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REVIEW

Bath salts and polyconsumption: in search of drug-drug interactions

Ana Belen Lopez-Rodriguez[1] · Maria-Paz Viveros[2]

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Abstract

Background and rationale Polydrug use is a widespread phenomenon, especially among adolescents and young adults. Synthetic cathinones are frequently consumed in combination with other drugs of abuse. However, there is very little information regarding the consequences of this specific consumption pattern.

Objectives The aim of this review is to introduce this topic and highlight the gaps in the existing literature. In three different sections, we focus on specific interactions of synthetic cathinones with alcohol, cannabinoids, and the stimulants nicotine and cocaine. We then dedicate a section to the existence of sex and gender differences in the effects of synthetic cathinones and the long-term psychophysiological consequences of adolescent and prenatal exposure to these drugs.

Major findings Epidemiological studies, case reports, and results obtained in animal models point to the existence of pharmacological and pharmacokinetic interactions between synthetic cathinones and other drugs of abuse. This pattern of polyconsumption can cause the potentiation of negative effects, and the dissociation between objective and subjective effects can increase the combined use of the drugs and the risk of toxicity leading to serious health problems. Certain animal studies indicate a higher vulnerability and effect of cathinones in females. In humans, most of the users are men and case reports show long-term psychotic symptoms after repeated use.

Conclusions The co-use of synthetic cathinones and the other drugs of abuse analyzed indicates potentiation of diverse effects including dependence and addiction, neurotoxicity, and impaired cognition and emotional responses. The motivations for and effects of synthetic cathinone use appear to be influenced by sex/gender. The long-term consequences of their use by adolescents and pregnant women deserve further investigation.

Keywords Bath salts · Polyconsumption · Drug interactions · Novel psychoactive substances

Abbreviations

3-FMC	3-Fluoromethcathinone
4-CMC	4-Chloromethcathinone
5-HT	Serotonin
α-PHP	Alpha-pyrrolidinohexiophenone
α-PVP	α-Pyrrolidinovalerophenone
AB-CHMINACA	N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide
AB-FUBINACA	N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide)
BrdU	5-Bromo-2′-deoxyuridine
CNS	Central nervous system
CPP	Conditional place preference
CXCL12	C-X-C Motif Chemokine Ligand 12
DA	Dopamine
DAT	Dopamine transporter
EPC	Environmental place conditioning
EtOH	Ethanol
fMRI	Functional magnetic resonance imaging
L-SPD	Stepholidine
MDMA	3,4-Methylenedioxymethamphetaminen
MDPV	4-Methylenedioxypyrovalerone
MEPH	Mephedrone, 4-methylmethcathinone
METH	Methylone, 3,4-methylenedioxy-N-methylcathinone
mPFC	Medial prefrontal cortex

✉ Ana Belen Lopez-Rodriguez
lopezroa@tcd.ie

[1] School of Biochemistry and Immunology, Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin 2, Ireland

[2] School of Biological Sciences, Complutense University, Madrid, Spain

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NA	Noradrenaline
NAc	Nucleus accumbens
nAChR	Nicotinic acetylcholine receptor
NPS	Novel psychoactive substances
PND	Post-natal day
SERT	Serotonin transporter
THC	Delta-9-tetrahydrocannabinol
WIN	WIN 55,212–2

Introduction

Synthetic cathinones ("bath salts") are among the most prevalent novel psychoactive substances (NPS), also known as designer drugs. They are psychostimulants related to the naturally occurring parent compound cathinone, a monoamine alkaloid found in the khat plant (*Catha edulis*). A growing body of literature refers that many cathinone NPS show significant abuse liability and potential for addiction (Watterson and Olive 2017). These designer drugs are a high-public risk because of their potency and dangerous effects on the central nervous system (CNS) or the cardiovascular function, among others. The ability of cathinones to produce multiple organ system toxicities and death in humans is well-documented (Baumann and Volkow 2016; Watterson and Olive 2017). They are easy to buy over the internet, labeled under misleading descriptions such as "legal drugs" and "not for human consumption".

First-generation synthetic cathinones are the most used NPS and include 4-methylmethcathinone (mephedrone) (MEPH), 3,4-methylenedioxy-N-methylcathinone (methylone) (METH), and 4-methylenedioxypyrovalerone (MDPV). They are classified as "euphoric stimulants" because they act through the monoamine transporters (norepinephrine, dopamine, or serotonin transporters) in two ways: either as monoamine uptake inhibitors or as transporter substrates that increase the release of these neurotransmitters (Luethi and Liechti 2018). Based on their structural similarity and/or analogous mechanism of actions on neurotransmitters, MEPH and MDPV exert similar actions to methamphetamine and cocaine, respectively, while METH shows a pharmacological profile that more closely resembles 3,4-methylenedioxymethamphetamine (MDMA) (German et al. 2014; Weinstein et al. 2017). Synthetic cathinones and classical stimulants share some functional analogies regarding the main effect on the dysregulation of monoamine systems, the behavioral effects (psychostimulant and hallucinogenic effects), and the abuse liability, but there is much less information about the synaptic, systemic, or behavioral mechanisms by which synthetic cathinones act in comparison with the classical psychostimulants. Cathinones present structural differences in their backbone and in the substitute groups that make them to be considered a unique family of drugs. MEPH and METH act as monoamine transporter substrates, inducing an increase of the monoamine's release and a blockage of the reuptake from the synapses (German et al. 2014) whereas MDPV, like cocaine, blocks the dopamine transporter (DAT) and enhances the activity of dopamine and norepinephrine with no apparent effect on the release. However, it is important to note that despite some of the structural analogies and behavioral effect similitudes with classical psychostimulants, MDPV shows greater potency, selectivity, and functional upregulation of DAT (Lopez-Arnau et al. 2018) and induces greater locomotor activation, tachycardia, and hypertension than cocaine in rats (Baumann et al. 2013). The regulation and legal control of these types of substances are in fact very difficult since new analogues evolve rapidly. The speed with which these new compounds or "second-generation synthetic cathinones" enter the black market exceeds the ability to legislate on their illegalization, and due to this unprecedented proliferation of NPS, the investigation of their specific effects, mechanisms of action, pharmacokinetics, and clinical toxicology is still under development.

