Clinical Pharmacology of the Synthetic Cathinone Mephedrone

Esther Papaseit, José Moltó, Robert Muga, Marta Torrens, Rafael de la Torre, and Magí Farré

Abstract 4-Methyl-*N*-methylcathinone (mephedrone) is a popular new psychoactive substance (NPS) that is structurally related to the parent compound cathinone, the β-keto analogue of amphetamine. Mephedrone appeared on the street drug market as a substitute for 3,4-methylenedioxy-*N*-methylamphetamine (MDMA, ecstasy) and was subsequently banned due to the potential health risks associated with its use. Nevertheless, mephedrone continues to be widely consumed among specific populations, with unique patterns of misuse. To date, most information about the biological effects of mephedrone comes from user experiences, epidemiological data, clinical cases, toxicological findings, and animal studies, whilst there are very few data regarding its human pharmacodynamics and pharmacokinetics. This chapter reviews the available published data on patterns of mephedrone use, its acute and

E. Papaseit, R. Muga, and M. Farré (✉)
Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain

Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallés, Spain
e-mail: mfarre.germanstrias@gencat.cat

J. Moltó
Hospital Universitari Germans Trias i Pujol (IGTP), Badalona, Spain

Fundació Lluita contra la Sida, Badalona, Spain

M. Torrens
IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

Institut de Neuropsiquiatria i Adiccions, Barcelona, Spain

Universitat Autònoma de Barcelona (UAB), Cerdanyola del Vallés, Spain

R. de la Torre
IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain

Universitat Pompeu Fabra (UPF), Barcelona, Spain

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chronic effects, and its pharmacokinetic properties. More human research is needed to elucidate the safety, toxicity, and addiction potential of mephedrone and related NPS.

Keywords 3,4-Methylenedioxy-*N*-methylamphetamine (MDMA ecstasy) • 4-Methyl-*N*-methylcathinone (4-MMC mephedrone) • New psychoactive substance (NSP) • Synthetic cathinones

Contents

1 Synthetic Cathinones and Mephedrone

Synthetic cathinones are man-made derivatives of the parent compound cathinone, a naturally occurring psychostimulant found in the khat plant, *Catha edulis*. Cathinones are phenethylamine derivatives, structurally and pharmacologically similar to amphetamine, 3,4-methylenedioxy-*N*-methylamphetamine (MDMA, ecstasy), and other related substances [1]. All cathinones possess a β-keto substituent in their chemical structure, which defines the properties of this class of compounds [2]. The most relevant compounds of the group are *N*-methylcathinone (ephedrone), 4-methyl-*N*-methylcathinone (mephedrone, 4-MMC) – considered to be the prototypical ring-substituted synthetic cathinone derivative, 3,4-methylenedioxypyrovalerone (MDPV, bath salts), and α-pyrrolidinovalerophenone (α-PVP, flakka) [3]. Synthetic cathinones represent the second largest group of new psychoactive substances (NPS) in the street drug market [4–6].

Mephedrone, initially described in 1929 by Saem de Burnaga, remained in obscurity for decades. In the early 2000s, however, clandestine chemists began altering the chemical structure of the cathinone template to synthesize unscheduled compounds [7], and mephedrone was rediscovered and first reported online in 2003. In subsequent years, the popularity of mephedrone increased due to a number of factors including competitive pricing, widespread online availability, and perceived low potential for harm, together with the shortage of MDMA [8, 9]. As a consequence, mephedrone rapidly became a replacement for MDMA and was marketed as a 'legal high' [10]. In this scenario, mephedrone was sold openly on the grey market (online vendors from surface and deep websites) and in head shops as a number of authentic commercial products. It was typically marketed and sold as 'bath salts', 'incense', and 'plant food/fertilizer', and advertised as 'not for human consumption' to circumvent potential legislative control [8, 11–13].

In 2008, mephedrone was first identified on internet web sites and in products confiscated by law enforcement [14]; soon after, the misuse of mephedrone became

a particularly widespread and problematic concern in Australia, the United States (USA), and several European countries. For example, during 2009–2010 in the United Kingdom (UK), the distribution and consumption of mephedrone experienced a rapid increase which exceeded even that of ecstasy [3, 15, 16]. The higher prevalence of use was associated with reports of numerous hospital admissions and related overdose deaths. As a consequence of media attention and an official risk assessment, mephedrone was made illegal in the UK and classified as a Class B substance under the Misuse of Drugs Act on April 16, 2010. Subsequently, other European countries and the USA also adopted control measures [5, 17], and it was banned in 2010 and 2011, respectively.

2 Patterns of Use

In 2009–2010, a non-representative internet survey investigating mephedrone use among readers of *MixMag*, a UK clubbers' magazine, estimated a 42% life-time use and a 34% past-month use (2,295 respondents) [18]. One year later, life-time and past-month use of mephedrone increased to 61% and 51%, respectively (2,560 respondents) [16]. Immediately after mephedrone was banned, estimated overall rates of use remained low but stable, ranging from 0 to 6.3% life-time prevalence depending on age and country (Table 1). Nevertheless, mephedrone consumption among certain subgroups including drug users, club scene participants, readers of music and clubbing magazines, and the gay community continued to be considerable and much greater in comparison to the general population. In 2011–2012, past-year use of mephedrone was 19.5% among the UK *MixMag* survey respondents, and 30% in a subset of regular clubbers [19]. Mephedrone was the 11th most prevalent drug amongst clubbers, in terms of life-time use, when it was legal (42%), moving up to 4th place (61%) after being banned. In spite of the legislative ban on mephedrone, 42% of the respondents to an online survey of mephedrone users reported still trying to obtain it, and 53% said that the ban had not affected availability in their area [20]. Immediately after its prohibition in the UK, mephedrone had become the most popular drug in London among men who have sex with men, with over half the clubbers having tried it [12].

To date, the latest official epidemiological data indicate that mephedrone continues to be one of the most relevant NPS used in recreational nightlife settings according to indirect estimations. It is remarkable that mephedrone is currently involved in 50% of all hospital emergency presentations related to NPS misuse in Europe [5, 21], particularly in England where the number of individuals requiring treatment for mephedrone has more than doubled from 953 in 2010–2011 to 2,024 in 2014–2015 [22]. With respect to fatalities, in 2015 the number of cases in which mephedrone was implicated ($n = 34$, 1.5%) was comparable to that of MDMA ($n = 28$, 1.2%). According to these recent data, all mephedrone-associated deaths in 2015 were in men, 68% of whom were men who had sex with other men [23].

