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Use of cognitive enhancers: methylphenidate and analogs

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Abstract. – OBJECTIVE: In the last decades, several cognitive-enhancing drugs have been sold onto the drug market. Methylphenidate and analogs represent a sub-class of these new psychoactive substances (NPS). We aimed to review the use and misuse of methylphenidate and analogs, and the risk associated. Moreover, we exhaustively reviewed the scientific data on the most recent methylphenidate analogs (methylphenidate and ethylphenidate excluded).

MATERIALS AND METHODS: Literature search was performed on methylphenidate and analogs, using specialized search engines accessing scientific databases. Additional reports were retrieved from international agencies, institutional websites, and drug user forums.

RESULTS: Methylphenidate/Ritalin has been used for decades to treat attention deficit disorders and narcolepsy. More recently, it has been used as a cognitive enhancer and a recreational drug. Acute intoxications and fatalities involving methylphenidate were reported. Methylphenidate was scheduled as an illegal drug in many countries, but NPS circumventing the ban and mimicking the psychostimulant effects of methylphenidate started being available: ethylphenidate, 3,4-dichloromethylphenidate, 3,4-dichloroethylphenidate, 4-fluoromethylphenidate, 4-fluoroethylphenidate, methylnaphthidate, ethylnaphthidate, isopropylphenidate, propylphenidate, 4-methylmethylphenidate, and N-benzylethylphenidate have been available in the past few years. Only little data is currently available for these substances. Many intoxications involving methylphenidate analogs were reported. To date, ethylphenidate was involved in 28 fatalities, although it was reportedly directly related to the cause of death in only 7 cases; 3,4-dichloroethylphenidate was involved in 1 death.

CONCLUSIONS: The rapid expansion of methylphenidate analogs onto the drug market in the past few years makes likely the occurrence of intoxications and fatalities in the next years. Careful monitoring and systematic control of methylphenidate analogs should be undertaken to reduce the uprising threat, and education efforts should be made among high-risk populations.

Key Words:
Cognitive enhancers, Methylphenidate, Ritalin, Ethylphenidate, Methylphenidate analogs, New psychoactive substances.

Introduction

Consumption of various pharmaceutical drugs by healthy individuals in an attempt to improve cognitive faculties is on the rise, whether for academic or recreational purposes[1]. These substances are stimulants that preferentially target the catecholamines of the prefrontal cortex of the brain to induce their effects (e.g., methylphenidate and analogs, modafinil and analogs, and amphetamine)[2,3]. However, scientific studies supported only small benefits from cognition-enhancing drugs[4] while the risks to health are serious and include dependence, tolerance, and cardiovascular, neurologic, and psychological disorders, with a risk of overdose leading to death[5]. As a consequence, many of these substances are controlled internationally[6]. Like other new psychoactive substances (NPS), new molecules mimicking the psychoactive effects of the scheduled drugs are being synthesized to evade the legislation. Little information on the pharmacology and the toxicology of the new substances is known when they first emerge. Methylphenidate (MPH) is one of the most popular cognitive enhancers[4] and several analogs appeared on the drug market during the last years. However, little or no scientific data on these new analogs is available.

In this mini-review, we aimed to report the current trends in the use and misuse of cognitive en-

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hancers within the sub-class of methylphenidate (MPH) and analogs. We performed an exhaustive review of the scientific data on MPH analogs that first appeared on the drug market in the last five years, i.e. all MPH analogs with the exception of MPH and ethylphenidate. Finally, we compiled the fatalities associated with the consumption of MPH analogs reported in the literature.

Materials and Methods

A literature search was performed on MEDLINE, EMBASE, and CENTRAL (Cochrane Central Register of Controlled Trials) using the keywords methylphenidate intoxication, methylphenidate fatality, methylphenidate death, methylphenidate analog, ethylphenidate, nopaine, dichloromethylphenidate, 3,4-CTMP, 3,4-DMPH, dichloroethylphenidate, fluoromethylphenidate, 4F-TMP, fluoroethylphenidate, methylnaphthidate, HDMP-28, ethylnaphthidate, HDEP-28, isopropylphenidate, IPH, propylphenidate, PPH, methylmethylphenidate, and benzylethylphenidate, with the aim of identifying relevant articles published in English, up to December 2018. Further research manuscripts were retrieved through reference lists of selected articles. Additional reports were found on international agencies or institutional websites including the European monitoring centre for drugs and drug addiction (EMCDDA) and drug user forums.