In the last few years, the number of studies on first-generation synthetic cathinones like MDPV or MEPH has rapidly increased. Very interesting recent data show that the stimulant and rewarding effects of MDPV (2 mg/Kg) are reduced in a dose-response manner by AMD3100 (1, 2.5, 5, 10 mg/Kg), a selective antagonist of the chemokine receptor CXCR4 (Oliver et al. 2018). CXCR4 is the main receptor for C-X-C motif chemokine ligand 12 (CXCL12), which is the CNS chemokine most linked to addiction and has been shown to enhance the release of dopamine (DA) in the mesolimbic regions producing a higher reward, reinforcement, and hyperlocomotion. Acute treatment with cocaine (25 mg/Kg) increases CXCL12 plasma levels in male mice (PND 42), and it shows a correlation with cocaine abuse and dependence in humans (Araos et al. 2015). The results obtained by Oliver et al. 2018 suggest that CXCR4 blockage reduces the effect of CXCL12 on the mesolimbic release of DA and is supported by the fact that the intracerebral injection of CXCL12 (25 ng/4 μl) increases cocaine (20 mg/Kg) hyperlocomotion (Trecki and Unterwald 2009). New insights on the interactions with the dopaminergic system are described in (Hicks et al. 2018) using male Sprague Dawley rats (250–275 g). The authors show that the reinstatement effect of MDPV (self-administered at 0.056 mg/Kg/infusion) is reduced in a dose-dependent manner by stepholidine (L-SPD), a Chinese herbal extract that binds to D1-like receptor (agonist) and D2-like receptor (antagonist). The highest dose of L-SPD (10 mg/Kg) decreased the reinstatement of the conditional place preference (CPP) and sucrose seeking induced by MDPV but did not modulate the hyperlocomotion. Further studies using functional magnetic resonance imaging (fMRI) and graph theory metrics have been performed in adult Long-Evans male rats (250–300 g) to assess in vivo brain functional network organization. This work shows that the effect of MDPV (1–

3 mg/Kg) on DAT causes their internalization and alters the homeostasis of the DA system and functional brain network reorganization. These changes persisted at least for 24 h and resulted in increased drug-seeking behavior, impaired functional connectivity, and reduced social interaction and ultrasonic vocalizations (Colon-Perez et al. 2018).

The pharmacokinetic profile and behavioral effects of MEPH have been addressed by Šíchová et al. (2017) in male Wistar rats (180–250 g). The authors show that MEPH (2.5, 5, or 20 mg/Kg) increased the locomotion and impaired the spatial distribution in a dose-dependent manner up to 40 min after administration and induced a long-lasting increase in body temperature that persisted 3 h after the injection. These effects were also reflected in brain pharmacokinetics where the maximum concentration of MEPH was found 30 min after the treatment, showing a mean brain:serum ratio of 1:1.19.

Second-generation synthetic cathinones were not subject to regulations when they first arose, and this group includes pentedrone, pentylone, 3-fluoromethcathinone, or α-pyrrolidinovalerophenone. Similarly to first-generation synthetic cathinones, they interact with monoamine transporters as monoamine uptake inhibitors or transporter activators, producing elevations of these neurotransmitters in the synaptic cleft (Gannon et al. 2018; Luethi and Liechti 2018). The pharmacokinetic profile, molecular mechanisms, and behavioral studies have been conducted in male and female Wistar rats using an implanted radiotelemetry system. The second-generation synthetic cathinones pentedrone and pentylone dose-effect curves were contrasted with METH (males, postnatal day (PND) 231 and females, PND 84). All drugs (0.5–10 mg/Kg) produced an increase in locomotion in a dose-dependent manner in both sexes but lasted longest after pentedrone. Females (PND 70) self-administered more infusions (0.025–0.3 mg/Kg/inf) of pentedrone or pentylone in comparison with METH which indicates a greater abuse liability of the second-generation synthetic cathinones (Javadi-Paydar et al. 2018). Studies with some of the newest second-generation synthetic cathinones show that 3-fluoromethcathinone (3-FMC) increases oxidative stress, autophagy, and apoptosis in neuronal cell lines (Siedlecka-Kroplewska et al. 2018). The pharmacokinetic and pharmacodynamics of alpha-pyrrolidinovalerophenone (α-PVP), also known as "flakka" or "zombie drug", have been reviewed in Nóbrega and Dinis-Oliveira (2018). In this review, the authors state that α-PVP exerts powerful cocaine-like stimulant effects, high brain penetration, and high liability for abuse by indirect activation of D1 and D2 dopamine receptors (Kaizaki et al. 2014; Marusich et al. 2014; Rickli et al. 2015). Alpha-PVP belongs to N-pyrrolidine cathinone derivatives and undergoes a complex metabolism pathway that results in different metabolites like β-hydroxy-α-PVP and α-PVP lactam. It is a potent inhibitor of DA and noradrenaline (NA) transporters (DAT and NAT), and it induces tachycardia, agitation, hypertension, hallucinations, delirium, mydriasis, self-injury, aggressive behavior, and suicidal ideations in humans; being cardiac arrest and/or pulmonary edema/arrest the main cause of death associated with it; however, very little is known about their short and long-term effects, which indicates the need of more preclinical and clinical studies.

The present review focuses on the first-generation cathinones, MEPH, METH, and MDPV, in particular on polydrug use, sex and gender differences, and long-term effects, three aspects we consider very relevant for a better understanding of synthetic cathinones. We will use the term "sex differences" as referred to differences between males and females attributable to biological factors, whereas "gender differences" involve socio/cultural factors. However, it is worth mentioning that complex interactions between neurobiological factors and social influences can occur (Becker et al. 2017).

Polydrug use

Polydrug use and abuse are a very widespread phenomenon. Psychophysiological aspects might influence motivation for polydrug use and abuse, for example, the transient relief exerted by one drug of some undesired effects caused by the other substance. Another reason for polydrug use is to potentiate the rewarding effects of one drug by the use of others, and both can have additive or synergistic effects that make their consumption even more dangerous. It is important to analyze the possible functional and pharmacological interactions between drugs that are consumed in combination. A report released on the Morbidity and Mortality Weekly Report in 2011 showed that a high percentage of bath salts users (94%) also tested positive for other common drugs such as marijuana, opiates, benzodiazepines, cocaine, or amphetamines (MMWR 2011).

