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From Clinical Application to Cognitive Enhancement: The Example of Methylphenidate

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Abstract: Methylphenidate (MPD) is a central nervous system (CNS) stimulant, which belongs to the phenethylamine group and is mainly used in the treatment of attention deficit hyperactive disorder (ADHD). However, a growing number of young individuals misuse or abuse MPD to sustain attention, enhance intellectual capacity and increase memory. Recently, the use of MPD as a cognitive enhancement substance has received much attention and raised concerns in the literature and academic circles worldwide. The prescribing frequency of the drug has increased sharply as consequence of the more accurate diagnosis of the ADHD and the popularity of the drug itself due to its beneficial short-term effect. However, careful monitoring is required, because of possible abuse.

In this review different aspects concerning the use of MPD have been approached. Data showing its abuse among college students are given, when the drug is prescribed short term beneficial effects and side effects are provided; moreover studies on animal-models suggesting long lasting negative effects on healthy brains are discussed. Finally, emphasis is given to the available formulations and pharmacology.

Keywords: Abuse, ADHD, cognitive enhancement, long-term effects, methylphenidate.

1. INTRODUCTION

Methylphenidate (MDP) is a central nervous system (CNS) stimulant, of the phenethylamine class, available on the market with the following trade names: Ritalin, Equasym XL, Concerta, Quillivant XR, Methylin, Metadate and Focalin. Its street names are the following: Bennies, Black Beauties, Cat, Coke, Crank, Crystal, Flake, Ice, Pellets, R-Ball, Skippy, Snow, Speed, Uppers, and Vitamin R. The drug was first synthesized in 1944 and launched as Ritalin by Ciba-Geigy Pharmaceutical Company in 1954. It was originally used, after licensed in 1955 by the U.S. Food and Drug Administration (FDA), for the treatment of lethargy, narcolepsy, chronic fatigue, disorders associated with depression and what was then known as hyperactivity [1]. However, its most impressive beneficial effect has been the decrease of the symptoms noticed in attention deficit hyperactivity disorder (ADHD), which is one of the most common behavioral disorders in childhood and may persist into adulthood [2, 3] found in approximately 3% to 5% of the general population of school-age children, occurring more frequently in boys [4-6]. Its prevalence may rise up to 17% when less strict criteria are used [7]. In 1990, when diagnosis of the ADHD became more broadly accepted the MDP became the drug of choice for the treatment of this disorder with its prescription exceedingly increasing [4, 8-11]. In general, MPD is safe when used as prescribed and produces limited side effects when used orally in therapeutic doses [12-15]. Although, MPD's safety, efficacy and cost effectiveness have been documented in many studies [16, 17] there is still a gap of knowledge regarding its long-term effects on brain function and structure and its influence on brain development.

Historically, in 1937, Charles Bradley reported a positive effect of stimulant medication in children with various behavior disorders [18]. Many of the children previously mentioned would probably be diagnosed with ADHD today [19]. Bradley discovered the beneficial effects of stimulants on children behavior symptomatically, in his attempt to treat their headaches produced after pneumoencephalograms as result of a considerable loss of spinal fluid. Benzedrine, "the most potent stimulant available at the time" was used by Bradley to treat the headaches. Although benzedrine had only a tiddley effect on the headaches, it caused an astonishing improvement in behavior and school performance in some of the children. Subsequent trials of Bradley led to the same conclusion *i.e.* the use of benzedrine improved the school performance of approximately half the children and they "were more interested in their work and performed it more quickly and accurately" [19]. However, his revolutionary observations had no influence on practice at the time since the assumption that behavioral disorders require psychological interventions was predominant [20]. Posterior studies for example by Denhoff *et al.* [21] produced growing interest in

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stimulant treatment of hyperkinetic children. At present, stimulant medication is the most frequently used treatment for children with ADHD and MPD is the stimulant of first choice, [9, 22] while benzedrine, which was the first stimulant used for the same purpose, is no longer in use [8].

