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# Tolerability of Chronic Extremely High-dose Use of Methylphenidate. Description of A Clinical Case

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## ABSTRACT

*Methylphenidate (MPH) is frequently employed off-label and at high uncontrolled dosages, even beyond the scope of attention deficit hyperactivity disorder (ADHD) treatment. Intoxications appear to be infrequent and are documented in only a few case reports, with monitoring of plasma concentrations not consistently conducted. In the literature, there are no case reports or studies on the tolerability of high-normal doses of MPH.*

*Here we present a case of prolonged and excessive use of MPH without side effects before the patient was admitted to our psychiatric facility, following the consumption of illegal substances and a brief episode of acute confusion. Surprisingly, after admission, the patient's symptoms improved rapidly, before we substantially reduced the dose.*

## Keywords

Methylphenidate, ADHD, Tolerabilité, Tolerance, High-dose, Plasma concentrations, Substance abuse, Cocaine interaction.

## Introduction

MPH is a central nervous system stimulant medication that is commonly used to treat ADHD. The usual dosage is 20-30 mg/day with a maximum dose of 60 mg/day. Tolerance development rarely occurs, necessitating higher dosages [1]. However, tolerability development seems to be intensified by higher dosage [2] or simultaneous consumption of cocaine [3]. High-dose therapies over an extended period, up to a maximum of 180 mg/day, are described in the literature [4].

We present a case involving the use of extremely high doses of MPH (> 1000 mg/day) over a period of several months at the time when she was admitted to the hospital due to an acute state of confusion unrelated to MPH intake. In the literature, no case with such prolonged administration of maximal doses of MPH has been described, and there is no information available regarding dosage reduction or the risk of withdrawal symptoms. Therefore, we opted for a very gradual dose reduction under controlled conditions. The corresponding measured plasma concentrations were significantly elevated, exceeding 300 ng/mL. According to the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) consensus guidelines for TDM in Neuropsychopharmacologythe reference range of MPH for adults is 12-79 ng/mL in samples taken 2 h after dosing for immediate release (20 mg) or 4-6 h after dosing for extended-release formulations (40 mg) [5,6].

## A Case

Ms A, a 22-year-old, was brought to the psychiatric emergency department by her mother after exhibiting violent agitation at home. During the initial interaction, the patient appears calm and cooperative. However, after admission, Ms A experienced fluctuating confusion, hypoactivity, and hyperactivity. Symptoms included impaired vigilance, temporal-spatial disorientation, psychomotor slowing, speech disturbances and delusional persecution and attention. Normalization began on the 3rd day, and acute confusion resolved completely by the 5th day of hospitalization (Figure 1). Cardiovascular and neurological investigations, including cranial nuclear magnetic resonance, electroencephalogram, and electrocardiogram (QTc interval 432

ms (Bazett formula)) revealed no critical pathological findings. The blood pressure remained stable around 120/80 mmHg. Medication regimen on admission included long-acting MPH 1620 mg/day (Concerta®, 10 tablets of 54 mg three times per day), bupropion 600 mg/day (two tablets of 300 mg in the morning), lisdexamfetamine (LDX) 140 mg/day (two tablets of 70 mg in the morning), mianserin 60 mg/day in the evening, and diazepam 20 mg/day (5mg four times per day). Toxicological screening on the 3rd day after admission was found positive for amphetamines and benzodiazepines, negative for opioids, cocaine, cannabis, benzodiazepines, barbiturates, buprenorphine, and methadone.