It is noteworthy that polyuse is particularly common among adolescents and young adults. Adolescence represents a critical developmental phase during which the CNS shows unique plasticity. During this period, maturation and rearrangement of major neurotransmitter pathways are still taking place and therefore, the adolescent brain is particularly vulnerable to diverse insults, including drugs of abuse. In fact, the adolescent period appears to be critical in relation to the use and abuse of addictive drugs in humans. In rodents, periadolescence is defined as the ontogenetic period that encompasses the 7–10 days preceding the onset of puberty (at 40 days of age) and the first few days thereafter. Adolescent animals exhibit a particular behavioral repertoire that includes high levels of exploration, novelty and sensation seeking, impulsivity, and risk-taking that resemble behavioral characteristics of the human adolescent population, and several adolescent animal models have been used to analyze the effects of

drugs of abuse (Marco et al. 2009; Viveros et al. 2012; Pavón et al. 2016; Spear 2016; Jordan and Andersen 2017).

As mentioned above, the vast majority of synthetic cathinone users are polydrug consumers (Spiller et al. 2011; Winstock et al. 2011; Vandrey et al. 2013; Assi et al. 2017a, b), and in most intoxication cases, other illegal drugs or their metabolites are present in blood samples (Marinetti and Antonides 2013). However, in comparison with the literature investigating the interactions of classical psychostimulants with other frequently consumed drugs such as alcohol or cannabinoids and the effects of their polyconsumption, much less is known about their possible interactions with synthetic cathinones. Therefore, here, we have focused precisely on the existing data in relation with the interaction of synthetic cathinones with alcohol, cannabis, nicotine, and cocaine and we compared in parallel the available information on animal models and human reports.

Interactions of synthetic cathinones with alcohol

The interactions of alcohol and different psychostimulants such as methamphetamine, cocaine, nicotine, or MDMA have been reviewed in Althobaiti and Sari (2016). They present current information about animal and clinical studies. According to this review, the high prevalence and motivation for co-abuse of alcohol with psychostimulants might be the potentiation of rewarding effects, which may lead to the observed potentiation of drug-seeking behavior and the decrease of the detrimental subjective effects of either alcohol or the other drugs of abuse. Co-abuse of alcohol with psychostimulants can lead to several neural dysfunctions including a decrease in brain antioxidant enzymes, depletion of several neurotransmitters, and impaired learning and memory processes. In addition, cardiovascular dysfunctions have been also described including increases in myocardial oxygen consumption, heart rate, and blood pressure. As we discuss below, for the case of co-abuse of alcohol and synthetic cathinones, pharmacokinetic factors might be involved in these effects since it has been shown that alcohol increases the blood concentration of different psychostimulants and its active metabolites. The important increased risks for the fetus (critical brain structural and functional abnormalities) derived from the consumption of alcohol with the above-mentioned psychostimulants by pregnant women are also highlighted (see Althobaiti and Sari 2016 for review). There is less information available about interactions of synthetic cathinones and alcohol; however, there are some useful data obtained from both animal models and human studies that point to the consequences of this pattern of consumption and the potential underlying mechanisms.

Animal studies

A recent microdialysis study in awake adult male Sprague Dawley rats (250–300 g) has analyzed the effects of MEPH alone (25 mg/Kg) or in combination with ethanol (EtOH, 1 g/Kg) on serotonin (5-HT) and DA release in the nucleus accumbens (NAc) and the medial prefrontal cortex (mPFC) (López-Arnau et al. 2018). In the NAc, they observed only a tendency to potentiate the DA release in the MEPH + EtOH group in comparison with the MEPH group. On the other hand, they reported a significant potentiation of MEPH-induced 5-HT release by EtOH in this same brain area. In the mPFC, the increased release of 5-HT lasted longer in the MEPH + EtOH group than that in the group receiving only MEPH. In addition, EtOH potentiated the psychostimulant effect of MEPH measured as locomotor activity, and the higher hyperlocomotion periods coincided with the peaks in the levels of neurotransmitters (López-Arnau et al. 2018). Because of the implication of these neurotransmitters in impulsivity-related behaviors, it is likely that the combination of EtOH with MEPH might increase impulsivity and perhaps, their abuse liability. Moreover, given the significant potentiation of 5-HT release by MEPH, the combination of MEPH with antidepressants (especially inhibitors of 5-HT reuptake such as zimelidine, amitriptyline, or fluoxetine) may cause a potent and dangerous reaction including the occurrence of the serotonergic syndrome. To the best of our knowledge, this matter has not been experimentally addressed yet.

Since alcohol and psychostimulants are frequently co-abused by the adolescent population, the studies about the effects of synthetic cathinones in combination with EtOH during the adolescent period are of special relevance. A study in male adolescent mice (PND 35–42) has shown that EtOH (1 g/Kg) significantly increases the hyperlocomotion induced by MEPH (10 mg/Kg). In this experiment, the mice were only tested once in the apparatus after receiving a treatment. The effect of EtOH on the CPP induced by MEPH was also analyzed. During the conditioning phase (days 2, 4, 6, and 8), the mice were treated with MEPH (10 or 25 mg/Kg), MEPH + EtOH (10 or 25 mg/Kg + 0.75 g/Kg), EthOH (0.75 g/Kg), or saline, 20 min before being confined into one of the two conditioning compartments for 30 min. On days 3, 5, 7, and 9 of the conditioning phase, the animals received saline and were confined to the opposite compartment. EtOH, at a dose that did not elicit CPP on its own (0.75 g/Kg), increased the place conditioning induced by the two doses of MEPH (10 and 25 mg/Kg) (Ciudad-Roberts et al. 2015). In another study, this same research group (Ciudad-Roberts et al. 2016) analyzed the effects of MEPH and EtOH (24 h or 7 days after treatment) on diverse signs of neurotoxicity, neurogenesis, and

learning in adolescent CD-1 male mice (PND 35–42). First, they evaluated the effect of MEPH (25 mg/Kg; administered four times in one day, every 2 h), EtOH (2, 1.5, 1.5, 1 g/Kg), and their combinations on the decreases of the DAT and 5-HT transporters (SERT), considered a measurement of neurotoxicity. EtOH potentiated the neurotoxic effect of MEPH in the hippocampus (SERT) and frontal cortex (DAT) and increased the MEPH-induced lipid peroxidation in these brain regions, suggesting a potentiation of oxidative stress-induced neuronal damage. Spatial learning and memory were assessed in a Morris water maze (MWM) 1 week after treatment, and following the MWM test, neurogenesis (5-bromo-2′-deoxyuridine, BrdU staining) was measured 28 days after treatment. EtOH potentiated MEPH-induced negative effects on learning and memory in the MWM, a task that highly depends on the hippocampus and hippocampal neurogenesis (Ciudad-Roberts et al. 2016). From the above studies, it is important to note that the combined use and abuse of synthetic cathinones and alcohol can involve significant risks in terms of dependence and addiction, neurotoxicity, and detrimental effects on cognition. Another important aspect that deserves further research is the possibility of long-term effects of the co-abuse of these two types of drugs when they are consumed in critical stages of development such as the adolescent period or by pregnant women.

