Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: https://www.tandfonline.com/loi/ierj20

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To cite this article: Fabrizio Schifano, G. Duccio Papanti, Laura Orsolini & John M. Corkery (2016) Novel psychoactive substances: the pharmacology of stimulants and hallucinogens, Expert Review of Clinical Pharmacology, 9:7, 943-954, DOI: 10.1586/17512433.2016.1167597

To link to this article: https://doi.org/10.1586/17512433.2016.1167597

EXPERT REVIEW OF CLINICAL PHARMACOLOGY, 2016
VOL. 9, NO. 7, 943–954
http://dx.doi.org/10.1586/17512433.2016.1167597

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REVIEW

Novel psychoactive substances: the pharmacology of stimulants and hallucinogens

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ABSTRACT

There are increasing levels of concern relating to the rapidly evolving novel psychoactive substances/NPS and web markets' scenarios. The paper aims at providing an overview of the clinical pharmacological issues related to some of the most popular NPS categories, e.g. stimulants and hallucinogens. NPS intake is typically associated with the imbalance of a complex range of neurotransmitter pathways/receptors, namely: dopamine; cannabinoid/CB1; and 5-HT_{2A}. The intake is almost invariably undetectable with standard screening tests. Hence, it may frequently occur that the acute management of NPS misusers will need to focus on decreasing levels of both self/outward-directed aggression and agitation. Benzodiazepines may be considered as first line treatment. Alternatively, propofol and/or antipsychotics can be administered. Focus will be as well on treatment of possible rhabdomyolysis and hyperthermia. Indeed, future studies should inform better tailored management/treatment strategies.

ARTICLE HISTORY
Received 15 February 2016
Accepted 15 March 2016
Published online
1 April 2016

KEYWORDS
Novel psychoactive substances; synthetic cannabimimetics; synthetic cathinones; hallucinogenic drugs; phenethylamines; psychiatric disturbances; drug misuse

Introduction

Over the last decade, the drug scenario has shown significant levels of changes, with the emergence of a range of novel psychoactive substances (NPS). NPS are typically defined as new narcotic/psychotropic drugs which are not controlled by the United Nations' 1961 Narcotic Drugs/1971 Psychotropic Substances Conventions, but which may pose a public health threat [1]. However, 'novel' typically refers to molecules that have recently become a reason of current/potential public health concern. At times, although misleading, the terms 'legal highs' or 'research chemicals' have been used as well to describe such substances, with the web playing a major role in shaping this unregulated market [2]. Overall, there are increasing levels of concern about both the complex pharmacodynamics of these drugs and the appearance of acute/chronic medical and psychopathological manifestations associated with NPS intake [1]. A concurrent use of a range of different NPS, and/or medications, is frequently being reported and this may be a reason of further concern.

The present paper aims at providing an overview of the clinical pharmacological issues related to some of the most popular NPS categories, for example stimulants and hallucinogens (for a rapid overview, see Table 1).

Methods

We searched Medline/PubMed for studies using the terms 'new psychoactive substances,' 'NPS,' 'legal highs,' 'designer drugs,' 'research chemicals,' 'smart drugs,' 'emerging drugs of abuse,' 'emerging drugs of misuse,' 'stimulants,' 'hallucinogenic drugs,' 'psychedelics,' 'synthetic cannabimimetics (SC),' 'synthetic cannabinoids,' and 'spice.'

The search was filtered by 'English and human' and limited by publication dates to the last 5 years. In total, 4159 references were identified; of these, 363 were considered potentially relevant. Some further 35 references were retrieved from specific websites identified by typing the index substance keywords on Google, with selection and analysis of fora posts/threads; and from national/international agencies' reports. After a further thorough screening for eligibility, some 82 papers/documents had finally been considered here as suitable and consistent with the aims of the paper.

Stimulants: synthetic cathinones; 4,4′-dimethylaminorex (4-4′-DMAR); methylphenidate (MPH)-like NPS; amphetamine-type stimulants; aminoindanes; and cocaine analogs.

Synthetic cathinones

The only cathinones under international control (United Nations Convention on Psychotropic Substances 1971) are amfepramone, cathine, cathinone, mephedrone, methcathinone, and pyrovalerone. Although mephedrone (4-methylmethcathinone) was originally synthesized in 1929, it first appeared on the drug scene in 2008 [3], and synthetic cathinones currently account for the second largest group of substances monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Of the hundred or so cathinones notified to date to the EMCDDA, those which are a reason of particular concern are mephedrone, 4-MEC/4-Methylethcathinone, alpha-PVP/α-pyrrolidinopentiophenone, flephedrone, 3′,4′-Methylenedioxy-α-pyrrolidinobutyrophenone (MDPBP), Methylenedioxypyrovalerone (MDPV), methedrone, methylone, naphyrone, and pentedrone and pyrovalerone.

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Table 1. Stimulant and hallucinogenic novel psychoactive substances (NPS), chemical structure, pharmacodynamics, gergal/colloquial names, psychoactive effects, and medical/psychopathological consequences.

