REVIEW

# Neuronal and peripheral damages induced by synthetic psychoactive substances: an update of recent findings from human and animal studies

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***Funding:*** *GC was supported by the PRIN 2015 (Pr. 2015R9ASHT) and PON AIM (PON RICERCA E INNOVAZIONE 2014-2020, - AZIONE I.2. D.D. N.407 DEL 27 FEBBRAIO 2018 - "ATTRACTION AND INTERNATIONAL MOBILITY"); MDL was supported by Autonomous Region of Sardinia (RAS-FSC 2018, Codice intervento: RC_CRP_034; CUP RASSR03071); NS was supported by Fondazione di Sardegna (Progetti Biennali UniCA, Annualità 2017).*

## Abstract

Preclinical and clinical studies indicate that synthetic psychoactive substances, in addition to having abuse potential, may elicit toxic effects of varying severity at the peripheral and central levels. Nowadays, toxicity induced by synthetic psychoactive substances poses a serious harm for health, since recreational use of these substances is on the rise among young and adult people. The present review summarizes recent findings on the peripheral and central toxicity elicited by "old" and "new" synthetic psychoactive substances in humans and experimental animals, focusing on amphetamine derivatives, hallucinogen and dissociative drugs and synthetic cannabinoids.

***Key Words:*** *cannabinoids; dissociatives; hallucinogens; ketamine; MDMA; methamphetamine; methoxetamine; neuroinflammation; neurotoxicity; NPS*

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***doi:*** *10.4103/1673-5374.268895*

***Received:*** *July 1, 2019*
***Peer-review started:*** *July 3, 2019*
***Accepted:*** *July 30, 2019*
***Published online:*** *November 4, 2019*

## Introduction

Synthetic psychoactive substances are used as recreational drugs worldwide, although usage patterns significantly vary according to geographic areas, lifestyles and availability of novel derivatives. Synthetic psychoactive substances may possess abuse liability and their recreational use has long been a source of concern due to the possible development of addiction. Further worry on synthetic psychoactive substances comes from the evidence that their use may induce either lethality or toxic effects of varying severity. Central toxicity of synthetic psychoactive substances has emerged as a major issue, since reports in users have documented neurological and/or psychiatric complications that may persist after drug discontinuation.

Among synthetic psychoactive substances, the amphetamine derivatives methamphetamine (METH), also known as "ice" or "speed", and 3,4-methylenedioxymethamphetamine (MDMA), also known as "ecstasy", are those whose toxic effects have been more extensively characterized, both substances having long been used as either therapeutics or recreational drugs (**Figure 1**). *In vitro* and *in vivo* studies have demonstrated that METH and MDMA may elicit toxic effects in peripheral organs, as well as in brain regions that regulate movement and/or superior brain functions (Moratalla et al., 2017). Besides, clinical studies have shown that METH and MDMA can induce brain abnormalities in users. Although therapeutic use of METH has been drastically reduced, the substance is still utilized for the treatment of attention deficit hyperactivity disorder and obesity, while MDMA is now being repurposed as a therapy for post-traumatic stress disorder (Mithoefer et al., 2018). Furthermore, the European Monitoring Centre for Drugs and Drug Addiction has recently reported a resurgence in the use of amphetamine derivatives as recreational drugs (EMCDDA, 2016). On this basis, it appears important to thoroughly characterize the short- and long-term toxicity of METH and MDMA to disclose the risks associated with their use, either medical or recreational.

The emergence of the so-called "novel psychoactive substances (NPS)" has raised further concern on the toxicity associated with recreational substance use. NPS are intoxicating synthetic compounds, typically not controlled by the United Nations drug convention, that are continuously developed to mimic the effects of well-established drugs of abuse. Among NPS, hallucinogen drugs, dissociative drugs and synthetic cannabinoid receptor agonists (SCRAs) are emerging as major sources of social and clinical concern, since their use has been associated with numerous fatalities and intoxications.

Animal and human studies demonstrate that hallucinogen drugs alter consciousness and induce sensory/perceptual disturbances, while dissociative drugs alter the users' mental state and behavioral performance and induce feelings of detachment from reality. Hallucinogens, also known as 'psychedelics', include lysergamides (e.g., LSD), tryptamines (e.g., psilocybin, psilocin) and phenethylamines (e.g., mescaline, Bromo-DragonFly), and typically connote drugs acting as agonists at the serotonin 5-HT2A receptor. Yet, some NPS,

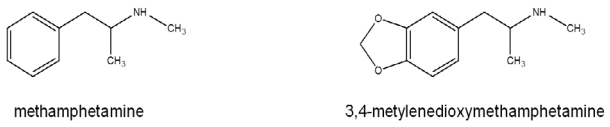


**Figure 1 Chemical structures of methamphetamine and 3,4-methylenedioxymethampetamine.**

such as dissociative anesthetics, like ketamine or phencyclidine and the more recent dissociative drug methoxetamine, are not classified as 'serotonergic hallucinogens' but may produce some hallucinogenic effects. Notably, animal studies indicate that dissociative anesthetics may elicit neurotoxic effects.

To date, researches by pharmaceutical companies have failed to design SCRAs with satisfactory therapeutic potential (De Luca and Fattore, 2018). Indeed, considerable adverse effects have increasingly been reported with the progression of chemically different generations of SCRAs. Regrettably, the illegal market switched SCRAs into potent recreational drugs with higher risk of developing dependence and severe neurological and/or psychiatric complications. Accordingly, the neurotoxicity of SCRAs is currently under investigation.

This review summarizes the most recent findings of preclinical and clinical studies that evaluated the toxic effects of synthetic psychoactive substances, focusing on METH, MDMA, hallucinogen drugs, dissociative drugs and SCRAs. Rather than providing a systematic review of all animal and human studies performed so far with these substances (which are already available for each specific class of drugs), we aim at providing a PubMed based overview of the most recent (last 5 years) studies on their toxic effects discussed in light of the existing literature. Results of earlier studies were also reviewed, when relevant.

## Toxic Effects of Methamphetamine Demonstrated in Preclinical Studies

### Overview of toxic effects

Rodent studies show that METH may elicit hypertension as well as toxicity in the heart, lung and liver (Wells et al., 2008; Halpin and Yamamoto, 2012; Tomita et al., 2013; Hassan et al., 2016). A recent investigation in C57Bl/6 mice demonstrated that chronic and escalating parenteral METH administration (5–40 mg/kg) caused cardiotoxicity, which shared many similarities with that observed in METH addicts. Indeed, METH increased heart weight and induced dilated cardiomyopathy associated with lower survival rates in male than female mice (Marcinko et al., 2019), in agreement with the clinical findings showing that men are more susceptible than women to METH-induced cardiotoxicity (Dluzen and Liu, 2008). Marcinko et al. (2019) also reported that escalating doses of METH affected the transcription of genes that were previously found to be dysregulated in studies of METH-induced neurological impairment and that are likely to participate in METH-induced cardiotoxicity.

Another effect of METH commonly observed in experimental animals is hyperthermia. In addition to being itself a major cause of lethality, hyperthermia has been implicated in several of the toxic effects of METH. Thus, hyperthermia exacerbates METH-induced neurotoxicity (Bowyer and Ali, 2006; Bowyer and Hanig, 2014), and studies in rats treated with single or multiple parenteral doses of METH (2–10 mg/kg) have shown that hyperthermia contributes to liver damage, increase in peripheral ammonia, leakage from blood brain barrier and vascular edema elicited by METH (Kiyaktin and Sharma, 2007, 2015; Halpin et al., 2013). Finally, single or multiple parenteral administrations of METH (1–40 mg/kg) induce symptoms of neurological toxicity in experimental animals, such as seizures and tremor (Izumi et al., 1984), as well as behavioral abnormalities reminiscent of anxiety-like, depressive-like or psychotic-like phenotypes (Silva et al., 2014; Wearne et al., 2016; Etaee et al., 2017; Struntz and Siegel, 2018). **Table 1** provides further details about the toxic effects of METH in experimental animals demonstrated by studies from the past 3 years.