Table 1 National estimates of mephedrone use in the general population in European countries from 2010 to 2015

Year	Country	Prevalence (%) Age of population	Life-time Total	Previous year Total	Previous month Total	Source
2010	Slovakia	15–64	0.0	0.10	0.0	Annual report questionnaire
		15–19	1.7	n/a	n/a	2011 National Report to EMCDDA
2010	Spain	14–18	0.4	0.3	0.2	ESTUDES 2010
2010/2011	Ireland	15–64 15–34	2 4.3	1.1 2.2	0.1 0.1	Drug Prevalence Survey 2010/2011: Regional Drug Task Force and Health and Social Care Trust
2010/2011	United Kingdom	16–59	n/a	1.3	n/a	2010/2011 Crime Survey for England and Wales
		16–24	n/a	4.4	n/a	
	Malta	15–16	3.5	5.0	2.0	Annual report questionnaire
2011	Spain	15–64	0.1	0.0	0.0	EDADES 2011
		15–24	0.3	0.2	0.0	
	Hungary	16	6	n/a	n/a	Annual report questionnaire
2011/2012	United Kingdom	16–59	n/a	1.0	n/a	2011/2012 Crime Survey for England and Wales
		16–24	n/a	3.3	n/a	
2012	Spain	n/a	0.5	0.3	0.2	ESTUDES 2012
2012	Croatia	n/a	0.3	1.5	n/a	2012 National Report to EMCDDA
2012/2013	United Kingdom	16–59	1.9	0.5	n/a	2012/2013 Crime Survey for England and Wales
		16–24	4.5	1.6	n/a	
2013	Australia	≥14	n/a	0.4	n/a	National Drug Strategy Household Survey 2013
2013	Spain	15–64	0.1	0.6	0.0	EDADES 2013
		15–24	0.1	0.0	0.0	
2013/2014	United Kingdom	16–59	2.3	0.6	n/a	2013/2014 Crime Survey for England and Wales
		16–24	6.3	1.9	n/a	
2014	Spain	14–18	0.5	n/a	n/a	ESTUDES 2014
2014/2015	United Kingdom	16–59 16–24	2.2 5.3	0.5 1.9	0.2 0.5	2014/2015 Crime Survey for England and Wales

n/a not available

Furthermore, from the total amount of mephedrone seized in the European Union, almost all of it was in the UK in accordance with historically high estimates of its use in that country [5, 24].

Over the past few years, forensic evidence from confiscated drug products shows that mephedrone is typically available as a fine white, off-white or yellowish powder, or as tablets and capsules with a very high purity (around 99%). The powder can be directly taken by the intra-nasal route, or it can be easily dissolved in

water for oral/rectal use and intravenous/intramuscular injection. Although mephedrone can be administered by any of these routes, it is predominantly consumed intra-nasally, orally, and by intravenous injection [12, 25]. Nasal insufflation ('snorting') is a common route of administration, but unwanted effects including nasal burning, clogging of nasal passages, nasal dripping, and nasal bleeding have led some users to switch to oral ingestion [26]. By the oral route, mephedrone is typically swallowed by 'dabbing' with a moistened finger or 'bombing' wrapped in thin cigarette paper, or ingested directly as tablets and capsules. The combination of both routes, nasal and oral, has been frequently reported as an alternative to avoid undesirable local reactions whilst maintaining sustained psychoactive effects [27, 28].

Mephedrone injection has become a common pattern of use among high-risk drug users, mainly experienced intravenous drug consumers, and more recently, among some sub-groups of men who have sex with men [4, 5, 29]. A new trend, known as 'slamming', consists of the intravenous injection of a combination of mephedrone with methamphetamine, gamma-hydroxybutyric acid (GHB), cocaine or sildenafil during the so-called chemsex parties which can last for many hours. The drug cocktail is injected as a means to sustain and enhance sexual experiences [30–32]. Consequently, intravenous mephedrone use in conjunction with unprotected sexual activity is associated with a highly elevated risk of blood-borne and sexually transmitted diseases, in addition to adverse effects of the drug itself [4, 33]. Anecdotally, other routes of administration such as intrapulmonary (smoking), rectal ('booty bumping' or 'plugging'), subcutaneous, and intramuscular have also been described [14, 34–36].

Based on recreational user reports, mephedrone is initially consumed in single doses although repeated doses (re-dosing or 'bingeing'), in a similar manner to MDMA, is common practice in order to maintain pleasurable effects [37]. A typical drug use session lasts for approximately 8–10 h during which 5–6 mephedrone doses are taken, equivalent to a total median dose of 1–1.9 g [18, 36, 37]. Mephedrone oral dosage ranges from 15 to 300 mg, whereas nasal insufflation dosage is somewhat lower and ranges from 5 to 200 mg. Intravenous/intramuscular injection has been reported at approximately half or one-third of oral dosage, whilst 100 mg is described as a usual rectal dose [26, 38]. The initial impact is felt by recreational users approximately 30 min after oral ingestion, with effects lasting for 2–5 h [39]; in contrast, intravenous and rectal administration produce earlier onset of action and shorter duration [40]. Like other classical drugs of abuse, intravenous injection produces the most intense acute pleasurable effects, which are characterized by an initial rush of approximately 5 min followed by euphoric effects which can last for 60 min [9].

3 Pharmacodynamics of Mephedrone in Human Subjects

Mephedrone, like other amphetamines and MDMA, has a chiral centre in its structure, so exists as two enantiomers, *R*-mephedrone and *S*-mephedrone. Importantly, racemic mephedrone is the most common form of the substance available in the street drug market [41]. The molecular mechanism of action for mephedrone is most comparable to MDMA. Like MDMA, mephedrone is a non-selective releaser and reuptake inhibitor at monoamine transporters in the brain and periphery [42–45]. Another chapter of this volume is focused on the mechanism of mephedrone and other synthetic cathinones at human monoamine transporters (see [46]).

Preclinical studies performed in rodents and invertebrate models have evaluated acute mephedrone effects [39, 47]. In rats, mephedrone induces locomotor hyperactivity, increases in blood pressure and heart rate, and changes in temperature [48–52]. There is a paucity of data on the pharmacodynamics of mephedrone after administration to humans in laboratory conditions, with the exception of a recently published study from our group [53]. Most information regarding psychological and subjective effects related to mephedrone is based on user reports posted on internet web sites and blogs, surveys and questionnaires, whilst data concerning acute clinical toxicity has been provided from emergency department cases and toxicological consultations [37, 54, 55].