Stimulant NPS				
Class	Structure	Action	Gergal/Colloquial names	Psychoactive effects and medical/psychopathological consequences
Synthetic cathinones	Analogs of beta-ketoamphetamine cathinone	Substrates for DAT, SERT, and NET Monoamine transporter substrates with DAT-selective profiles Non-substrate transporter inhibitors	'Meow Meow;' 'Bubbles'; Mephedrone; Methylone; MPDV; α-PVP, and many others	• Euphoria, mood enhancement, openness, empathy, mental clarity, elation, increased libido • Restlessness, anxiety, hallucinatory experiences, psychosis • Tachycardia, hypertension, abdominal pain, chills, flushing, sweating, hyperthermia, renal failure, rhabdomyolysis, seizures, serotonin syndrome • Chronic use: paranoid ideation and mood disturbances
Aminorex derivatives	*Para*-methyl derivative of 4-methylaminorex and analogs	DA/NA releasing action and SERT inhibition	'Serotoni;' '4,4'-dimethylaminorex/DMAR	• Elation, increased alertness, anxiety, agitation • Increased body temperature, cardiorespiratory issues
Methylphenidate-like NPS	Ethyl-homologue of methylphenidate	Potent DAT and NERT inhibition	'El Burst;' 'El Blanco;' Ethylphenidate	• Euphoria; elation; increased arousal; improved concentration, sociability, and sexual drive • Muscle tension, palpitations, sweating, appetite loss, anxiety and restlessness • Insomnia, paranoia, hallucinations • Bizarre and violent behavior, suicidality, psychosis, relapse of psychotic disorder
Novel Amphetamine type stimulants	Analogs of amphetamine and methylamphetamine	Variable levels of SERT, NET, and DAT inhibitory potencies	PMA;PMMA; 4-MTA; DMA; MPA; diclofensine	• Euphoria; increased energy and sexual drive, improved sociability, color and sound amplification • Increased alertness and anxiety levels, loss of appetite • Tachycardia, increased body temperature
Synthetic cocaine substitutes	Benzoic acid esters	DAT inhibition	Dimethocaine	• Increased concentration and attention, talkativeness • Tachycardia, diaphoresis, muscle twitching, nausea, vomiting, peripheral vasoconstriction
			p-FBT	• Hypertension, tachycardia • Anxiety, temporary psychosis
	3-Phenyltropane analogs	SERT, NET, and DAT inhibitory properties	RTI-111, RTI-121, RTI-126	• Euphoria, talkativeness • Increased alertness, anxiety, paranoid, ideation • Insomnia, crash-like symptoms
Aminoindanes	Aminoindane analogs	Serotonin release and SERT inhibition	MDAI, 5-IAI, ETAI	• Euphoria, elation, mood enhancement, openness, empathy, mental clarity, increased energy and libido • Eye and skin irritation, gastrointestinal, and respiratory disturbances • Serotonin syndrome

Table 1. (Continued).

Hallucinogenic NPS				
Class	Structure	Action	Gergal/Colloquial names	Psychoactive effects and medical/ psychopathological consequences
Synthetic cannabimimetics	Large class of compounds with different chemical structures	CB1, CB2 receptor full agonism;5-HT, nicotinic, glycine, and NMDA receptors' interaction	'Spice,' 'K2,' 'Bonzai,' 'clockwork orange,' 'psyclone,' JWH-018, HU-210, XLR-11, 5F-AKB48, PB-22, ADB-PINACA, MAB-CHMINACA, and many others	• Visual and auditory hallucinations, paranoid ideation • Anxiety/panic attacks, agitation, behavioral dyscontrol, excited delirium • Suicidal ideation, manic-like symptoms, relapse of bipolar disorders • Temporary psychosis, relapse of psychotic disorders, persisting psychotic disorders/ 'Spiceophrenia' • Tachycardia, hypertension, dyspnea/tachypnea, mydriasis, nausea, vomiting, hypokalemia • Acute kidney injuries, myocardial infarction, liver failure • Nystagmus, seizures, encephalopahy, stroke • Rhabdomyolysis, hyperthermia, serotonin syndrome possible
Psychedelic phenethylamines	2C-B difuran analog	5-HT_{2A} agonism, 5-HT_{2B}, and 5-HT_{2C} affinity	'Bromodragonfly'	• Long standing hallucinations, paranoid ideation, mood elevation, confusion, anxiety, flashbacks • Convulsions, respiratory issues, liver failure, kidney failure, vasoconstriction
	2C-B derivatives	5-HT_{2A} affinity; D_2 low affinity; monoamine transporters' low inhibitory activity levels	'2C-series,' 'Nexus,'2C-D, 2C-E, 2C-N, 2C-H, and others	• Hallucinations; dysphoria; severe agitation • Mydriasis; seizures; headache; apnea
	N-benzyl substituted phenethylamines	5-HT_{2A} and 5-HT_{2C} full agonism; α_{1A}, α_{2A}, and H_1 high binding affinity; D_2 and D_3 low-affinity	'N-bomb,' 25B-NBOMe, 25C-NBOMe, 25I-NBOMe	• Visual, auditory, olfactory, and tactile hallucinations • Euphoria, increased sociability, empathy • Depersonalization, dissociation, derealization • Panic, severe agitation, insomnia, aggressiveness • Nausea, vomiting, headache, seizures, muscle rigidity, rhabdomyolysis, tremors • Renal failure, cardiopulmonary arrest
	MDA benzofuran analogs	5-HT_{2A} and 5-HT_{2B} agonism; DAT, α_{2c} affinity; SERT inhibition	'BenzoFury,' 5-APB, 6-APB, and others	• Euphoria, elation, entactogenic properties, hallucinations • Agitation, panic attacks, insomnia • Severe paranoia, psychosis • Unpleasant come-down, depression • Nausea, hot flushes, headache, jaw clenching • Serotonin syndrome possible

(*Continued*)

Table 1. (Continued).

Hallucinogenic NPS				
Class	Structure	Action	Gergal/Colloquial names	Psychoactive effects and medical/ psychopathological consequences
Tryptamines	Tryptamine derivatives	5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C} agonism; VMAT2, σ-1, SERT, TAR interactions	4-HO-DALT, 5-MeO-DMT, 5-MeO-DIPT, 5-Meo-DALT, and others	• Visual hallucinations common, auditory hallucinations possible • Intensification of colors, distortion of body image, depersonalization • Euphoria, marked mood lability, relaxation, entactogenic properties • Anxiety, panic disorder, agitation, restlessness, paranoia, excited delirium • Tachyarrhythmia, hyperpyrexia, Hypertension • Nausea, vomiting, muscle tension • Serotonin syndrome possible
Ergolines	LSD-related compounds	5-HT_{2A} agonism and/or other 5-HT_2 receptors agonism/interactions	LSZ, 1-P-LSD, ETH-LAD, PRO-LAD, AL-LAD	• Hallucinations, time distortion, body image alterations • Bad trips, flashbacks • Headache, nausea, mydriasis, tachycardia, hyperpyrexia, hypertension

DAT: Dopamine transporter; SERT: serotonin transporter; NERT: norepinephrine transporter; VMAT2: vesicular monoamine transporter 2; TAR: traceamine-associated receptors; LSD: lysergic acid diethylamide.

