Psychiatria Danubina, 2021; Vol. 33, Suppl. 4 (part III), pp 1240-1242
Conference paper
Case report

HIGH-DOSE METHYLPHENIDATE USE PRIOR TO HOSPITALIZATION EXACERBATES THE WITHDRAWAL SYNDROME IN INPATIENTS TREATED FOR OPIOID AND SEDATIVE-HYPNOTIC CO-DEPENDENCE - CASE SERIES AND REVIEW OF THE LITERATURE

Suzana Jonovska[1,2], Tom Sugnet[1] & 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

* * * * *

INTRODUCTION

Methylphenidate (MPD) is a psychostimulant with dopamine and noradrenaline reuptake inhibition characteristics, frequently prescribed for treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD). Synthesized in 1944, and subsequently marketed in 1954, it was initially used for treatment of hypotension, narcolepsy and sedative-induced coma. From the 1960ies, it has been prescribed for the treatment of ADHD, and this is most common indication of the drug, even not without controversy. Presently, it is among the fifty most prescribed medications in the USA, but less so in other countries. Similar to other stimulant psychotropic drugs, the abuse of MPD is common (Bjarnadottir et al. 2016), especially among students, long-distance drivers and in people with substance use disorder.

Acutely, mixing psychostimulants and central nervous system depressants can lead to initial euphoria, which can give way to subsequent overdose due to continual upping of doses of CNS-depressants whose effects are not readily felt, but overshadowed by the intensive effects of stimulants. In the long run, users may self-medicate psychostimulant withdrawal symptoms with CNS-depressants and vice versa. Stimulant/depressant co-dependence can influence withdrawal length or severity. The most investigated co-dependence of this type is cocaine/alcohol co-dependence. Cocaine co-dependence was not found to affect intensity of alcohol withdrawal symptoms (Kampman et al. 2002). Among cocaine/alcohol co-dependent subjects, cocaine use severity seems a better predictor of a successful detoxification than alcohol use severity (Kampman et al. 2004). In cocaine users on maintenance opioid therapy, a two component model was noticed: cocaine use was found to provoke opioid withdrawal-like symptoms in subjects on high maintenance opioid doses (e.g. 6 mg of buprenorphine or 120 mg of methadone) but had no effect on subjects receiving low-dose opioid maintenance therapy (Stine & Kosten 1994). Sedative-hypnotics were found to influence the abuse potential of other drugs through direct and indirect actions on hypothalamic–pituitary–adrenal axis and the mesocorticolimbic system (Schelp et al. 2018). The impairing effects during everyday activities, like driving, were found more prominent in amphetamines/benzodiazepines co-dependent subjects that in those who used either drug in isolation (Høiseth et al. 2014). Among methadone maintenance treatment patients, higher benzodiazepine use rate was found to correlate with testing positive for MPD (Peles et al. 2014).

We present two cases of inpatients treated for co-morbid opioid and sedative use disorder, in which prolonged use of high-dose MPD prior to hospitalization adversely affected duration and severity of withdrawal syndrome of co-morbid opioid and GABAergic addiction.

CASE SERIES

Case 1

A 38-year-old female, healthcare worker, with a daily intake of up to 300 mg zolpidem in the last three years, along with up to 1000 mg tramadol a day. She reported workplace stress as the trigger for her sedative/opioid co-dependence. She started self-medicating herself with a low dose of diazepam (2 mg daily) but gradually augmented the dose. Eventually, she found zolpidem more to her liking. Paradoxically, she managed to remain functional on high dose zolpidem (300 mg a day) which she described as “euphoric” and “energizing”. Around one year prior to admission, she started taking tramadol, in order to enhance the effects of zolpidem which she thought was “losing efficacy”. She sought help of a private practice psychiatrist to whom she presented with symptoms of depression, trouble concentrating and distractibility. She was started on MPD (18 mg a day). She continued taking high doses of zolpidem and tramadol along with MPD. Gradually, she started upping the dose of MPD, up to 540 mg a day. Two months before admission she experienced seizures and was started on lamotrigine. Upon

admission to the drug rehabilitation department of our hospital, her psychopharmacologic regimen consisted of lamotrigine (50 mg, twice daily), diazepam (10 mg, three times a day) and tramadol (100 mg, twice daily). The Hamilton Anxiety Rating Scale (HAM-A) on admission showed severe anxiety (46). She also reported craving for MPD, as well as somnolence, fatigue, and memory problems. During a 12-week-long stay she was motivated to complete the inpatient rehabilitation program, including tapering off tramadol and diazepam. Anxiety symptoms (as measured on HAM-A), including those due to withdrawal or rebound anxiety, were gradually subdued: 40 at the 4th week, 31 at the 8th week and 23 at the 12th week (time of discharge). Still, they were higher than what we usually see in non-MPD-dependent sedative/opioid co-dependent patients. This patient's therapy on discharge included lamotrigine (100 mg, twice daily), fluvoxamine (100 mg, once daily) and amisulpride (50 mg, twice daily). On subsequent checkups, the patient claimed full functionality, and reported no cravings for zolpidem, tramadol or MPD.