2. MATERIALS AND METHODS

Some databases, from 1957 to 2015, were searched: Medline, Cochrane Central, Scopus, Web of Science, ScienceDirect, EMBASE and Google Scholar, using the following keywords: Methylphenidate, cognitive enhancement, ADHD, abuse, long-term effects, Ritalin, Concerta, Metadate, Methylin and Focalin. The main key word "Methylphenidate" was individually searched in association to each of the others. Among the 7305 sources found after the initial screening in order to exclude duplicate sources, 134 references, taking into consideration the aims of the paper, were selected.

3. PHARMACOLOGY AND AVAILABLE FORMULATIONS

ADHD and other related disorders are considered to be associated with dopamine and norepinephrine sub-performance in the brain, particularly in the prefrontal cortex (PFC) [23]. As already mentioned, ADHD is a common developmental disorder that affects school–age children [24] and impairs the functioning of the frontal lobes, specifically the PFC, which is responsible for self-regulatory functions, including among others motivation, memory and inhibition. Executive function (EF) refers to the mental control procedures, encompassing cognitive, physical and emotional control, that are requested to maintain effective goal-directed behavior, which includes problem solving, planning and organizing skills [23]. Deficits in EFs have been suggested to lead to cognitive difficulties experienced by children with ADHD [25, 26]. Deficits in working memory (WM), which is a key EF, have been cited in individuals with ADHD [27, 28]. Moreover, a lot of studies have indicated that WM impairments are central to ADHD [29, 30].

Since MPD's mechanism of action implicates the inhibition of catecholamine reuptake, principally as a dopamine reuptake inhibitor, the drug is considered efficient for the control of the symptomatology of ADHD, which is mostly consistent with the dysfunction of the PFC. MPD acts by blocking both dopamine and norepinephrine transporters, which leads to increased extracellular dopamine and norepinephrine concentrations in PFC [31] and dopamine in the striatum [32-36]. It has been shown that working memory performance is facilitated after a low dose of MPD infusion in PFC, whereas infusion of MPD into striatum has no reaction on this PFC-dependent cognition task [37], suggesting that PFC is a main site for MPD's therapeutic action [38, 39]. *In vivo*, acute administration of MPD exerts excitatory actions on the PFC neurons by an indirect activation of alpha2-adrenoceptors and D1 receptors [38, 40-42], while *in vitro*, the drug could enhance excitability of pyramidal PFC neurons by activating alpha-2 receptors located in interneurons [43]. Zhang *et al.* found that MPD facilitates NMDA-receptor mediated excitatory synaptic transmission through σ1 receptors *via* PLC/PKC signaling [44]. Evidence also suggests that alpha2A adrenoceptor gene is involved with the MPD-induced improvement in ADHD [45].

MPD is highly effective in improving the core symptoms of ADHD [46]. Pietrzak *et al.* suggested that MPD improved response inhibition, attention control and sustained attention in approximately 70% of the studies examined [47]. Moreover, WM is improved by MPD through dopaminergic transmission facilitation [48]. Although, the most recent findings suggest that impairments in visuospatial WM (VSWM) is common to individuals with ADHD [29, 49], there is a limited number of studies investigating the effectiveness of MPD on VSWM in children with ADHD [50, 51].

MPD (structure is shown in Fig. **1**) can be found on the market in various forms under numerous brand names and formulations including tablets, capsules, oral suspension (liquid syrup) and adhesive-based matrix transdermal system (patch). The drug is currently administered either as extended [52-54], instant-release or as an osmotically controlled-released formulation [55, 56].

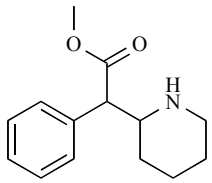

Fig. (1). Methylphenidate chemical structure.