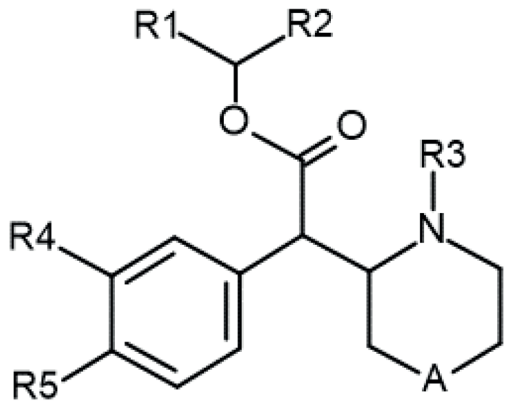
Results

Methylphenidate

Methylphenidate (MPH) (methyl phenyl (2-piperidinyl)acetate) is a sympathomimetic drug that was first synthesized in 1944 and established as a psychostimulant in 1954. Its 2-benzyl piperidine structure resembles that of catecholamines and phenylethylamines, with a piperidine group substituting the amine (Figure 1). As such, MPH's structure is closely related to that of amphetamines[7].

Similarly to amphetamines, MPH competes with catecholamines in the central nervous system and blocks dopamine (DA) and norepinephrine (NE) transporters (DAT and NET, respectively), resulting in elevated synaptic extracellular DA and NE levels[8-10]. MPH was shown to modulate cognition: e.g., improved planning and spatial working memory performance – although it impairs previously established performance – and reduced regional blood flow in different parts of the brain[3,11]. MPH administration increases attention and cognition in healthy subjects through DA and NE increase in the striatum of the subcortical basal ganglia, the dorsolateral prefrontal cortex, and the posterior parietal cortex of the brain[3]. It was initially used for the treatment of depression, chronic fatigue syndrome, and narcolepsy because of its stimulating and exciting effect, tiredness and inhibitions elimination, physical efficiency increase for a short time[12-15]. The sale of MPH is approved in some European countries, such as the United Kingdom and Germany, but the number of prescriptions is significantly lower than the US and it is commonly prescribed under the brand name Ritalin[16], which is used in the treatment of attention deficit hyperactivity disorder (ADHD), with limited effectiveness[17].

MPH is also a substance under international control, in accordance with the Convention on Psychotropic Substances of 1971[6]. MPH is among the substances the most commonly misused by individuals seeking to extend their capacities for alertness and cognition[18,19]. A recent systematic review assessed MPH effect on cognitive performances in healthy subjects including 46 trials and several meta-analyses of studies that tested the effects of MPH[20]. It was found that a single dose of MPH (5 to 40 mg or 0.25 to 0.5 mg/kg) had a significant effect on memory but no effect on attention and executive functions. When taken for a prolonged period, MPH presents a risk of addiction, and possibly physical dependence[21]. In sport, the substance is considered a doping substance and is therefore prohibited. Within the last decade, Ritalin's production almost increased tenfold due to its misuse as brain doping substance and party drug. Indeed, the drug is one of the most misused cognitive enhancer, especially in US college campuses, with a prevalence from 7 to 25%[22,23]. Several studies investigated MPH misuse in college and University Students starting from the first years of new century[24-26]. In 2000, a study showed that more than 16% of 283 students of the Massachusetts College of Liberal Arts had tried MPH recreationally[24]. A larger study carried out at the University of Michigan found that approximately 3% 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.



R1	R2	R3	R4	R5	A	Name
H	H	H	H	H	C	Methylphenidate
CH_3	H	H	H	H	C	Ethylphenidate
H	H	H	H	H	C	Dexmethylphenidate
H	H	H	Cl	Cl	C	3,4-Dichloromethylphenidate
CH_3	H	H	Cl	Cl	C	3,4-Dichloroethylphenidate
H	H	H	H	F	C	4-Fluoromethylphenidate
CH_3	H	H	H	F	C	4-Fluoroethylphenidate
CH_3	H		H	H	C	N-Benzylethylphenidate
H	H	H			C	Methylnaphtidate
CH_3	H	H			C	Ethylnaphtidate
CH_3	CH_3	H	H	H	C	Isopropylphenidate
H	H	H	H	CH_3	C	4-Methylmethylphenidate
CH_2CH_3	H	H	H	H	C	Propylphenidate
H	H	H	H	H	O	Methylmorphenate

Figure 1. Structural formula of methylphenidate and analogs.