### Neurotoxic effects

Studies *in vitro* have demonstrated that METH (100 μM–3 mM applied for 24 hours) is toxic for dopaminergic cell lines like neuroblastoma-derived SH-SY5Y cells and pheochromocytoma-derived PC12 cells (Moratalla et al., 2017). Moreover, studies in experimental animals have demonstrated overt toxic effects of METH on the dopaminergic and serotonergic systems. In rodents, either single administration or "binge" regimens of parenteral METH may induce marked neurotoxicity especially in the nigrostriatal dopaminergic system. METH (2.5–30.0 mg/kg) damages neuronal bodies, since it reduces the numbers of dopaminergic neurons in the substantia nigra pars compacta (Hirata and Cadet, 1997; Granado et al., 2011a, b; Ares-Santos et al., 2014). When administered at the same doses, METH may also damage dopaminergic terminals, since it reduces the levels of tyrosine hydroxylase and dopamine transporter, as well as of dopamine and its metabolites dihydroxyphenilacetic acid and homovanillic acid (Granado et al., 2010, 2011a, b; Ares-Santos et al., 2014). METH-induced damage of dopaminergic terminals appears most evident in the striatum but also occurs, albeit at low levels, in other regions that receive dopaminergic innervation, such as the cortex, thalamus, hypothalamus and hippocampus (Guilarte et al., 2003; Krasnova and Cadet, 2009; Granado et al., 2010; Ares-Santos et al., 2012). Conversely, multiple parenteral administration of METH (7.5–60 mg/kg) induce widespread damage of serotonergic terminals in rodents, revealed by reduced levels of serotonin, serotonin transporter and tryptophan hydroxylase in the hippocampus, frontal cortex and striatum (McFadden and Vieira-Brock, 2016; Moszczynska and Callan, 2017). Neurotoxic effects of METH in the dopaminergic and serotonergic systems have also been demonstrated in non-human primates (Yuan et al., 2006; Melega et al., 2008). Notably, single or multiple doses of METH (0.1–40 mg/kg) that induce neurotoxic damage may as well impair social behavior, recognition memory and learning in experimental animals (Melega et al., 2008; Avila et al., 2018; Gutierrez et al., 2018). These effects of METH have been observed after either oral intake or parenteral administration and suggest a causal link between neurotoxicity

**Table 1 Overview of the toxic effects of methamphetamine demonstrated in studies from the past 3 years**

| Site affected | Species | Toxic effect | Reference |
|---|---|---|---|
| Blood brain barrier | Rats ( 8 × 15 mg/kg, i.p.) | Increased permeability | Xue et al., 2019 |
| Cerebellum | Rats (2 mg/kg, i.p., 3 days + 5 mg/kg, i.p., 4 days) | Reduced volume of cerebellar layers (molecular, granular, and Purkinje), decreased volume of white matter, increased astrogliosis | Eskandarian Boroujeni et al., 2019 |
| Colon | Rats (0.1 mg/kg/0.1 mL infusion self-administered 3 h/d for 14 days) | Increased levels of α-synuclein, and decreased levels of parkin, tyrosine hydroxylase, and dopamine-β-hydroxylase in the myenteric plexus | Flack et al., 2017 |
| Heart | Mice (escalating i.p. administrations to reach 35–40 mg/kg in 2–5 months) | Increased heart weight and induction of dilated cardiomyopathy | Marcinko et al., 2019 |
| Heart | Humans | Induction of cardiomyopathy | Schürer et al., 2017 |
| Heart | Rats (1–5 mg/kg, i.p., 14 days) and humans (isolated cardiomyocytes) | Induction of apoptosis and decrease in the levels of melusin, which is implicated in maintaining normal heart function | Sun et al., 2019 |
| Heart | Humans | Reduction of coronary sinus flow | Wei et al., 2018 |
| Heart and vessels | Humans | Elevation in blood pressure, increase in left ventricular mass index and impairment in diastolic function | Zheng et al., 2019 |
| Hippocampus | Cynomolgus monkeys (2 mg/kg, i.m., acute, or 0.1 to 0.75 mg/kg for 4 weeks and 0.75 mg/kg for other 4 weeks) | Induction of volumetric atrophy of the hippocampus, downregulation of genes associated with cytoskeleton organization and phagocytosis | Choi et al., 2018 |
| Hippocampus | Rats (2 × 50 mg/kg, i.p., 3 days) | Induction of enduring hippocampal cell damage, reduction of mature brain-derived neurotrophic factor protein content | García-Cabrerizo et al., 2018 |
| Liver | Rats | Increase in the activity of seral alanine aminotransferase and aspartate aminotransferase | Zhang et al., 2019 |
| Liver and kidney | Mice (10 mg/kg i.p., 3 times/week for 1 month) and humans | Increased serum level of alanine aminotransferase, creatine kinase and creatinine. | Zhang et al., 2018 |

i.m.: Intramuscular; i.p.: intraperitoneal.

and behavioral abnormalities induced by METH.

Dopaminergic damage induced by METH appears to stem from the interaction among different mechanisms. These include oxidative stress, that may arise from the auto-oxidation of extracellular dopamine that is released by METH, excitotoxicity and glia activation (Moratalla et al., 2017). Conversely, little is known about the mechanisms underlying METH-induced neurotoxicity on serotonergic terminals, although evidence exists to suggest that dopaminergic mechanisms take part in serotonergic damage (Gross et al., 2011). Interestingly, rodent studies have demonstrated that METH-induced neurotoxicity is dose- and time-dependent. Damage of dopaminergic terminals may appear shortly (within 24 hours) after the administration of high doses of METH and decreases in the striatal levels of tyrosine hydroxylase and dopamine transporter may recover over time. However, recovery is often incomplete and damage may persist months after METH discontinuation (Kousik et al., 2014; Granado et al., 2018).

## Toxic Effects of Methamphetamine Demonstrated in Human Studies

### Overview of toxic effects

Case reports indicate that fatalities related to METH are more frequent in individuals who consume high amounts of the drug, and that most common reasons of death are multiple and/or pulmonary congestion, pulmonary edema, ventricular fibrillation, acute cardiac failure, cerebrovascular hemorrhage, leukoencephalopathy or hyperthermia (Darke et al., 2017; Mu et al., 2017; Callaghan et al., 2018). Other causes of fatalities related to METH are accidents, suicides and homicides, accounting for the manifestation of psychological and behavioral disturbances in users (Auckloo and Davies, 2019). Indeed, epidemiological studies have reported that about the 40% of METH users may display psychiatric symptoms (Glasner-Edwards and Mooney, 2014), albeit most of them are transient in individuals who do not take METH on a regular basis (Gan et al., 2018). METH users often display psychiatric symptoms of the "positive" type, like delusions, hallucinations and hostility, but less frequently show psychotic symptoms of the "negative" type (McKetin et al., 2018). Psychiatric symptoms may persist up to six months or longer after METH discontinuation in a significant percentage of users (up to the 30%) (Deng et al., 2012), and these enduring symptoms may stem from heightened sensitivity to the drug or dosing escalation (Hsieh et al., 2014). **Table 1** provides further details about the toxic effects of METH in humans demonstrated by studies from the past 3 years.