Newer long-acting formulations include an immediate-release ingredient to ensure the instant onset of action and an extended-release ingredient, which continues acting throughout the day. Thus, a rapid onset of action can be achieved with one dose per day. Different technologies are used for the numerous MPD formulations aiming to control the symptoms for at least 8 hours and incorporate different proportions of instant and extended-release MPD. For instance, Focalin XR® and Ritalin LA® use Spheroidal Oral Drug Absorption System (SODAS®) technology to supply 50% of the MPD dose instantly and 50% as extended release [57].

dl-threo-Methylphenidate exists as two enantiomers, l-threo-methylphenidate (l-MPD) and d-threo-methylphenidate (d-MPD). d-MPD has been developed as a medicine to treat ADHD itself. dl-threo-Methylphenidate undergoes enantioselective metabolism in the liver, resulting in remarkable variations in the plasma concentrations of its isomers, depending on both the formulation administered and the route of administration. Plasma d-MPD concentrations are higher than those of l-MPD when dl-threo-methylphenidate is taken orally. Nevertheless, with the newly developed methylphenidate transdermal system (MTS), 'first-pass' metabolism is circumvented and consequently, plasma d-MPD concentrations are consistent with those reached after oral administration, but the relative l-MPD concentrations are much higher, *i.e.* 50-60% of those of d-MPD. However,

even in this case, it is more possible that the contribution of l-MPD to both the adverse effects and effectiveness of the racemate is no higher than 5-10% of the total. Transdermal drug delivery is considered an effective and safe mean of administering MPD to individuals with ADHD [58].

According to Heal and Pierce [36] d-MPD and l-MPD have the same pharmacological profile as the parent racemate, *i.e.* acting as catecholamine-selective reuptake inhibitors. However, d-MPD is approximately 10 times more abundant than l-MPD in this regard. Ritalin LA® contains racemic MPD (ie. both *d*-MPH and *l*-MPH isomer), like most MPD formulation do. Taking into account that when the *l*-MPH is orally administered it is metabolized promptly *via* first pass through hepatic circulation, *d*-isomer is thought to be the main pharmacological contributor in the treatment of the disorder. Taking all this into consideration Focalin XR® developed a formulation containing only the d-MPH isomer.

The abilities of these drugs not only to improve the cognitive and behavioral impairment but also to modulate the common side effects is due to their capacity to potentiate noradrenergic and/or dopaminergic function in the central and peripheral nervous systems. The authors concluded that between the two isomers, d-MPD, which is more abundant and potent, contributes more to both the effectiveness and the adverse effects, irrespective of the route of administration or the formulation of the racemate [36].

MPD's, formulated as hydrochloride salt, high solubility in the fluids of the gastrointestinal tract, leads to rapid and extensive absorption from the intestine to the colon [59, 60]. Thus, it is more likely that the gastric emptying time is the main factor in controlling MPD absorption after immediate-release intake, whereas for the various controlled-release formulations, programmed drug release and the dissolution pattern are considered to be the factors which control the drug's absorption. Because of extensive first-pass metabolism followed by oral administration, the absolute bioavailability is low and variable [61].

Once MPD reaches the systemic circulation, it is promptly distributed to various tissues, with a steady-state volume of distribution of approximately 2 L/kg [62].

MPD is primarily metabolized to the inactive [63] metabolite ritalinic acid [59, 64, 65] by deesterification. This simple process leads to absolute bioavailability of 11-53% [66]. The circulating concentrations of the metabolite significantly exceed the concentrations of the parent drug [67-70]. Urinary elimination of ritalinic acid accounts for 60-80% of the dose [59, 64, 65].

Clearance of the drug is also speedy, with little or no accumulation of MPD from day to day, even with the controlled-release formulations [68]. Nonlinearity, possibly related to first-pass metabolism saturation may be noticed at higher oral doses [71]. Half-life has been reported to be 2-6 hours after immediate-release or intravenous dosing with most studies reporting an average of 2-3 hours. Longer half-life is reported for extended-release formulations, but this is most probably related to prolonged absorption [72].