Case 2

A 35-year-old male, employed in family business, with a long history of polydrug abuse. He started taking marijuana and amphetamines at the age of sixteen, cocaine at the age of seventeen, and opioids at the age of twenty. He has been in sporadic in- and outpatient psychiatric treatment for more than fifteen years but has not been able to achieve abstinence lasting more than a few weeks. In the last few years, one could note a shift from illicit drug use to use of supratherapeutic doses of legal psychoactive drugs, including buprenorphine, benzodiazepines, pregabalin, bupropion and MPD. His family history is positive for borderline personality disorder and polydrug abuse in his sister as well as anxiety disorder in his mother. He enrolled in our drug rehabilitation program in order to taper off benzodiazepines which exerted negative effects on his mood and cognition. His psychopharmacologic regimen upon admission consisted of diazepam (20 mg, three times daily), pregabalin (300 mg, three times a day), buprenorphine (16 mg, once daily), venlafaxine (150 mg, once daily), fluvoxamine (150 mg, once daily) and sulpiride (50 mg, PRN). He denied having taken any other psychoactive substance other than high doses of MPD, in the past three months. The Hamilton Anxiety Rating Scale (HAM-A) on admission showed prominent anxiety (40). He was in a somber mood, preoccupied, exhausted, with trouble concentrating. During an 11-week-long stay he was motivated to complete the inpatient rehabilitation program, including tapering off diazepam. A slow taper, with the help of lamotrigine (titrated up to 2x75 mg a day), was gradually started. Anxiety symptoms (as measured on HAM-A) became less intense: 36 at the 4th week. Nonetheless, into the seventh week of his stay, patient suffered from severe rebound anxiety (when diazepam was tapered down to 25 mg a day) and asked to stop the taper. Anxiety symptoms (as measured on HAM-A) were 39 at the 8th week, and 35 at the 11th week (final week of his stay). This kind of scenario seems common in long-term polydrug users, but we cannot rule out the influence of high-dose MPD use prior to admission on this patient's unsuccessful benzodiazepine taper, in light of use of appropriate antianxiety therapy (pregabalin, venlafaxine, fluvoxamine) and a mood-stabilizing anticonvulsive drug (lamotrigine). Presently, the patient is still not able to reach abstinence; he remains non-functional and suffers from memory problems.

DISCUSSION

In our case studies, we found that continuous use of high doses of MPD prior to hospitalization, lead to more prominent GABAergic discontinuation withdrawal symptoms, especially in the form of rebound anxiety.

Current guidelines do not recommend co-prescribing of sedative-hypnotics together with opioids or psychostimulants. Their concomitant use has been proven to increase mortality in substance use population. Chronic use of benzodiazepines and Z-drugs should be discouraged, especially in substance users. Inpatient and outpatient benzodiazepine tapering programs should be promoted and made easily available. Anticonvulsant mood stabilizers like carbamazepine and lamotrigine can reduce benzodiazepine-related cravings and prevent potential seizures while non-abusable drugs with antianxiety features, such as clonidine, propranolol, low-dose sulpiride or amisulpride should be preferred to abusable antianxiety drugs. We should also raise the question of appropriateness of prescribing of MPD in substance users, especially in patients with no history of ADHD. MPD was supposed to curb cravings in cocaine- or amphetamine- users, but its effect has not been superior to that of modafinil, a eugeroic with minimal abuse potential, which remains a more recommendable solution in this population.

CONCLUSION

Overall, the use of MPD may be on the rise in general population and in the population of substance users. Its use may have effects on the consumption of other drugs. MPD use, as a factor affecting outcomes and severity of withdrawal in co-morbid opioid and benzodiazepine use disorder, should be examined in larger studies.

Acknowledgements: None.

Contribution of individual authors:

All authors contributed to writing of this paper equally.

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).

References

1. *Bjarnadottir GD, Haraldsson HM, Rafnar BO, Sigurdsson E, Steingrimsson S, Johannsson M: Prevalent intravenous abuse of methylphenidate among treatment-seeking patients with substance abuse disorders: a descriptive population-based study. J Addict Med 2016; 9:188-94*
2. *Høiseth G, Andås H, Bachs L, Mørland J: Impairment due to amphetamines and benzodiazepines, alone and in combination. Drug Alcohol Depend 2014; 145:174-9*
3. *Kampman KM, Pettinati H, Volpicelli J, Kaempf G, Turk E, Insua A et al.: Concurrent cocaine withdrawal alters alcohol withdrawal symptoms. J Addict Dis 2002; 21:13-26*
4. *Kampman KM, Pettinati HM, Volpicelli JR, Oslin DM, Lipkin C, Sparkman T et al.: Cocaine dependence severity predicts outcome in outpatient detoxification from cocaine and alcohol. Am J Addict 2004; 13:74-82*
5. *Peles E, Schreiber S, Linzy S, Domani Y, Adelson M: Differences in methylphenidate abuse rates among methadone maintenance treatment patients in two clinics. J Subst Abuse Treat 2015; 54:44-9*
6. *Schelp SA, Brodnik ZD, Rakowski DR, Pultorak KJ, Sambells AT, España RA et al.: Diazepam concurrently increases the frequency and decreases the amplitude of transient dopamine release events in the nucleus accumbens. J Pharmacol Exp Ther 2018; 364:145-155*
7. *Stine SM & Kosten TR: Reduction of opiate withdrawal-like symptoms by cocaine abuse during methadone and buprenorphine maintenance. Am J Drug Alcohol Abuse 1994; 20:445-58*

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