

Cannabis and Methylphenidate-Induced Manic Symptoms

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Abstract

Methylphenidate (MPH) prescription rates have been increasing steadily in the last few years, and diversion of the drug is becoming an issue, especially among young people. As is commonly known from scientific literature, high doses of stimulants may induce symptoms similar to those typical of mood disorders or schizophrenia, but with a wide range of variability in symptoms severity, duration and presentation. Poly drug abuse represents another under-evaluated issue, especially with regards to MPH and Δ -9-tetrahydrocannabinol. Here we present a case of methylphenidate and cannabis-induced manic-like episode, involving a 23-year-old male student. The case presentation and management is described in details, and poly drug abuse-related problems are discussed. In conclusion, future studies should explicitly examine the effects of the combination of MPH and THC as well as other possible new patterns of poly drug intake, in order to fully understand their synergistic desirable effects and associated clinical and toxicological implications.

Keywords Methylphenidate; Δ -9-Tetrahydrocannabinol; Poly abuse; Manic episode

Introduction

The significant increase in methylphenidate (MPH) prescription rates over the last 15 years has led to controversy about abuse, misuse, and diversion of the drug [1]. A number of studies report that stimulant diversion is a common problem in many countries, especially among young students [2]. The prevalence of prescription stimulants misuse appears to be higher among individuals between 12 and 25 years of age, ranging from 0.9% to 10.0% across studies [2]. It is known that high doses of stimulant medications can induce manic and psychotic symptoms that may resemble those of bipolar disorder or schizophrenia [3]. Indeed, predicting who is at risk of stimulant-induced psychosis is extremely difficult. Case reports are notable for the broad range of patients' ages, the variety of medications involved, the wide range of duration of exposure, the symptoms reported, and the symptoms severity [3]. Another important issue that has to be taken into account is that users of illicitly prescribed stimulants, including MPH, seem to have higher rates of alcohol and other drugs abuse, especially cannabis [4]. To date, poly abuse of MPH and Δ -9-tetrahydrocannabinol (THC)-the primary psycho active component of smoked hashish and marijuana- has not been closely examined in its peculiar psychoactive effects, as well as in its potential to induce mania or psychosis [2]. In this paper we report a case of methylphenidate/cannabis-induced manic-like symptoms, discussing the clinical aspects and the possible risk factors associated with this and other new peculiar patterns of poly abuse (Table 1).

Basic metabolic panel	
Blood glucose	102 mg/dL
Creatinine	0.90 mg/dL
Estimated Glomerular Filtration Rate	>90 mL/min/1.73 mg
Total Bilirubin	0.40 mg/dl
Direct Bilirubin	0.20 mg/dl
Indirect Bilirubin	0.20 mg/dl
Amylase	64U/L
Lipase	108 U/L
Sodium	139 mmol/L
Potassium	3.85 mmol/L
Calcium	2.50 mmol/L
AST	29 U/L
ALT	16 U/L
Troponine	<0.015
Complete Blood Count (CBC):	
White Blood Cell	7.70 * 10 ³ /ul
Red Blood Cell	4.38 * 10 ⁶ /ul
Hemoglobin	13.1 g/dl
Hematocrit	38.2%
Mean corpuscular volume	87.2 fl

Electrocardiographic Measures	
Heart rate	76 bpm
QTc	396 msec
PQ interval	102 msec

Mean corpuscular hemoglobin	29.9 pg
Mean corpuscular hemoglobin Concentration	34.3 g/dl
Platelet Count	220 * 10 ³ /ul
Procalcitonin	0.22%
Red Cell Distribution Width-SD	43.2 fl
Red Cell Distribution Width-CV	13.5%
Platelet Distribution Width	12.1 fl
Mean Platelet Volume	10.1 fl
P-LCR	26.5%
Hepatitis B testing	Negative
Hepatitis C testing	Negative

Table 1: Electrocardiographic measures, basic metabolic panel and complete blood count did not reveal any abnormalities in our patient.