In addition, an association between MPH and alcohol and drugs' use was found[25]. A national US survey reported that 2.3% high school seniors declared past-year use of Ritalin in 2003, while 1.9% used methamphetamine[27]. The same survey, carried out in 2006, showed that the use of MPH among young adults and college students was 2.6% and 3.9%, respectively[28]. According to White et al, 16% students of a northeastern US university misused or abused stimulant medications[29]. Of this category, 96% reported Ritalin as their stimulant of choice. More than 50% of the students using Ritalin reported 2 or 3 administrations per year, 34% reported 1 or 2 administrations per month, and 15.5% reported 2 or 3 administrations per week. Outside colleges or campus, the potentiality of abuse of MPH was considered in the early 1960s in a case report of a patient who was taking 125 tablets of MPH per day[30].

MPH adverse effects include pupil dilation, loss of hair, depression, anorexia, headaches, im-

pairment of libido, insomnia, restlessness, anxiety, and hypersensitivity[31-35]. In cases of high doses, anorexia and tachyarrhythmia are more common. Oral MPH abuse included reports of MPH paranoia, hallucinations, delusional disorder, and euphoria[36-39]. Intravenous abuse of MPH associated with psychosis was reported in 1963 and the early 1970s[36,37,40]. Moreover, it has been reported that the consumption of MPH was associated with a 1.8-fold increase in risk of sudden death or ventricular arrhythmia[41]. In 1986, Levine et al reported the first case of MPH fatal overdose, following intravenous injection of Ritalin; post-mortem blood concentration was 2,800 ng/mL[42]. Another fatality following MPH parenteral administration was subsequently reported[43]. In 1999, Massello and Carpenter reported the first case of MPH fatality by intranasal abuse of Ritalin[44]. In 2014, Cantrell reported the first fatality resulting from MPH ingestion; post-mortem peripheral blood concentration was 1,100 ng/mL and central blood concentration was 980 ng/mL[45].

Dexmethylphenidate (*d*-MPH) is the active dextrorotatory enantiomer of racemic MPH (R,R) (Figure 1). It is sold under the trade names Focalin among others as a central nervous system stimulant that is used in the treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy. *d*-MPH is a stimulant with similar effects, addiction liability, and dependence liability to those of amphetamine[21,46].

Ethylphenidate

Ethylphenidate (EPH) is the ethyl acetate analog of MPH (ethyl phenyl(2-piperidinyl)acetate, Figure 1). It is an amphetamine-like stimulant that inhibits DA and NE reuptake in the central nervous system through DAT and NET inhibition. EPH affinity to DAT and inhibition potency are similar to those of MPH, but its affinity to NET and inhibition potency are much lower (7-fold factor)[47,48]. Like MPH, EPH *threo* form (*d*-EPH) (R,R) binds DAT and NET with a much higher affinity (10-fold factor)[47]. The drug was patented in 2003 as a potential treatment for attention deficit disorders and narcolepsy, with lower abuse potential compared to MPH[49]. It was first notified as an NPS in the European Union in 2011[50].

Soussan and Kjellgren[51] and Ho et al[52] compiled Internet reports from drug user forums on the subjective effects of EPH intake. EPH is mainly used for recreational purposes. It is described as a potent stimulant with euphoric and arousing effects, increased (or decreased) focus and concentration, increased socialness[51,52]. EPH is marketed as a powder, a pellet, or a crystal and is mainly taken by insufflation (10 to 100 mg), although it can be administrated orally or anally in a capsule form, through the inhalation of evaporating fumes, or injected intramuscularly or intravenously[51,52]. It is associated with a high risk of drug abuse and addiction (redose is frequent)[51,52]. Onset of action reportedly ranges from 0 to 35 min with nasal insufflation, 5 to 31 min with oral ingestion, 0 to 2 min with intravenous injection, and 2 to 10 min with rectal administration[52]. Duration of effects reportedly ranges from 15 to 300 min[52]. Adverse effects following EPH intake may include tachycardia, hypertension, palpitations, endocarditis, fever, mydriasis, insomnia, irritability, paranoia, anxiety, and delusional thoughts. Recovery after acute intoxication is slow, as it can take several days[51-56]. Several deaths associated with EPH were reported (Table I)[57-59]. Maskell et al reported a fatal case of EPH intoxication where EPH was the sole cause of the death. EPH concentration in the post-mortem femoral blood was 2,180 ng/mL – no other drugs were detected[59]. EPH was seemingly directly involved in several causes of death[57,58]. EPH is a controlled drug in several European countries, in Canada, and in China[60,61]. EPH schedule in the United Kingdom drastically reduced the number of hospital admissions for EPH intoxication in Scotland from 15 to 1 per month[62,63].