### Neurotoxic effects

Neuroimaging and postmortem studies have revealed abnormalities in the brain of METH users, such as reduced densities of dopamine transporter, vesicular monoamine transporter and of dopamine D2 receptors, as well as decreased levels serotonin and serotonin transporter (Moszczynska and Callan, 2017). METH users may also display abnormalities in behavioral functions (e.g., executive functions, learning) that are regulated by monoamines. These findings may suggest that METH induces neurotoxic damage in monoaminergic pathways that may become evident at the behavioral level. However, the existence of neurotoxic effects of METH in humans is disputed (Kish et al., 2017). Thus, human studies do not always show a clear correlation between the amount of METH consumed and the severity of behavioral deficits; moreover, certain monoaminergic deficits may recover after METH discontinuation (Moszczynska

and Callan, 2017). While these findings seem to downplay the existence of METH-induced neurotoxicity in humans, it should be considered that the divergent results obtained in animal and human studies may be influenced by possible confounders, such as protocols of METH administration in experimental animals and variability in METH purity and/or polydrug use in humans (Moszczynska and Callan, 2017). In addition, it is noteworthy that recovery of monoaminergic deficits in the human brain could depend on compensatory mechanisms, like sprouting and branching of the remaining neuronal fibers (Volkow et al., 2015; Boileau et al., 2016).

Another source of concern related to the possible neurotoxicity of METH in the dopaminergic system is the suggested link between METH use and later manifestation of Parkinson's disease. Rodent studies have demonstrated that METH preferentially damages the dopaminergic nigrostriatal pathway, which degenerates in Parkinson's disease (Moratalla et al., 2017). Moreover, some epidemiological studies have reported a higher risk of Parkinson's disease in METH users than in the general population (Callaghan et al., 2012; Curtin et al., 2015; Rumpf et al., 2017; Lappin et al., 2018), which could be explained by hypothesizing that METH use favors the demise of mesencephalic dopaminergic neurons. However, other studies have questioned the hypothesis that METH may be a causative factor for Parkinson's disease. Thus, it has been reported that METH users seldom display cardinal motor symptoms of Parkinson's disease, even in the presence of dopaminergic deficiency (Marshall and O'Dell, 2012). Moreover, METH users exhibit more marked dopamine deficiency in the caudate than in the putamen, whereas Parkinson's disease features more marked dopamine deficiency in the latter nucleus (Kish et al., 2017). Finally, it is still unclear whether in humans METH induces damage of nigral neurons and gliosis, two pathological hallmarks of Parkinson's disease (Kish et al., 2017).

## Toxic Effects of 3,4-Methylenedioxymethamphetamine Demonstrated in Preclinical Studies

### Overview of toxic effects

The toxic effects of MDMA that have been more exhaustively characterized in experimental animals are cardiovascular damage and hyperthermia; however, hepatotoxicity, nephrotoxicity and disruption of the blood brain barrier have also been reported (Green et al., 2003; Texeira-Gomez et al., 2016; Perez-Hernandez et al., 2017).

In rats, single or repeated parenteral administrations of MDMA (0.001–20.0 mg/kg) increase blood pressure and induces tachycardia, although bradycardia may also be observed (O'Cain et al., 2000; Alsufyani and Docherty, 2015). Besides, MDMA (20 mg/kg, single administration) damages the cardiac muscle by activating the autophagy-lysosomal pathway (Shintani-Ishida et al., 2014), increases the levels of pro-inflammatory cytokines in heart and plasma (Neri et al., 2010), and alters the cardiac gap junction protein Cx43 (Zhuo et al., 2013). In mice, single or repeated parenteral administrations of MDMA (5 or 20 mg/kg) transiently increases blood pressure in anaesthetized animals (Vandeputte and Docherty, 2002) and markedly activate cardiac sympathetic pathways in awake animals, an effect that may lead to heart damage (Navarro-Zaragoza et al., 2015, 2019). Repeated parenteral administrations of MDMA (40 mg/kg) also induce widespread epigenetic changes in DNA methylation in the heart muscle of mice, which could play a role in cardiotoxicity (Koczor et al., 2015).

Hyperthermia has been consistently demonstrated in experimental animals treated with MDMA (Green et al., 2003). In addition to be a life-threatening event itself, hyperthermia seems to participate in other toxic effects of MDMA, such as hepatotoxicity and glia activation (Colado et al., 1995; Turillazzi et al., 2010; Frau et al., 2016a). Moreover, intracerebroventricular administration of MDMA (125–500 μg) may induce neurological adverse effects (e.g., seizures, tremor) (Hanson et al., 1999), whereas single parenteral administration of MDMA (2–10 mg/kg) may elicit a phenotype reminiscent of the human serotonin syndrome (Ma et al., 2013). Furthermore, single or repeated parenteral administration of MDMA modifies the behavior of rodents in tests used to study anxiety, depression, cognition and motivation, although variable results have been reported according to the administration regimen used (Navarro and Maldonado, 2002; Ho et al., 2004; Clemens et al., 2007; Costa et al., 2014; Simola et al., 2014). **Table 2** provides further details about the toxic effects of MDMA in experimental animals demonstrated by studies from the past 3 years.

### Neurotoxic effects

Studies *in vitro* have demonstrated that MDMA (100-800μM applied for 24 or 48 hours) is toxic for cortical neurons and SH-SY5Y cells (Moratalla et al., 2017), and neurotoxic effects of MDMA have been demonstrated in experimental animals as well (Lyles and Cadet 2003).

In rats and primates, single or repeated administrations of MDMA by the oral or parenteral route (10–80 mg/kg) reduce serotonin levels in several brain regions, including the hippocampus, hypothalamus, striatum, and neocortex (Commins et al., 1987; Scallet et al., 1988; Scheffel et al., 1998). Moreover, single administration of MDMA (2.5–30 mg/kg) by oral or parenteral route may damage serotonergic cell bodies in the raphe nucleus (Ricaurte et al., 1988) as well as tryptophan hydroxylase-positive fibers in frontal cortex, hippocampus, thalamus, septum, and amygdala (Adori et al., 2006; Kovács et al., 2007). Serotonergic damage induced by MDMA may be persistent, since reduced markers of neuronal viability and function have been detected months or years after drug discontinuation (Crawford et al. 2006). Nevertheless, serotonergic axonal sprouting has been observed in rats and primates that received single or repeated parenteral administration of MDMA (10–40 mg/kg) (Ricaurte and McCann, 1992; Fischer et al., 1995), which may suggest recovery of damage over time. Finally, repeated parenteral administration of MDMA (10 mg/kg) may induce GABAergic damage in the rat brain (Anneken et al., 2013).