Case Presentation and Management

The police found P., a 23-year-old Caucasian young male, while he was wandering naked and in a confusional state within the University Campus of Chieti (Italy); P. was therefore referred to the Emergency Department (ED) of the local "Maria SS. Annunziata" hospital. In the ED, a first psychiatric assessment was performed, and forced hospitalization was required due to the psychomotor agitation and lack of insight shown by patient. Lorazepam 1mg was administered and P. was promptly transferred to the psychiatric acute ward of "Maria SS. Immacolata" hospital, located in Guardiagrele (Italy), under the order of a mandatory inpatient treatment for mentally ill lasting one week. At the mental status examination, the patient was formally cooperative. Motor activity was notably increased; grooming and personal hygiene resulted fairly neglected. He was alert, with a slight spatial and temporal disorientation. His sustained attention was altered and he was easily distractible. P. showed no signs of cognitive impairment, but he manifested an extreme talkativeness and his speech was very rapid and loud in volume. He declared a very euphoric mood ("I am very happy and in peace with the universe"), often laughing inappropriately during the clinical interview. Affective state appeared to be congruent, markedly hyperthymic. The patient experienced delusional thought content, characterized by ideas of grandiosity (he was convinced he had the mission to save the world). Thought process was accelerated, with flight of ideas. Perceptual disturbances were present in the form of auditory hallucinations (he affirmed to hear the voice of God supporting him and investing him of special powers, so that he could be able to save other individuals). He did not lack impulse control and showed no signs of aggressive behaviour or self-harm intentions. Physical examination and electrocardiography monitoring did not reveal any abnormalities (Table 1). Venipuncture was performed to collect blood samples for laboratory investigations (Table 1). Basic metabolic panel and complete blood count resulted within normal range (Table 1). A urine sample was collected to perform enzyme-multiplied immune test to detect common drugs of abuse, including ecstasy, amphetamines/methamphetamines, barbiturates, benzodiazepine, cocaine, methadone, opiates and cannabis (Table 2). The patient tested positive for THC and benzodiazepines (the latter ones had been administered

under clinical supervision as previously mentioned) (Table 2). The parents of the patient were then interviewed: they referred that has two siblings, one brother and one sister, both older than him, and no family psychiatric history. According to his parents, P. had a normal neurodevelopment; the onset of his behavioural issues dated back to childhood, and was characterized by attention deficit, impulsivity and hyperactivity. The patient was diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) by a private specialist; methylphenidate at a dosage of 30 mg per day was prescribed since P. was 16 years old, with a positive response and subsequent good levels of global functioning. P. had no previous history of mood disorders or any other psychiatric and medical comorbidity. Afterwards, the patient admitted that since he has started University two years before (attending Medical school), he had stopped taking MPH regularly as prescribed and had saved prescriptions in order to abuse the drug in higher doses before the exams. During exam seasons, he used to intake up to 90-120 mg of MPH per day, averagely a10 mg tablete very 2-3 hours, to enhance his cognitive performances. Cannabis consumption had been stable in the previous two years, with an average of 3 joints per day and an increase during exam seasons. P. was treated with a conservative approach, including hydration and lorazepam (1 mg/day). After 4 days of hospitalization, a significant clinical improvement was obtained, and mood was euthymic with restored insight. Forced hospitalization was reviewed and mandatory inpatient treatment order ceased. The day after, P. decided, in agreement with his family, to be discharged and to be followed as an outpatient by a private psychiatrist. Final diagnosis was substance-induced (MPH+THC) manic episode.

Ecstasy (MDMA)	Negative	Cut off 500
Amphetamine/Methamphetamine	184 ng/ml	Cut off 1000
Barbiturates	23ng/ml	Cut off 200
Benzodiazepine	Over	Cut off 200
Cocaine	Negative	Cut off 300
Methadone	Negative	Cut off 300
Opiates	Negative	Cut off 300
Cannabis	Over	Cut off 500

Table 2: Urinary drug screen to detect common drug of abuse, performed using enzyme-multiplied immune test, revealed to be positive to THC and benzodiazepine (1 mg of lorazepam has been previously administered).

Discussion and Conclusions

In Europe, misuse of prescription drugs to gain neuroenhancement does not appear to be as common as in the United States or in Canada [5]. To the best of our knowledge, no systematic data regarding this phenomenon exists on Italian young adult population, and this appears to be the first Italian case report describing such a pattern of drug diversion and poly drug abuse. This could highlight that MPH misuse may clearly be underreported if not specifically investigated. On the other hand, the use of prescription and illicit drugs for the purpose of pharmacological neuroenhancement has been attracting a growing amount of attention internationally [6,7]. Specifically, psychostimulants such as methylphenidate (MPH) seem to be among the most prevalent substances used for the purpose of improving

