

# Illicit use of Methylphenidate: the other side of the medical prescription

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## ABSTRACT

**Introduction/Objective:** Attention Deficit Hyperactivity Disorder is the most common neurobehavioral disorder of childhood. Parallel to the progress in the diagnosis, the prescription of psychostimulants, namely Methylphenidate (MPH), has also increased. The aim of this review is to promote reflection and debate on this issue, displaying its actual relevance in order to prevent and properly diagnose such cases in Portugal.

**Results:** In recent years, illicit use or misuse of MPH for recreational purposes or as a cognitive stimulant to improve academic achievement, has become a focus of concern. Easier accessibility, false belief that it is safer than illegal drugs because it's prescription based as well a less social stigmatization promote this practice. Thus, treatment with MPH requires adequate medical indication and supervision, not only for its potential cardiovascular side effects and exacerbation of psychiatric disorders, but also due to the risk of illicit use and intoxication.

**Conclusion:** This article reviews the literature concerning MPH misuse. In order to counteract this emerging problem, of still unknown proportions in Portugal, it is crucial to invest in the information and awareness of adolescents, parents, health professionals, and educational community in general.

**Keywords:** Attention deficit hyperactivity disorder; illicit use; intoxication; methylphenidate; pediatric age

## USO ILÍCITO DE METILFENIDATO: O OUTRO LADO DA PRESCRIÇÃO MÉDICA

### RESUMO

**Introdução/Objetivo:** A Perturbação de Hiperatividade com Défice de Atenção é a perturbação neurocomportamental mais frequente na criança em idade escolar. Paralelamente ao aumento do seu diagnóstico, também a prescrição de psicoestimulantes, nomeadamente o Metilfenidato (MFD), tem aumentado. O objetivo desta revisão é promover a reflexão e discussão sobre esta problemática, salientando a sua relevância atual, bem como a necessidade de prevenção e diagnóstico adequado destes casos em Portugal.

**Resultados:** Nos últimos anos, o uso ilícito de MFD para fins recreativos ou como estimulante cognitivo para melhorar os resultados académicos, tornou-se num foco de preocupação. A acessibilidade facilitada, a falsa crença de que por ser prescrito é mais seguro do que drogas ilegais e a menor estigmatização social promovem esta prática. Assim, o tratamento com MFD requer uma indicação médica e vigilância adequadas, não só pelos seus potenciais efeitos secundários cardiovasculares e exacerbção de transtornos psiquiátricos, mas também pelo risco de uso ilícito e intoxicação.

**Conclusão:** Este artigo revê a literatura relativa à problemática do uso ilícito de MFD. Para combater este problema emergente, cuja dimensão ainda é desconhecida em Portugal, é crucial investir na informação e consciencialização dos adolescentes, pais, profissionais de saúde e comunidade educativa em geral.

**Palavras-Chave:** Idade pediátrica; intoxicação; metilfenidato; perturbação de hiperatividade com défice de atenção; uso ilícito

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## INTRODUCTION

In Portugal, the use of medicine, with or without medical prescription, for recreational use has not been an important subject of reflection by health professionals. However, in other countries, especially in the USA, where prescribed drug intoxication in the Emergency Department (ED) services has exceeded that of illicit drugs, there is a growing alarm for this issue, which affects one in every five adolescents. Between 2004 and 2009, 19% of prescribed drug intoxications occurred in those under 20 years of age.<sup>1</sup> A study conducted in school-aged children in 2014, 2.5% of 3751 Portuguese adolescents admitted to the illicit use of medicines.<sup>2</sup>

Methylphenidate (MPH) is a psychostimulant widely used in the pharmacologic treatment of Attention Deficit Hyperactivity Disorder (ADHD), the most common neurobehavioral disorder of childhood.<sup>3-12</sup> In 2005, it was the third most commonly drug prescribed in the USA and between 2005 and 2009 its worldwide consumption increased by 30%.<sup>1,13</sup> Consequently, as a result of this expanded prescription, the risk of accidental or intentional exposure and its illicit use increased as well.<sup>1,3,6-9,14-17</sup>

MPH has been used for its stimulating effect, above all to control attention deficit and impulsivity symptoms of ADHD, but also as an appetite suppressant and cocaine substitute stimulant.<sup>1,6</sup> The Drug Enforcement Administration (DEA) released a statement declaring that a significant portion of MPH prescriptions are being diverted to illicit use. Similarly, the World Health Organization reinforces the need for an effective prevention of this situation.<sup>6,18</sup>

MPH intoxication leads to a sympathomimetic response, which can have serious, even fatal consequences, depending on the dose, route of administration and multiple drug intake.<sup>18-21</sup>

With this article, the authors intend to recommend the reflection and discussion of this subject, sensitizing health professionals to the importance of a correct diagnosis of ADHD, pharmacological treatment and its adequate monitoring, in order to minimize the risk of abuse and/or intoxication with MPH. It is also intended to draw attention to the need to invest in information on the consequences of this undue consumption and in epidemiological studies in Portugal in order to promote future prevention strategies, since there is no data available in the literature revised.