Our group had the opportunity to evaluate the pharmacodynamics effects of mephedrone for the first time in humans in a randomized, double-blind, crossover, and placebo-controlled trial [53], where a single oral dose of 200 mg mephedrone was compared to 100 mg MDMA and placebo. The mephedrone dose was selected after a series of pilot studies, which tested doses ranging from 50 to 200 mg [56]. The administration of mephedrone by the oral route at a dose of 200 mg produced significant increases in arterial blood pressure and heart rate, a modest increase in pupil diameter, and slight changes in oral temperature. These effects were similar in intensity to those induced by 100 mg MDMA, except for mydriasis that was lower with mephedrone. Mephedrone induced subjective feelings of euphoria, wellbeing, pleasure, stimulant-like effects and mild changes in perception, but not hallucinations or psychotic symptoms, these effects were similar in magnitude to those induced by MDMA. Both substances were well tolerated and no serious adverse events were presented [53]. Under laboratory conditions, physiological and subjective effects produced by 200 mg of oral mephedrone started at 30–45 min and lasted 2–3 h, in the case of 100 mg of MDMA the effects started at 45 min–1 h and lasted 3–5 h. As a summary, the pharmacological effects of mephedrone were similar to MDMA but with a more rapid onset and a shorter duration of effects, probably related to its brief half-life (see Sect. 4). Mephedrone impaired short-term memory in a similar manner to MDMA, while it improved critical tracking tasks but did not change reaction times or divided attention tasks in laboratory tests assessing driving-related skills [57].

According to consumers' experiences and preferences, mephedrone effects are characterized by sympathomimetic, psychostimulant, and empathogen–entactogen reactions that resemble MDMA, amphetamines, and cocaine [14, 20, 36, 58, 59]. In spite of the differences in doses and routes of administration employed, recreational mephedrone consumers (according to surveys, questionnaires, interviews, forums, etc.) consistently describe pleasurable effects such as euphoria, increased energy, mood enhancement, talkativeness, increase music sensitivity, empathy, sociability, sensory enhancement, moderate sexual arousal, and perceptual distortions ([8, 11, 12, 14, 60, 61]). In contrast, the undesirable effects include jaw clenching, bruxism, body sweats, palpitations, anxiety, tremor in extremities, blurred vision, shortness of breath, headache, cold or numb extremities, nausea and vomiting, agitation, anxiety, aggressiveness, paranoia, and panic [37, 59, 60], most of which are slight or moderate and do not require medical assistance. Post-drug recovery effects include craving, decreased appetite, lack of motivation, paranoia, insomnia, and irritability, all of which ameliorate after a few days ('feeling normal' after 4 ± 2 days) [37, 60]. Such symptoms concur with those self-reported in counselling services and emergency department admissions.

Acute toxic effects induced by mephedrone include the enhancement of cardiovascular response and neuropsychiatric effects and, in some cases, life-threatening reactions requiring medical assistance/hospitalization. In this respect, multiple cases have been reported of hypertension, cardiac arrhythmia, chest pain, paranoia, psychosis, hallucinations, agitation, aggressive behaviour, and suicidal ideation attributed to mephedrone use ([62–70]; Sivagnanam et al. 2013), although only a few cases have had the presence of mephedrone confirmed by forensic analysis (Table 2).

Upon administration of mephedrone in controlled clinical settings or self-administration in recreational settings, mephedrone effects are characterized by a rapid onset and a short-lasting duration. The pharmacodynamic response to mephedrone reported after experimental administration in humans could partially justify the pattern of use among mephedrone consumers in real-life conditions [60].

Regarding the possible long-term toxicity of mephedrone, the fact that the drug possesses structural and pharmacological similarities to MDMA, amphetamines, and cathinone suggests the likelihood that repeated and/or prolonged use produces similar consequences on neurochemical and neuropsychological function. From the limited results to date, it should be pointed out that repeated mephedrone administration in experimental animals has not shown evidence of neurotoxicity to monoaminergic systems in the brain [42, 88–91]. It should be kept in mind that further research with mephedrone in humans is required to first establish safety aspects, and the potential for long-term toxicity remains an important research question.

Table 2 Mephedrone concentrations in blood from human subjects based on findings from human performance, toxicological assessments, and postmortem cases

Subjects	Concentration of mephedrone	Reference
$N = 1$	0.5 mg/L, 198 mg/L (urine)	[71]
$N = 1$[a]	0.15 mg/L (serum)	[68]
$N = 1$ (Case 2)	3.3 mg/L, 4.2 ng/mg, and 4.7 ng/mg (hair)	[72]
$N = 1$ (Case 1)	22 mg/L	
$N = 1$	13.2 μg/g (antemortem), 8.4 μg/g (postmortem)	[73]
$N = 10$	26.8 ng/mg (0.2–313.2) (hair)	[74]
$N = 1$	193 mg/L	[75]
$N = 1$ (Case 1)	0.98 mg/L	[64]
$N = 1$ (Case 2)	2.24 mg/L	
$N = 1$ (Case 3)	0.13 mg/L	
$N = 1$ (Case 4)	0.23 mg/L	
$N = 1$ (Case 1)	51 μg/kg, 560 μg/kg (urine)	[76]
$N = 1$ (Case 2)	28 μg/kg	
$N = 1$ (Case 3)	29 μg/kg	
$N = 1$ (Case 1)	1 μg/kg	
$N = 1$	0.5 mg/L, 14.8 mg/L (urine), 38 mg/L (gastric), 1.9 mg/L (bile)	[77]
$N = 36$[b]	1.586 mg/L (<0.01–22 mg/L)	[78]
$N = 1$	21.11 pg/mg	[79]
$N = 32$	0.21 mg/L (0.01–0.74)	[80]
$N = 9$	0.27 mg/L (0.08–0.66)	
Case 2	2.1 mg/L	
Case 6	1.94 mg/L	
$N = 1$	5,500 and 7,100 ng/mL (vitreous humor)	[81]
$N = 6$	161 ng/mL (39–370 ng/mL)	[82]
$N = 1$	1.33 mg/L, 144 mg/L (urine), 4.52 mg/L (gastric), 1.29 mg/L (bile), 0.89 mg/L (brain), 0.25 ng/mg (hair)	[83]
$N = 1$ (case 2)	412 ng/mL	[84]
$N = 2$	50–59 pg/mg (hair)	[85]
$N = 5$[c]	1,774 ng/mL (13–5,500)	[86]

(continued)

Table 2 (continued)

Subjects	Concentration of mephedrone	Reference
$N = 1$	2,600 ng/mL	
$N = 1$	692 ng/mL	
$N = 1$	52 ng/mL	
$N = 1$	13 ng/mL	
$N = 4$	1.7 mg/L (0.19–3.30)	[87]
$N = 8$	1.34 mg/L (0.07–2.24)	

[a]4 g (200 mg by oral and 3.8 g by intramuscular injection)
[b]2009–2011
[c]2012–2014

4 Pharmacokinetics of Mephedrone in Humans

Most of the information concerning the pharmacokinetics of mephedrone in humans has arisen from toxicological cases, been extrapolated from preclinical pharmacokinetic and toxicokinetic data, or come from in vitro and in vivo metabolism findings [92]. There are very few data available related to human mephedrone pharmacokinetics under controlled conditions. It is noteworthy that there is no widely available commercial test to rapidly determine the presence of mephedrone or other cathinones in urine and blood. However, there are sophisticated analytical methods, such as gas/liquid chromatography coupled to mass spectrometry, for the determination of mephedrone concentrations in human tissue specimens for toxicological services, drugged driving cases in police departments, and clinical case reports [93]. Among the suspected cases of mephedrone exposure (case reports, driving under the influence of drugs, and fatalities) the dose, purity, route of administration, pattern of use, and concentrations leading to intoxications or fatal clinical consequences are usually unknown (Table 2).