4. ADVERSE SIDE EFFECTS

Although MPD is effective in the majority of children in the short term, there is considerable variation in individual response to treatment, with a minority not managing sufficient symptom control whereas others are unable to tolerate the adverse effects of the drug [73-75].

The adverse effects of MPD include among others: pupil dilation, [76] loss of hair, depression, anorexia, headaches, impairment of libido, insomnia, restlessness, anxiety and hypersensitivity [77-80]. Data obtained by Auger *et al*. [81], demonstrate that patients treated with high-dose stimulants, used in the treatment of excessive somnolence disorders, showed a significant increase of the occurrence of psychosis, psychiatric hospitalizations and substance misuse compared to the patients treated with standard doses of the same stimulants. In addition, anorexia and tachyarrhythmia were more common in the high-dose treated group compared to controls. Occasionally, stimulant psychosis can occur during long-term therapy with MPD. Thus, regular psychiatric monitoring of individuals treated with MPD has been recommended [82].

Recent large-scale studies by the US FDA suggest that, serious adverse cardiovascular events such as sudden death, myocardial infarction, and stroke are not associated with the medical use of MPD, amphetamine or other customarily prescribed ADHD stimulants in children, young adults, and adults [83, 84]. On the other hand, some studies suggest a small but significant impact of MPD on the cardiovascular system including increases in heart rate and blood pressure and sudden cardiac death [85, 86].

Aktepe *et al.* [87], investigated the side effects of MPD in ADHD children (n=126). In 55.5% of cases, MPD was used alone, whereas in 26.9% of cases, it was used in combination with other medications. Side effects were recorded in 51.6% of cases and no side effects in 48.4%. MPD treatment had to be ceased in only 5.5% of cases. The side effects resulting in the cessation of the treatment with MPD are as follows: weight loss, irritability, hyperactivity, exacerbation of tics and papular rash. The side effects reported are shown in Fig. **2**. MPD was used at a dose of 10-20 mg/day in 89.6% of cases.

Moreover, MPD has been associated with the risk of long lasting and often painful erections, known as priapism. Thus, FDA updated patient medication guides and MPD labels to provide information about the rare but important risk of priapism. If the previously mentioned disorder is not treated immediately, it can result in permanent harm to the penis. Priapism is more likely to occur in male patients treated with atomoxetine than those treated with MPD. However, due to limitations in available information, it is not known how frequently priapism appears in patients treated with MPD. Cases of a prepubertal child and a 14-year-old male who developed priapism after therapy with MPD have been reported in literature [88, 89]. It is recommended that healthcare professionals should inform male patients about the symptoms and signs of priapism and emphasize the necessity for immediate treatment, since younger males may