mental performances, as emerges by preliminary quantitative surveys. The prevalence rates of psychostimulants use among university students may be particularly high, ranging broadly from 1 to 38% [6-12]. Moreover, some authors underline that 5% of nonmedical users of prescription stimulants meet the criteria for abuse or dependence [13]. However, the short- and long-term risks of abuse and addiction among subjects taking stimulants for neuroenhancement purposes are yet to be cleared [6,14]. Surely, the potential of stimulants to induce psychosis-like or manic-like symptoms has been known for at least 35 years, since Lucas and Weiss (1971) reported three cases of "methylphenidate hallucinosis" [15]. The terms "hallucinosis" and "toxicosis" are often used to distinguish transient symptoms associated with stimulant use from longer-lasting symptoms of schizophrenia and bipolar disorder [3]. The minimum dose necessary to produce psychotic symptoms varies considerably. Some abusers may experience severe toxic effects after multiple doses (a concept similar to sensitization), while others experience comparable effects after the consumption of just minimal doses (reverse tolerance) [16]. Again, the case we present in this paper confirms that stimulant diversion, here with high doses of methylphenidate, may cause manic-like symptoms. As a key message, clinicians should be very cautious while prescribing stimulant medications, always providing an adequate and close follow-up, including patients and caregivers education. Before prescribing stimulants, a complete assessment should be performed, and mood disorder history and past or current substance abuse should be carefully evaluated. With regard to treatment, discontinuation of the stimulant drug during acute intoxication was confirmed to be the best approach [3]. According to evidences, stimulant-induced adverse effects might last shortly, with recovery typically occurring almost always within 7 days of medication discontinuation [3]. It seems ascertained that those who misuse MPH are more likely than their peers to misuse various other substances, and MPH misuse frequently occurs in the context of simultaneous poly drug use [4]. Not surprisingly, the combination of MPH and THC appears to be particularly common [4]. One explanation could be that cannabis is still the most produced, consumed and seized drug worldwide [14]. Use of cannabis has kept rising in recent years, and there are also indications that the number of people requiring treatment for cannabis use is increasing globally [14]. Thus, evidence suggests that a growing number of drug users are suffering from cannabis use disorders, and recent researches suggest that cannabis may be even becoming more harmful per se [14]. Our case report represents just another little proves to confirm the common pattern of poly abuse MPH+THC. Indeed, a limitation most studies share is not having differentiated between concurrent use (use of more than one drug within a specified time period; e.g., past 12 months) and simultaneous use (co-ingestion of more than one drug at the same time) [2]. The studies that have made this distinction again suggest that MPH+THC might be a very common form of simultaneous poly abuse; one study found that 52% of undergraduate students who were illicit MPH users reported simultaneous use with marijuana [4]. In our case, as well as in a pharmacological perspective, it is difficult to determine how the two substances have interacted to cause manic symptoms. An interesting aspect of the present study is the qualitative description of the patient's subjective experience: in line with preliminary evidences, it confirms that the additive effects of THC and MPH might be peculiar and noteworthy on users. Preliminary data show that MPH+THC might have unique effects on cardiovascular function, subjective reactions and performance measures [2]. Specifically, it is possible that both MPH and THC significantly increase subjective drug effects compared

to placebo [2]. The combination of stimulants and THC may therefore be a desirable "cocktail" for young adults looking for euphorogenic effects of marijuana without adversely impacting cognitive performance [2]. Some authors suggest that the use of cannabis in these cases may also be considered as a form of neuroenhancement [5]. In this scenario and according to our patient's qualitative description, cannabis consumption with the purpose of relaxing, turning off reoccurring thoughts and falling asleep, appears a desirable add-on especially during stressful period, and would allow the subject to be more vigilant and to increase concentration the day after. It is here highlighted that, as proved by the clinical case, this pattern of poly abuse might carry serious risks.