Simmler and colleagues [4] have identified three categories of cathinones: (a) substrates for the dopamine (DAT), serotonin (SERT), and norepinephrine/noradrenaline (NET/NE) transporters with 3,4-methylenedioxy-methamphetamine (MDMA)-like profiles, for example mephedrone, methylone, butylone, ethylone, 4-MEC; (b) monoamine transporter substrates with DAT-selective profiles similar to amphetamine and methamphetamine, for example cathinone, methcathinone, flephedrone. Naphyrone and 1-naphyrone have very high potencies and some degree of selectivity for DAT; and (c) non-substrate transporter inhibitors, for example MDPV.

Methcathinone (ephedrone) selectively generates a release of dopamine (DA) higher than that of serotonin (5-HT). MDPV is a DA selective uptake inhibitor, but selectively blocks the uptake of DA more than 5-HT, and presents with a high abuse potential [5]. MDPV inhibits monoamine uptake at the DA, 5-HT and NET transporters, similarly to cocaine [6,7]. The behavioral effects of mephedrone and MDPV are similar to methamphetamine and cocaine, respectively, whilst methylone's are closer to MDMA [8]. MDPV, mephedrone, methcathinone, and naphyrone are potent NET inhibitors [9].

Synthetic cathinones are typically sold as pills, capsules, and powders. They are usually snorted/sniffed (insufflated), taken orally by 'bombing' (swallowing the powder wrapped in a cigarette paper), mixed in a drink, or through intravenous injecting.

Synthetic cathinones are often used by consumers for various reasons, including: hallucinogenic experiences, euphoria, mood enhancement, openness, empathy, mental clarity, stimulation, increased energy, and increased libido [10]. Mephedrone possesses a re-dosing risk due to half-life being as short as 1 h [11]. By contrast, MDPV is thought to have a half-life of 3–5 h. Several different cathinones are often used together, and this could cause synergistic effects, for example as with MDPV and mephedrone [9].

The most common cathinones' adverse reactions are restlessness and anxiety, ranging from mild agitation to severe psychosis. Furthermore, tachycardia, hypertension, abdominal pain, chills, flushing, sweating, hyperthermia, renal failure, rhabdomyolysis, and seizures can also be observed [1,12–14]. Paranoid ideation and mood disturbances have been observed in chronic users of both natural and synthetic cathinones [13–16]. Many synthetic cathinones users report tolerance, dependence, and withdrawal symptoms [17].

Injecting use of synthetic cathinones has emerged among specific subpopulations' segments of at least 10 EU countries [18]. In some areas in Europe (e.g. eastern Europe), such injectors account for more than half of all drug injectors, with problem drug users now switching from heroin. The intake of cathinones can occur with high frequency levels, for example up to 10–20 times injections per day. MDPV, mephedrone, and 4-MEC are all reported to be injected. A more recent development is the injecting of α-PVP in Ireland [19]. Within the 'Chemsex' (e.g. the use of misusing drugs to increase levels of libido/sexual performances) context, drugs including synthetic cathinones/mephedrone are described as having a significant influence on the risk-taking behavior of 'men who have sex with men' population [20].

Some 83 deaths involving synthetic cathinones had been registered by the end of 2014 in England and Wales [21]. Although most fatalities involved mephedrone, increasing numbers of α-PVP and pentedrone deaths are being reported in the EU. Cathinones are typically involved in hangings or other mechanical suicides [13,14].

4,4′-DMAR

4,4′-DMAR ('Serotoni'), a derivative of aminorex, is a powerful dopamine/NE releaser whilst inhibiting the SERT as well. It may be snorted, or ingested, to achieve levels of both elation and increased alertness. The relating anxiety/agitation may last for a number of hours, with the risk of increase in body temperature and cardiorespiratory problems [22]. 'Serotoni' has recently been associated with some 35 fatalities in Europe [1].

MPH-like NPS

Ethylphenidate (EPH; sold under a range of brandnames such as '*Burst*,' '*El Blanco*,' '*Gogaine*') is the ethyl-homologue of MPH. It appeared in the UK market in 2011 and has now become one of the most popular NPS. Both EPH and MPH are stimulant drugs, being potent inhibitors of both DA and NE reuptake, although EPH is almost five times less potent against NE than DA and MPH is less selective [23]. Other MPH-derived compounds have recently appeared on the market, such as 3,4-dichloromethylphenidate (3,4-DCMP), methylnaphthidate (HDMP-28), propylphenidate, and isopropylphenidate. 3,4-DCMP is claimed to be more potent than MPH, with a slower onset of action and longer duration [23]. HDMP-28 acts as a triple receptor reuptake inhibitor (DA, NE, and 5-HT) in a manner similar to cocaine; it is also claimed to have several times the potency of MPH, but with a shorter duration of action [23].