There are some exceptions, for example, in reports of fatalities directly attributed to mephedrone toxicity, and impaired driving cases with high mephedrone concentrations [80, 87]. These mephedrone-associated events occurred mainly in recreational drug users who had used mephedrone in combination with alcohol or other recreational drugs (cocaine, amphetamine, or MDMA) and among intravenous drug users combining mephedrone with heroin. Lately, confirmed mephedrone fatalities have been detected in combination with other drugs among men who have sex with men due to the widespread chemsex phenomenon. The collective evidence indicates that mephedrone is only directly implicated as a principal cause in a limited number of deaths, though it undoubtedly plays a role in fatalities secondary to poly-drug exposures.

Since saliva, sweat, and hair samples can be more easily obtained as alternatives to blood or urine, reliable analytical methods have been developed in these matrices to detect a number of drugs such as MDMA, amphetamines, and certain NPS. Mephedrone concentrations from recreational users have been determined in hair, whilst published analysis methods for its detection in saliva have not yet been

applied to human specimens [94–97]. Mephedrone is a weak base with a relatively low molecular weight, which results in easy diffusion across cell membranes before incorporation into hair. In fact, after repeated consumption in a similar manner to amphetamines, mephedrone concentrations in hair have been detected in the range of nanogram per milligram [79, 85], in agreement with the amounts of the drug detected in other biological matrixes from intoxications and fatalities [72, 74, 83] (Table 2).

Regarding experimental studies in humans, we recently carried out the first controlled clinical trial to evaluate mephedrone pharmacokinetic parameters in humans [53]. The administration of an oral dose of 200 mg in 12 healthy male recreational drug users produced a mean maximal plasma concentration (C_{max}) value of 134.6 ng/mL (range 51.7–218.3 ng/mL). Concentrations decreased to one-half at 2 h and were undetectable at 24 h post-administration (Fig. 1). In spite of high inter-individual variability observed after oral administration, peak plasma concentration (T_{max}) was attained at 1.25 h, earlier than most psychostimulant drugs. Mean elimination half-life ($T_{1/2}$) was 2.15 h, significantly faster than MDMA, amphetamine, and methamphetamine ($T_{1/2}$ of 8, 10–12, and 15 h, respectively), and more similar to cathinone ($T_{1/2}$ of 4 h). The clinical pharmacokinetic data obtained after controlled mephedrone administration are congruent with the rapid onset and short duration of effects described after oral mephedrone use in recreational settings.

In same clinical trial mentioned above, urine samples were collected over a 4-h period after mephedrone administration to characterize the human metabolism of mephedrone [98]. These new in vivo data provide an important comparison to previous analyses performed in post-mortem samples [76] and in vitro models [99]. The findings confirmed the involvement of three main hepatic pathways of mephedrone metabolism: (1) *N*-demethylation to form 4-methylcathinone (nor-mephedrone), (2) phenyl ring hydroxylation to form 4-hydroxytolylmephedrone (4-OH-mephedrone), and (3) β-keto

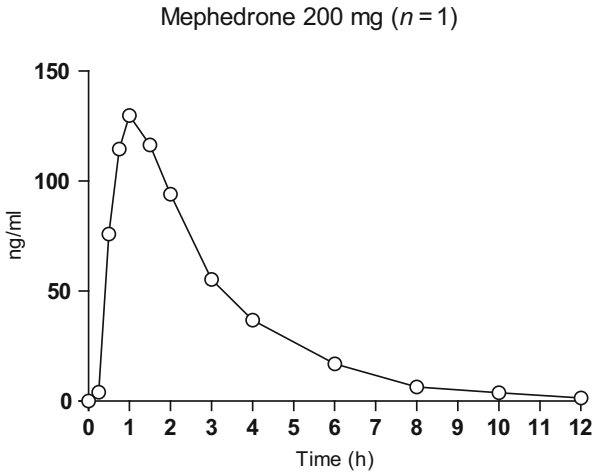

Fig. 1 Time course of plasma mephedrone concentrations after controlled administration of an oral dose of 200 mg in one study participant [53]

reduction to form dihydro-mephedrone. All of the identified phase I metabolites are reported to act as non-selective substrates at plasma membrane transporters for dopamine, norepinephrine, and serotonin, similar to mephedrone. Importantly, dihydro-mephedrone is a much weaker transporter substrate in comparison to nor-mephedrone and 4-OH-mephedrone [100]. In vitro studies suggest that mephedrone metabolic disposition (phase I) is regulated mainly by cytochrome P450 isoenzyme 2D6 (CYP2D6) [76]. For instance, human polymorphisms in CYP2D6, as well as co-administration of mephedrone with specific drugs also metabolized through CYP2D6 (or inhibitors), could increase potential risk of toxicity. At present, no studies have examined the interaction of mephedrone with other susceptible drugs commonly used among recreational drug users [e.g. MDMA, antiretroviral drugs, selective serotonin reuptake inhibitors (SSRIs)]. In contrast to the various metabolites reported in animals [101, 102], a number of unique phase I and phase II metabolites are found in humans including *N*-desmethyl-mephedrone-3 carboxylic acid, hydroxylmephedrone-3-*O*-glucoronide, *N*-succinyl nor-mephedrone, and hydroxyl nor-mephedrone-3-*O*-glucoronide (Fig. 2).

In forensic cases, nor-mephedrone and dihydro-mephedrone have been detected in blood and urine, whilst 4-OH-mephedrone, the most abundant mephedrone metabolite, has only been reported in urine. Taken together with in vitro data, it has been suggested that nor-mephedrone possesses lipophilic properties that may allow it to penetrate through the blood–brain barrier and act on the central nervous system, similar to the parent compound. In fact, in vivo studies in rats have confirmed that nor-mephedrone is the only bioactive mephedrone metabolite to exert effects on extracellular dopamine and locomotion [100]. Currently, the potential role of nor-mephedrone and other metabolites on human mephedrone effects is unknown and, consequently, more research on this topic is warranted.

Overall, the initial results regarding the human pharmacology of mephedrone under controlled administration confirm previous extrapolation from non-experimental human data and preclinical studies. However, it is still unclear whether the pharmacokinetics and/or metabolism of mephedrone, including its active metabolites, might have implications in the particular susceptibility of some subjects to develop acute mephedrone intoxication.