The interactions of low doses of MDPV (0.1–0.3 mg/Kg), another first-generation synthetic cathinone that acts as a selective DA transporter blocker, with EtOH (1 g/Kg) have also been assessed in the adult male rats (250–300 g). By behavioral and neurochemical studies, López-Arnau et al. 2017 evaluated whether EtOH could modify the psychostimulant (locomotor activity) and CPP of MDPV. In locomotor activity assays, EtOH induced a reduction in the stimulant effect induced by low doses of MDPV. In contrast, the rewarding properties of MDPV were unaltered by EtOH. Pharmacokinetic analyses indicated that the combination of MDPV (0.3 mg/Kg) and EtOH (1 g/Kg) decreased blood and brain MDPV concentrations during the first 20 min after injection. Complementary in vitro assays in rat liver microsomes showed that depending on the MDPV/EtOH ratio, there were different effects of EtOH on the metabolism of MDPV. The treatment of liver microsomes with a high concentration of MDPV (10 μM) and EtOH (1 μM) resulted in the inhibition of the MDPV metabolism in a dose-dependent manner. However, a low MDPV concentration (1 μM) and EtOH (1 μM) resulted in an increase of the metabolic rate of MDPV, demonstrating a biphasic effect of EtOH depending on the MPDV concentration. The increase of MPDV metabolism would explain the decrease in the blood and brain MPDV levels observed in vivo when animals were treated with a low dose of MPDV, as mentioned before (López-Arnau et al. 2017).

Human studies

Regarding clinical studies, de Sousa Fernandes Perna et al. 2016 analyzed the neurocognitive performance upon acute MEPH (single doses of 200 mg) in combination with alcohol (0.8 g/Kg). Eleven participants received MEPH, with and without alcohol, and were assessed on neurocognitive aspects by means of the divided attention task, critical tracking task, and the spatial memory test. The results showed that MEPH intoxication impaired short-term spatial memory 1 h after administration. When MEPH was combined with alcohol, the reaction time decreased in comparison to alcohol alone. Alcohol intoxication impaired both short- and long-term spatial memory, and stimulatory effects of MEPH did not compensate for the impairing effects of alcohol on most performance parameters.

Interactions of synthetic cathinones with cannabis and synthetic cannabinoids

Animal studies

To the best of our knowledge, there are no preclinical (animal) studies that directly investigate the interaction between synthetic cathinones and cannabinoid derivatives. Diverse reports show that both cathinones and cannabinoids affect anxiety-like behaviors, analgesia, depression, aggression, and feed behaviors by parallel and contrasting mechanisms (see Geresu 2015 for review), but the interaction itself is barely assessed. As mentioned in the "Introduction" section, the first-generation synthetic cathinones MEPH, METH, or MDPV show pharmacological similarities with the more classical stimulants methamphetamines, MDMA, and cocaine, respectively (Weinstein et al. 2017), and diverse studies have shown interactions between these traditional stimulants and cannabinoid compounds (see Table 1 containing some illustrative results). Based on these two sets of evidence, we propose that there is a high possibility of potential interactions between synthetic cathinones and cannabinoid compounds and that the experimental analysis of such interactions could contribute to explain the consequences of their combined use. We are aware that, at this very early stage and with the lack of animal studies to support it, this presumption is speculative. However, we find very important to point out the urgent necessity of specific and systematic experimental studies that deeply analyze the interactions between synthetic cathinones and cannabinoids in appropriate animal models.

Human studies

In humans, apart from emergency departments or user reports, the information on the interactions of cannabinoid derivatives and synthetic cathinones is also limited. The "Alcohol and

Table 1 Examples of animal studies assessing the effects of combining cannabinoids with the classical stimulants methamphetamine, cocaine, and MDMA

Stimulant	Combination	Effect	Test/Assay
Methamphetamine	THC (Castelli et al. 2014)	THC reduced methamphetamine-induced brain damage (nNOS) and astrocyte activation (GFAP).	Semi-quantitative immunohistochemistry
	WIN (Bortolato et al. 2010)	Methamphetamine increased CB1 receptor expression. WIN induced anxiolytic-like effects after methamphetamine exposure. Methamphetamine decreased the impact of WIN on the attenuation of exploratory behaviors and short-term memory.	Quantitative immunofluorescence, open field, object exploration and recognition, startle reflex, habituation, and prepulse inhibition
Cocaine	WIN (Aguilar et al. 2017)	WIN treatment in adolescence prevented the anxiogenic-like effects after cocaine abstinence and increased depressive-like symptoms following cocaine removal in adulthood.	Prepulse inhibition, object recognition, elevated plus maze, and tail suspension
	Cannabidiol (Gobira et al. 2015) (Mahmud et al. 2017)	Cannabidiol pretreatment increased the latency and reduced the duration of cocaine-induced seizures through the activation of the mTOR pathway and the reduction in glutamate release.	Seizures observations, synaptosomes isolation, ELISA microplates attached to a spectrofluorometer
		Cannabidiol induced anxiolytic-like effects at a high dose (10 mg/Kg) but did not affect cocaine intake or relapse.	Operant conditioning chambers, elevated plus maze
MDMA	THC (Touriño et al. 2007) (Llorente-Berzal et al. 2013) (Lopez-Rodriguez et al. 2014)	Acute and chronic MDMA decreased the severity of THC withdrawal and increased the levels of extracellular 5-HT.	Withdrawal and dependence paradigm, locomotor activity and microdialysis
		Adolescent exposure to MDMA with or without THC induced long-term and sex-dependent psychophysiological alterations, involving hippocampus and hypothalamic regions	Hole-board, elevated plus maze, novel object test, prepulse inhibition, plasma (ELISA), immunoblotting, PCR
		THC and MDMA alone or in combination induced changes in glial activation (GFAP and Iba-1) and alterations in the serotonergic (SERT) and cannabinoid systems (CB1 receptor). These changes showed sexual dimorphisms.	Immunohistochemistry
	WIN (Manzanedo et al. 2010)	Low dose of WIN (0.1 mg/Kg) increased the rewarding effects of a low dose of MDMA (1.25 mg/Kg). A higher dose of WIN (0.5 mg/Kg) decreased the conditional place preference induced by a higher dose of MDMA (5 and 2.5 mg/Kg).	Conditional place preference paradigm