EPH can also be found as an extra ingredient in psychoactive compounds' mixtures, together with methiopropamine (MPA), ephedrine, phenylethylamine, and remaining stimulants [23,24]. EPH intake can occur orally, intranasally, rectally, or through intramuscular/intravenous injection. Commonly reported dosages are 10–100 mg for oral or intranasal administration and 5–50 mg for injection [25]. The mean onset time for the EPH 'high' is around 15 min for intranasal and 25 min for oral administration; the mean duration of the effects is 120 min for all routes of administration. It has been suggested that, at low doses, EPH encourages increased levels of motor/mental productivity, whilst at higher dosages this may result in a general lack of motor control [26]. EPH can be found in powder, crystalline, and tablet form. Common desired effects reported by users include euphoria, stimulation/increased arousal, improved concentration, sociability, and sexual drive. Conversely, adverse effects reported include muscle tension, palpitations, sweating, appetite loss, anxiety/restlessness, insomnia, paranoia, and auditory/visual hallucinations [24]. EPH intake has been associated with bizarre/erratic and violent behavior, suicidality, psychosis, and clinical worsening of paranoid schizophrenia [23]. Tolerance to EPH has been described. Many users report a concurrent intake of a range of substances and in particular of sedative drugs such as alcohol, benzodiazepines, and/or opiates used as 'downers,' together

with EPH. A 'crash'-like phase after the end of an EPH binge session, with a period of mood lowering and fatigue, has been described [27]. As it might be expected from a short half-life stimulant which boosts DA levels, users report a strong urge/compulsion to re-dose [23,27,28]. A significant outbreak of severe soft-tissue infections among drug users who report injecting EPH repeatedly has been recently identified [23]. Twenty-eight fatalities associated with analytically confirmed EPH ingestion, mostly in combination with other drugs, have been described.

Amphetamine-type stimulants/novel stimulants

Amphetamine-type substances include PMA (4-methoxyamphetamine), PMMA (4-methoxymeth-amphetamine), 4-MTA (4-methylthioamphetamine/'*flatliners*'), DMA (2,5-dimethoxyamphetamine), diclofensine, MPA, etc. [1,29].

PMA and PMMA (aka '*red Mitsubishi*'/'*pink ecstasy*'/'*Mitsubishi turbo*'/'*Dr. Death*') are similar to MDMA, although these molecules are already extremely active at lower doses. They may determine a fatal rise in body temperature, euphoria, a sense of full energy, an amplification of sounds/colors, and feelings of love/sociability. An increasing number of fatalities have been described following their consumption [30].

Diclofensine is a stimulant that acts as a DA/NE/5-HT reuptake inhibitor [31]. It was originally developed as an antidepressant, but eventually abandoned due to possible concerns about its potential for abuse [32].

MPA ('*Blow*') was firstly synthetized in 1942 but advertised on the Internet as a 'research chemical' in the late 2010 [33–36]. It acts as a selective NE/DA reuptake inhibitor [37]. It may be ingested, snorted, or smoked. At low doses, it is a stimulant associated with mild euphoria, alertness, sexual arousal, loss of appetite, tachycardia, anxiety, etc. Adverse effects include a significant hangover after extended use with nausea, headache, dizziness, lack of energy, skin irritation, and difficulty urinating [1].

Aminoindanes

The UNODC [38] reports that up May 2015 the most commonly reported aminoindanes were 5,6-methylenedioxy-2-aminoindane (MDAI; '*MDAI gold*'), 5-iodo-2-aminoindane, and 2-aminoindane (2-AI; *Blurberrys*,' '*Groove-e*,' '*Pink Champagne*'). Other aminoindanes available as NPS include *N*-methyl-2AI, 1-aminoindane, and ETAI (*N*-ethyl-5-trifluoromethyl-2-aminoindane). Although some of these molecules are controlled in specific countries, none of them are subject to control under the UN International Drug Conventions. The aminoindanes' potential to affect serotonin release and reuptake [39] is likely to be associated with the ability to engender entactogenic and empathogenic effects akin to those of MDMA [40].

Most aminoindanes are available from a range of sources, including the web, as powder, and capsules/tablets, which can be either ingested or snorted.

Aminoindanes are used by consumers in search of a range of psychoactive effects, including hallucinogenic experiences, euphoria, mood enhancement, openness, empathy, mental clarity, stimulation, increased energy, and increased libido [41].

Aminoindanes are reported to cause eye and skin irritation, as well as gastrointestinal disturbances with nausea, vomiting/diarrhea, and respiratory tract concerns. Three deaths associated with MDAI use, either alone or in combination, were identified in the United Kingdom during 2011–2012, all involving symptoms consistent with serotonin syndrome [42].

Synthetic cocaine analogs

Dimethocaine and 4-fluorotropacocaine (*p*FBT), typically found as white powder, act as DA reuptake inhibitors, resulting in mild stimulant effects. Similar to cocaine, both substances are being insufflated since following ingestion they would be hydrolyzed by the digestive system esterases. Dimethocaine users report a short-lasting rush, together with levels of increased attention/concentration, talkativeness, and the desire to re-dose. Adverse/unwanted effects include peripheral vasoconstriction, tachycardia, diaphoresis, muscle twitching, nausea, and vomiting [41]. *p*FBT is anecdotally reported to cause hypertension, tachycardia, anxiety, and temporary psychosis [41]. Further cocaine analogs include RTI-111 (e.g. a potent stimulant acting as an inhibitor of 5-HT, DA, and NE reuptake [43]), RTI-121, and RTI-126. RTI-121 is a potent/long-lasting stimulant acting as a selective DA reuptake inhibitor [44]. RTI-126 [45], on the other hand, may present with a potency which is 5-fold higher than that of cocaine. When snorted, these compounds are associated with alertness, euphoria, talkativeness, insomnia, prolonged residual tension/anxiety, and crash-like symptoms [1].

Hallucinogens: SC, psychedelic phenetylamines, and tryptamines.