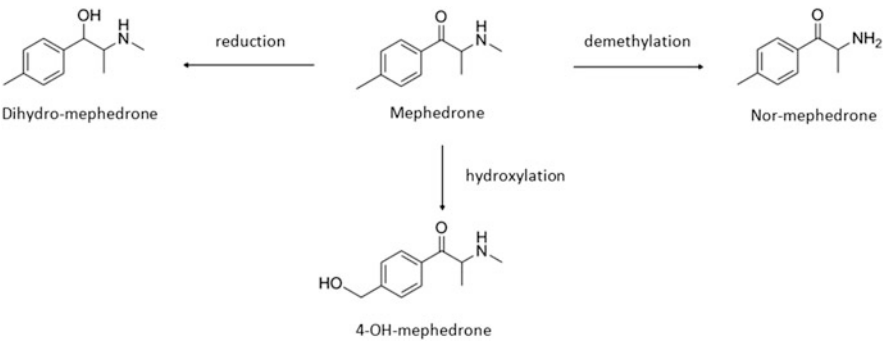

Fig. 2 Proposed pathways of mephedrone metabolism in humans

5 Abuse Liability

Predictions about the human abuse liability of mephedrone are based on user experiences, clinical reports, and extrapolation of preclinical studies, and have been recently confirmed by the first clinical trial described above [53]. To date, the potential abuse liability of mephedrone has been assessed in experimental models through a number of approaches and direct comparison with other well-known drugs of abuse (MDMA, amphetamine, cocaine) and/or NPS such as 3-methyl-*N*-methylcathinone (3-MMC), MDPV, methylone, naphyrone, flephedrone, and butylone [51, 103–109]. Systemic administration of mephedrone in laboratory animals produces elevations in the extracellular concentrations of dopamine, serotonin, and norepinephrine leading to self-administration, place preference, and locomotor hyperactivity [39, 43, 52, 110, 111]. Furthermore, mephedrone shares with other stimulant drugs of abuse the ability to activate the mesolimbic dopamine reward circuit as a main mechanism involved in the positive-reinforcing effects produced (euphoria, pleasure, well-being, happiness). At the same time, feelings of euphoria and stimulation can lead to high abuse liability similar in magnitude to that observed after controlled administration of MDMA, one of the drugs preferred by users in recreational settings.

In humans, data about the pharmacology of mephedrone are scant and findings are variable depending on the route of administration used. Evidence from questionnaires, online-surveys and even some case reports related to long-term mephedrone consumption have indicated addiction potential and dependency symptoms, cravings, and withdrawal syndromes [34, 37, 60, 112–115]. Some epidemiological data highlight the prevalence of self-reported tolerance, impaired control, continued mephedrone consumption despite physical and psychological problems, strong urges, and bingeing [36, 37, 60, 112], whilst tiredness, insomnia, nasal congestion, and impaired concentration are described as the most common withdrawal-related effects. Intranasal users considered mephedrone to be more addictive than cocaine [60]. The transition from nasal to injection route, and intravenous injection use, is associated with a compulsive consumption pattern. Hence, mephedrone addicts commonly report re-injecting of the drug with excessive binge use over long periods of time [9, 114, 116]. The potential of mephedrone for cravings, compulsive re-dosing, and uncontrollable binge use have been attributed to its self-reported high and short duration effects [8, 117]. For intranasal and/or intravenous administration, no human clinical trials have been conducted. As previously explained in other sections, relative mephedrone abuse liability has been assessed in a double blind, double dummy, placebo, and positive comparator controlled and crossover clinical trial [53]. Mephedrone produced similar effects to MDMA on standardized questionnaires developed to measure abuse potential in humans ([118]; Visual Analog Scale, 49-item Addiction Research Center Inventory-ARCI, and Evaluation of Subjective Effects of Substances with Abuse Potential questionnaire-VESSPA-SEE), but with a faster onset of the desired high and shorter duration of action [53]. Even though preclinical and human clinical findings are limited, overall data suggest that the shorter half-life and duration of

effects induced by mephedrone may lead to more compulsive drug-taking behaviour in order to maintain euphoria.

6 Summary

To conclude, mephedrone is perhaps the most representative synthetic cathinone in the recent NPS phenomenon. The misuse of mephedrone in recreational settings has been related to serious medical problems which have negative impacts on global public health, especially after binge use, intravenous administration or in the context of chemsex scenarios. The known effects of mephedrone on dopamine and serotonin systems in the brain confer psychostimulant-like effects that resemble those of other amphetamine-compounds and MDMA. Further human clinical pharmacology research focused on pharmacodynamics and pharmacokinetics is essential to better understand mephedrone effects, as well as the potentially life-threatening medical complications associated with its consumption, in order to provide more effective interventions.

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References

1. Valente MJ, Guedes de Pinho P, de Lourdes Bastos M, et al. (2014) Khat and synthetic cathinones: a review. Arch Toxicol 88:15–45
2. Hill SL, Thomas SH (2011) Clinical toxicology of newer recreational drugs. Clin Toxicol (Phila) 49:705–719
3. Karila L, Megarbane B, Cottencin O, et al. (2015) Synthetic cathinones: a new public health problem. Curr Neuropharmacol 13:12–20
4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2014) European drug report 2014: trends and developments. http://www.emcdda.europa.eu/system/files/publications/963/TDAT14001ENN.pdf
5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2016) 2016 EU drug markets report: strategic overview. http://www.emcdda.europa.eu/publications/eu-drug-markets/2016/strategic-overview
6. Papaseit E, Farré M, Schifano F, et al. (2014) Emerging drugs in Europe. Curr Opin Psychiatry 27:243–250
7. United Nations Office on Drugs and Crime (UNODC) (2016) Laboratory and scientific section portals. Synthetic cathinones. https://www.unodc.org/LSS/SubstanceGroup/Details/67b1ba69-1253-4ae9-bd93-fed1ae8e6802
8. Brunt TM, Poortman A, Niesink RJ, et al. (2011) Instability of the ecstasy market and a new kid on the block: mephedrone. J Psychopharmacol 25:1543–1547