EPH is mainly metabolized by human carboxylesterase 1c and is converted in ritalinic acid (hydrolysis) and MPH (transesterification)[64,65]. Conversely, EPH is formed after co-ingestion of MPH and ethanol via hepatic transesterification, and EPH can be detected in blood and urine specimens (< 3% MPH concentration in blood)[66,67]. *l*-MPH is more extensively converted (to *l*-EPH) than *d*-MPH (to *d*-EPH)[47,68].

Other Methylphenidate Analogs

Other MPH analogs are being marketed as NPS for their nootropic and stimulant effects. Most of these substances are substituted with a halogen atom at positions 3- or/and 4- of the phenyl ring, for potential increased potency (and addiction liability)[69]. These substances are taken to mimic MPH cognitive effects while circumventing the legislation ("legal high"). Due to their recent availability on the drug market, only little information on MPH analogs is available in the scientific literature to date. Other active MPH analogs exist but, to the best of the authors' knowl-

Table I. Fatalities associated with methylphenidate analogs' use. F, female; M, male; PM, post-mortem; AM, ante-mortem.

MPH analog involved	Victim	MPH analog concentration	Co-administration	Cause of death	Ref.
EPH	M/32	PM femoral blood 110 ng/mL, liver 180 ng/g, pericardium fluid 131 ng/mL, urine 987 ng/mL, stomach content 20.7 ng/mL (200 mL)	Methadone, EDDP, morphine, fentanyl, MPH, and ritalinic acid (2140 ng/mL in blood)	Mitral valve endocarditis in combination with a pneumonia; EPH might have contributed to the death	59
EPH	M/38	PM femoral blood 23 ng/mL	Pregabalin, fentanyl, norfentanyl, and ritalinic acid (943 ng/mL in blood)	Aspiration of stomach content; EPH might have contributed to the death	59
EPH	M/38	PM femoral blood >2,000 ng/mL	Tramadol, paracetamol, morphine and metabolites, 6-monoacetylmorphine, and acetone	Acute haemorrhage related to an abscess	60
EPH	F/33	PM femoral blood 1,900 ng/mL	Methadone, procyclidine, propranolol, morphine and metabolites, diazepam, temazepam, and metabolites, cannabis metabolite, pregabalin, and methylthienylpropamine	Polydrug toxicity and acute pyelonephritis	60
EPH	F/31	PM femoral blood 1,200 ng/mL	Alcohol, morphine and metabolites, and diazepam and metabolites	Polydrug toxicity	60
EPH	M/27	PM femoral blood 760 ng/mL	Alcohol, diazepam and metabolite, and methylthienylpropamine	Unascertained cause	60
EPH	M/37	PM femoral blood 610 ng/mL	Diazepam and metabolite and mirtazapine	Empyema; chronic drug abuse might have contributed to the cause of death	60
EPH	F/31	PM femoral blood 470 ng/mL	Lignocaine, methadone, mirtazapine, and promethazine	Bronchopneumonia and chronic drug abuse; methadone and EPH intoxication might have contributed to the cause of death	60
EPH	M/34	PM femoral blood 410 ng/mL	Alcohol, methadone, diazepam and metabolites, and cannabis metabolite	Multiple injuries	60
EPH	M/38	PM femoral blood 350 ng/mL	α-Methyltryptamine, etizolam, and diphenhydramine	α-Methyltryptamine and EPH toxicity	60
EPH	M/20	PM femoral blood 320 ng/mL	Fluoxetine and metabolite, pregabalin, zuclopenthixol, morphine and metabolites, etizolam, pyrazolam, 2-MeO-diphenidine	EPH, methoxyphenidine, morphine, pyrazolam, and etizolam toxicity	60
EPH	M/40	PM femoral blood 250 ng/mL	Methadone, olanzapine, diazepam and metabolites, cannabis metabolite	Polydrug toxicity; coronary artery atherosclerosis might have contributed to the cause of death	60
EPH	M/35	PM femoral blood 140 ng/mL	Methadone	Unascertained cause	60
EPH	F/33	AM blood 460 ng/mL; PM femoral blood 130 ng/mL	Dihydrocodeine, hydrocodone, morphine, desmethyldiazepam, ketamine, morphine, paracetamol, and alfentanil	Sepsis/multiple organ failure and bronchopneumonia; Chronic drug abuse might have contributed to the cause of death	60