Synthetic cannabimimetics

SC ('Spice') were first detected in Europe toward the end of 2008 and, at the time of writing, constitute the largest group (about 30%) of NPS monitored by the EMCDDA. SC belong to a range of chemically different families of compounds. Some are cannabinoid receptors' agonists whilst others are compounds targeting enzymes involved in the metabolism and transportation of endocannabinoids [46]. Many SC contained in Spice drugs are full-agonists, possess large levels of receptors' affinity, and hence elicit maximal activity at cannabinoid receptors [47]. Conversely, THC effects in cannabis are modulated/dampened by the presence of other natural compounds such as terpenoids, cannabidiol, and tetrahydrocannabivarin [46], but no such 'modulating' compounds are generally detected in Spice products [48]. Several SC have been found to interact with a range of remaining receptors, including 5-HT, nicotinic acetylcholine, glycine, and/or ionotropic glutamate (NMDA), and it is possible that SC produce their complex effects through their actions at non-cannabinoid receptors as well [48]. A number of SC compounds incorporate indole-derived moieties active on 5-HT receptors, either as components of the structure or as substituents. It has been suggested that, at high doses, SC compounds may also possess some monoamine oxidase, and 5-HT reuptake, inhibitory properties [49]. These complex pharmacodynamic elements may further increase the risk of serotonin syndrome

occurrence in SC misusers [10,46]. Furtherly, it has been suggested that the chronic activation of CB-2 receptors results in the upregulation of 5-HT_{2A} receptors in the prefrontal cortex of mice [50]. Modification in 5-HT_{2A} receptors' neurotransmission has been associated with hallucinations/delusions/psychosis [51].

'Spice' preparations are composed by both a dried plant base, to mimic the 'grass effect' of female cannabis dried inflorescences, and a mixture of SC which are sprayed on it. SC dispersed in the grass preparation look like marijuana, with capsules and e-liquid formulations being available as well. SC have also been found in tablets and sprayed on herbal cannabis. SC can be found on the web, from 'head–shops,' gas stations, and from an ever expanding range of other outlets [52].

Their intake can occur through inhalation from a joint/bhong/pipe or using a vaporizer. Other ways of intake include insufflation, oral ingestion, rectal administration, and injection [1]. Misusers are often young males, choosing Spice instead of cannabis for its low cost; favorable legal status [41]; easy availability; misperception that SC are natural, and not synthetic, molecules; and undetectability in routine urine screening tests [53,54]. The non-detectability of SC make also Spice very attractive for subpopulations undergoing regular drug tests [10].

Spice products are almost always laced with multiple SC in a single preparation [1]. Hence, there is a potential for drug–drug interactions between multiple SC in a single product, and this may contribute to the abuse-related and synergistic effects of these compounds. Some SC metabolites, furthermore, retain levels of both affinity and activity for CB-1 receptors, hence contributing to the toxicity of the products [55]. The recent trend of SC fluorination may increase the compounds' lipophilicity, hence promoting the absorption through biological membranes/blood–brain barrier, possibly enhancing the SC overall toxicity [55].

The total lack of product quality control may lead to significant differences in concentration ('hot-spots') of SC present in herbal incenses or e-liquids [46,55]. In comparison with cannabis, use of SC may be characterized by quicker 'kick off' effects; significantly shorter duration of action; larger levels of hangover effects; and more intense visual hallucinations, paranoid feelings, and behavioral dyscontrol [46,56]. The acute SC intoxication is characterized by a short-lived clinical picture with reported signs/symptoms of elevated heart rate/blood pressure levels, visual/auditory hallucinations, mydriasis, agitation/anxiety, hyperglycemia, dyspnea/tachypnea, and nausea/vomiting [1].

Other psychiatric, neurologic, and somatic effects include suicidal ideation/self-injurious behavior, aggressive behavior, panic attacks, cognitive impairment, thought disorganization, psychosis, agitated/excited delirium, nystagmus, seizures, hyperemesis, encephalopathy, acute kidney injury, rhabdomyolysis, hyperthermia, serotonin syndrome, toxic hepatitis/liver failure, coma, severe dysrhythmias/cardiotoxic effects, and stroke [1,56].

Long-term SC misuse may also be associated with tolerance, dependence, and a severe prolonged withdrawal syndrome, characterized by drug craving, tachycardia, tremor, profuse sweating and diarrhea, nightmares/insomnia, headache, anxiety/irritability, mood swings, feelings of emptiness/depressive symptoms, and somatic complaints [1]. SC intake has been associated with a range of psychotomimetic disturbances (e.g. paranoia, delusions, hallucinations), the occurrence of florid/acute transient psychosis, relapse/worsening of a preexisting psychosis, persistent psychotic disorder/'Spiceophrenia' [56], and relapse of a preexisting bipolar disorder [57]. A number of deaths have been related to SC ingestion, either on their own or in combination in analytically confirmed reports [1]. Very recently, a phase I clinical trial for the development of a painkiller drug akin the ones found in Spice was abruptly terminated due to severe neurological adverse effects and one death among a number of human volunteers [58].

Psychedelic phenetylamines

Phenethylamines include a wide range of natural or synthetic substances which own psychostimulant, entactogenic, and hallucinogenic effects. Mescaline, isolated from peyote cactus (*Lophophora williamsii*) and traditionally chewed by Indians in Mexico as a religious sacrament, represents the prototype psychoactive phenethylamine compound. A variety of methoxylated amphetamine compounds are derived by mescaline and include TMA (3,4,5-trimethoxyamphetamine), DOM (3-methoxy-4,5-methylenedioxyamphetamine), DOET (2,4,4-trimethoxyamphetamine), DOI (4-iodo-2,5-dimethoxyam-phetamine), DOC (4-chloro-2,5-dimethoxyamphetamine), etc. [59]. Alongside these substances, the group of phenethylamines also include a total of 179 'classical' phenethylamines, such as MDMA-like drugs (e.g. MDA [3,4-methylenedioxy-amphetamine], MDEA [3,4-methylenedioxyethamphetamine], MBDB [*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine]) and the latest generation phenethylamine derivatives for example 'Bromodragonfly' (1-(8-bromobenzo[1,2-b; 4,5-b']difuran-4-yl)-2-aminopropane); *N*-benzyl substituted phenethylamine (NBOMe) derivatives; indanes; benzofurans; and the class of 2C-molecules, such as 2,5-dimethoxy-4-bromophenethylamine (2C-B), 2,5-dimethoxy-4-iodophenethylamine (2C-I); and 2,5-dimethoxy-4-ethylphenethylamine (2C-E) [1].