nNOS neuronal nitric oxide synthase, *GFAP* glial fibrillary acidic protein, *CB1* cannabinoid receptor type 1, *WIN* WIN 55,212-2, *mTOR* mammalian target of rapamycin, *MDMA* 3,4-methylenedioxymethamphetamine, *Iba-1* ionized calcium-binding adapter molecule 1

Drug Foundation" has described that the combination of synthetic cathinones + alcohol + cannabis produces nausea and vomiting (www.adf.org.au), and in another study, it has been calculated that 29% of synthetic cathinone users combine them with plant or synthetic cannabinoids (MMWR 2011). In a report from Northern Ireland, the combination of MEPH and cannabinoids was present in 5 of the 12 cases of sudden death and in 4 of 23 cases of impaired driving MEPH, and cannabinoids combined were also found (Cosbey et al. 2013). An extensive record of MDPV use in Germany during 2014–2016 described 23 cases of MPDV use from which 87% were men, in an age range from 23 to 49 years. In most cases, the co-consumption of other psychotropic drugs was frequent, particularly opiates and cannabinoids in the 22% of the cases, followed by benzodiazepines and cocaine (17%) (Grapp et al. 2017). One of the most recent reports describes an intoxication case of a 38-year-old man who attempted suicide by taking a mix of five different designer drugs including the novel synthetic cannabinoids AB-CHMINACA (N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(cyclohexylmethyl)-1H-indazole-3-carboxamide), AB-FUBINACA (N-(1-amino-3-methyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1H-indazole-3-carboxamide), and the second-generation synthetic cathinones α-PHP (alpha-pyrrolidinohexiophenone), α-PVP (α-pyrrolidinovalerophenone), and 4-CMC (4-chloromethcathinone). The observed symptoms included increasing somnolence and unresponsiveness to painful stimuli, dilated pupils, sinus tachycardia, and strong dehydration. All of these substances, except for 4-CMC, were detectable in the stomach (Klavž et al. 2016).

Accumulating evidence indicates that one of the main reasons for combining MEPH and MPDV with other drugs is to counteract the undesired effects. In particular, cannabis is consumed in combination with synthetic cathinones to reduce anxiety, agitation, and overstimulation (Zawilska and Wojcieszak 2013). However, the users reported/showed an increase in delusions and hallucinations (MMWR 2011; Zawilska and Wojcieszak 2013), more episodes of memory blackouts when MEPH was used in combination with cannabis, and increased panic/delirium attacks when the second-generation synthetic cathinone α-PHP was combined with synthetic cannabinoids (Assi et al. 2017b). This wide spectrum of effects might reflect the high variability in the chemical composition of the synthetic compounds.

From demographic studies and the above data, it appears that synthetic cathinones are mainly consumed by young men and very often in combination with cannabis derivatives (Sutherland et al. 2016; Papaseit et al. 2017). In 2010–2011, over 200 surveys taken in Spain showed that 74.4% of the NPS users (40.1% METH and 35.2% MEPH users) were male. Among them, 68.6% of the survey participants sporadically consumed the synthetic cathinones in combination with cannabis and 38.7% reported a regular co-use (González et al. 2013). Similarly, combinations with synthetic cannabinoids have been reported in cathinone users describing that 87% of the users had consumed marijuana or synthetic cannabinoids (not specified) in 6 months before the first cathinone use (Wagner et al. 2014). Another study on an Australian cohort which was followed during the interval 2010–2015 revealed that polydrug pattern was significantly associated with synthetic cathinone use and 16% of users reported daily cannabis consumption (Sutherland et al. 2016).

Interactions of synthetic cathinones with nicotine

Animal studies

As highlighted in the previous sections, polydrug use and abuse constitute the most frequent pattern among synthetic cathinone users. Preclinical studies using male mice (20–25 g) have addressed the influence of the acute co-administration of MEPH (0.05, 0.1, 0.25, 1, 2.5, 5, and 10 mg/Kg) and nicotine (0.05 and 0.5 mg/Kg) on anxiety-like behaviors, cognition, and nicotine-induced sensitization (Budzynska et al. 2015). This study revealed that the co-administration of subthreshold, nonactive doses of MEPH and nicotine (0.5 mg/Kg) induced a clear anxiety-like profile in the elevated plus maze test (a classical test that evaluates anxiety-like responses). The administration of MEPH alone at a dose that is known not to affect locomotor activity (1 mg/Kg) enhanced the expression of nicotine-induced locomotor sensitization. The authors also found interesting results in relation to the oxidative status of the brain. Thus, MEPH and nicotine administered alone exerted strong pro-oxidative effects when compared to saline-treated groups, as revealed by increases of malondialdehyde and decreases in catalase activity and in the total anti-oxidant status in hippocampus and prefrontal cortex. The co-treatment with MEPH and nicotine exacerbated these oxidative changes in both brain regions (Budzynska et al. 2015). A more recent study with adult male rats (200–225 g) has shown that reward function is potentiated by MDPV self-administration in a nicotinic acetylcholine receptor (nAChR)-dependent manner following a self-administration protocol of MDPV for 10 days (0.03 mg/Kg/inf, 1 h per session), 5 days per week. Immediately after MDPV self-administration, the reward threshold was decreased, which is indicative of increased brain reward function, and this effect was prevented when animals were treated with an antagonist of nAChR (mecalymine hydrochloride, 1 ml/Kg body weight) (Geste et al. 2018).