Continued

Table I (Continued). Fatalities associated with methylphenidate analogs' use. F, female; M, male; PM, post-mortem; AM, ante-mortem.

MPH analog involved	Victim	MPH analog concentration	Co-administration	Cause of death	Ref.
EPH	M/54	PM cardiac blood 41 ng/mL	Dihydrocodeine	Unascertained cause	60
EPH	M/45	PM femoral blood 40 ng/mL	Diazepam and metabolites, methadone, morphine and metabolites, and 6-monoacetylmorphine	Methadone and heroin toxicity	60
EPH	M/44	PM femoral blood 28 ng/mL	Methadone and diazepam and metabolites	Pneumonia and methadone toxicity; cachexia might have contributed to the cause of death	60
EPH	M/42	PM femoral blood 15 ng/mL	Alcohol, dihydrocodeine, morphine and metabolites, and diazepam and metabolite	Head injury	60
EPH	F/46	PM femoral blood 10 ng/mL	β-Hydroxybutyrate, mirtazapine, codeine, morphine, diazepam and metabolite, fluoxetine and metabolite, and paracetamol	Disseminated Staphylococcus pyogenes infection and heroin and EPH use	60
EPH	M/25	PM femoral blood 10 ng/mL	Diazepam and metabolite, paracetamol, codeine and metabolites, morphine and metabolites, 6-monoacetylmorphine, and mirtazapine	Heroin and codeine toxicity and acute liver failure	60
EPH	M/45	AM blood 30 ng/mL, serum 8 ng/mL; PM femoral blood 8 ng/mL	Alcohol, morphine and metabolites, 6-monoacetylmorphine, paracetamol, methadone, and desmethyldiazepam	Intracerebellar haematoma and EPH toxicity	60
EPH	M	PM femoral blood 2,180 ng/mL	None	EPH toxicity	61
EPH	M	PM femoral blood 1,370 ng/mL	Benzoylecgonine, sertraline, and diphenhydramine	Hanging	61
EPH	M	PM femoral blood 870 ng/mL	Dothiepin, Methiopropamine, and ethanol	Hanging	61
EPH	M	PM femoral blood 110 ng/mL	Methadone, EDDP, zopiclone, sertraline, aripiprazole, dehydroaripiprazole, 2-aminoindane, and ethanol	Methadone and 2-aminoindane toxicity	61
EPH	M	PM femoral blood 140 ng/mL	Morphine, codeine, ketamine, cocaine, benzoylecgonine, venlafaxine, and O-desmethylvenlafaxine	Heroin toxicity	61
EPH	M	PM femoral blood 30 ng/mL	Methiopropamine and 5-APB/6-APB	Polydrug toxicity	61
EPH	M	PM femoral blood 110 ng/mL	Diazepam, nordiazepam, temazepam, oxazepam, morphine, and codeine	Polydrug toxicity	61
4F-TEP	-	-	-	4F-TEP involvement in the cause of death 89 is not documented	

edge, they are not reported by NPS users (e.g., 3-bromomethylphenidate, 4-bromomethylphenidate, 3-chloromethylphenidate, 4-hydroxymethylphenidate)[69,70].

3,4-Dichloromethylphenidate

3,4-Dichloromethylphenidate (3,4-CTMP) is a halogenated analog of MPH *threo* form (R,R) (methyl(3,4-dichlorophenyl)(2-piperidinyl)acetate, Figure 1) that was first synthesized in 1996 as a potential treatment for cocaine addiction[69]. It was first marketed as an NPS in the United Kingdom in 2013 and is sold as a powder or a tablet to be taken orally or snorted (up to 10 mg)[71,72]. It was first detected in illegal products in Japan in 2013[73,74]. 3,4-CTMP subjective effects are reported by consumers on drug forums[71].