MDMA has generally been reported to induce little or no toxic effects in catecholaminergic systems of rats and primates (Moratalla et al., 2017). However, recent evidence suggests that MDMA may be toxic for the dopaminergic system

**Table 2 Overview of the toxic effects of MDMA demonstrated in studies from the past 3 years**

| Site affected | Species | Toxic effect | Reference |
|---|---|---|---|
| Blood brain barrier | Rats (12.5 mg/kg, i.p., acute) | Induction of edema due to bood brain barrier disruption | Pérez-Hernández et al., 2017 |
| Cerebral cortex | Mice (5–10 mg/kg, s.c., increasing doses 3 × day, once a week × 8 weeks) | MDMA can contribute to the cortical amyloid cascade in the APP/PS1 dE9 model of Alzheimer's disease | Abad et al., 2019 |
| Heart | Humans | Genetic polymorphisms of the noradrenaline transporter gene (SLC6A2) weakly moderates the acute cardiovascular response to MDMA | Vizeli et al., 2018 |
| Heart | Humans (internal mammary artery, *in vitro*, 10–1360 mM) | Increase in serotonin-dependent vasoactivity, especially in hyperthermic conditions | Fonseca et al., 2017 |
| Hippocampus | Rats (15 mg/kg, i.p., acute) | Prolonged depression of new neurite formation | Petschner et al., 2018 |
| Kidney | Rats (10 or 40 mg/kg, i.p., acute) | Increased levels of reactive oxygen species, increased water absorption | de Bragança et al., 2017 |
| Liver | Primary mouse hepatocytes (0.203 and 0.472 mM) | Subtoxic concentrations alter metabolic pathways, as revealed by metabolomics | Araújo et al., 2018 |
| Retina | Mice (2 mg/kg, i.p., daily × 3 months) | Induction of retinal dysfunction mediated by apoptosis of photoreceptor cells | Lv et al., 2019 |
| Retina | 661W photoreceptor cells and RAW264.7 macrophages | Promotion of macrophage polarization to M1 and induction of inflammatory response | Liu et al., 2018 |
| Striatal muscle | Rats (10 or 40 mg/kg, i.p., acute) | Rhabdomyolysis | de Bragança et al., 2017 |
| Testis | Rats (5 or 10 mg/kg, i.p., × 16 days) | Increased immunoreactivity for the heat shock protein (HSP70), increased apoptosis | Mobaraki et al., 2018 |

i.p.: Intraperitoneal; MDMA: 3,4-methylenedioxymethamphetamine; s.c.: subcutaneous.

of rats. Thus, repeated parenteral administrations of MDMA (5 mg/kg) to adolescent rats induce dopaminergic damage that is evident at adulthood and consists in reduced numbers of tyrosine hydroxylase-positive neurons in both the substantia nigra pars compacta and ventral tegmental area, along with decreased immunoreactivity for tyrosine hydroxylase and dopamine transporter in the striatum and nucleus accumbens (Cadoni et al., 2017). Moreover, acute parenteral administration of MDMA (20 mg/kg) to adult rats increases nitrosative stress in dopaminergic pathways of the prefrontal cortex (Schiavone et al., 2019).

In mice, MDMA causes little serotonergic damage but induces marked toxicity in dopaminergic pathways. When administered by the parenteral route in "binge" dosing (1–30 mg/kg), MDMA decreases the numbers of dopaminergic neurons in the substantia nigra pars compacta, reduces the densities of fibers positive for the dopamine transporter and tyrosine hydroxylase in the dorsal striatum, and dampens the striatal concentrations of dopamine, dihydroxyphenilacetic acid and homovanillic acid (O'Shea et al., 2001; Granado et al., 2008; Costa et al., 2013). Interestingly, Granado et al. (2008) reported degeneration of dopaminergic fibers in the dorsal striatum but not nucleus accumbens, which suggested that the nigrostriatal system is the major target of MDMA-induced dopaminergic damage. This hypothesis has recently been confirmed and extended by a study in mice repeatedly treated with increasing numbers of parenteral MDMA administrations (10 mg/kg) (Costa et al., 2017). That study showed that MDMA reduced the numbers of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta and the densities of fibers positive for the dopamine transporter and tyrosine hydroxylase in the striatum. MDMA also reduced the density of dopamine transporter-positive terminals in the medial prefrontal cortex, and the density of tyrosine hydroxylase-positive fibers in the medial prefrontal cortex and hippocampus, which suggests that MDMA damages the mesolimbic and mesocortical dopaminergic systems. The severity of dopaminergic damage increased with the number of MDMA administrations; however, only the nigrostriatal system appeared damaged when mice were evaluated 3 months after treatment discontinuation (Costa et al., 2017). The same study also showed that repeated parenteral administrations of MDMA (10 mg/kg) may induce GABAergic damage, as revealed by reduced numbers of neurons positive to glutamic acid decarboxylase-67 (GAD-67) in the striatum and hippocampus and by reduced density of GAD67-positive fibers in medial prefrontal cortex (Costa et al., 2017). Furthermore, a subsequent study showed that repeated parenteral administration of MDMA (10 mg/kg) may trigger nitrosative stress, as revealed by increased numbers of neurons positive to neuronal NO synthase in the striatum and substantia nigra pars compacta (Costa et al., 2018). The magnitude and topography of the modifications in the immunoreactivity for GAD-67 and neuronal NO synthase varied with the number of MDMA administrations; moreover, these effects persisted up to 3 months after MDMA discontinuation (Costa et al., 2017, 2018). Interestingly, MDMA has been found to induce parallel modifications in the immunoreactivity for markers of dopaminergic function, GAD-67 and neuronal NO synthase (Costa et al., 2017, 2018). This finding may suggest a possible relationship among dopaminergic damage, GABAergic damage and increased nitrosative stress induced by MDMA (Costa et al., 2017, 2018).

Recent studies in rodents have provided important insights into MDMA-induced neurotoxicity, which may be relevant when translating preclinical results to the human setting. For example, it has been found that the noxious effects of MDMA in the brain are stereospecific and mediated by the S(+) enantiomer. In fact, repeated parenteral administrations of S(+)-MDMA (10 mg/kg) activate microglia and astroglia in the striatum of mice, whereas repeated parenteral ad-

ministrations of R(–)-MDMA (10 mg/kg) do not (Frau et al., 2013). In line with these findings, another study in mice found that repeated parenteral administrations of R(–)-MDMA (50 mg/kg) induced neither hyperthermia nor neurotoxicity (Curry et al., 2018). Moreover, MDMA may reciprocally interact with other neurotoxic/psychoactive substances to cause brain damage. In this regard, studies in mice showed that repeated parenteral administrations of MDMA (10 mg/kg) during adolescence exacerbated dopaminergic damage, glia activation and recognition memory deficits induced by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered at adulthood (Costa et al., 2013, 2014). Moreover, the noxious effects of MDMA may be amplified when the drug is co-administered with psychoactive substances like caffeine or ethanol. In mice, caffeine may potentiate glia activation and generation of pro-inflammatory mediators, as well as damage of dopaminergic neurons and fibers and of nuclear DNA that are induced by repeated parenteral administrations of MDMA (10–20 mg/kg) (Frau et al., 2016b; Górska et al., 2018). Similarly, ethanol co-administration amplifies the dopaminergic damage and behavioral abnormalities induced by repeated parenteral administration of MDMA (10–20 mg/kg) (Ros-Simò et al., 2012; Vidal-Infer et al., 2012). Studies in rats have confirmed that caffeine and ethanol may exacerbate the neurotoxicity induced by acute or repeated parenteral administration of MDMA (5–20 mg/kg), although these noxious effects were observed in the serotonergic system (Izco et al., 2007; Vanattou-Saïfoudine et al., 2012), but not in the dopaminergic system (Cadoni et al., 2017). Furthermore, another study in mice has shown that the noxious central effects elicited by repeated parenteral administrations of MDMA (20 mg/kg) may vary with the experimental setting, in fact glia activation induced by MDMA has been found to be amplified when the drug is administered in crowded cages or at high environmental temperature (Frau et al., 2016a). To complicate the matter, age, gender and genetic background of animals, as well as interaction of these factors critically regulate the effects of MDMA in the brain. Thus, the neurotoxic effects elicited by the repeated parenteral administrations of MDMA (5–20 mg/kg) may be more marked in adult and aged animals than in young animals (Reveron et al., 2005; Frau et al., 2016b; Feio-Azevedo et al., 2018). Besides, a recent study in mice that do not express the protein Ras homolog enriched in striatum (Rhes) has demonstrated that repeated parenteral administrations of MDMA (20 mg/kg) caused more pronounced dopaminergic neurodegeneration and glia activation in male than in female $Rhes^{-/-}$ mice (Costa et al., 2019).