Human studies

Studies in humans demonstrate that the multidrug abuse tends to be either binary or ternary mixtures and also includes nicotine (Assi et al. 2017b). The use of synthetic cathinones and natural khat derivatives presents a significant association with daily tobacco use (Sutherland et al. 2016). Different studies reveal higher prevalence of tobacco smoking among khat users relative to non-khat users (Ayana and Mekonen 2004; Ali et al. 2011) and describe a range between 42% (Bawazeer et al. 1999) and 62% (Alem et al. 1999; Tesfaye et al. 2008) of khat chewers that were heavy smokers (more than 20 cigarettes per day). There is also a significant positive association between levels of khat dependence and nicotine dependence in a UK resident Yemeni khat-chewing population (Kassim et al. 2011). Also, in this case, a gender difference has been found with men consuming khat and tobacco more intensely and frequently than women (Maziak et al. 2004; The World Bank 2007; Nakajima et al. 2013). Users of the first-generation synthetic cathinone MDPV in combination with tobacco describe painful urination (Assi et al. 2017b) and sleep disturbances associated with dysregulation in emotional and physiological functions (Nakajima et al. 2014b). However, apart from these few case reports, the mechanisms underlying such interactions in humans are still poorly investigated and understood.

Interactions of synthetic cathinones with cocaine

Another drug frequently used in combination with synthetic cathinones is cocaine (Assi et al. 2017b), a powerfully addictive stimulant substance derived from the leaves of the coca plant native to South America.

Animal studies

The interactions between cocaine and synthetic cathinones have been analyzed in different ways and using different animal models. Simmons et al. (2018) analyzed the rewarding and reinforcing properties of cocaine (0.56 mg/Kg/infusion, self-administered) in comparison with MDPV (0.56 mg/Kg/infusion, self-administered) in adult male Sprague Dawley rats (250–275 g). Animal ultrasonic vocalization rates (50 kHz) and persistence were used as an indication of positive effects of the drugs. The results showed that MDPV-treated rats showed greater and more persistent rates of vocalizations than the cocaine group, which was interpreted as a high-abuse risk by the authors. This study supports that MDPV has very high rewarding and reinforcing effects that are tenfold higher than those of cocaine. Stereochemical studies have shown that S-MEPH (10, 30 mg/Kg) induced a reduction in anxiety- and depression-like behaviors associated with cocaine (10 mg/Kg) and MDPV (1 mg/Kg) withdrawal in the adult male rats (250–300 g) (Philogene-Khalid et al. 2017). Other studies with mammals have used rodents to address the interactions of cocaine and MEPH. To study the effects of pre-exposure to MEPH on cocaine efficacy, the adult male rats (260–290 g) were injected for 5 days with either saline or MEPH (15 mg/Kg), and 10 days later, they were challenged with cocaine (15 mg/Kg). In this same study, they investigated the effects of prior cocaine exposure on MEPH efficacy by injecting the animals with either cocaine (15 mg/Kg) or saline for 5 days, and 10 days later, they received MEPH (15 mg/Kg). The results showed that cocaine challenge induced greater locomotor activity following MEPH pretreatment than following saline pretreatment. However, the locomotor activity in animals challenged with MEPH was not affected by the cocaine pretreatment (Gregg et al. 2013). The specific interaction of first-generation synthetic cathinones and cocaine has been also assessed in an invertebrate animal model. The use of planarians (*Dugesia dorotocephala*) (a simple CNS model) has enabled the study of the pharmacology of the S-enantiomer of MEPH. Vouga et al. (2015) analyzed the effects of racemic MEPH, S-mephedrone (S-MEPH), and R-mephedrone (R-MEPH) (100 μM) on cocaine-induced (1 μM) reward (environmental preference) and withdrawal. In this animal model, reward was evaluated by the environmental place conditioning test in which planarians are exposed for a certain time to an environment in the presence of a rewarding substance and later are given the choice of two different environments, one of them in the presence of the rewarding substance. Withdrawal experiments consist of placing the animals in a jar with the drug of interest for a period of time and then put them back into a petri dish containing water to quantify the decrease in motility, which is a characteristic withdrawal response of planarians. The results showed that planarians conditioned with cocaine displayed significant environmental place conditioning (EPC) in comparison with control animals, and this EPC was significantly reduced when S-MEPH was included in the environment. Regarding cocaine withdrawal response, planarians treated with cocaine and then withdrawn in water showed decreased motility in comparison with that of the control group. However, when cocaine-conditioned animals were withdrawn with a solution of S-MEPH (100 μM), the decreased motility was less pronounced in comparison with those animals withdrawn in water. This interaction was not present when a 100-fold lower concentration of S-MEPH (1 μM) was tested, indicating that the S-enantiomer of this synthetic cathinone attenuates the cocaine withdrawal effects in a dose-dependent manner. Given the simplicity of the animal model used, the interpretation of the results may be open to question and we should be cautious when translating them into mammal models, but these invertebrate alternative models can be useful to provide complementary data and help to progress in the field.

Human studies

In a clinical report from emergency departments, 35 patients were evaluated after the consumption of drugs sold as bath salts (not specified) and it was found that 11% of them had used cocaine in addition to synthetic cathinones (MMWR 2011). A study of an Australian cohort over a period of 5 years (2010–2015) revealed that cocaine use was associated with recent synthetic cathinone use (last 6 months previous to the interview and data collection of this study), although this did not reach statistical significance for the multivariate logistic regression (Sutherland et al. 2016). Different toxicological studies and case reports have described the use of MEPH in combination with cocaine (Hondebrink et al. 2015), MEPH, cocaine, and alcohol (Gerace et al. 2014) and the co-use of MEPH in combination with MDPV and cocaine (Spiller et al. 2011). It has been shown that among individuals that consumed MEPH for the first time, 17 of 89 users (19.1%) also consumed cocaine, whereas in experienced users, the proportion increased to 26 of 82 participants (31.7%) (Winstock et al. 2011). Apart from these studies describing consumption patterns, little is known about direct interactions between synthetic cathinones and cocaine in humans; there is one case report describing increased effects on tachycardia when MDPV was combined with cocaine (Assi et al. 2017b), which appears to indicate additive effects.