3,4-CTMP was shown to increase electrically evoked DA efflux in the nucleus accumbens (NAc) of rat brain slices[75], as observed with MPH[75,76] and drugs of abuse with rewarding properties[77]. Interestingly, potency was much higher than that of MPH[75] (as previously suggested by Deutsch et al with *in vitro* experiments[69] and Wayment et al in rat striatal tissues[78] (more than 15 times as potent as MPH)) and cocaine[79]. Moreover, the *threo* form (R,R) displays higher affinity for DAT than its *erythro* diastereoisomer (R,S), as demonstrated *in vitro* and *ex vivo* in rats' brain slices[80,81]. 3,4-CTMP was also shown to increase electrically evoked NE efflux in the bed nucleus of the stria terminalis of rat brain slices[75]. Taken together, these results suggest that 3,4-CTMP may induce a tolerance and a cocaine-like abuse liability. Luethi et al[48] confirmed 3,4-CTMP DAT and NET inhibition in human embryonic kidney cells, with a 2- and 10-fold higher potency than MPH (18- and 48-fold higher than cocaine), respectively. It also shows a high affinity for serotonin (5-HT) transporters (SERT), responsible for 5-HT reuptake from the synaptic cleft in the central nervous system, which suggests that 3,4-CTMP may modulate depression[48].

3,4-CTMP is subject to a temporary class drug order, along with MPH and several analogs (class B drugs), under the Misuse of Drugs Act 1971 in the United Kingdom[82]. It is also scheduled in Sweden, China, and Canada[61,83,84]. Nuclear magnetic resonance (NMR), gas chromatography–electron ionization-mass spectrometry (GC-EI-MS), and electrospray ionization-high resolution tandem mass spectrometry (ESI-HRMS/MS) spectra were reported for analytical determination[73,74,85].

3,4-Dichloroethylphenidate

3,4-dichloroethylphenidate (3,4-CTEP) is a chlorinated analog of EPH *threo* form (R,R), and the ethyl acetate isomer of 3,4-CTMP (ethyl(3,4-dichlorophenyl)(2-piperidinyl)acetate, Figure 1). 3,4-CTEP is a DAT and NET inhibitor with a lower potency than MPH and cocaine, as shown in human embryonic kidney cells[48]. Like 3,4-CTMP, it also binds SERT with a high affinity[48]. 3,4-CTEP products were seized by the German authorities in 2017[87]. The drug is banned in the United Kingdom[82]. 3,4-CTEP NMR, GC-EI-MS, and ESI-HRMS/MS characterization was reported[85].

4-Fluoromethylphenidate

4-Fluoromethylphenidate (4F-TMP) is another halogenated derivative of MPH *threo* form (R,R) in the position 4- of the phenyl ring (methyl(4-fluorophenyl)(2-piperidinyl)acetate, Figure 1). Like 3,4-CTMP, 4-fluoromethylphenidate (4F-TMP) was first synthesized in 1996 as a potential treatment for cocaine addiction[69]. 4F-TMP is taken orally or snorted and its effects are described on drug user forums[71]. *In vitro* studies and *ex vivo* studies in rats suggest that MPH potency is twice as low as that of MPH and cocaine as a DAT inhibitor[69,80]. Luethi et al recently showed that 4-TMP DAT and NET inhibition potency is similar to that of MPH in human embryonic kidney cells[48]. 4-TMP *threo* diastereoisomer (R,R) is a much more potent inhibitor of DAT and NET than its *erythro* form (R,S) in rat synaptosomes, yet 4-TMP is marketed both in its *threo* form (R,R) and as a *threo*/*erythro* mixture[88]. 4F-TMP is currently scheduled in United Kingdom as a class B drug[82]. NMR, GC-MS, liquid chromatography-MS (LC-MS), X-ray crystallography, and infrared spectroscopy characterization of 4F-TMP and its *erythro* form (R,S) were reported[88].