Different mechanisms are thought to participate in the neurotoxicity induced by MDMA in experimental animals, such as hyperthermia, increase in oxidative and nitrosative stress, activation of glia cells (Moratalla et al., 2017). In addition, dopamine receptors and drug metabolism seem to critically influence the neurotoxic effects of MDMA. In fact, studies in mice show that antagonism or inactivation of dopamine receptors attenuates MDMA-induced neurotoxicity (Granado et al., 2014) and that administration of MDMA directly in the striatum does not induce dopaminergic damage, even at doses (1–100 μg) that are comparable to those that elicit neurotoxicity when administered systemically (Escobedo et al., 2005). Nevertheless, the precise cascade of events leading to MDMA-induced neurotoxicity has not been elucidated, neither have the mechanisms that underlie the differential neurotoxicity of MDMA in rats and primates compared with mice.

## Toxic Effects of 3,4-Methylenedioxymethamphetamine Demonstrated in Human Studies

### Overview of toxic effects

Hyperthermia and cardiovascular problems are the toxic effects of MDMA that have been more frequently associated with admissions to emergency rooms and fatalities (Parrott et al., 2013; Bonsignore et al., 2019).

Hyperthermia induced by MDMA may be severe, with core temperatures higher than 43°C (Jahns et al., 2018), and may precede other toxic effects, such as disseminated intravascular coagulopathy, rhabdomyolysis, multiple organ failure, or acute renal failure (Capela et al., 2009). Although MDMA-induced hyperthermia is often associated with poor prognosis, survival is possible if patients are rapidly subjected to intensive care (Davies et al., 2014; Jahns et al., 2018). Regarding the cardiovascular system, MDMA may increase blood pressure and induce vasoconstriction by means of serotonin-dependent mechanisms (Silva et al., 2016), an effect that seems to be more marked in hyperthermic than normothermic conditions (Fonseca et al., 2017). Moreover, MDMA may alter heart rhythm and induce myocardial infarction and sudden cardiac death (Bonsignore et al., 2019). Toxicity of MDMA on heart and vessels is more pronounced in individuals with pre-existing cardiovascular conditions (Vizeli and Liechti, 2017).

Other signs of toxicity involving peripheral organs that have been documented in MDMA users are hyponatremia, elevation in cortisol levels, altered cortisol reactivity, pulmonary edema, and liver failure (Schifano, 2004; Parrott et al., 2013; Thakkar et al., 2017). Furthermore, MDMA users may experience the serotonin syndrome, a potentially lethal condition requiring prompt treatment, whose symptoms include agitation, hyperthermia, sweating, tremor, increased reflexes, dilated pupils, and diarrhea. Finally, MDMA users may display signs of neurological toxicity (i.e., ataxia), sleep disturbances, psychiatric distress and neurocognitive deficits that may persist after drug discontinuation (Smithies et al., 2014; Parrott et al., 2017). Nevertheless, the association between use of MDMA and manifestation of neurocognitive deficits has recently been questioned (Amoroso, 2019). **Table 2** provides further details about the toxic effects of MDMA in humans demonstrated by studies from the past 3 years.

### Neurotoxic effects

Some neuroimaging studies have demonstrated that heavy MDMA users may exhibit decreased levels of serotonin transporter (Benningfield and Cowan, 2013), increased cortical excitability (Bauernfeind et al., 2011), or altered cortical serotonergic signaling (Di Iorio et al., 2012). However, other neuroimaging studies have reported little or no abnormali-

ties involving serotonergic pathways in the brain of MDMA users (Garg et al., 2015; Mueller et al., 2016), a finding that may question the existence of MDMA-induced neurotoxicity in humans.

The issue of serotonergic damage in the brain of MDMA users has recently been reexamined by meta-analysis studies of the existing investigations of neuroimaging. A first meta-analysis found that MDMA reduced the availability of the serotonin transporter in MDMA users (Roberts et al., 2016a). Albeit the overall effect size was moderate and large heterogeneity was observed, significant reductions in the availability of serotonin transporter were found in cortical regions (frontal, parietal, temporal, occipital), hippocampus, amygdala, and thalamus. Conversely, no effects of MDMA on serotonin transporter were observed in the caudate, putamen and midbrain. The same meta-analysis also revealed that upregulation of serotonin 5-HT2A receptors may take place in neocortical brain areas of MDMA users (Roberts et al., 2016a). Reductions in serotonin transporter densities in the brain of MDMA users have been confirmed by another recent meta-analysis study (Müller et al., 2019). Interestingly, decreased serotonin transporter densities were found in cortical regions, thalamus and hippocampus, but not in the basal ganglia, in agreement with earlier findings (Roberts et al., 2016a). Reduction in serotonin transporter density may account for the existence of neurotoxic effects of MDMA in humans. However, it may be also conceivable that decreases in the levels of serotonin transporter may reflect downregulation due to MDMA-induced serotonergic stimulation (Müller et al., 2019). Interestingly, Müller et al. (2019) observed no relationship between lifetime episodes of MDMA use and reduction in the density of the serotonin transporter. Conversely, they found a significant positive association between the latter marker and time of MDMA abstinence, which may suggest that the effects of MDMA on serotonin transporter are potentially reversible, as hypothesized by earlier studies (Reneman et al., 2001; Buchert et al., 2006; Benningfield and Cowan, 2013). Finally, another meta-analysis has demonstrated that MDMA users may display deficits in executive functions, such as access to semantic memory, mental switching, and information updating (Roberts et al., 2016b). Since executive functions are regulated by serotonin-rich prefrontal cortical areas, deficits in these functions may provide behavioral correlates of possible serotonergic damage induced by MDMA (Roberts et al., 2016b).

Dopaminergic abnormalities in the brain of MDMA users have been hypothesized. An earlier investigation found that administration of the dopamine D2 receptor agonist bromocriptine led to more marked secretion of growth hormone in control subjects than in MDMA users, which may suggest dopaminergic dysfunction in the latter (Gerra et al., 2002). Moreover, an imaging study demonstrated increased striatal $^{18}$F-DOPA reuptake in MDMA users, which may indicate a striatal hyperdopaminergic state; however, this effect was influenced by polydrug use (Tai et al., 2011). Furthermore, a recent investigation that applied untargeted metabolomics screening approaches demonstrated decreased calcitriol plasma levels after acute MDMA intake (Boxler et al., 2018). Since calcitriol modulates the upregulation of trophic factors that have protective effects on dopaminergic neurons (Cass et al., 2006), decreased calcitriol after use of MDMA may suggest that the drug is toxic for the dopaminergic system. Nevertheless, several other studies found no evidence of dysfunctions involving dopaminergic pathways in the brain of MDMA users (reviewed in Vegting et al., 2016), and the existence of MDMA-induced dopaminergic damage in humans remains controversial.

## Toxic Effects of Hallucinogen and Dissociative Drugs

### Preclinical studies

Studies *in vitro* have demonstrated that both acute and prolonged exposure to hallucinogen phenethylamines (2.4–100 μM) inhibit neuronal activity in rat primary cortical cultures (Zwartsen et al., 2018). Similarly, studies in users have demonstrated toxic effects of serotoninergic hallucinogens, including the newest ones, which have been frequently associated with acute serotonin syndrome, hyperthermia, seizures, hyponatremia and sympathomimetic toxicity (Hill and Thomas, 2011). Degree of symptoms can range from mild to severe; complications may include seizures and extensive muscle breakdown. Animal studies have described the behavioral components of the serotonin syndrome induced by hallucinogen drugs which include lateral head weaving, hind limb abduction, backward locomotion, and lower lip retraction (Halberstadt and Geyer, 2011; Gatch et al., 2017).

Ketamine is a non-competitive antagonist of glutamate N-methyl-D-aspartate (NMDA) receptors that induces dissociative anesthesia and analgesia at clinical doses; however, at recreational doses of subanesthetic levels, ketamine may produce an intense psychedelic experience. Accordingly, although present on the drug market for long time, ketamine continues to be abused worldwide, and its consumption among adolescents is particularly worrying. A study in Cynomolgus monkeys has shown that repeated parenteral administrations of a recreational dose of ketamine (1 mg/kg) induce neurotoxic effects, involving the activation of apoptotic pathways in the prefrontal cortex, that lead to irreversible deficits in brain functions (Sun et al., 2014). In line with this, repeated parenteral administrations of sub-anesthetic doses of ketamine (5–50 mg/kg) increased cell death in hippocampal cornu ammonis area 3, caused irreversible changes in both brain structure and function in young adult mice (Majewski-Tiedeken et al., 2008) and induced apoptotic and necrotic neuronal cell death in the perinatal rhesus monkey (Slikker et al., 2007).

Methoxetamine is an NPS structurally related to ketamine and phencyclidine, designed to mimic the psychotropic effects of its parent compounds (Zanda et al., 2016) and increasingly available on the Internet as 'legal ketamine' (EMCDDA, 2014). Methoxetamine acts as a NMDA receptor antagonist, but also potently inhibits neuronal activity and alters monoamine metabolism in *in vitro* models (Hondebrink et al., 2018). Moreover, acute repeated parenteral administration of methoxetamine (0.125–5 mg/kg) considerably stimulates the mesolimbic dopaminergic transmission in rats (Mutti et al., 2016), and affects brain functions and

behavior in rodents (Zanda et al., 2017). A recent study in mice (Ossato et al., 2018) found that acute parenteral administration of methoxetamine (0.01–30 mg/kg) induced alterations in sensory function processing that resembled those reported by users (Kjellgren and Jonsson, 2013) and persisted for hours when methoxetamine was administered at high doses. Moreover, another recent study in rats found that repeated parenteral administrations of methoxetamine (0.1–0.5 mg/kg) induced persistent behavioral abnormalities in tests used to evaluate anxiety-like states and recognition memory (Costa et al., 2019). The same investigation also demonstrated that methoxetamine induced persistent damage of dopaminergic fibers and neurons in the nigrostriatal and mesocorticolimbic systems as well as of serotonergic fibers in the nucleus accumbens core (Costa et al., 2019). **Table 3** provides further details about the toxic effects of hallucinogen and dissociative drugs demonstrated by preclinical studies from the past 3 years.

**Human studies**

In 2007, tryptamine derivatives were listed as 'narcotics' or 'designated substances' and were quickly replaced on the online drug market by cathinones, phenethylamines, and piperazines. Yet, several novel tryptamines continue to appear on the online drug market as 'legal highs', which include AMT, 5-MeO-AMT, 4-HO-DALT and 5-MeO-DALT (**Figure 2**). In addition to visual and auditory hallucinations, these drugs may induce agitation, tachyarrhythmia, hyperthermia and death (Wood and Dargan, 2013).

According to the EMCDDA (2015), some phenethylamines with hallucinogenic properties are very popular in the current drug market, including the so-called 2C series (e.g., 2C-B/'Nexus') and the NBOMe series drugs (e.g., 25I-NBOMe, **Figure 2**). Their use has been associated with serotonergic and sympathomimetic toxic effects, including vomiting/diarrhea, metabolic acidosis, mydriasis, convulsions, thrombocytopenia, renal failure, hyperthermia and coma (Schifano et al., 2017). Fatalities and hospitalizations have been reported following use of 25I-NBOMe and symptoms of acute toxicity included tachycardia, hypertension, agitation/aggression and seizures, while laboratory tests detected elevated level of creatinine kinase, leukocytosis and hyperglycaemia (Suzuki et al., 2015). Rhabdomyolysis is a relatively common complication of severe NBOMe toxicity, an effect that may be linked to NBOMe-induced seizures, hyperthermia, and vasoconstriction. Slightly different from 25I-NBOMe, 25C-NBOMe was found to induce aggression, unpredictable violent episodes, dissociation and anxiety (Lawn et al., 2014). Although studies on the pharmacology of hallucinogenic phenylethylamines from the 2C series are

**Table 3 Overview of the toxic effects of hallucinogen and dissociative drugs demonstrated in studies from the past 3 years**

| Site affected | Species | Toxic effect | Reference |
|---|---|---|---|
| Adipose tissue | Rats (25B-NBOMe; 0.25 mg/kg, i.p., acute) | Induction of hyperthermia and increased thermogenesis | Nakamura et al., 2018 |
| Cerebral cortex | Mice (ketamine; 30 mg/kg, i.p., + dexmedetomidine, 20 μg/kg, acute) | Induction of apoptosis that displays features similar to those of physiological apoptosis and can be regulated by neuronal activity | Wang et al., 2017 |
| Dorsolateral prefrontal cortex | Humans (methoxetamine) | $^{18}$F-fluorodeoxyglucose positron emission tomography revealed significant bilateral deficits of the tracer uptake after injection of methoxetamine | Moccia et al., 2019 |
| Heart | Rats (methoxetamine in isolated cardiomyocytes, 10 μM) | Induction of harmful effects on cardiomyocytes mediated by the altered expression and function of the P21 protein (Cdc42/Rac)-activated kinase 1 | Yoon et al., 2019 |
| Heart, bronchial tissues and striatum | Rats (ketamine; 30 mg/kg, i.p., acute) | Induction of oxidative stress | Ahiskalioglu et al., 2018 |
| Heart and CNS | Mice (methoxetamine and ketamine; 1 and 30 mg/kg, i.p., acute) | Alteration of cardiorespiratory parameters, systolic and diastolic blood pressure | Ossato et al., 2018 |
| Heart and monoaminergic neurons | Zebrafish (ketamine; 2.0 mM × 2 hours or 20 hours) | Induction of adverse effects on development, heart rate and monoaminergic neurons. | Robinson et al., 2018 |
| Hippocampus | Mice (ketamine; 75 mg/kg, i.m. × 4 administrations) | Early exposure in the postnatal period impairs axonal pruning in the developing hippocampus | Obradovic et al., 2018 |
| Hippocampus | Rats (ketamine in primary hippocampal neurons, (0.1–1000 μM × 3–24 hours) | Activation of cell cycle entry and alteration of early and late apoptosis by inhibition of the PKC/ERK pathway | Jiang et al., 2018 |
| Hippocampus and frontal cortex | Rats (ketamine; 20 mg/kg, s.c.) | A single neonatal exposure induces a short-term reduction in hippocampal cellular viability, and long-term alterations in hippocampal glutamate transport, along with short-term recognition memory impairment | Sampaio et al., 2018 |
| Hippocampus and frontal cortex | Rats (ketamine; self-administration of 0.5 mg/kg/infusion × 5–6 weeks) | Impaired homeostasis of glutamatergic synapses | Caffino et al., 2017 |
| Isolated cells | SH-SY5Y, PC12, and SN4741 cells (25C-NBOMe; 25–400 μM × 24 hours) | Reduction of cell viability | Xu et al., 2019 |
| Prefrontal cortex | Mice (5-MeO-AMT; 0.3–10 mg/kg, i.p., once a day × 7 days) | Induction of head-twitch responses through the activation of 5-HT2A receptors | Abiero et al., 2019 |
| Reproductive system | Rats (ketamine; 20–60 mg/kg, i.p., every 3 days × 7 administrations) | Toxicity on the reproductive system mediated by the breaking of the hypothalamic-pituitary-testicular axis. | Qi et al., 2017 |
| Striatal muscle | Humans (25I-NBOMe) | Single ingestion may cause massive rhabdomyolysis. | Waldman et al., 2018 |

CNS: Central nervous system; i.m.: intramuscular; i.p.: intraperitoneal; s.c.: subcutaneous.

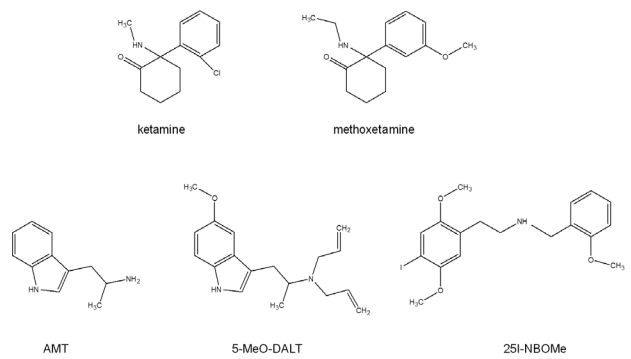


**Figure 2 Chemical structures of some hallucinogen/dissociative substances used as recreational drugs.**
AMT: α-Methyltryptamine; 5-MeO-DALT: N-allyl-N-[2-(5-methoxy-1H-indol-3-yl)ethyl]prop-2-en-1-amine; 25I-NBOMe: 4-Iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine.

still scarce, it has been demonstrated that they may act either as agonists or antagonists of G-protein-coupled serotonin and α-adrenergic receptors (Villalobos et al., 2004; Fantegrossi et al., 2008) and some of them (i.e., 2C-C, 2C-D, 2C-E, and 2C-I) were found to act as full agonists at 5-HT2A/2C receptors (Eshleman et al., 2014).

Use of methoxetamine by humans has been recently associated with acute neurological (Elian and Hackett, 2014; Fassette and Martinez, 2016) and cerebellar toxicity (Shields et al., 2012), including psychomotor agitation and altered motor coordination (Craig and Loeffler, 2014). Case reports described intoxicated patients with hypertension and tachycardia following use of methoxetamine (Thornton et al., 2017), ketamine (Kalsi et al., 2011), phencyclidine (Akmal et al., 1981) or methoxylated phencyclidine analogs (Bäckberg et al., 2015). Induction of gastrointestinal and urinary toxicity by ketamine have also been described (Wei et al. 2013). **Table 3** provides further details about the toxic effects of hallucinogen and dissociative drugs demonstrated by clinical studies from the past 3 years.

Due to the numerous medical issues associated with the use of new hallucinogen and dissociative drugs, being aware of the toxicity of these compounds is of primary importance for health professionals. Since it is not always possible to know the exact compound(s) consumed, management of toxicity should be based on clinical symptoms that an individual presents with and training of medical staff should focus on the management of the pattern of toxicity, rather than on the specific drug(s) used. This view is supported by a recent study revealing that physicians and nurses have less confidence in managing acute toxicity related to the use of NPS compared with classical recreational drugs (Wood et al., 2016).

## Toxic Effects of Synthetic Cannabinoid Receptor Agonists

### Preclinical studies

Studies *in vitro* have explained why SCRAs elicit more marked toxicity, compared with $\Delta^9$-tetrahydrocannabinol (THC). Recently, Hutchison et al. (2018) showed that the abused synthetic cannabinoid AB-PINACA displays peculiar pharmacodynamic properties at CB1 cannabinoid receptors, showing similar affinity as to $\Delta^9$-THC but higher efficacy for G-protein activation and greater potency for adenylyl cyclase inhibition. This finding is of particular toxicological interest, since subsequent chemical generations of SCRAs have become increasingly potent. For instance, derivatives of third generation Spice/K2 cannabinoids, such as BB-22, 5F-PB-22, 5F-AKB-48 and STS-135 (**Figure 3**), are high affinity ligands and potent full super-high CB1 receptor agonists, compared to the first-generation prototypical compound JWH-018 (De Luca et al., 2015). Data obtained by [$^3$H]CP-55,940 assay for evaluating affinity towards CB1 receptors showed that BB-22 and 5F-PB-22 displayed the lowest $K_i$ of binding to CB1 receptors (0.11 and 0.13 nM), which is respectively 30 and 26 times lower than that of JWH-018 (3.38 nM). Moreover, data obtained in the CB1 receptor-induced [$^{35}$S]GTPgS binding assays for evaluating potency and efficacy showed that BB-22 and 5F-PB-22 have a potency ($EC_{50}$, 2.9 and 3.7 nM, respectively) and efficacy ($E_{max}$, 217% and 203%, respectively) as CB1 receptor agonists higher than JWH-018 ($EC_{50}$, 20.2 nM; $E_{max}$, 163%). $^5$F-AKB-48 and STS-135 showed greater $K_i$ for CB1 receptor binding, greater $EC_{50}$ and decreased $E_{max}$ as CB1 receptor agonists than BB-22 and 5F-PB-22, but still higher compared with JWH-018 (De Luca et al., 2016). In addition, studies *in vitro* showed that 5F-ADBINACA, AB-FUBINACA and STS-135 (3-60 μM) induced neurotoxicity in murine neuro-2a cells mediated by a reduction in mitochondrial membrane potential (Canazza et al., 2017). Furthermore, AKB-48 (62.5-1000 μM) has been recently found to exert toxic effects in human bone marrow neuroblastoma SH-SY5Y cells by inducing oxidative damage and increasing the production of interleukin-6 and tumor necrosis factor-α (Oztas et al., 2019).

Studies in mice have shown that SCRAs induce anxiety-, depression-, and aggression-like phenotypes, increase pain threshold, and cause seizures, myoclonia, bradycardia, hypothermia, and hyperreflexia (Banister et al., 2015; Ossato et al., 2016; Canazza et al., 2016, 2017; Pryce and Baker, 2017; Wilson et al., 2019). Behavioral and neurological effects of SCRAs appear to be mediated by CB1 receptors, since they are prevented by the selective CB1 receptor antagonist/inverse agonists AM 251 (Ossato et al., 2016; Canazza et al., 2016, 2017; Pryce and Baker, 2017; Wilson et al., 2019). Moreover, recent evidence in rats showed that repeated administration of JWH-018 (0.25 mg/kg) modifies the activity of dopamine neurons and induces differential changes in the responsiveness of dopamine transmission to motivational stimuli in terminal areas (De Luca et al., 2018), similar to previous results obtained in a rat model of disruption of cortical dopaminergic transmission (Bimpisidis et al., 2014). Interestingly, these neurochemical and behavioral observations are associated with a neuroinflammatory phenotype, as indicated by reactive microgliosis and astrogliosis in dopaminergic brain areas such as the dorsal and ventral striatum and the medial prefrontal cortex (De Luca et al., 2018). **Table 4** provides further details about the toxic effects of SCRAs in experimental animals demonstrated by studies from the past 3 years.

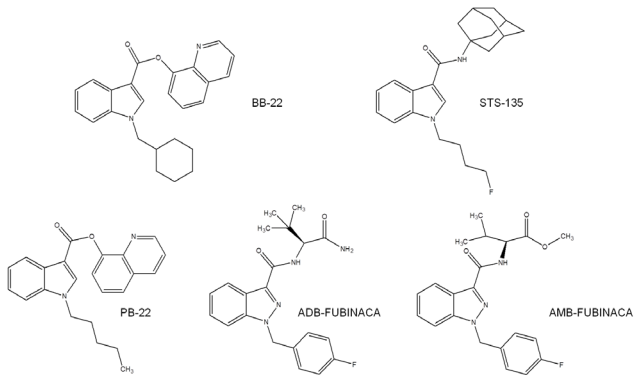


**Figure 3 Chemical structures of some SCRAs used as recreational drugs.**
ADB-FUBINACA: (S)-N-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluoroben-zyl)-1H-indazole-3-carboxamide; AMB-FUBINACA: methyl 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoate; BB-22: 1-(cyclohexylmethyl)-1H-indole-3-carboxylic acid, 8-quinolinyl ester; PB-22: 1-pentyl-1H-indole-3-carboxylic acid 8-quinolinyl ester; STS-135: N-(Adamantan-1-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide; SCRAs: synthetic cannabinoid receptor agonists.

### Human studies

Even though various products containing SCRAs (i.e., joints, powders, liquids for electronic cigarettes and inhalation devices) are advertised as "safe and legal" alternatives to marijuana, they induce severe adverse effects that are different from those of marijuana (Ford et al., 2017). SCRAs intoxication is very complex to diagnose and manage, since it may involve diverse symptoms ranging from seizures, hallucinations, agitation and irritability to psychotropic disturbances, paranoia and anxiety (EMCDDA, 2018). Current information on the toxicity of SCRAs mainly derives from emergency and forensic cases. An earlier report described a simultaneous human and canine neurological toxicity associated with PB-22 (QUPIC) (Gugelman et al., 2014). A 22-year-old man and his dog had generalized tonic-clonic seizures that appeared due to the fact that the man smoked three packages of a product labeled "Crazy Monkey" daily for several weeks, likely in the presence of the animal. Indeed, laboratory analysis of specimens obtained from the product as well as from serum and urine of both human and canine patients revealed the presence of PB-22 (**Figure 3**) along with metabolites of UR-144, another SCRA. Subsequent reports have documented the toxicity of ADB-FUBINACA and AMB-FUBINACA (**Figure 3**). A case report (Nacca et al., 2018) described a 38-year-old man admitted to the emergency room with altered mental status and bradycardia. Later, he showed progressive encephalopathy and seizures accompanied by autonomic instability, respiratory failure, hypotension, hypothermia, and hypoglycemia. A computer tomography scan revealed multiple packages in the patient's stomach and rectum that were removed by laparotomy. Analysis of the patient's serum, urine, and matter from the packages identified cannabis and ADB-FUBINACA. Importantly, prior rodent studies support the ability of ADB-FUBINACA to cause the reported toxidrome (Banister et al., 2015). Another study has described a mass intoxication (33 persons) with AMB-FUBINACA in the New York city area, that was characterized by depressant "zombie-like" effects (i.e., blank stare, slow response, lethargy, mechanical movements, groaning) (Adams et al., 2017). The current evidence also indicates that toxicity of SCRAs becomes more severe after the concurrent ingestion of other NPS (Miliano et al., 2016), in particular synthetic cathinones (Klavž et al., 2016; Assi et al., 2017; Grapp et al., 2017). **Table 4** provides further details about the toxic effects of SCRAs in humans demonstrated by studies from the past 3 years.

## Conclusions

Toxicity of synthetic psychoactive drugs is alarming, since it may result in either fatalities or functional impairments in the brain and/or peripheral organs. Moreover, preclinical studies suggest that synthetic psychoactive substances may damage neuronal bodies and terminals, although no conclusive evidence of neurotoxicity has been obtained so far in humans. However, it should be noted that human studies of drug-induced neurotoxicity may be affected by confounding factors, such as polydrug use and/or differences in drug purity (Davidson et al., 2001; Reneman et al., 2002; Morefield et al., 2011; Tai et al., 2011), which may lead to results dissimilar to those observed in animal studies. Further investigations are warranted to ascertain whether synthetic psychoactive substances elicit actual neurotoxic effects in the human brain particularly with regard to NPS, since little is known about the human neurotoxicology of these substances. The number of NPS that have recently emerged onto the recreational drug scene is very impressive although quite difficult to estimate with a certain precision (**Table 5**). With this review we aimed to provide an overview of the pharmacology of the most commonly used classes of synthetic psychoactive substances and to discuss the acute and chronic harm and toxicity associated with their use.

**Table 4 Overview of the toxic effects of SCRAs demonstrated in studies from the past 3 years**

| Site affected | Species | Toxic effect | Reference |
|---|---|---|---|
| CNS | Humans (5F-PB-22, PB-22, BB-22 and 5F-SDB-005) | Users may display agitation, aggressiveness, reduced consciousness, hallucinations with paranoid features and seizures | Hill et al., 2018 |
| CNS | Mice (CUMYL-4CN-BINACA; 0.3 mg/kg, i.p.) | Pro-convulsant effects | Kevin et al., 2019 |
| Heart and kidney | Humans (5F-PB-22, PB-22, BB-22 and 5F-SDB-005) | Users may display acidosis, tachycardia, hypertension and increased creatine kinase | Hill et al., 2018 |

CNS: Central nervous system; i.p.: intraperitoneal; SCRAs: synthetic cannabinoid receptor agonists.

**Table 5 Overview of popular synthetic psychoactive drugs, their mechanisms of action and toxic effects**

| Class | Drugs and mechanisms of action | Toxic effects |
|---|---|---|
| Cannabinoids | CB1/CB2 cannabinoid receptor agonists – activation of cannabinoid receptors | Anxiety, chest pain, hallucinations, inability to feel pain, paranoid delusions, respiratory failure, severe agitation, severe psychosis, significant withdrawal syndrome, total memory loss |
| Depressants | Opioids, Benzodiazepines – agonists of k and m opioid receptors, antagonists of k and d opioid receptors, modulators of GABA-A receptors | Addiction, confusion, impaired cognition, overdose, respiratory depression, seizures after withdrawal |
| Hallucinogens | Psychedelics, Dissociatives – agonists of 5-HT2A serotonin receptors, NMDA glutamate receptor antagonists, blockers of serotonin transporter | Acute cerebellar toxicity, cardiovascular toxicity, delirium, hypertension, hyperthermia, near-death experience, psychosis, respiratory failure, tachycardia, urinary tract damage |
| Stimulants | Amphetamines, Cathinones, Piperazines – increase synaptic levels of dopamine, noradrenaline, serotonin | Disorientation, hallucinations, hyperreflexia, hypertension, hyperthermia, kidney and liver failure, mydriasis, reduced level of consciousness, seizures, severe psychosis and agitation, tachycardia, tremor |

GABA: γ-Aminobutyric acid; NMDA: N-methyl-D-aspartic acid receptor.

**Author contributions:** *All authors wrote the manuscript. NS approved the final manuscript.*
**Conflicts of interest:** *We declare no conflicts of interest.*
**Financial support:** *GC was supported by the PRIN 2015 (Pr. 2015R9ASHT) and PON AIM (PON RICERCA E INNOVAZIONE 2014-2020, - AZIONE I.2. D.D. N.407 DEL 27 FEBBRAIO 2018 - "ATTRACTION AND INTERNATIONAL MOBILITY"). MDL was supported by Autonomous Region of Sardinia (RAS-FSC 2018, Codice intervento: RC_CRP_034; CUP RASSR03071). NS was supported by Fondazione di Sardegna (Progetti Biennali UniCA, Annualità 2017).*

**Additional file:** *Abbreviations and chemical names of compounds not defined in the text.*

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