, leading to a coma, but had not received psychiatric care other than for acute GBL withdrawal. This was their first voluntary psychiatric hospitalization.

Case 1

A 46-year-old woman, with a ten-year history of GBL use, was admitted to the hospital. She started using GBL in the context of poly-drug abuse, initially in order to enhance the euphoric effects of 3,4-methylenedioxymethamphetamine (MDMA). She reported not using any other psychoactive substance except GBL for the last two years, once or twice a week. She voluntarily enrolled the inpatient drug rehabilitation program at our hospital. Upon admission, she reported a strong craving for GBL, which was interpreted as the primary obstacle to her achieving abstinence from this drug. She had no concomitant psychiatric illness, except for subclinical elements of borderline personality disorder which were revealed by means of psychological testing. The patient's family history was unremarkable.

Case 2

A 35-year-old man, with a five-year history of GBL use, was transferred from a regional general hospital after a four-week-long treatment of protracted GBL withdrawal. He had generally used GBL simultaneously with other substance (like MDMA or cocaine), to boost their effects, but in the last months prior to admission, he reportedly had no access to other drugs, and used

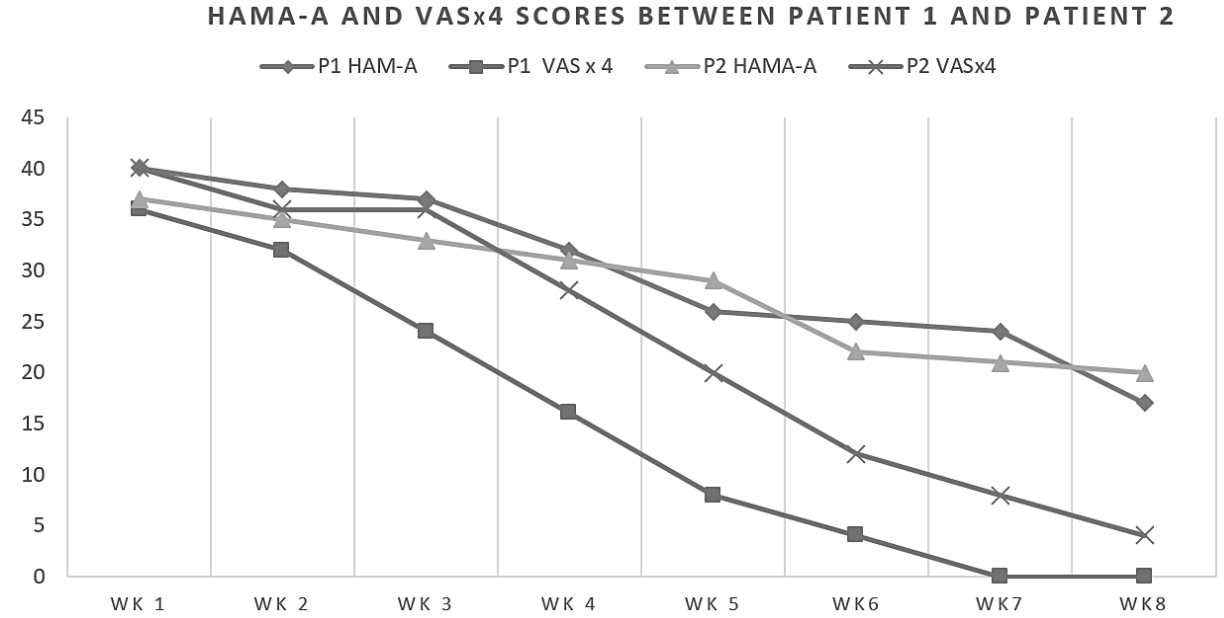
GBL exclusively, mainly for stress relief, several times a week. Upon admission, he showed no residual symptomatology of acute GBL withdrawal, but reported cravings for GBL. Psychological testing revealed that his personality was characterized by impatience, irritability, and propensity for impulsive reactions. The patient's family history was positive for anxiety disorder and chronic benzodiazepine use, in his mother.