Bromo-Dragonfly (aka '*DOB-Dragonfly*'/'*3C-Bromo-Dragonfly*' [60]) displays a high affinity for 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors [61]. Its effects are associated with long-standing hallucinations, mood elevation, paranoid ideation, confusion, anxiety, and flashbacks. In addition, a number of related acute intoxications with convulsions, respiratory problems, liver and kidney failure, severe vasoconstriction, and fatalities have been described [60].

The 2C-series compounds, including 2C-B ('*Nexus*'), but also 2,5-dimethoxy-4-methylphenethylamine (2C-D), 2C-E, 2,5-dimethoxy-4-nitrophenethylamine (2C-N), 2,5-dimethoxyphenethylamine (2C-H), *N*-ethyl-2C-B, etc. [29] act primarily at the 5-HT_{2A} receptors, also displaying low-affinity binding to D_2 receptors and a low inhibitory activity to monoamine transporters (for a thorough review, see Rickli and colleagues [62]). Adverse effects include headache, dysphoria,

hallucinations, mydriasis, seizures, severe agitation, and apnea. Several related deaths have been reported as well [1].

Recently, several highly active NBOMes have entered the NPS market and include: 25B-NBOMe (2-(4-bromo-1,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine); 25C-NBOMe ((2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine) aka '*N-Bomb*'/'*Pandora*'); and 25I-NBOMe ((4-iodo-2,5-dimethoxy-*N*-(2-methoxybenzyl)phenethylamine) aka '*N-bomb*') [29,63,64]. *In vitro* receptor studies have demonstrated that NBOMe compounds act as potent full agonists at the 5-HT_{2A} and 5-HT_{2C} receptors [65]. In addition, 25I-NBOMe and 25C-NBOMe are pharmacologically active at very low, submilligram doses [29]. They also display high binding affinity to adrenergic α_{1A} and α_{2A}, as well as histamine H_1, receptors. They show as well low-affinity binding levels to D_2 and D_3 receptors [62]. Their higher 5-HT_{2A} receptor affinity, compared to the 2C-derivatives, explain the frequent associated reports of hallucinations and delusions. NBOMe-containing products are usually available as tablets, capsules, powder, liquid, spray, and blotters. They are usually taken sublingually/orally or via nasal insufflation [29]. Some of them are sold as lysergic acid diethylamide (LSD) replacement [29,63]. Depending on the route of administration, their effects may last 3–10 h. Psychotropic effects commonly reported include euphoria, increased sociability, visual/auditory/olfactory/tactile perceptual disturbances, empathy, depersonalization, dissociation, and derealization. Their adverse effects may include nausea, vomiting, headache, panic/severe agitation, aggressiveness, seizures, insomnia, muscle rigidity/rhabdomyolysis with renal failure, tremors, and cardiopulmonary arrest [29,63]. Several fatalities have been reported following the intake of NBOMe compounds [66].

Benzofurans, which are phenethylamines structurally related to MDMA and MDA, include several compounds, for example 6-APB (6-[2-aminopropyl] benzofuran; aka '*BenzoFury*'); 5-APB (s [5-(2-aminopropyl)benzofuran]); 6-APDB (6-[2-Aminopropyl]-2,3-dihydrobenzofuran; aka '*4-Desoxy-MDA*'); 5-APDB (5-[2-Aminopropyl]-2,3-dihydrobenzofuran; aka '*3-Desoxy-MDA*'); etc. [29]. They are typically ingested, since nasal insufflation may be painful. Their intake may be associated with stimulant, entactogenic, and hallucinogenic effects. Adverse effects may include dry mouth, nausea, jaw/teeth clenching, insomnia, diarrhea, light hypersensitivity, hot flushes, headache, drowsiness, panic attacks/anxiety, depression, severe paranoia, and psychosis. An unpleasant 'comedown,' lasting several days, has been reported [67]. Several deaths related to 5- and 6-APB have been identified [68].

Tryptamines

Tryptamines have been classified in two groups: (1) '*simple tryptamines*,' structurally derived from tryptamine and (2) '*ergolines*,' structurally related to the semisynthetic lysergic acid diethylamide/LSD [69].

Simple tryptamines

Apart from *N,N*-dimethyltryptamine (DMT); other tryptamine derivatives include 5-MeO-DMT/5-methoxy-*n,n*-dimethyltryptamine, found in some *Delosperma* species; psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine); and psilocin (4-hydroxy-*N,N*-dimethyltryptamine), which are identified in hallucinogenic fungi (aka '*magic shrooms*' or '*mushies*'); bufotenin (5-hydroxy-*N,N*-dimethyltryptamine/5-OH-DMT); and 5-hydroxy-indolethylamines, common constituents of venoms of the genre *Hyla, Leptodactylus*, Rana, and *Bufo alvarius* [70]. Tryptamines psychoactive effects are due to their agonism at 5-$HT_{1A,}$ 5-HT_{2A} and 5-HT_{2C} receptors [71]. Other receptors implicated in the tryptamine pharmacodynamics include vesicular monoamine transporter 2 (VMAT2), σ-1, serotonin transporter (SERT) and traceamine-associated (TAR) receptors [71].

DMT (aka '*Dimitri*'/'*businessman's trip*') has been found in the leaves of *Psychotria viridis*, which are traditionally combined by the indigenous Amazonian tribes with *Banisteriopsis caapi*, source of the monoamine oxidase inhibitors (MAOi) β-carboline alkaloids harmine, harmaline, and tetrahydroharmine, to produce Ayahuasca. DMT has been also found in other plant sources, e.g. *Phalaris arundinacea* and *Mimosa hostilis* [72]. DMT produces strong hallucinogenic LSD-like effects, powerful entheogenic experiences/intense visual hallucinations, and euphoria. Since DMT is inactive after oral administration unless combined with MAOis, it is usually injected, snorted, or smoked. If smoked, its effects last for a short period of time (5–30 min) [73].