## METHODS

We conducted a literature search in Medline (PubMed) database, including all articles published between 2000 and 2015 written in English or Portuguese. Literature search was updated in 2016 and no new relevant articles were found.

A classic Boolean search was performed using a combination of keywords and Medical Subject Headings (MeSH). The MeSH terms used for the research were "Attention Deficit Disorder with Hyperactivity" and "Methylphenidate". For the purposes of this article, illicit use is considered when a higher than medically recommended dose is taken, when a different form of administration than prescribed is used or when MPH is taken without a prescription. "Misuse", "non-medical use", "diversion" or

"abuse" are other terms used in literature to convey the sense of illicit use of MPH that is outside of the bounds of normal therapeutic use. So, the MeSH terms were combined with this additional terms.

The reference list of the identified articles and Portuguese literature were manually searched for additional potential bibliography not indexed, including five references.

The following exclusion criteria were applied: publication before 2000, articles that analyzed adult population, articles focusing on psychostimulants as a class and not on methylphenidate individually and articles that did not analyze illicit use of methylphenidate.

The title and abstract of these articles were evaluated, and those that did not discuss the proposed topic were excluded. Selected articles were read entirely, and of those that met the established criteria - 40 articles, were included.

Articles included in the review were analyzed in relation to the prevalence of illicit use of MPH, demographic variables among misusers (gender, age, undergraduates or graduates), reasons for use, possible benefits, period in which MPH use began, route of administration, knowledge about the drug, side effects and intoxication, risk factors and prevention of MPH misuse.

## ADHD AND METHYLPHENIDATE

ADHD is one of the most common neurobehavioral disorders in the pediatric age.<sup>11,22</sup> It is estimated that 3-7% of school-aged children and 2-5% of adults have this condition, and 56% are under pharmacological treatment between 4-17 years.<sup>7,13,16</sup> In response to increased psychostimulant therapy, prescription and production rates of MPH, the most widely used drug, have increased significantly in the past two decades. As a result, accidental or intentional exposure and its illicit use, possibly underdiagnosed, also increased.<sup>6,7,11,13,17,18,23-27</sup>

MPH is marketed in Portugal in pill form, such as Rubifen® (immediate action), Ritalina® (intermediate action) and Concerta®, or the generic Methylphenidate LA (prolonged action).<sup>28</sup> In other countries it's also available as a patch for transdermal application.<sup>5,7</sup> Despite its clinical benefit, the DEA classifies MPH as a Schedule II substance, just as cocaine, given the potential for abuse and risk of dependence.<sup>7,11,18,20,23,24,29</sup> However, studies show that when patients with ADHD comply with the recommended dosage, MPH is safe and effective, and does not cause addiction.<sup>1,10,18-20</sup>

The exact mechanism of action of MPH is not yet fully understood, but it is thought to act similarly to cocaine by stimulation of the Central Nervous System, through the blockade of the reuptake of dopamine and noradrenaline, with consequent increase of these neurotransmitters in the extraneuronal space.<sup>5,8,14,16,17,19,25,30-33</sup> However, MPH detaches itself from the dopamine transporter three times slower than cocaine, which decreases the need for repeated ingestion as well as the risk of dependence.<sup>10</sup> Nevertheless, since it alters the function of the mesocorticolimbic dopamine system, there is a potential risk of abuse.<sup>16,25</sup>

MPH is not approved for use in children under six years of age and the recommended dose is 0.3-1 mg/kg/day, in two or three

doses, with a maximum daily dose of 2mg/kg or 60mg.<sup>4,5,17,19,30,34</sup> It should be initiated with immediate-acting formulations, at a dose of 5 mg one to three times daily and increasing over the period of two weeks, if deemed necessary to the effective dose. It can subsequently be replaced by long-acting formulations.<sup>35</sup>

The abuse of MPH occurs mostly by oral intake (60%), but also by inhalation or intravenous administration of crushed pills, leading to a rapid increase in concentration and bioavailability.<sup>5,16,19</sup> Immediate action forms are preferred for misuse, because of its quick start of action, therefore long-term deliveries have been presented as a measure against misuse, given their lower risk of potential abuse.<sup>16,20,30</sup> However, when these pills are chewed, the maximum concentration is higher and reached faster than the formulations of immediate release.<sup>35</sup> In the case of oral administration, the combination with alcohol accelerates the absorption of MPH, forming the active metabolite ethylphenidate, with an increased risk of serious cardiovascular effects.<sup>5,11,19</sup>