The patient's history reveals a diagnosis of narcissistic and borderline personality disorders at the age of 18. Subsequently, she had experienced several short-term hospitalizations due to conflicts in relationships and substance abuse involving cannabis, tramadol, paracetamol, and laxatives. Since the age of 20, Ms A has been consuming cocaine daily at a dosage of 1.5 grams, she also has occasionally used other substances such as LSD or MDMA. Four months before the current admission, a diagnosis of ADHD was made in an outpatient setting, and treatment with MPH was initiated. With the intention of simultaneously addressing the cocaine use, the dosage of MPH was increased to 1620 mg/day within a month (Figure 1). The rapid dosage increase was reported to be well-tolerated by the patient, and she was able to partially reduce her cocaine consumption. During the current inpatient phase in our departement and after the disappearance of the confusion symptoms on the 5th day post-admission, she had no further episodes of confusion symptoms. The patient reported refraining from substance use throughout her hospital stay, and regular urine screenings consistently showed negative results. During hospitalization, plasma concentrations of hydroxybupropion (major active metabolite of bupropion), dexamphetamine (active metabolite of LDX) and MPH were determined using an ultra-performance tandem mass spectrometry method used for therapeutic drug monitoring on a routine basis in an accredited environment (ISO 15189). (Detailed procedure available upon request). Three days after admission, trough plasma concentration of hydroxybupropion (911 ng/mL) was found to be in the reference range (850-1500 ng/mL) defined for unipolar depression [6]. Plasma concentration of dexamphetamine was measured on the 3rd (47 ng/mL, 24 hours after last drug intake) and 6th (217 ng/mL, 4 hours after last drug intake) days after admission. Four days after admission, MPH dose was reduced from 1620 mg/day to 1296 mg/day. Plasma concentration of MPH was measured 6, 24 and 60 days after admission. Due to the short half-live of MPH (2 hours), steady-state conditions were reached for all measurements. Because long acting MPH was given three times per day and concentration should be measured 6 hours after last drug intake [7] to be compared with reference values, blood samplings were performed at 2 pm without administration of MPH at noon (administered after blood sampling). Plasma concentrations of MPH ranges between 391 and 331 ng/mL (FIG. 1, red diamonds), suggesting a low intra-individual variability (coefficient of variation of 8.8%). Plasma concentration of bupropion, dexamphetamine and MPH are in accordance with the dosages, ruling out the hypothesis that these high dosages were prescribed to compensate for an increased drug elimination. Regular psychiatric evaluations did not reveal any signs of typical symptoms of MPH overdose after the 5th day of admission. During her hospitalization, the medical team never suspected any problems with her medication adherence. One month before discharge, the patient experienced mild depressive symptoms (attributed to the obtention of a placement in a medically supervised institution outside her parents' home), supporting an increase of bupropion to 450 mg/day.

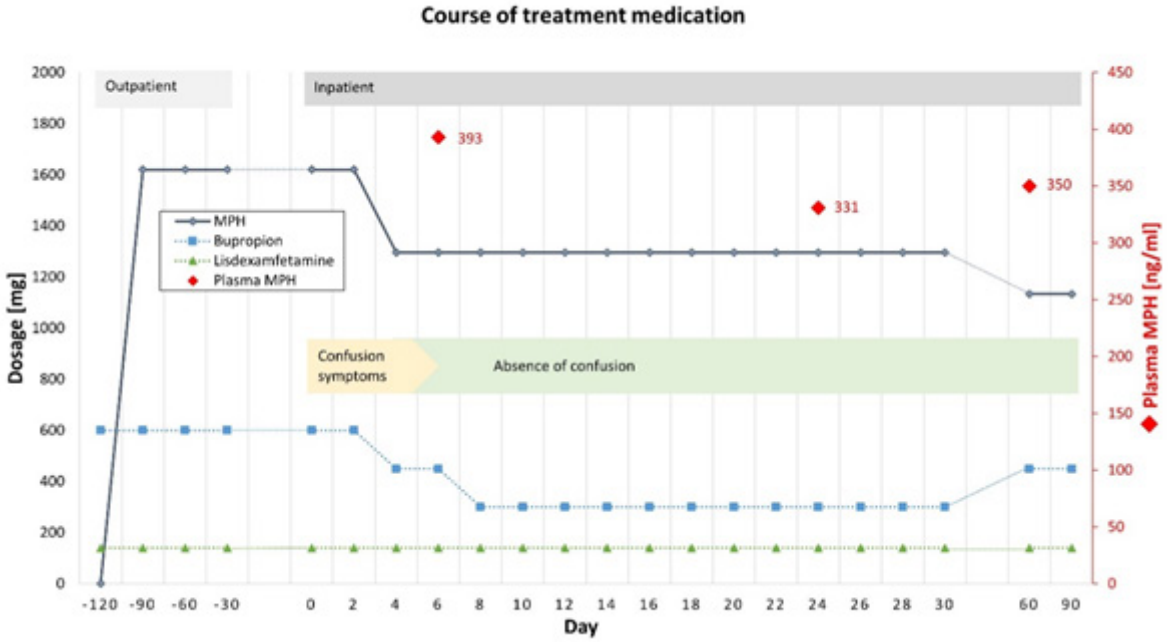


**Figure 1:** Daily dosage (left y axis) of methylphenidate (MPH, grey line), bupropion (blue line) and lisdexamfetamine (green line) from 3 months before hospitalization until discharge. Plasma concentration of MPH (right y axis) are presented with red diamonds.