A priori, it could be tempting to expect that the combination of synthetic cathinones with cocaine would produce additive stimulant effects because of the nature of the drugs. However, the results discussed above suggest that the interactions are more complex. This emphasizes the urgent need for

more pharmacological and clinical studies to identify the nature and mechanisms underlying the interactions of these stimulants and to provide more information to quickly identify intoxication cases in human and prevent fatal consequences.

Table 2 summarizes the main studies discussed in this review that analyze interactions between synthetic cathinones and other frequently used drugs in both human and animal studies.

Sex/gender differences and long-term effects

Sex/gender differences

The existence of sex/gender differences in addiction-related processes is well-known and has been demonstrated in human and animal studies. Whereas these differences apply to diverse drugs of abuse, including classic psychostimulants such as

Table 2 Human and animal studies addressing the effects of cathinone combinations with other used and abused drugs

Drug	Combination	Effect
MEPH	Alcohol	•Animals: EtOH enhanced the increased locomotor activity and CPP induced by MEPH. EtOH impaired the decrease of DAT and SERT induced by MEPH as well as potentiated the negative effects of MEPH on learning and memory. (Ciudad-Roberts et al. 2015, 2016; López-Arnau et al. 2018).
		•Human: Reaction time decreased when MEPH was combined with alcohol as compared to alcohol alone. Stimulatory effects of MEPH did not compensate the impairing effects of alcohol on neurocognitive tasks. (de Sousa Fernandes Perna et al. 2016).
	Cannabis	•Human: Cathinones are often taken in combination with cannabis. MEPH was detected in different concentrations (up to 0.74 mg/L) in fatal and impaired driving cases; the subjects were mostly young adult men and it was consumed in combination with classical drugs such as cannabis or alcohol (Cosbey et al. 2013; Assi et al. 2017b)
	Cannabis and MPDV	•Human: Accumulating evidence indicates that MEPH and MDPV are often combined with cannabis to counteract anxiety and overstimulation induced by the cathinones (MMWR 2011; Zawilska and Wojcieszak 2013).
	Nicotine	•Animals: The administration of subthreshold doses of MEPH and nicotine (0.05 mg/Kg each) induced anxiety-like effects in the plus maze and exerted pro-cognitive action in the passive avoidance paradigm. The combination of both drugs decreased the general antioxidant status, catalase activity, and antioxidant activity in the brain. MEPH alone enhanced the expression of nicotine-induced locomotor sensitization Budzynska et al. 2015).
	Cocaine	•Animals: Prior exposure to MEPH enhanced cocaine-induced locomotor activation suggesting that MEPH cross-sensitizes to cocaine and increases cocaine efficacy; however, this cross-sensitization was not bidirectional. The S-enantiomer of MEPH reduces the anxiety- and depressant-like effects observed in cocaine abstinence (Gregg et al. 2013; Philogene-Khalid et al. 2017).
		•Human: Several patients combined NPS with more commonly used illicit drugs, including cocaine. Survey participants' first MEPH session lasted an average of 6 h, and it was taken together with cocaine in 17 out of 88 participants (Winstock et al. 2011; Hondebrink et al. 2015).
MDPV	Alcohol	•Animals: EtOH reduced the stimulant effect of low doses of MDPV and decreased its concentration in blood and the brain. Depending on the ratio, MDPV/EtOH, EtOH increased MPDV metabolic rate in the microsomes of the liver. In contrast, no effects of EtOH on the rewarding properties of MDPV were found (López-Arnau et al. 2017).
	Nicotine	•Animals: Pretreatment with an antagonist of nAChR decreased the self-administration of MDPV and prevented the decrease in reward thresholds (Geste et al. 2018).
		•Humans: Tobacco is taken very often in combination with cathinones, some of the secondary effects include painful urination when combining it with MPDV (Assi et al. 2017b).
	Cocaine	•Animals: MDPV increased ultrasonic vocalizations at greater rates and persistence than cocaine, and the latency to begin self-administration was shorter than the latency to begin cocaine self-administration (Simmons et al. 2018).
		•Human: Users of MDPV refer to it as "legal cocaine", and a large number of participants reported abuse of cocaine or methamphetamine prior to bath salts consumption. The high incidence of neurological/psychiatric changes after MPDV use occurred in a population that had preexisting experience with other drugs such as cocaine (Spiller et al. 2011).
	Cannabis	•Human: In a review of NPS from 2014, MDPV was one of the most prevalent drugs and was taken in combination with cannabis in 21% of the cases, followed by benzodiazepines and cocaine in 17% of participants (Grapp et al. 2017).
Khat	Nicotine	•Human: 68% of the tobacco smokers were also regular khat users and the 32% reported themselves as episodic khat smokers. Users described a higher impact of khat when combined with tobacco. The level of severity of dependence on khat chewing positively correlated with nicotine dependence (Ayana and Mekonen 2004; Kassim et al. 2011).
α-PHP	Synthetic cannabinoids	•Human: Users have reported that the combination of α-PHP and synthetic cannabinoids (unspecified) induces intense panic and delirium effects (Assi et al. 2017b).

EtOH ethanol, *CPP* conditioned place preference, *MEPH* mephedrone, *DAT* dopamine transporter, *SERT* serotonin transporter, *MDPV* 4-methylenedioxypyrovalerone, *NPS* novel psychoactive substances, *α-PHP* alpha-pyrrolidinohexiophenone

cocaine and MDMA (Andersen et al. 2012; Soleimani Asl et al. 2015; Becker 2016; Lazenka et al. 2017; Becker et al. 2017), there are still very few data regarding sex/gender differences in the effects of synthetic cathinones. However, certain occasional data from both human and animal models point to the existence of differences between males and females whereas in animal studies, these differences are attributable to biological factors (sex differences), in humans, not only biological but also cultural/social factors have to be considered (gender differences).