## EPIDEMIOLOGICAL ASPECTS

Several studies have pointed to the problem of improper use of MPH.<sup>11,13,18,20,23,24,29,36</sup> Non-medical use of psychostimulants is the second most common form of illicit drug use in university, second only to marijuana.<sup>5</sup> In Switzerland, in 2009, MPH exposure exceeded that of ecstasy and was only lower than the use of cocaine.<sup>14,15</sup>

Calls to the American Association of Poison Control Centers (PCC) motivated by misuse of medication for ADHD, rose 76% between 1998 and 2005.<sup>23</sup> In 2004, 1.7/100,000 of visits to the ED between children aged 12-17 years were due to illicit use of MPH.<sup>1,23</sup> In another study, in 2004, MPH was responsible for 1414 drug-related ED outflows, and in 2005 for 3212.<sup>18,20</sup>

PCC data show MPH intoxication in pediatric age ranges between 80% to 87%.<sup>30</sup> In children up to the age of 12, exposure is often accidental, due to errors in the administration and, in the majority of cases, asymptomatic. Among adolescents however, about half present symptoms and most of the exposures are intentional, mainly due to illicit use and attempted suicide.<sup>30,31</sup> In 2004, in an American CCV, there were 8,336 cases of ingestion of MPH (72% accidental) and 19% of children involved were under the age of six. The toxicity was moderate in 11% and severe in 1%.<sup>5</sup>

In literature, annual rates of MPH used amongst secondary school students vary between 5-10%, and in college students between 5-36%, depending on the level of academic requirement of the college they attend.<sup>6,9,11,16,18,29,32,33,37,38</sup>

## MOTIVES AND ACCESSIBILITY

Recently, improper use of MPH for recreational purposes or as a cognitive stimulant has become a focus of increasing concern. The easy access, the false belief that it's safer due to be a drug prescribed in pediatric age and the lack of perception of the parents and relatives of its non-therapeutic use contribute to the misuse.<sup>1, 14, 15, 18, 24</sup>

Most adolescents have little prior information about MPH and its use is easy and not socially reprehended.<sup>28</sup> High school

and college students may be attracted to its stimulant effects, such as enhanced concentration, euphoria and appetite suppression. MPH is considered one of the "study drugs" and is also dubbed "vitamin R", "kiddy coke", "Poor Man's Cocaine" and "the smart drug".<sup>32</sup> In the Infarmed's patient information leaflet it's mentioned that Ritalin LA® can *help improve attention (deviations of attention), concentration and reduce impulsive behavior*; potentially appealing results for students, who often devalue adverse effects.<sup>40</sup> For college students the main reason for MPH use is to improve academic performance (30% to 94%), mainly in periods of assignment delivery or assessments, to combat fatigue and enhance attention, interest and memory; followed by recreational reasons (20% to 70%), such as increasing sociability and euphoria and potentiating the effects of alcohol, decreasing its depressant effect and, in a reduced minority, to suppress appetite.<sup>11, 18, 24, 29, 33, 37 -39, 41, 42</sup>

The limitations associated with the short duration of a medical consultation, facilitated access to information via the Internet, the possible simulation or exaggeration of complaints by adolescents for the purpose of being medicated, etc., are factors that increase the risk of over diagnosis and the consequently excessive prescription of MPH.<sup>11,35</sup> In addition, the extension of pharmacological treatment to adults may also facilitate access to this therapy.<sup>10,22,35</sup>

MPH has been associated with street sales and theft in pharmacies, although the majority (up to 78%) acquire it through family members or colleagues with a doctor's prescription.<sup>1, 11, 16,18,20,23,24,32,37</sup> This exchange is frequently performed within the educational institution, probably at a higher rate than what has been recognized.<sup>18</sup> Several studies have shown that 16-54% of patients receiving MPH have already been approached to sell, give or exchange their medication with other students and 11% to 49% effectively do so.<sup>11,13,18,32,35,36,38,39,43</sup> According to the students, patients who are medicated have extra tablets because they do not take them daily, i.e. they only take medication on school days and when the workload is significant, stopping at weekends and holidays.<sup>29</sup> Thus, about 85% of university students consider that obtaining MPH is relatively easy and that selling it is an advantageous and a morally irrelevant deed.<sup>29</sup>

Illicit use among patients with ADHD who are medicated with MPH is a poorly studied reality.<sup>13,18,36</sup> Apparently, those who use their own medication illegally have a higher hyperactivity score, although more studies are needed to confirm this; and those who correctly take the medication have more negative expectations regarding psychostimulants, sometimes requiring supervision to maintain adherence to therapy.<sup>10,13</sup> The phenomenon of "doctor shopping", in which the patient seeks several doctors to obtain medication for illicit use, has also been described.<sup>18</sup> In the Portuguese medical reality this can be easily identified, provided that this possibility is taken into account by the access to the electronic emission of prescriptions (PEM) and health data platform (PDS), which allows to consult patient's prescribed medication.