## Conclusions

To the best of our knowledge, this is the first publication documenting extremely high dosages of MPH confirmed through multiple plasma concentration measurements. MPH overdose can result in acute confusion, as observed in our patient. However, unlike most cases of overdose, excessive sympathetic activity, which primarily affects the neurological and cardiovascular systems was not observed in our patient. [8] The confusion observed in our patient may be attributed to the irregular intake of MPH, possibly mixed with MDMA before hospitalization. Due to cross-reactivity, our screening tests were unable to differentiate between LDX and MDMA, while other toxic substances showed negative results. The cause of acute confusion was probably due to consumption of MDMA, but improvement in symptoms were observed before reducing the daily dose of MPH. What is striking and has never been published before is that Ms A remained symptom-free for weeks until discharge at a dosage of MPH exceeding 1000 mg/day and plasma concentrations exceeding 300 ng/mL (Figure 1). While there are no specific therapeutic reference ranges for MPH in ADHD, a mean plasma concentration of 9 ng/mL (SD+/-2.7) and 17.9 ng/mL (SD+/-6.52) were reported after administration of 54 mg and 108 mg respectively [9]. Her measured concentrations thus suggest that she does not have exceptionally increased enzymatic metabolism of MPH, as MPH concentration can vary up to 25 times between individuals but usually remain constant within each individual [9]. Plasma concentrations consistently exceeding 300 ng/mL are significantly higher than the concentrations typically reported in cases of accidental or suicidal intoxications [10,11].

The development of such tolerability raises questions. The patient did not exhibit side effects or specific ADHD symptoms, and regular urine screenings confirmed the absence of substance use, although the testing methods used could not differentiate between the use of MDMA and the prescribed amphetamines. In a recently published study, it was demonstrated in children that an intolerance to MPH exists for normal dosages in only 1.2-4.1% of cases. An asymptomatic elevation in cardiovascular parameters can be observed in approximately 10% of cases, necessitating continuous monitoring during ongoing treatment. So far, no article has been published regarding the tolerability of extremely high doses of MPH. However, tolerance developments to MPH have been documented in contrast. Tolerance to MPH is more likely to occur with higher dosages, but the available data on tolerance development is uncertain. Studies have reported tolerance rates ranging from 2.7% to 24.7% at therapeutic doses, and up to 60% in patients receiving doses exceeding 60 mg/day [1] and faster onset of tolerance at higher dosage [2].

Considering our patient's extremely high dosage, it is highly probable that tolerance has developed. It is important to note that the patient also took the stimulants LDX at twice the maximum recommended daily dosage and bupropion at a dosage of 300-450 mg/day. The development of tolerance appears to be influenced by the prior or concurrent use of other stimulants like MDMA or cocaine, and it has been demonstrated that individuals with a coexisting cocaine use disorder require a 40% higher dosage of MPH to achieve the same therapeutic effect [3]. Accordingly to this observation are results of a study showing that ADHD patients with treatment up to 180 mg/day resulted in reduced positive drug tests [4]. However, the dosage used in this study was considerably lower than the dosage administered to our patient. While the study supports the link between MPH dosage and tolerance, it does not clarify the influence of substances like cocaine on tolerance development [4]. Laboratory studies have demonstrated that higher doses of MPH have a greater effectiveness in reducing the positive effects of cocaine and decreasing the preference for cocaine over monetary rewards [12]. Conversely, normal doses of MPH do not show a significant effect in this regard [13]. Thus, there is a link between the development of tolerance and the prior or concurrent use of cocaine. However, it cannot be ruled out that the extreme dosage over 20 times the maximum recommended dose itself contributes to the development of tolerance.

We would like to emphasize at this point that the patient arrived with the mentioned medications and dosages, and we do not endorse uncontrolled off-label treatments. For this study, written informed consent and human subjects research committee approval were obtained.

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