Recently, beyond "classic" substances of abuse, a number of novel psychoactive substances (NPS) is determining a sanitary issue of growing importance [14]. The term novel psychoactive substance has been legally defined by the European Union as a new narcotic or psychotropic drug, in either a pure form or a preparation, that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but which may pose a public health threat comparable to that posed by substances listed in those conventions (Council of the European Union decision 2005/387/JHA) [14]. In parallel with a stabilization in the use of many internationally controlled drugs, the market of NPS is dramatically on the rise, year by year and worldwide: the total number of substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) currently results in more than 450 - close to double the number of substances controlled under the United Nations International drug control conventions-with more than half of these new substances being reported in the last three years [17,18]. There is now a growing body of clinical evidence to demonstrate the potential acute and chronic health harms associated with the use of NPS [19,20]. However, NPS are still often unknown to health professionals, mainly due to the lack of evidence-based sources of information [21,22]. Among NPS, synthetic cannabimimetics play a major role, and ethylphenidate, the derivative of its parent drug methylphenidate, is listed among those new compounds [14]. Recently, ethylphenidate, with its legal ambiguity and large online availability, has attracted an increasing number of nonmedical, users in pursuit of cognitive enhancement and pleasurable effects [23]. New evidences suggest ethylphenidate misuse as possibly underestimated, and define this compound as a highly potent recreational drug with psychostimulant properties and relevant harm potential [23,24]. On the other hand, synthetic cannabimimetics (SC), currently largely available online and in head- and smart- shop, are hundreds of different molecules, preparations, formulations and packages: they possess high/very high cannabinoid receptor binding affinity levels, with a significantly higher dose-response efficacy than THC itself [19]. In addition, some SC show further pharmacological actions, which may be per se a reason of clinical concern in terms of toxicological and psychopathological effects, especially in case of poly drug use [19,25,26]. A big issue is that synthetic cannabinoids are not usually detected by conventional drug screening tests [27]; advanced tests, like liquid chromatography-tandem mass spectrometry (LC/MS/MS), may identify specific compounds, but these are not generally available in the average acute care setting [27].

The evaluation of an adolescent or young adult presenting to the emergency department with an altered mental status can be dramatically challenging for clinicians. The differential diagnosis is extensive, comprising a wide range of psychiatric and physical conditions, but acute intoxication due to substances of misuse,

including medical products and NPS, should always be considered [28]. This latter possibility should always be carefully evaluated both clinically and by means of an anamnesis focused on drug consumption, although this may not always be possible because of the patient conditions or reticence. Clinicians should be aware that routine drug screening tests may detect the presence of the most common substances of misuse, but positive and negative results do not always confirm or confute a diagnosis, and further evaluation may be needed. A positive result does not necessarily mean that the observed signs and symptoms are caused by the detected substance; similarly, a negative result does not rule out intoxication by other, undetected, psychoactive substances [25]. Focused and direct questions about the nature and the particular patterns of drug intake, including medical products diversion and consumption of NPS naming them with their common street names (e.g. Spice, K2, Black Mamba etc. for Synthetic Cannabinoids), should be included in a comprehensive and complete clinical assessment [28]. Given that nowadays poly drug use represents the norm rather than the exception, the simultaneous misuse of drugs should also be actively investigated, identified and well discriminated. Future studies should explicitly examine the effects of the combination of MPH and THC as well as other possible new patterns of poly drug intake, including NPS, to better understand their synergistic desirable effects and associated clinical and toxicological implications. Our patient's descriptions regarding the pattern and motivations of MPH +THC poly drug use seemed reliable and genuine; the family lately reported to have found several empty blisters of methylphenidate in P.'s garbage at his current apartment. On the other hand, the absence of further laboratory confirmation still represents a limitation for this case; we did not have the possibility to confirm the declared poly abuse through more sensitive, reliable, and highly specific confirmatory methods. Our local psychiatric acute ward is linked with a laboratory equipped to perform only the enzyme-multiplied immune test, the most frequently used urinalysis for screening "classic" drugs of abuse. Over time, our clinical groups have complained about the relatively high rates of false positives using this analytic methodology and about the missed chances to eventually confirm the screened substance of abuse or detect other NPS. Indeed, the lack of financial resources and the complex specific protocols to deliver samples to more sophisticated laboratories still represent issues difficult to solve in our Region. To the best of our knowledge, liquid chromatography-tandem mass spectrometry (LC/MS/MS) is a rapid, sensitive, reliable, and highly specific method for detecting methylphenidate and its metabolite [29]. Moreover, both the cost and performance of LC/MS/MS method seem to be more convenient than GC/MS or ELISA, and it allows the use of a single, rapid procedure for both screening and confirmation [29]. It is here strongly recommended to invest in the development of more reliable analytic investigations in local psychiatric services. This may have a substantial impact on clinical implementation of diagnosis as well as on pharmacological research, especially to understand and discriminate toxicological mechanisms and interactions in cases of poly abuse.

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