9. Van Hout MC, Bingham T (2012) "A costly turn on": patterns of use and perceived consequences of mephedrone based head shop products amongst Irish injectors. Int J Drug Policy 23:188–197
10. Prosser JM, Nelson LS (2012) The toxicology of bath salts: a review of synthetic cathinones. J Med Toxicol 8:33–42
11. Deluca P, Schifano F, Davey Z, et al. (2009) Mephedrone report. Institute of Psychiatry, King's College London, London http://www.psychonautproject.eu
12. Measham F, Moore K, Newcombe Z, et al. (2010) Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. Drugs Alcohol Today 10:14–21
13. Winstock AR, Mitcheson L, Marsden J (2010) Mephedrone: still available and twice the price. Lancet 376(9752):1537
14. Schifano F, Albanese A, Fergus S, Psychonaut Web Mapping, ReDNet Research Groups, et al. (2011) Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology (Berl) 214:593–602
15. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2015) European drug report 2015. http://www.emcdda.europa.eu/attachements.cfm/att_239505_EN_TDAT15001ENN.pdf
16. Winstock AR (2011a) Drugs survey. MixMag 238:49–59
17. Advisory Council on the Misuse of Drugs (ACMD) (2015) ACMD report on definitions for the Psychoactive Substances Bill, 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/454039/Definitions_report_final_14_august.pgl
18. Dick D, Torrance C (2010) Drugs survey. MixMag 225:44–53
19. Winstock A (2012) Global drug survey. MixMag 251:68–73
20. Carhart-Harris RL, King LA, Nutt DJ (2011) A web-based survey on mephedrone. Drug Alcohol Depend 118:19–22
21. Wood DM, Heyerdahl F, Yates CB, et al. (2014) The European Drug Emergencies Network (Euro-DEN). Clin Toxicol (Phila) 52:239–241
22. Public Health England (2015) Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 1 April 2014 to 31 March 2015. Public Health England, London https://www.ndtms.net/Publications/downloads/Adult%20Substance%20Misuse/adult-statistics-from-the-national-drug-treatment-monitoring-system-2014-2015.pdf
23. Hockenhull J, Murphy KG, Paterson S (2016) Mephedrone use is increasing in London. Lancet 387:1719–1720
24. United Nations Office on Drugs and Crime (UNODC) (2015) World drug report 2015. https://www.unodc.org/documents/wdr2015/World_Drug_Report_2015.pdf
25. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2011) Report on the risk assessment of mephedrone in the framework of the council decision on new psychoactive substances. http://www.emcdda.europa.eu/system/files/publications/571/TDAK11001ENC_WEB-OPTIMISED_FILE_280269.pdf
26. Van Hout MC (2014) An Internet study of user's experiences of the synthetic cathinone 4-methylethcathinone (4-MEC). J Psychoactive Drugs 46:273–286
27. Psychonaut Web Mapping Research Group (2009) Mephedrone report. Institute of Psychiatry, King's College London, London http://194.83.136.209/documents/reports/
28. The Vaults of Erowid (2016) https://www.erowid.org/chemicals/4_methylmethcathinone/4_methylmethcathinone.shtml
29. Péterfi A, Tarján A, Horváth GC, et al. (2014) Changes in patterns of injecting drug use in Hungary: a shift to synthetic cathinones. Drug Test Anal 6:825–831
30. Bourne A, Reid D, Hickson F, Torres-Rueda S (2015) "Chemsex" and harm reduction need among gay men in South London. Int J Drug Policy 26:1171–1176
31. Daskalopoulou M, Rodger A, Phillips AN, et al. (2014) Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. Lancet HIV 1:e22–e31

32. McCall H, Adams N, Mason D, et al. (2015) What is chemsex and why does it matter? BMJ 351:h5790
33. Hope VD, Cullen KJ, Smith J, et al. (2016) Is the recent emergence of mephedrone injecting in the United Kingdom associated with elevated risk behaviours and blood borne virus infection? Euro Surveill 21(19). doi:10.2807/1560-7917.ES.2016.21.19.30225
34. Dargan PI, Sedefov R, Gallegos A, Wood DM (2011) The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone). Drug Test Anal 3:454–463
35. Russo R, Marks N, Morris K, et al. (2012) Life-threatening necrotizing fasciitis due to 'bath salts' injection. Orthopedics 35:e124–e127
36. Winstock AR, Mitcheson LR, Deluca P, et al. (2011b) Mephedrone, new kid for the chop? Addiction 106:154–161
37. Jones L, Reed P, Parrott A (2016) Mephedrone and 3,4-methylenedioxy-methamphetamine: comparative psychobiological effects as reported by recreational polydrug users. J Psychopharmacol (Epub a head)
38. World Health Organization (WHO) (2014) Mephedrone. Critical Review Report. 36th ECDD (2014) Agenda ítem 4.12. http://www.who.int/medicines/areas/quality_safety/4_12_review.pdf
39. Green AR, King MV, Shortall SE, et al. (2014) The preclinical pharmacology of mephedrone; not just MDMA by another name. Br J Pharmacol 171:2251–2268
40. Karch SB (2015) Cathinone neurotoxicity ("The "3Ms"). Curr Neuropharmacol 13:21–25
41. Gibbons S, Zloh M (2010) An analysis of the 'legal high' mephedrone. Bioorg Med Chem Lett 20:4135–4139
42. Baumann MH, Ayestas Jr MA, Partilla JS, et al. (2012) The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. Neuropsychopharmacology 37:1192–1203
43. Baumann MH, Partilla JS, Lehner KR (2013) Psychoactive "bath salts": not so soothing. Eur J Pharmacol 698:1–5
44. Saha K, Partilla JS, Lehner KR, et al. (2015) 'Second-generation' mephedrone analogs, 4-MEC and 4-MePPP, differentially affect monoamine transporter function. Neuropsychopharmacology 40:1321–1331
45. Simmler LD, Buser TA, Donzelli M, et al. (2013) Pharmacological characterization of designer cathinones in vitro. Br J Pharmacol 168:458–470
46. Simmler LD, Liechti ME (2016) Interactions of cathinone NPS with human transporters and receptors in transfected cells. Curr Top Behav Neurosci (Epub ahead of print)
47. Zawilska JB (2014) Mephedrone and other cathinones. Curr Opin Psychiatry 27:256–262
48. Meng H, Cao J, Kang J, et al. (2012) Mephedrone, a new designer drug of abuse, produces acute hemodynamic effects in the rat. Toxicol Lett 208:62–68
49. Shortall SE, Macerola AE, Swaby RT, et al. (2013) Behavioural and neurochemical comparison of chronic intermittent cathinone, mephedrone and MDMA administration to the rat. Eur Neuropsychopharmacol 23:1085–1095
50. Shortall SE, Green AR, Swift KM, et al. (2013) Differential effects of cathinone compounds and MDMA on body temperature in the rat, and pharmacological characterization of mephedrone-induced hypothermia. Br J Pharmacol 168:966–977
51. Varner KJ, Daigle K, Weed PF, et al. (2013) Comparison of the behavioral and cardiovascular effects of mephedrone with other drugs of abuse in rats. Psychopharmacology (Berl) 225:675–685
52. Wright Jr MJ, Angrish D, Aarde SM, et al. (2012) Effect of ambient temperature on the thermoregulatory and locomotor stimulant effects of 4-methylmethcathinone in Wistar and Sprague-Dawley rats. PLoS One 7:e44652
53. Papaseit E, Pérez-Mañá C, Mateus JA, et al. (2016) Human pharmacology of mephedrone in comparison to MDMA. Neuropsychopharmacology 41:2704–2713