Psilocin hallucinogenic effects occur within the first 2 h after oral intake and last up to 4–8 h [74]. Psilocin is a partial 5-HT_{2A} agonist, with little dopaminergic or noradrenergic activity [75,76].

Bufotenin (aka '*5-OH-DMT*') is found in the skin of various species of the toad *Bufo* genus; in mushrooms such as Amanita; and in plants such as *Anadenanthera* and *Piptoderma peregrina* [77]. It acts on 5-HT_{2A} receptors [78].

Alongside these naturally occurring tryptamines, a rapidly increasing number of tryptamine derivatives, such as 5-Meo-DALT (*N*-diallyl-5-methoxy-tryptamine), AMT (α-methyltryptamine), AET (α-ethyltryptamine), 5-Meo-AMT (5-methoxy-α-methyltryptamine), 4-HO-DALT (*N,N*-diallyl-4-hydroxytryptamine), 5-MeO-DIPT (5-methoxy-diisopropyl-tryptamine; aka '*foxy*' or '*foxy methoxy*'), DET (*N,N*-diethyl-tryptamine), and 5-IT (5-(2-aminopropyl)indole), have recently entered the market. These tryptamine derivatives are usually available as capsules, tablets, powder, or liquid formulations and may be ingested, snorted, smoked, or injected [41]. The main clinical effects are visual hallucinations, alterations in sensory perception, intensification of colors, distortion of body image, depersonalization, marked mood lability, euphoria, relaxation, entactogenic properties, and anxiety. Adverse effects include agitation, tachyarrhythmias, hyperpyrexia, serotoninergic neurotoxicity, and death [41].

AMT (aka '*Day Tripper*'/IT-290) and AET (aka '*Love Pearls*'/ET) possess central stimulant and hallucinogenic properties. AMT desired effects, peaking in 3–4 h and lasting up to 12–24 , include euphoria, distortion of color/shapes and visual hallucinations. AET is a reversible MAOi and 5-HT/DA releasing molecule. AET onset of action occurs within 30–90 min; its adverse effects may include: facial flushing, headache, gastrointestinal disorders, irritability, insomnia and, at times, hyperthermia and agitated delirium. Although it may be

made available as an LSD alternative, due to its amphetamine-like structure 5-MeO-AMT presents with a range of sympathomimetic effects. It owns a strong binding activity at 5-HT_{1A} and 5-HT_{2A} receptors whilst inhibiting as well the monoamines' reuptake [79]. 5-MeO-DIPT (aka '*foxy*/'*foxy methoxy*'/5MEO), structurally related to DMT and bufotenin, is an agonist at 5-HT_{2A}, 5-HT_{1A}, and 5-HT_{2C} receptors. Its adverse effects include nausea, vomiting, mydriasis, auditory and visual hallucinations, formication, tachycardia, hypertension, echolalia, paranoia, restlessness/agitation and muscle tension [36]. DET significantly inhibits monoamine oxidase. It produces hallucinogenic effects similar to DMT or mescaline. Adverse effects include anxiety, tremors, nausea/vomiting, mydriasis, disinhibition, visual distortions, and increased blood pressure.

Ergolines

LSA has been found in the seeds of *Argyreia nervosa* and *Ipomoea violacea*. It is traditionally used during shamanic and ceremonial practices. LSD appears as a crystalline powder soluble in water which is made available as sugar cubes or small squares of papers or stamps which are typically ingested. Its effects are rapid and include headache, raised pulse rate, dilated pupils, nausea, blood pressure alterations, and sometimes an increase in body temperature. Its effects vary according to both the subject expectation/mood and the setting, including idiosyncratic perceptual disturbances such as stationary objects appearing to move and changing shape, synesthesia, distortions of body image, and perception of time, etc. Tolerance, dependence, and withdrawal experiences have been described by users. Adverse effects may include '*bad trips*,' that is an unpleasant, often terrifying, post-intake drug experience. Spontaneous recurrence of the drug-induced experience (i.e. flashbacks) is fairly common after LSD use. Some novel LSD derivatives have recently reached the market, such as LSZ (lysergic acid 2,4-dimethylazetidide), 1-P-LSD (1-propionyl-D-lysergic acid diethylamide hemitartrate), ETH-LAD (6-ethyl-6-nor-lysergic acid diethylamide), PRO-LAD (6-propyl-6-nor-lysergic acid diethylamide), and AL-LAD (6-allyl-6-nor-lysergic acid diethylamide). They produce effects resembling those of LSD, having similar pharmacological action at 5-HT_{2A} receptors, but possessing different potencies, kick-off effects and duration [29].

Expert commentary: NPS use as a clinical challenge for emergency physicians

The constantly and rapidly evolving NPS drug scenario represents a challenge for medicine, and especially so for both emergency physicians and mental health professionals. Indeed, NPS intake is typically associated with the imbalance of a range of neurotransmitter pathways/receptors. Hence, this may be followed by a range of psychopathological disturbances [1], whose occurrence has been related to (a) increased central dopamine levels, associated with the intake of most of these substances, including novel psychedelic phenethylamines, stimulants, synthetic cathinones and 4,4'-DMAR; (b) cannabinoid CB1 receptor activation, achieved with synthetic cannabimimetics; and (c) intense 5-HT_{2A} receptor activation, reported with both NBOMe compounds and latest tryptamine derivatives.