In literature, there are percentages between 15% and 64% for misuse of the medication itself, mainly due to dose

increase, and concomitant abuse of other drugs or behavioral disturbance.<sup>11,13,14,18,36</sup> However, it is important to emphasize that most adolescents with ADHD who are medicated with MPH do not use their medication unduly, making it necessary to be careful not to stigmatize this group and devalue the beneficial effects of pharmacological treatment.<sup>16,18,36</sup>

### **SIDE EFFECTS AND INTOXICATION**

There is few information regarding the accidental exposure of MPH and the potential medical complications associated with overdose, and the effect of high doses in humans is unknown.<sup>4,14,31</sup> In addition, in a questionnaire conducted at different PCCs, only three in 15 had guidelines for intoxication with MPH.<sup>5</sup>

The risk of adverse effects is dose-dependent and varies depending on the route of administration and multiple drug intake.<sup>18,20,31</sup> The oral route is the most common among those who use MPH to improve academic performance.<sup>8, 18,24,28,37,42</sup> Those who consume it for recreational purposes do so more often through the intranasal route, promoting a faster effect with polydrug use (alcohol, tobacco, cocaine, marijuana and ecstasy). Subjective effects are described as “cocaine-like” in supratherapeutic doses, although expectations regarding the effects of a psychostimulant might act as a placebo.<sup>6,35</sup>

Information about long-term side effects of psychostimulants is limited.<sup>1,11,25</sup> The most immediate and frequent adverse effects are abdominal pain, tachycardia, insomnia and anorexia, and less frequently nausea, headache and hypertension. The manifestations of MPH overdoses are similar to those of sympathomimetic agents: psychiatric and neurological effects are manifested by headache, agitation, depression, abnormal movements or rigidity, mood or behavior changes, hallucinations and paranoia; cardiovascular manifestation include hypertension, tachycardia, arrhythmias and chest pain, and the main gastrointestinal manifestation are vomiting and/or abdominal pain. Analytically, there may be an increase of serum transaminases or creatine kinase and thrombocytopenia. Mydriasis, tachypnea, hyperthermia, rhabdomyolysis and convulsions are also described.<sup>1,3,8,11,19,21,22,30,34,40</sup> There is a report of oral dyskinesia, a rare presentation of Ritalin® intoxication, which was solved with lorazepam<sup>19</sup>. At high doses it may cause anxiety, altered respiratory rate, cardiac arrhythmia, psychosis, mania, depression and suicidal ideation.<sup>1,5,8,11,13,18,21,30,32</sup> Although it is very rare, there is a record of cardiomyopathy, acute myocardial infarction, and sudden death associated with the illicit use of MPH.<sup>11,18,32,34</sup> Psychostimulants have been associated with sudden cardiac death due to prolonged ventricular repolarization, reflected as prolongation of QT interval, which predisposes to *torsade des pointes* tachycardia. However, there are studies that do not find correlation with a substantial alteration of the QRS or QT interval.<sup>34</sup> Complications associated with parenteral injection, such as local infections, inflammatory and ischemic complications, endocarditis, and pulmonary hypertension may also occur.<sup>14</sup>

Data from PCC suggest that the acute toxicity of MPH is rarely associated with severe symptomatology, being mostly

mild to moderate.<sup>8,14,21</sup> However, MPH demonstrates high pharmacokinetic variability among individuals and is not linear at high doses and may be idiosyncratically toxic at low doses.<sup>3,4,31</sup> Some studies suggest that MPH doses less than 1 mg/kg are not associated with adverse events at pediatric age, although the toxic dose of immediate or extended-release formulations remains unknown.<sup>30,31</sup>

Deaths from the parenteral and intranasal illicit use of MPH are described because these routes of administration produce a rapid and cocaine-like effect.<sup>1,8,18,30</sup> The most common cause of death after intoxication of stimulants agents is ventricular tachycardia or ventricular fibrillation.<sup>30</sup> In literature, cases of suicide attempts through ingestion of MPH have also been described, but none of the cases had sequelae or fatal outcome.<sup>4,14,30</sup>