4-Fluoroethylphenidate

4-Fluoroethylphenidate (4F-TEP) is the ethyl acetate analog of 4F-TMP, but it is not clear whether the *threo* (R,R), the *erythro* form (R,S), or a *threo*/*erythro* mixture is used (ethyl(4-fluorophenyl)(2-piperidinyl)acetate, Figure 1). No information about the drug was found in the scientific literature, although it is available on the drug market since 2015[71]. The National Records of Scotland reported a fatality involving 4F-TEP, which occurred in 2016, but no more data were provided (Table I)[87]. The drug is now controlled in the United Kingdom and Canada[61,82].

Methylnaphthidate (HDMP-28)

Methylnaphthidate (HDMP-28) is an analog of the *threo* form (R,R) of MPH, with a naphthyl group substituting the phenyl ring, that appeared on the drug market in 2014 (methyl 2-naphthyl(2-piperidinyl)acetate, Figure 1). Reported doses range from 10 to 50 mg when taken orally or snorted. Subjective effects are reported on user forums[71]. Like other MPH analogs, HDMP-28 displays high affinity to the DAT *in vitro*, the *threo* form (R,R) being more effective[81]. Interestingly, both diastereoisomers also display similar high affinity to SERT, suggesting that HDMP-28 may modulate depression[81]. HDMP-28 affinity for DAT and SERT was also shown *ex vivo* in rats' striatum and cerebellum, with a higher affinity than that of cocaine[89]. The same study showed that HDMP-28 has reinforcing effects *in vivo* in rhesus monkeys, MPH and cocaine producing similar effects[89]. HDMP-28 is currently scheduled in the United Kingdom, Switzerland, and Canada[61,82,90].

Ethylnaphthidate

Ethylnaphthidate (HDEP-28) is the ethyl acetate analog of HDMP-28 (ethyl 2-naphthyl(2-piperidinyl)acetate, Figure 1), with similar DAT and NET inhibition potency to that of MPH[48]. Although no study was conducted on HDEP-28 affinity to SERT, its structural analogy with HDMP-28 suggest that HDEP-28 also interact with the transporter[81,89]. It was first marketed in 2015 and its effects are described on drug user forums[71]. Klare et al reported HDEP-28 analytical characterization with NMR, GC-EI-MS, and ESI-HRMS/MS spectra[85]. HDEP-28 is banned in the United Kingdom, Switzerland, and Canada[61,82,90].

Isopropylphenidate

Isopropylphenidate (IPH) is the isopropyl acetate analog of MPH (isopropyl phenyl(2-piperidinyl)acetate, Figure 1). It appeared on the drug market in 2013 and users describe the effects as similar to those of EPH, with a fast onset of action[71]. IPH *threo* form (R,R) binds DAT and NET with an affinity similar to that of EPH in human embryonic kidney cells[89]. Markowitz et al showed that a 10 μM racemic IPH mixture inhibits 96% and 62% the reuptake of DA and NE, respectively, in *in vitro* experiments with human DAT and NET (NE inhibition was stronger with racemic MPH and racemic EPH). In the same study, *in vitro* metabolic experiments with human liver and intestinal miscrosomes showed that IPH is predominantly metabolized by carboxylesterases 1, although it seems to be a poor substrate for the enzyme. Finally, the authors showed that racemic IPH significantly increased the locomotor activity of rats over the entire 120 min study period following a 10 mg/kg intraperitoneal administration[91]. IPH is a controlled substance in the United Kingdom and Canada[61,82].

Propylphenidate

Propylphenidate (PPH) is the propyl analog of MPH (propyl phenyl(2-piperidinyl)acetate, Figure 1). Luethi et al[48] showed that IPH *threo* isomer (R,R) binding affinity to NET is similar to that of IPH and EPH in human embryonic kidney cells. However binding affinity to DAT is 4-fold lower, making it one of the MPH analogs with the lowest affinity to DAT (with *N*-benzylethylphenidate). Subjective effects are described as very mild on drug user forums[71]. However, it is a scheduled substance in the United Kingdom, Switzerland, Canada, and Sweden[61,82,90,92].

4-Methylmethylphenidate

4-methylmethylphenidate (4-MeTMP) is a derivative of MPH *threo* isomer (R,R), with a methyl in position 4- of the phenyl ring (methyl(4-methyl)(2-piperidinyl)acetate, Figure 1). Its use as a psychostimulant was first described in 2015 on drug user forums, where its effects are reported[71]. 4-MeTMP DAT and NET binding affinity and inhibition potency are similar to those of 4F-TMP[48,80,81]. 4-MeTMP NMR, GC-EI-MS, and ESI-HRMS/MS spectra were described in the literature[85]. The substance is controlled in the United Kingdom, Switzerland, and Canada[61,82,90].