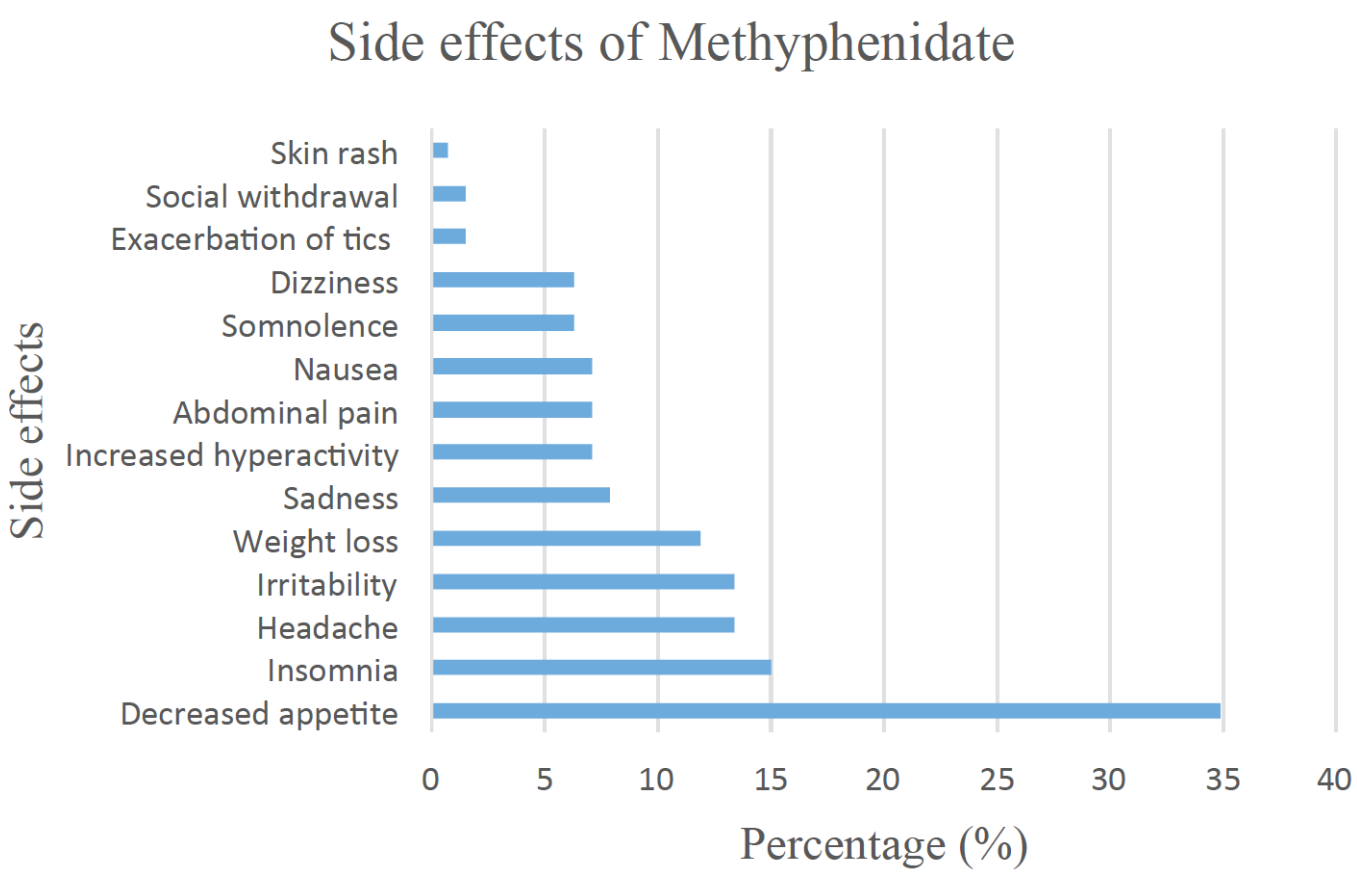

Fig. (2). Adverse side effects of Methylphenidate reported by Aktepe *et al.* [87].

not recognize the problem or be too embarrassed to tell anyone if it happens [90].

Hepatotoxicity is a rare adverse reaction to MPD. The literature review indicates some cases of liver failure attributed to MPD, that recovered after the treatment cessation. However, a recent study reported a liver failure case attributed to MPD, where liver transplantation was required. The probable mechanism of liver injury was MPD direct toxicity to hepatocytes. Thus, the monitoring of liver function is highly recommended in these cases [91].