Since there is no antidote for MPH intoxication, the treatment consists of supportive measures and should be individualized.<sup>1,5,31</sup> Serious symptoms such as agitation, delirium, dystonia and seizures can be controlled with benzodiazepines, phenobarbital or haloperidol.<sup>14,19,26,30,31</sup> Gastrointestinal decontamination with activated charcoal orally, has been performed in acute intoxication, although without clear resolution of symptoms or studies with scientific evidence.<sup>4,5,31</sup> Fever should be controlled, such as hypertension, which can be managed with alpha-adrenergic antagonists, vasodilators or calcium channel blockers. For arrhythmias administration of antiarrhythmics is advised; beta-blockers can further increase blood pressure as a result of unopposed alfa-adrenergic stimulation.<sup>30</sup>

Patients can be discharged from the ED in the absence of signs of toxicity and if oral intake occurred over three hours ago. This time frame is the most likely period to occur symptomatology, as the maximum concentration is reached after two hours.<sup>5,14, 19, 30</sup> Patients who are routinely medicated with MPH and who are on toxic intake should not take the medication within 24 hours of the episode.<sup>5</sup> Intensive care is indicated in cases of severe sympathomimetic toxicity, co-morbidity or polydrug use.<sup>14</sup>

### **RISK FACTORS AND PREVENTIVE STRATEGIES**

There are five groups of individuals at high-risk of MPH misuse: high school and university students, other young adults, substance abusers and patients treated with MPH.<sup>11,13,18,20,36</sup>

Although more research is required to obtain a profile of those who misuse MPH, significant risk is associated with males, caucasians, middle and upper social classes, high school students with no intentions on getting further education, university students (mostly from competitive institutions or those with low academic performance), other substance abusers and perfectionist or sensation-seeking personalities.<sup>9,11,13,14,18,20,22,29,37,38,41,42</sup>

The majority of the MPH misusers initiate their consumption at university, however preventive strategies should begin earlier since 19% and 2% starts while at high and middle school, respectively.<sup>18,29</sup> The initiation of substance abuse during adolescence increases the probability of developing future addiction, especially if it begins at an early age.<sup>25</sup>

The major obstacle to implementing preventive strategies seems to be the impact MPH has in improving attention skills and fatigue, as described by students. These effects become desirable according to the growing demands and competitiveness felt by students throughout their education.<sup>29</sup> Despite the absence of significant side effects, MPH does not have any result on intelligence quotient and the influence on cognitive skills appears to be limited to those with ADHD. It is also reasonable to consider placebo effect.<sup>6,11</sup> Nonetheless, more research is required on this matter, since not much is known about the physiologic effects of MPH on those with no disorder.<sup>11,29,45</sup>

Perhaps the most important preventive strategy should be careful prescription of MPH, since patients treated with this substance can inappropriately provide it to their friends or school colleagues. Thus, diagnosis and pharmacological treatment should only be carried out by a qualified physician, which ought to ensure the reliability of the person supervising the MPH administration. It is imperative to watch for signs of possible misuse, such as repeated requests for higher doses and a pattern of “lost” prescriptions.<sup>16,39,43</sup> Dosage has to be carefully monitored, avoiding excess, which enhances misuse.<sup>11,24,29,33,35-37</sup>

Providing proper information regarding the use of MPH and the risks of misuse is necessary, especially to those belonging to risk groups and their families, as there’s still a lack of knowledge regarding adverse effects. Information concerning legal implications of improper use of schedule II substances (like MPH) should also be provided.<sup>11, 13, 16, 20, 29, 30, 38</sup>

Reports to the PCC referring to motivation, dosage, formulation, beginning and type of symptoms are crucial for a proper evaluation of this issue and its consequences.

In conclusion, MPH misuse is considered a current and important issue, concerning, not only students, but also families, school institutions and the medical community. As MPH prescription for children and adolescents with ADHD increases, the risk of intentional and unintentional overdose, misuse and suicidal attempts increases too.<sup>4</sup>

Nonmedical use of MPH is erroneously considered harmless and morally accepted on both psychological and physical terms by the misusers. This acceptance is due to the motivation behind MPH misuse which is to improve academic performance, in opposition to the motivation behind the use of recreational substances. Living in a competition oriented society makes it difficult to persuade students not to misuse psychostimulant substances.

There are no Portuguese studies available regarding MPH misuse, but it can be assumed this is a concern in our country too, given the summarized information above. Thus, it’s important to identify a profile of MPH misusers, its prevalence, motivations and consequences, in order to develop an effective preventive program.

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