After a thorough literature review and psychoeducational intervention, patients were offered a twice-daily regimen of low-dose amisulpride monotherapy (50 mg in the morning, and 50 mg in the afternoon). Low doses of benzamide antipsychotics are widely used in many countries: amisulpride for dysthymia, sulpiride for depression and psychosomatic symptoms, tiapride for treating anxiety during acute alcohol withdrawal. These antidepressant and anxiolytic effects of low doses of benzamides are due to their blocking of inhibitory presynaptic dopamine autoreceptors. Since, in both patients, anxiety was a trigger factor for GBL use, a non-abusable drug, such as low-dose amisulpride seemed like a reasonable choice. But, in patients with substance use disorder, symptoms of anxiety are usually, intertwined with craving for a specific drug of abuse. Given that, in animal studies, benzamide antipsychotics were find to bind to the GHB receptor (GHBR) at therapeutically applicable concentrations (IC_{50} = 50 nM for amisulpride), we wanted to explore whether low-dose amisulpride reduced cravings for GBL as well, and not anxiety only. The patients were observed during their hospital stay (8 weeks) and they had their scores checked, once a week, on two scales: Hamilton Anxiety Rating Scale (HAM-A) and standardized visual analog scale (VAS from 0 to 10) for self-reported GBL-craving. Low-dose amisulpride regimen reduced anxiety and GBL-craving in both patients, but the reduction in GBL-craving seemed more marked, to the level of almost-extinction (Figure 1).

At the follow-up examination after twelve months, both patients reported abstinence from GBL. One patient is still taking amisulpride as prescribed. The other one only takes it PRN, in order to prevent possible GBL-cravings in situations he used to resort to GBL-use. No side effects were reported. Blood prolactin levels were checked during hospitalization, as well as on follow-up, and were within normal laboratory ranges.

DISCUSSION

Craving is one of the factors that can lead to a relapse in abstinent people. Naltrexone is usually indicated in the treatment of alcohol craving, and it has been tried in the treatment of GBL-related craving but its use is not without side effects, such as dysphoria and anhedonia, which are due to unspecificity of hedonic blockade of this drug (Mallik et al. 2017). Oftentimes, in people with substance use disorder, one can see substitution of one psychoactive drug for another (either voluntarily or due to iatrogenesis): people suffering from alcohol use disorder may end up suffering from benzodiazepine addiction, GBL addiction or baclofen addiction. Novel anticraving agents, with no abuse potential and with few or no negative effects on mood or cognition need to be found. In our case series, we found that low-dose amisulpride administration reduced craving in GBL/GHB use disorder, with no negative effects on mood or cognition.



HAMA-A - scores and self-reported VAS scores related to GBL - craving at the end of every week; VAS - scores were upscaled four times for visual enhancement; P1 – patient one; P2 – patient two; HAM-A – Hamilton anxiety rating scale; VAS – visual analog scale

Figure 1. Reported anxiety and GBL-craving during amisulpride treatment

CONCLUSION

Limitations of our study prevent us from reaching a definite conclusion. Studies with substantial number of patients, with control groups, as well as comparisons with placebo and other therapeutic measures will be needed in order to postulate that substituted benzamides could be viable GBL/GHB-anticraving drugs.

Furthermore, more effort needs to be put into research on endogenous GHB, the role of its GHB-receptors and its connection with GABAergic, dopaminergic and glutamatergic systems (Bosch et al. 2017).

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Conflict of interest:

All authors report no biomedical financial interest or potential conflicts of interest.
The publication of this study has been approved by the Ethics Committee of the institution within which the work was undertaken and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000).

Contribution of individual authors:

All authors contributed to writing of this paper equally.

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Correspondence:
Suzana Jonovska, MD, PhD
Department of Addictions and Psychotrauma, Psychiatric Hospital Rab
Kampor 224, 51 280 Rab, Croatia
E-mail: suzana.jonovska@gmail.com