N-benzylethylphenidate

N-benzylmethylphenidate (*N*-benzylTEP) is the *N*-benzyl analog of EPH *threo* form (R,R) (ethyl phenyl(2-piperidinyl-N-benzyl)acetate, Figure 1). *N*-benzylTEP acts as a DAT and NET inhibitor with a lower potency than MPH and cocaine, as shown in human embryonic kidney cells[48] and rat striatal tissue[78]. The *threo* form (R,R) shows higher affinity to DAT than the *erythro* form (R,S) *in vitro* and *ex vivo* in rats[80]. *N*-benzylTEP also binds SERT with a high affinity[48]. Illegal products containing *N*-benzylTEP were recently seized by the German authorities, attesting its presence on the drug market[87]. Consequently, although no intoxication cases were reported to date, the drug is scheduled in the United

Kingdom[82]. The analytical characterization of the stimulant was described in the literature (NMR, GC-EI-MS, and ESI-HRMS/MS)[85].

Social and ethical issues

Psychostimulants" or "cognitive enhancers" are pharmaceutical drugs developed to treat specific pathologies that impair the neurotransmitter systems, such as ADHD and narcolepsy[13,93]. They target the catecholamines of the central nervous system, namely dopamine, norepinephrine, and serotonin, to induce their effects. As such, they also stimulate alertness, sociability, and libido and have been abused by healthy individuals for recreational purposes for many years. Despite the enforcement of laws banning psychostimulants, their consumption is on the rise. They are widely used by students to "improve intelligence", under the illusion that these drugs will improve their grades. However, scientific studies showed only little to no benefits for cognitive enhancement. Worse yet, the consumption of such drugs can be highly addictive and proved hazardous to health with risks of psychological, neurologic and cardiovascular disorders that can be fatal[13,94].

Generally speaking, the use of pharmaceutical drugs in healthy subject to enhance physical and psychic performance have changed the concept of corporeity up to the possibility, for each individual, to design his/her own corporeity as desired. The concept of self-determination in medicine brought to excess could lead to dangerous choices, as in case of misuse of these substances. Even the doctor-patient relationship, which have considerably changed to the detriment of reputation and consideration of the doctor, left wide possibility to the patient/individual, until almost imagining that to overlap the figure of the doctor through incorrect information and immediate transposition.

In the new generations, the concept of personal improvement, immediate, with little effort and little perceived risk would make everything lawful. Consequently, the lack of perception of the dangerousness of these substances in question, makes them absolutely usable and lawful, exponentially increasing the social danger[13,95].

Conclusions

Like other NPS classes, psychostimulants use is spreading and new legal potent isomers are being synthesized and marketed rapidly. This is the case for the sub-class of MPH analogs, which has widely expanded during the last decade. Although originally produced to treat depression and ADHD, MPH has been used as a nootropic drug for the past 20 years to increase alertness and cognition or as a doping substance in sport. Consequently, it was scheduled as an illicit drug in many countries and new "legal highs" were synthesized. Only little or no data on the pharmacology and toxicology of the most recent MPH analogs is available, and few analogs, such as EPH and 3,4-CTMP, are currently controlled in few countries. Moreover, many cases of intoxication might go unnoticed, considering that there is only little data on the analytical detection of these compounds. Like other psychostimulants, many intoxication cases and several fatalities associated with MPH analogs were reported. Cardiac effects seem to play an important role in MPH analogs' toxicity. The development and the production of new and more potent and addictive cognitive-enhancing substances suggest that more cases of intoxication and death will occur in the future. To limit the consequences, education and communication efforts on the side effects and the dangerous nature of psychostimulants and MPH analogs should be made among high-risk populations, i.e. students and regular drug addicts. From a legal point of view, new MPH analogs should be systematically controlled, and new analytical methods should be developed to detect the newest drugs in biological specimens and seized products in forensic toxicology.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

JC, RG, FPB, and GR conceived the design of the manuscript. JC, MRV, and FP performed the literature search,

and RG and FPB revised it. All the authors have been involved in drafting the manuscript and revising it critically for important intellectual content, and all of them have given final approval to the version to be published.

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