54. Karila L, Billieux J, Benyamina A, et al. (2016) The effects and risks associated to mephedrone and methylone in humans: a review of the preliminary evidences. Brain Res Bull 126:61–67
55. Wood DM, Hill SL, Thomas SH, Dargan PI (2014) Using poisons information service data to assess the acute harms associated with novel psychoactive substances. Drug Test Anal 6:850–860
56. Farré M, Papaseit E, Pérez-Mañá C, Yubero-Lahoz S, et al. (2014) Pharmacokinetics and pharmacodynamics of mephedrone in humans. Res Adv Psychiatry 1(Suppl 1):19
57. de Sousa Fernandes Perna EB, Papaseit E, Pérez-Maná C, et al. (2016) Neurocognitive performance following acute mephedrone administration, with and without alcohol. J Psychopharmacol (Epub ahead of print)
58. Kapitány-Fövény M, Kertész M, Winstock A, et al. (2013) Substitutional potential of mephedrone: an analysis of the subjective effects. Hum Psychopharmacol 28:308–316
59. Wood DM, Davies S, Greene SL, et al. (2010) Case series of individuals with analytically confirmed acute mephedrone toxicity. Clin Toxicol (Phila) 48:924–927
60. Winstock A, Mitcheson L, Ramsey J, et al. (2011c) Mephedrone: use, subjective effects and health risks. Addiction 106:1991–1996
61. Deluca P, Davey Z, Corazza O, et al. (2012) Identifying emerging trends in recreational drug use; outcomes from the Psychonaut Web Mapping project. Prog Neuropsychopharmacol Biol Psychiatry 39:221–226
62. Durham M (2011) Ivory wave: the next mephedrone? Emerg Med J 28:1059–1060
63. James D, Adams RD, Spears R, National Poisons Information Service, et al. (2011) Clinical characteristics of mephedrone toxicity reported to the U.K. National Poisons Information Service. Emerg Med J 28:686–689
64. Maskell PD, De Paoli G, Seneviratne C, et al. (2011) Mephedrone (4-methylmethcathinone)-related deaths. J Anal Toxicol 35:188 Poster from The International Association of Forensic Toxicology
65. Nicholson PJ, Quinn MJ, Dodd JD (2010) Headshop heartache: acute mephedrone 'meow' myocarditis. Heart 96:2051–2052
66. Regan L, Mitchelson M, Macdonald C (2011) Mephedrone toxicity in a Scottish emergency department. Emerg Med J 28:1055–1058
67. Schifano F, Corkery J, Ghodse AH (2012) Suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone, "meow meow") in the United Kingdom. J Clin Psychopharmacol 32:710–714
68. Wood DM, Davies S, Puchnarewicz M, et al. (2010) Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. J Med Toxicol 6:327–330
69. Barrio P, Gaskell M, Goti J, et al. (2016) Persistent psychotic symptoms after long-term heavy use of mephedrone: a two-case series. Adicciones 28:154–157
70. Sivagnanam K, Chaudari D, Lopez P, et al. (2013) "Bath salts" induced severe reversible cardiomyopathy. Am J Case Rep 14:288–291
71. Dickson AJ, Vorce SP, Levine B, et al. (2010) Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. J Anal Toxicol 34:162–168
72. Torrance H, Cooper G (2010) The detection of mephedrone (4-methylmethcathinone) in 4 fatalities in Scotland. Forensic Sci Int 202:e62–e63
73. Wikström M, Thelander G, Nyström I, et al. (2010) Two fatal intoxications with the new designer drug methedrone (4-methoxymethcathinone). J Anal Toxicol 34:594–598
74. Martin M, Muller JF, Turner K, et al. (2012) Evidence of mephedrone chronic abuse through hair analysis using GC/MS. Forensic Sci Int 218:44–48
75. Mazoyer C, Boucher A, Gaillard Y et al (2011) Case report of driving under the influence of drugs (DUID) with mephedrone in France. Poster from Society of Forensic Toxicologists (SOFT) and The International Association of Forensic Toxicologists (TIAFT)

76. Pedersen AJ, Reitzel LA, Johansen SS, et al. (2013) In vitro metabolism studies on mephedrone and analysis of forensic cases. Drug Test Anal 5:430–438
77. Aromatario M, Bottoni E, Santoni M, et al. (2012) New "lethal highs": a case of a deadly cocktail of GHB and Mephedrone. Forensic Sci Int 223:e38–e41
78. Corkery JM, Schifano F, Ghodse H (2012) Mephedrone-related fatalities in the United Kingdom: contextual, clinical and practical issues. In: Gallelli L (ed) Pharmacology. InTech, ISBN: 978-953-51-0222-9. http://www.intechopen.com/books/pharmacology/mephedrone-related-fatalities-in-the-united-kingdom-contextual-clinical-and-practical-issues
79. Shah SA, Deshmukh NI, Barker J, et al. (2012) Quantitative analysis of mephedrone using liquid chromatography tandem mass spectroscopy: application to human hair. J Pharm Biomed Anal 61:64–69
80. Cosbey SH, Peters KL, Quinn A, et al. (2013) Mephedrone (methylmethcathinone) in toxicology casework: a Northern Ireland perspective. J Anal Toxicol 37:74–82
81. Adamowicz P, Tokarczyk B, Stanaszek R, et al. (2013) Fatal mephedrone intoxication – a case report. J Anal Toxicol 37:37–42
82. Burch HJ, Clarke EJ, Hubbard AM, et al. (2013) Concentrations of drugs determined in blood samples collected from suspected drugged drivers in England and Wales. J Forensic Leg Med 20:278–289
83. Gerace E, Petrarulo M, Bison F, et al. (2014) Toxicological findings in a fatal multidrug intoxication involving mephedrone. Forensic Sci Int 243:68–73
84. Maas A, Wippich C, Madea B, et al. (2015) Driving under the influence of synthetic phenethylamines: a case series. Int J Leg Med 129:997–1003
85. Salomone A, Gazzilli G, Di Corcia D, et al. (2016) Determination of cathinones and other stimulant, psychedelic, and dissociative designer drugs in real hair samples. Anal Bioanal Chem 408:2035–2042
86. Adamowicz P, Gieroń J, Gil D, et al. (2016) The prevalence of new psychoactive substances in biological material – a three-year review of casework in Poland. Drug Test Anal 8:64–71
87. Loi B, Corkery JM, Claridge H, Goodair C, et al. (2015) Deaths of individuals aged 16-24 years in the UK after using mephedrone. Hum Psychopharmacol 30:225–232
88. Angoa-Pérez M, Kane MJ, Francescutti DM, et al. (2012) Mephedrone, an abused psychoactive component of 'bath salts' and methamphetamine congener, does not cause neurotoxicity to dopamine nerve endings of the striatum. J Neurochem 120:1097–1107
89. Angoa-Pérez M, Kane MJ, Briggs DI, et al. (2013) Mephedrone does not damage dopamine nerve endings of the striatum, but enhances the neurotoxicity of methamphetamine, amphetamine, and MDMA. J Neurochem 125:102–110
90. den Hollander B, Rozov S, Linden AM, et al. (2013) Long-term cognitive and neurochemical effects of "bath salt" designer drugs methylone and mephedrone. Pharmacol Biochem Behav 103:501–509
91. Shortall SE, Green AR, Fone KC, et al. (2016) Caffeine alters the behavioural and body temperature responses to mephedrone without causing long-term neurotoxicity in rats. J Psychopharmacol 30:698–706
92. Ellefsen KN, Concheiro M, Huestis MA (2016) Synthetic cathinone pharmacokinetics, analytical methods, and toxicological findings from human performance and postmortem cases. Drug Metab Rev 1:1–29
93. Busardò FP, Kyriakou C, Napoletano S, et al. (2015) Mephedrone related fatalities: a review. Eur Rev Med Pharmacol Sci 19:3777–3790
94. Baciu T, Borrull F, Calull M, et al. (2016) Enantioselective determination of cathinone derivatives in human hair by capillary electrophoresis combined in-line with solid-phase extraction. Electrophoresis 37:2352–2362
95. de Castro A, Lendoiro E, Fernández-Vega H, et al. (2014) Liquid chromatography tandem mass spectrometry determination of selected synthetic cathinones and two piperazines in oral fluid. Cross reactivity study with an on-site immunoassay device. J Chromatogr A 1374:93–101