5. ABUSE/MISUSE

MPD has been broadly used as drug of abuse because of its psychostimulant properties. Moreover, MPD has been used by college students in order to achieve the so called cognitive enhancement (CE) which is defined as the usage (by healthy individuals) of psychoactive drugs aiming at enhancing cognition which includes among others concentration and memory. CE substances commonly used can be divided into three groups: 1) over-the-counter, such as caffeine tablets, energy drinks etc.; 2) drugs approved for the treatment of certain disorders, such as amphetamines and MPD and 3) illicit drugs, such as ecstasy and crystal meth [92]. According to users' reports on 'self-experiments' Internet forums, abusers either grind the commercially available tablets into powder and snort it or they convert it into liquid form, since the drug is water soluble, making it injectable (intravenous administration). Smoking and oral administration have also been reported. Moreover as referred in the same forum MPD can be abused in combination with other drugs, such as cannabis, oxycodone, amphetamines, alprazolam, alcohol and others [93].

Unlike other potent stimulants, there is no clandestine production of MPD and diverted pharmaceutical products are the only source for abuse purposes. MPD is obtained from fraudulent prescriptions, pharmacy theft, doctor shopping, and from friends or associates who have obtained the drug through a prescription [94].

The potentiality of abuse of MPD was considered in the early 1960s in a case report of a patient who was taking 125 tablets of MPD per day [95]. Reports of oral MPD abuse including reports of MPD paranoia [96], hallucinations [96, 97], delusional disorder [98] and euphoria [99], appeared later in the literature. Intravenous abuse of MPD related to psychosis was indicated in 1963 and subsequently intravenous abuse was reported in several studies in the early 1970s [96, 97, 100]. Afterward, a study depicted the intravenous abuse patterns, mortality, and morbidity related to MPD [101].

Studies on animals for evaluation of the long-term effects of abuse resulted in ambiguous outcomes; negative effects like the ones of methamphetamine in low doses and no effect in high doses. Additional studies to evaluate potential

neurotoxicity under such conditions is necessary. It has been proved that, the abuse of MPD, when in rare cases intravenously administered can even produce dopaminergic fibers maturation impairment in subcortical brain areas [102].

Many surveys have been conducted suggesting wide abuse of the drug as a cognitive enhancer among healthy college students. However, it is hard to define the actual trend of abuse [103]. According to Teter *et al.*, who conducted a research to investigate the motives, prevalence and routes of administration of illicitly used prescription stimulants among college students, 24.5% of the 269 students who declared past-year illicit use of prescription stimulants, reported MPD use. In the same survey, it was found that the motives for illicit use of prescription stimulants are the following: to assist with concentration, help study, heighten alertness, get high and experimentation. Although most users reported oral administration, a significant percentage (38%) of users reported intranasal administration [104].

Another study, reported that 2.3% of high school seniors declared past-year use of Ritalin, while 1.9% used methamphetamine [105]. A 2000 study, conducted within a liberal art college stated that more than 16% of the students who participated had tried MPD recreationally and approximately 13% had administrated the substance intranasally [106].

As reported by the U.S. Department of Health and Human Services, in Monitoring the Future National Survey Results on Drug Use, 1975-2006 [107], the use of MPD among young adults and college students in 2006 was 2.6% and 3.9%, respectively. A slight decrease in the use of MPD in both groups from 2002 to 2006 was also noted. However, compared to the trend of use of other phenethylamines commonly abused, such as amphetamines, MPD is less commonly abused by both categories.

A large study carried out at the University of Michigan; found that approximately 3% of the students (out of 2250 students who completed the survey) had declared past year illicit use of the drug. No significant differences between males and females percentages of misuse/abuse were found. In addition, an association between MPD misuse and use of alcohol and drugs was found. In particular, MPD misusers were considerably more likely to use drugs and alcohol [108].

According to White *et al.* [109] 16% of students of a northeastern US university have misused or abused stimulant medications. Of this category, 96% of those specified a medication, reported Ritalin as their stimulant of choice. More than 50% of the students misusing the drug, reported administration of the drug 2-3 times per year, 34% 1-2 times per month, while 15.5% of the misusers take the drug 2-3 times per week. Similar use patterns were reported by the two sexes. Reducing hyperactivity, improving attention and improving grades were the reasons which lead to misuse or abuse of the drug according to the participants.