Animal studies

Most of the experimental animal studies on synthetic cathinones have been performed in male mice and rats but occasional studies using both sexes suggest the existence of sex-related differences. As above indicated, MDPV is pharmacologically and behaviorally similar to cocaine and has been shown to have both aversive and rewarding effects. King et al. (2015) carried out a study to determine whether male and female Sprague Dawley rats (PND 71) differed in MDPV-induced (1.0, 1.8, or 3.2 mg/Kg) conditioned taste avoidance and CPP. Taste avoidance was clear in both sexes, and this avoidance was weaker in females compared to males. MDPV also produced place preferences in all drug-treated animals, but these preferences did not show sex differences. According to the authors, the weaker avoidance response in females compared to that in males suggests that females might be more vulnerable to use and abuse of MDPV. In another study also performed in male (230–300 g) and female (190–230 g) Wistar rats, cathinone (5 mg/Kg) was found to produce significantly greater increases in activity in female rats. In addition, the study describes complex interactions between caffeine (5 mg/Kg) and cathinone (5 mg/Kg) which also appears to be influenced by sex since the combination of both drugs significantly raised temperature acutely in male but not in female rats (Alsufyani and Docherty 2017).

Human studies

Diverse reports about the prevalence of NPS use indicate that the majority of the users are men (Romanek et al. 2017; Weinstein et al. 2017; Lauritsen et al. 2018). Other studies performed in Yemen showed that male and female adults chewed khat in approximately equal numbers, suggesting that prevalence of use may depend on sociocultural factors. However, the Yemen study also points to the existence of biological factors since male khat chewers reported more symptoms related to khat dependence than female chewers (Nakajima et al. 2013, 2014a). Furthermore, there are also differences related to the motivations for khat chewing; while men associate the use with recreational purposes, women report therapeutic use for headache or weight control (Stevenson et al. 1996). Thus, it is very important to further investigate the influence of both biological and socio/cultural factors not only on the effects of synthetic cathinones per se but also on their interactions with other co-abused drugs.

Long-term effects

An important issue is the analysis of long-term consequences of the use of synthetic cathinones during critical developmental phases of neurodevelopment, in particular, during the periadolescent and perinatal periods (consumption by pregnant women). The investigation in this area is still in its infancy and, since these drugs are relatively new, it will take a few years and much more research to have a good amount of data about the long-term impact of cathinone use in humans. In this context, animal studies in rats and mice are particularly useful, since the average duration of life in these species, about 2 years, allows to carry out developmental studies ranging from the prenatal period to aging in a relatively short time period.

Animal studies

Daniel and Hughes (2016) have investigated the long-term effects of adolescent exposure (PND 35–44, early adolescence or PND 45–54, late adolescence) of male and female rats to METH (8.0 mg/Kg) on anxiety and memory in adulthood (PND 90). METH-treated rats showed increased anxiety-related behavior in the open field as reflected in decreased ambulation, longer stay in the corners of the apparatus, and increased defecation, with this latter parameter being affected only in males. In addition, the METH-treated rats displayed signs of impaired short-term spatial memory in the Y-maze arm. Exposure to synthetic cathinones appears to affect responses to other drugs in the long term. Thus, it has been shown that MDPV exposure (1.5 mg/Kg, twice daily for 7 days) during adolescence in mice (PND 41–44) induced long-lasting changes related to enhanced responsiveness to cocaine (7.5 mg/Kg) in adulthood (PND 69–72). These results suggest that MDPV consumption by adolescents may cause a long-term sensitization to cocaine effects and perhaps a higher vulnerability to cocaine abuse (López-Arnau et al. 2017). Since pregnant women are among bath salts users (Gray and Holland 2014; Pichini et al. 2014), it is of extreme importance to analyze the long-term consequences of gestational exposure to synthetic cathinones. By using an animal pregnancy model, it has been shown that a single injection of "bath salts cocktail" (METH (5 mg/Kg), MEPH (10 mg/Kg), and MDPV (3 mg/Kg)) administered to pregnant mice (E17.5 gestation) resulted in measurable concentrations in the placenta and the fetal brain (Strange et al. 2017). The extensive presence of these substances in the fetal brain highlights the potential risk for the fetuses to present brain damage and altered

neurodevelopment. The effect of prenatal MDPV exposure (10 mg/Kg administered from the 8th to the 14th day of gestation) on the behavior of neonatal and preadolescent mice has also been addressed. Locomotor activity was measured at PND 7 and 21 and motor coordination on PND 21. Pups in the MDPV group showed increased spontaneous activity, described by the authors as frequent and erratic deflections in multiple directions that may reflect an increased motor excitation (agitation/hyperexcitability). On the other hand, no significant effect of the MDPV prenatal treatment on motor coordination was observed (measured as the latency of losing grip in the grip strength test). Maternal behavior was deteriorated in the MDPV-treated dams, mainly in the latency of complete pup retrieval. The birth rate and pup survival were reduced in animals exposed to MDPV due to stillbirth, premature birth, or cannibalism of dams (Gerecsei et al. 2018). It is important to mention that this study did not provide information about the sex of the pups. In any case, the results suggest that consumption of MDPV (and perhaps other synthetic cathinones) by pregnant mothers may have a negative impact on their ability to care for the newborns, possibly due to emotional alterations, and affect the survival, adequate development, and well-being of neonates.

Human studies

Knowledge of the long-term health consequences of consuming such dangerous drugs as synthetic cathinones is of vital importance. However, we have hardly found data in humans. There are case reports that reveal psychotic symptoms after repeated use of bath salts, and these symptoms may persist after discontinuation of drug use (Penders et al. 2013; Barrio et al. 2016). As a whole, these observations as well as the results obtained from animal models suggest that the use/abuse of synthetic cathinones may lead not only to acute toxicity but also to long-lasting health problems. Special attention should be paid to critical developmental periods of increased vulnerability.

Conclusions

The combined use and abuse of synthetic cathinones and the other drugs of abuse analyzed in this review indicate potentiation of diverse effects including dependence and addiction, neurotoxicity, and impaired cognition and emotional responses. Given the high rate of consumption of synthetic cathinones and cannabinoids and the wide spectrum of negative effects observed in humans, the lack of studies about the combination of both drugs in animal models is striking. It is urgent to carry out specific and systematic experimental studies that deeply analyze the interactions between these drugs. There are occasional data from both human and animal models that point to the existence of different effects of synthetic cathinones in males and females. Since such differences may be relevant for the establishment of appropriate prevention and therapeutic strategies, it is urgent to carry out more studies and deepen into the biological and socio/cultural factors involved. In addition, the enduring consequences of exposure to synthetic cathinones during critical developmental stages such as the adolescent and perinatal periods deserve special attention.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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