Due to the NPS complex pharmacodynamics here described, levels of debate are currently occurring in formal clinical fora to identify a range of proper, NPS-focused, management/treatment strategies. In fact, NPS consumers may present overnight to accident and emergency departments without disclosing their drug intake whilst it is also likely that the standard drug tests will show negative results. It is problematic to draw a detailed and universal management plan to cope with the behavioral and psychopathological disturbances related to the intake of the virtually few hundreds of substances currently available [80]. However, according to Velez and Benitez [81], the initial management of these patients should focus on decreasing levels of both self/outward-directed aggression and agitation. Verbal de-escalation can always be considered with more cooperative patients. However, given the complex, and at times unknown, pharmacology of the substances possibly ingested by the client, benzodiazepines may be considered as agents of choice [1]. Initially, due to lack of patient cooperation, the intravenous/IV access may be problematic. In those cases, Velez and Benitez have suggested to use either intramuscular/IM or intranasal midazolam (5–10-mg IM/intranasal or 2.5–5 mg IV), because of its fast absorption/onset of action; or lorazepam (4–8-mg IM; 2–4-mg IV) [81]. Diazepam should only be used IV, as it presents with erratic IM absorption [81]. Benzodiazepines, however, need frequent re-dosing/high dosages to achieve adequate sedative effect, and this may be a problem if clients have co-ingested alcohol.

Where patients cannot be controlled with benzodiazepines alone, propofol and/or antipsychotics (especially when paranoia and psychosis are being identified) may be considered, although this may further contribute to the acute toxicity effects of the abused substances. Both haloperidol and droperidol (5–10-mg IM or IV) have been suggested as reasonable options [81]. Aripiprazole, quetiapine, risperidone, and olanzapine can also be used, although the levels of evidence regarding their use for the undifferentiated agitation patient are limited [81].

Treatment of hyperthermia needs to be aggressively planned, and this typically involves cooling measures and, once an IV line is available, focus should be on control of rhabdomyolysis with intravenous fluid administration [1,81]. The serotonin syndrome is managed using benzodiazepines and cyproheptadine [1]. Inpatient admission, possibly to intensive care units, may at times be needed.

Five-year view

Indeed, future studies will provide better levels of NPS clinical and basic pharmacology-related knowledge, so that better tailored management/treatment guidelines can be made available.

Health professionals' education involving knowledge on NPS health harms, potential interventions, and referral pathways is lacking. Future NPS-related tutoring activities will allow clinicians to promote health prevention and education

activities, which in turn would reduce the negative social impact of NPS misuse, unnecessary hospital admissions, and avoidable fatalities [82]. Future approaches will consider as well the role of web-based preventative strategies in targeting youngsters/vulnerable individuals at risk of approaching the NPS market.

Although current general population surveys suggest relatively low levels of NPS use, at least if compared with well-known scheduled substances such as THC, cocaine and heroin, this may change. The online market of NPS is unfortunately developing far more rapidly than academic research. Hence, it is more than likely that over the next 5 years or so, the number of NPS will continue to rise. Similarly to Poland and Ireland, however, a brand new legislation focussing on NPS is expected to come into effect in the United Kingdom in April 2016. As a result of this, it is speculated that most of the so-called legal highs/research chemicals, now considered as technically 'legal,' will be outlawed. Since at present a sizeable proportion of the NPS are made available to customers through the most popular 'open web' search engines, one could hypothesize that over the next few years the NPS market will gradually expand and/or move to the 'deep web,' and especially to its most hidden portion, e.g. the 'DarkNet' [2]. It is hence here speculated that most transactions of NPS will occur in the future with the help of both 'ad hoc,' deep-web tailored, browsers and a range of 'crypto currencies,' some of which are already available for use. Current research activities, coordinated from our group, are already focussing on these possible future scenarios.

Key issues

- Over the last decade, the drug scenario has shown significant levels of changes, with the emergence of a range of NPS. The web may play a major role in shaping this unregulated market.
- An overview of the clinical pharmacological issues related to some of the most popular NPS categories, for example stimulants (e.g. synthetic cathinones, 4-4′-DMAR, methylphenidate-like NPS, amphetamine-type stimulants, aminoindanes, and cocaine analogs); and hallucinogens (synthetic cannabimimetics, psychedelic phenethylamines, and tryptamines) is here provided (see Table 1).
- NPS intake is typically associated with the imbalance of a range of neurotransmitter pathways/receptors, which in turn may be followed by the occurrence of a range of psychopathological disturbances, due to (a) increased central dopamine levels, associated with the intake of most of these substances, including novel psychedelic phenethylamines, stimulants, synthetic cathinones, and 4,4′-DMAR; (b) cannabinoid CB1 receptor activation, achieved with synthetic cannabimimetics; and (c) intense 5-HT2A receptor activation, reported with both NBOMe compounds and latest tryptamine derivatives.
- NPS intake usually fails to be identified with standard drug screening tests. Advanced tests can be performed, but they are not generally available in the acute setting and are used mainly for forensic investigations.
- The initial management of these patients should focus on decreasing levels of both self-/outward-directed aggression and agitation. Due to the complex, and at times unknown, pharmacology of the NPS/other psychoactives ingested by the client, benzodiazepines may be considered as agents of choice.
- It is more than likely that over the next 5 years or so the number of NPS will continue to rise. A brand new legislation focussing on NPS is expected to come into effect in the United Kingdom in April 2016. It is speculated that over the next few years the NPS market will gradually expand and/or move to the 'deep web,' and especially to its most hidden portion, e.g. the 'DarkNet.'

Financial & competing interests disclosure

This paper was supported in part by grants of the European Commission (Drug Prevention and Information Programme 2014-16, contract no. JUST/2013/DPIP/AG/4823, *EU-MADNESS project*). Further financial support was provided by the EU Commission-targeted call on cross border law enforcement cooperation in the field of drug trafficking - DG Justice/DG Migrations and Home Affairs (JUST/2013/ISEC/DRUGS/AG/6429) *Project EPS/NPS* (Enhancing Police Skills concerning Novel Psychoactive Substances; NPS). F Schifano is a ACMD member, UK; EMA Advisory Board Member. JM Corkery is a ACMD UK NPS group advisor. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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