When MPD is intranasally abused similar effects to intranasal use of crack cocaine and amphetamines are produced [110, 111]. Doses as high as 200mg have been reported for intranasal MPD abuse and 40mg-1000mg for intravenous abuse [4, 111, 112].

To sum up, comparative analysis is not recommended since the methodology used differs from study to study. However, data obtained suggest broad abuse/misuse of MPD as cognitive enhancer among college students, teenagers and young adults [113-115]. Table **1** summarizes the outcomes of studies conducted to determine the prevalence of MPD's abuse.

6. LONG-TERM EFFECTS OF MPD ON THE BRAIN

Several studies, involving both animals, mostly rats, and humans have been conducted in order to assess the possible enhanced cognitive effects of MPD on the normal brain [116-118]. It has been reported that high doses (5–10 mg/kg) when intraperitoneally administered in rats increase the locomotor activity and impair both performance and attention. On the other hand, improvement of the cognitive performance and reduced motor activity was noted after rats were intraperitoneally administered a low dose (0.5–2 mg/kg) of the drug. Moreover, the administration of even lower doses (0.25–1 mg/kg) of MPD in healthy rats heightens the attention skills without influencing motor activity [119].

MPD improves the performance of prefrontal cortex tasks in both "normal" college students [120] and in patients diagnosed with ADHD [121].

Since MPD is most commonly prescribed to children and adolescents with ADHD at a moment of crucial importance for the adolescent because of the development and the maturation of the brain, it is thought that drug exposure at

Table 1. Prevalence of MPD's abuse and common routes of administration when abused.

Author	Type of Survey	Percentage of Individuals Used MPD	Routes of Administration
Teter *et al*. [104]	Web-based	24,5% out of 269 past-year illicit users of prescription stimulants	Oral, intranasal
Babcock and Byrne [106]	Self -reported survey (10 yes-and-no questions)	16.6% out of 283 students	12.7% intranasal
Teter *et al*. [108]	Internet survey	3% out of 2250 students reported past-year illicit use	
White *et al*. [109]	Internet survey	16% reported abuse/misuse of stimulant medication. 96% of those reported Ritalin as the stimulant of choice	Orally, 40% intranasal

this period of life could result in lasting alterations that will persist into the adulthood. Lee *et al*. investigated the effects of the repeated drug administration on the locomotor diurnal rhythm activity patterns of female Sprague-Dawley (SD) rats during adolescence. The experiment involved 31 rats divided into the following groups: control, 0.6 mg/kg, 2.5 mg/kg, and 10 mg/kg MPD group. Saline was injected to all groups on the first day of experiment, whereas on days 2-7 rats were administered with either saline, 0.6 mg/kg, 2.5 mg/kg, or 10 mg/kg of MPD. A washout period followed (*i.e.* Days 8-10). The same dose used on days 2-7 was injected again on day 11 to the four groups, respectively. The obtained data illustrated that repeated administrations of both 2.5 mg/kg and 10 mg/kg of the drug could alter the locomotor diurnal rhythm patterns, suggesting that the previously mentioned doses exert long-term effects [122].

The cellular mechanisms of action of MPD and its eventual effect on prefrontal cortical circuitry are not fully established, in particular within the developing brain system. Urban *et al.* [123], involve in their experiments both adult SD rats and Juvenile (postnatal day [PD] 15), that were administered with either saline or MPD. Both neuronal excitability and synaptic transmission in pyramidal neurons of prefrontal cortex were examined. Moreover, recovery from the drug treatment was tested 1, 5 and 10 weeks after the last administration of the drug.

It was concluded, that either chronic treatment or a single dose of 1 mg/kg intraperitoneal MPD, could generate considerable depressive effects on pyramidal neurons in juvenile rat prefrontal cortex. Doses of 0.03 to 0.3 mg/kg also generated depressive effects in juvenile rats, in a linear dose-dependent way. Function recovery achieved within 1 week from chronic 1 mg/kg treatment, while depression of prefrontal neurons noticed on rats chronically treated with 3 and 9 mg/kg lasted 10 weeks and beyond. The obtained data suggest that the prefrontal cortex of the juvenile is supersensitive to the drug and the acceptable therapeutic range for adults is overestimated, since the chronic treatment with 1 mg/kg MPD is well correlated with the acceptable therapeutic range for adults. In general, juvenile treatment with MPD can produce long-lasting and potentially permanent changes to excitatory neuron function in the prefrontal cortex of juvenile rats [123].

Both meta-analyses and systematic reviews of magnetic resonance imaging studies suggest that long-term treatment with ADHD stimulants (particularly, MPD and amphetamine) reduces abnormalities in brain function and structure found in individuals with ADHD [124-126]. Furthermore, both the efficacy and the safety of long-term use of ADHD stimulants for subjects with ADHD have been established [127]. Specifically, the continual treatment efficacy and safety of both MPD and amphetamine have been evidenced in controlled drug trials with duration of several years [127].

Rats with ADHD-like behavior were employed in animal studies aiming to evaluate the safety of MPD on the developing brain. It was noted that both psychomotor impairments and liturgical and structural parameters of dopaminergic system were improved with treatment. Nevertheless, MPD produced long lasting alterations to the dopaminergic system of healthy control animals. Moreover, it was shown that rats treated with MPD grew up to be more emotional and stressed [102].

Bolaños *et al.* [128] observed that animals treated with MPD showed increased anxiety-like behavior, were considerably more sensitive to stressful situations, and had enhanced plasma levels of corticosterone, compared to controls. However, for the latest study, healthy rats were used thus remaining unclear whether MPD could cause adverse emotional effects on ADHD animal models [128].

7. CONCLUSIONS

Data suggest that MPD is a drug of great value that nicely fits the pharmacological demands to control dopamine dysfunctions in ADHD. However, long lasting alterations to the dopaminergic system in normal control animals suggest that if a child is misdiagnosed with ADHD he or she may be at risk of long lasting unfavorable effects in brain development. Thus, careful clinical diagnosis and assessment of ADHD symptomatology is required to assure that the drug is only prescribed to children with comprehensible ADHD symptomatology. Data obtained from animal studies illustrate that under the latest conditions MPD is supportive for the related behavior and brain development in children with ADHD. It is worth pointing out that medical malpractice suits, charging physicians with negligent misdiagnosis of ADHD and failure to obtain sufficient informed consent for the use of stimulants and inadequate information on side effects have been raised [129].

In addition, clinicians should be very attentive concerning the prescribing of dosages higher than the maximum guidelines since the latter could result in undesired effects. Moreover, due to the numerous formulations commercially available, clinicians should be very cautious in choosing the most suitable one, taking into account the patients' response to the drug and the different treatment needs of each individual. In general, a tailored approach is required in order to optimize the treatment of ADHD symptoms.

Summing up, the wealth of both human and animal data of MPD indicates the great significance of the drug, which has to be carefully handled in the right way. However, it is extremely difficult to compare the studies investigating long term effects because of the heterogeneity in data and duration which suggests the necessity of systematic monitoring of long-term safety of the drug [130].

Nevertheless, the use of MPD and other stimulants for the treatment of ADHD symptoms has been controversial [131, 132]. One such criticism is the prescription of psychostimulants medication to children in order to reduce ADHD symptoms [133]. The claim that MPD acts as a gateway drug has been discredited by multiple sources, according to which MPD rarely leads to addiction or abuse when taken appropriately as treatment for ADHD.

Data obtained from numerous studies (comparative analysis is not recommended, though) suggest broad abuse/ misuse of MPD as cognitive enhancer among college students, teenagers and young adults [134]. Results obtained

from studies concerning the effects of the stimulant on healthy individuals suggest its abuse is a concern on college campuses.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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