96. Mercolini L, Protti M, Catapano MC, et al. (2016) LC-MS/MS and volumetric absorptive microsampling for quantitative bioanalysis of cathinone analogues in dried urine, plasma and oral fluid samples. J Pharm Biomed Anal 123:186–194
97. Strano-Rossi S, Anzillotti L, Castrignanò E, et al. (2012) Ultra high performance liquid chromatography-electrospray ionization-tandem mass spectrometry screening method for direct analysis of designer drugs, "spice" and stimulants in oral fluid. J Chromatogr A 1258:37–42
98. Pozo ÓJ, Ibáñez M, Sancho JV, et al. (2015) Mass spectrometric evaluation of mephedrone in vivo human metabolism: identification of phase I and phase II metabolites, including a novel succinyl conjugate. Drug Metab Dispos 43:248–257
99. Khreit OI, Grant MH, Zhang T, et al. (2013) Elucidation of the Phase I and Phase II metabolic pathways of (±)-4′-methylmethcathinone (4-MMC) and (±)-4′-(trifluoromethyl) methcathinone (4-TFMMC) in rat liver hepatocytes using LC-MS and LC-MS^2. J Pharm Biomed Anal 72:177–185
100. Mayer FP, Wimmer L, Dillon-Carter O, et al. (2016) Phase I metabolites of mephedrone display biological activity as substrates at monoamine transporters. Br J Pharmacol 173:2657–2668
101. Martínez-Clemente J, López-Arnau R, Carbó M, et al. (2013) Mephedrone pharmacokinetics after intravenous and oral administration in rats: relation to pharmacodynamics. Psychopharmacology (Berl) 229:295–306
102. Meyer MR, Wilhelm J, Peters FT, et al. (2010) Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography-mass spectrometry. Anal Bioanal Chem 397:1225–1233
103. Aarde SM, Angrish D, Barlow DJ, et al. (2013) Mephedrone (4-methylmethcathinone) supports intravenous self-administration in Sprague-Dawley and Wistar rats. Addict Biol 18:786–799
104. Creehan KM, Vandewater SA, Taffe MA (2015) Intravenous self-administration of mephedrone, methylone and MDMA in female rats. Neuropharmacology 92:90–97
105. Gatch MB, Taylor CM, Forster MJ (2013) Locomotor stimulant and discriminative stimulus effects of 'bath salt' cathinones. Behav Pharmacol 24:437–447
106. Hadlock GC, Webb KM, McFadden LM, et al. (2011) 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. J Pharmacol Exp Ther 339:530–536
107. Karlsson L, Andersson M, Kronstrand R, et al. (2014) Mephedrone, methylone and 3,4-methylenedioxypyrovalerone (MDPV) induce conditioned place preference in mice. Basic Clin Pharmacol Toxicol 115:411–416
108. Lisek R, Xu W, Yuvasheva E, Chiu YT, et al. (2012) Mephedrone ('bath salt') elicits conditioned place preference and dopamine-sensitive motor activation. Drug Alcohol Depend 126:257–262
109. Vandewater SA, Creehan KM, Taffe MA (2015) Intravenous self-administration of entactogen-class stimulants in male rats. Neuropharmacology 99:538–545
110. Motbey CP, Clemens KJ, Apetz N, et al. (2013) High levels of intravenous mephedrone (4-methylmethcathinone) self-administration in rats: neural consequences and comparison with methamphetamine. J Psychopharmacol 27:823–836
111. Shortall SE, Spicer CH, Ebling FJ, et al. (2015) Contribution of serotonin and dopamine to changes in core body temperature and locomotor activity in rats following repeated administration of mephedrone. Addict Biol 21:1127–1139
112. Dargan PI, Albert S, Wood DM (2010) Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. QJM 103:875–879
113. Bajaj N, Mullen D, Wylie S (2010) Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. BMJ Case Rep 2010. doi:10.1136/bcr.02.2010.2780

114. Dolengevich-Segal H, Rodríguez-Salgado B, Gómez-Arnau J, et al. (2016) Severe psychosis, drug dependence, and Hepatitis C related to slamming mephedrone. Case Rep Psychiatry 2016:8379562
115. Uosukainen H, Tacke U, Winstock AR (2015) Self-reported prevalence of dependence of MDMA compared to cocaine, mephedrone and ketamine among a sample of recreational poly-drug users. Int J Drug Policy 26:78–83
116. Kapitány-Fövény M, Mervó B, et al. (2015) Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone? Hum Psychopharmacol 30:233–243
117. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2010) 2010 Annual report on the state of the drugs problem in Europe. http://www.emcdda.europa.eu/system/files/publications/926/EMCDDA_AR2010_EN_242720.pdf
118. Food and Drug Administration (FDA) (2010) Draft guidance "assessment of abuse potential of drugs". http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf