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New psychoactive substances: a review and updates

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***Abstract*:** New psychoactive substances (NPS) are a heterogeneous group of substances. They are associated with a number of health and social harms on an individual and societal level. NPS toxicity and dependence syndromes are recognised in primary care, emergency departments, psychiatric inpatient and community care settings. One pragmatic classification system is to divide NPS into one of four groups: synthetic stimulants, synthetic cannabinoids, synthetic hallucinogens and synthetic depressants (which include synthetic opioids and benzodiazepines). We review these four classes of NPS, including their chemical structures, mechanism of action, modes of use, intended intoxicant effects, and their associated physical and mental health harms. The current challenges faced by laboratory testing for NPS are also explored, in the context of the diverse range of NPS currently available, rate of production and emergence of new substances, the different formulations, and methods of acquisition and distribution.

Keywords: laboratory testing, new psychoactive substances, NPS, synthetic cannabinoid receptor agonists, synthetic hallucinogens, synthetic opioids, synthetic stimulants

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Introduction

New psychoactive substances (NPS) are a complex and diverse group of substances often known as either designer or synthetic drugs, or by the more popular but misleading colloquial term of '*legal highs*'.[1,2] They tend to be either analogues of existing controlled drugs and pharmaceutical products or newly synthesised chemicals, created to mimic the actions and psychoactive effects of licensed medicines and other controlled substances.[3–5] By their number, nature and composition, NPS pose significant challenges for drug consumers, clinicians – both in drug services and, more broadly, researchers, forensic toxicologists, healthcare systems and drug control policy globally – and have been described as a 'growing worldwide epidemic'.[6,7]

The United Nations Office for Drugs and Crime (UNODC) has defined NPS as 'substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat'.[8] However, definitions of NPS can vary between countries, reflecting differences in national legislation, rather than pharmacological or structural classification. Although some former NPS have been subject to international control under the UN Conventions (e.g. mephedrone in 2015; the synthetic cannabinoid ADB-FUBINACA in 2019), different approaches have been taken to legal control at national level.[2,9,10] This has included the use of existing controlled drug legislation, new NPS-specific legislation, or extension of generic public health and medicines legislation. In the United Kingdom (UK), for example, the Psychoactive Substances Act 2016 introduced legislation that made it an offence to produce, supply, offer to supply, possess with intent to supply, possess on custodial premises, import or export psychoactive substances, but did not make it an offence to possess for personal use outside of a custodial setting.[11] In principle this created a 'blanket ban' of all current and future NPS (with certain exemptions). However, the legislation has been criticised for the imprecise definition of psychoactivity, its

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blanket nature covering compounds with quite differing harm profiles, difficulties in enforcement, and exemptions that meant that popular NPS such as nitrous oxide can still be purchased.[4,12,13] Early evaluation of the Act suggested that whilst the availability of NPS had decreased, there was no evidence of a reduction in NPS-related harms.[14]

By 2018, a total of 892 individual NPS, reported by 119 countries, were being monitored by the UNODC early warning system,[15] and by the end of 2018, over 730 NPS had been notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).[16] The rapid proliferation at which new NPS have emerged on the global drugs market is unparalleled,[17] and it was estimated that at its peak in 2015, new NPS appeared at a rate of at least one new substance per week.[18] The number of new NPS detections has decreased in recent years and, in addition, the nature of the market has changed, with a relative decrease in the number of new stimulants and synthetic cannabinoids detected, and an increase in the numbers of new opioids and benzodiazepines available.[16] The rapidly changing profile of the NPS market raises concerns over uncertainty and ambiguity regarding their chemical, metabolic and toxicity profiles, and the associated physical, social and mental health harms.[19–21]

Despite a large number of NPS being detected and actively monitored, estimates of general population use are relatively low compared with other type of controlled drugs, and use has fallen over the previous 5 years as result of factors such as legal control, market dynamics, substance trends and fashions, and changes in the availability of other controlled drugs.[22] NPS epidemiology is under-developed, and differences in definition and methodologies means that it is difficult to gain accurate estimates of use. The 2018/2019 Crime Survey for England and Wales (CSEW) reported around 0.5% of adults aged 16–59 years (approximately 152,000 people) had used NPS in the last year, and that around half of all NPS users were aged 16–24 years (encompassing approximately 86,000 young adults). Regarding frequency of use, of those who had consumed any NPS in the last year, about half had consumed at least twice that year, around one in four had used NPS two or more times a month and around 8% had used NPS daily.[23] Whilst individual NPS are not included in the CSEW, the most popular forms of substance were powders, crystals or tablets (31.0%); herbal smoking mixtures (24.1%); liquids (17.9%); or 'another substance' (31.0%). Prevalence of nitrous oxide ('laughing gas') has remained relatively high and stable over the past few years (despite legal control in 2016), and 2.3% of 16–59 year olds and 8.7% of 16–24 year olds report use in the previous year. Amongst 16–24 year olds, nitrous oxide is now the second most prevalent drug after cannabis (reported by 17.3% of 16–24 year olds).[23]

Although research suggests that NPS are associated with harms in key populations such as people who are homeless or prisoners,[24] there are no robust estimates of levels of use. For example, the 2018/2019 Crime Survey for England and Wales described above is based on self-reporting by users. Data on adult drug treatment in England suggests that whilst there has been a recent increase in presentations (1223 in 2018–1363 in 2019; 11% increase), this was largely in service users taking NPS alongside opioids (and not solely NPS); it only represents 1% of all service users in treatment; and numbers have fallen from a peak in 2015/2016 (2042; a 33% decrease).[25] The Office for National Statistics (ONS) reported that there were 125 deaths registered in England and Wales in 2018 where NPS were mentioned on the death certificate. Although this represented only 2.9% of all drug-related poisonings, it was the highest number yet recorded.[26]

The term new psychoactive substance is a legal definition and there is no universally agreed way to categorise NPS.[27] Traditionally established recreational drugs and NPS have been functionally categorised into three broad categories (stimulants, hallucinogens and depressants) based on the features seen with acute unwanted effects; more recently with the evolution of the NPS they have often been considered in four, somewhat overlapping functional categories related to their chemical structure, and psychopharmacological desired and unwanted effects: stimulants, cannabinoids, hallucinogens and depressants.[27,28]

This narrative review paper aims to provide a robust overview of the current trends and developments with NPS, including their chemical structures, mechanism of action, modes of use, intended intoxicant effects, and their associated physical and mental health harms. The current challenges faced by laboratory testing for NPS is also explored. The paper will adopt the 'four

category' classification, with the caveat that some new compounds do not neatly fit into these and their effects cross these boundaries. However, it is the authors' experience that this model provides a utilitarian framework, especially for the generalist and clinician, who can often find the scale and rapidity of change in the field of NPS overwhelming. Inevitably, in a paper of this scope, there are limitations to the amount of information that can be provided about individual compounds. References on further reading will be provided for the interested reader. A final caveat is that some authorities and experts do not typically consider the compounds nitrous oxide and ketamine to fall under the definition of NPS; they do fall within the UNDOC definition, and thus the authors have kept them within this piece.

Synthetic stimulants

Synthetic stimulants comprise of a diffuse group of base compounds, which include cathinones, aminoindanes, phenethylamines, piperazines and tryptamines, of which synthetic cathinones are by far the largest group and the most studied.[29] Currently, they represent the largest group of NPS that are monitored by the UNODC and EMCDDA.[16,17] They are designed to replicate the effects of traditional stimulant controlled drugs, such as cocaine, MDMA and amphetamines.[30] They can be made into a variety of formulations and be insufflated, swallowed (often wrapped in paper, known as 'bombing'), inhaled, smoked, injected or used rectally, the most common route being taken in pill/tablet form.[31] Synthetic stimulants promote an increase in synaptic availability of neurotransmitters, mainly dopamine (DA) and serotonin (5HT). DA plays an important role in motivation, arousal, learning and reward, whereas 5HT is a contributor to feelings of happiness and a sense of emotional connectedness ('entactogenic').[32] Synthetic stimulants act on the two neurotransmitter systems to different extents, accounting for their differing range of desired and unwanted effects.[26,33] These include sought after experiences such as euphoria, increased feelings of empathy and compassion, sense of inner peace and relaxation, enhanced self-confidence, sociability and libido, and boosted energy and alertness.[33,34] Synthetic stimulants have also been associated with adverse effects such as high addiction potential, severe intoxications linked to cardiac, metabolic, neuropsychiatric and neurological complications and an increasing number of fatalities.[35–37]

Chemical structures

Common first generation synthetic cathinones (natural cathinone being the main psychoactive compound found in khat leaves) include methcathinone, 4-methylmethcathinone (mephedrone, 4-MMC, and first developed in the 1920s), 3,4-methylenedioxy-N-methylcathinone (methylone) and 3,4-methylenedioxypyrovalerone (MDPV) followed by a second generation consisting of 4-methyl-N-ethylcathinone (4-MEC), 4-fluoromethcathinone (flephedrone, 4-FMC), its positional isomer 3-fluoromethcathinone (3-FMC) and α-PVP (α-pyrrolidinopentiophenone). Synthetic cathinones are similar in structure to amphetamine type stimulants and are chemically referred to as β-ketone analogues because of the carbonyl (=O) group in β carbon.[38,39] The common pharmacophore group responsible for the psychoactive effect observed in synthetic stimulants is phenethylamine,[32] and its derivatives are reported to represent at least 37% of the NPS available on the illicit drug market.[40]

Synthetic stimulants structurally similar to pyrovalerone (a psychoactive drug once used in the treatment of chronic fatigue and lethargy) such as MDPV,[41] are highly lipophilic compared with other synthetic stimulants, and so have a high blood–brain barrier penetration and volume of distribution, resulting in longer plasma and tissue half-lives.[42,43] The presence of electrophilic groups such as fluorine also increases the lipophilic nature of synthetic stimulants analogues thereby making them more potent, a quality sought after by users who want to experience the ultimate new 'party drug' which is more potent, longer acting and delivers a better 'high'.[44]

Mechanism of action

Synthetic stimulants increase the monoamine neurotransmitters DA and 5HT and to a lesser extent noradrenaline (NE) concentration in the synaptic cleft, which then mediate the stimulatory effects.[45] Two distinct mechanisms are responsible for the increase in monoamine concentration in the synaptic cleft. Firstly there is stimulation of non-exocytotic neurotransmitter release by inhibiting the vesicular monoamine transporter-2 (VMAT2) and reversing the transporter influx, thereby stimulating neurotransmitter release from the cytosolic pool or synaptic vesicles.[46] Secondly, there is inhibition of the uptake of neurotransmitters from the synaptic cleft by inhibiting the plasma membrane transporters, which are responsible for the uptake of DA, 5HT and NE.[47–50]

Harms and adverse effects

Historically synthetic stimulants were developed to treat patients with Parkinsonism, obesity or depression, but these were soon withdrawn due to concerns regarding their abuse and harm potentials.[29,51] Some have recently been reported to have been used as cognitive enhancers or 'nootropics' (classically to help students with their exams, with some reports of professionals using them to maintain attention at work in stressful environments) and as part of weight loss regimens.[52,53] The acute physical and mental health harms associated with the use of synthetic stimulants are due to sympathomimetic toxicity, which may present as agitation, nausea, vomiting, headache, palpitations, tachycardia, hypertension and hyperthermia, and less frequently as paranoia, hallucinations, seizures and collapse.[54] Less commonly, severe adverse effects such as significant peripheral organ damage and rhabdomyolysis have been reported, whilst deaths have been linked to hypertensive crises, hyperthermia, cardiac arrest and/or serotonin syndrome.[55] Functional magnetic resonance imaging (fMRI) of rodents has shown that administration of MDPV results in desynchronisation of functional connectivity between the pre-frontal cortex and striatum, nucleus accumbens and the insular cortex.[56] More recent *in vitro* studies in neuronal, skeletal muscle and hepatic cells have demonstrated potentially cytotoxic effects of synthetic stimulant exposure, including mitochondrial dysfunction, glutathione depletion, oxidative stress and apoptosis pathway activation, which are aggravated under hyperthermic conditions; however, the extent to which these mechanisms are relevant to their effects *in vivo* remains unclear.[56–58]

Case reports have shown synthetic stimulants can induce acute intra-parenchymal and subarachnoid haemorrhages as well as ischemic infarction,[58] and α-PVP has been implicated in ST-elevation myocardial infarction (STEMI) with multiple intra-cardiac thrombi.[59] Intravenous methcathinone (M-CAT) use has been associated with the rare syndrome of manganese-associated Parkinsonism (as the preparation of M-CAT involves use of potassium permanganate) and cognitive impairment, which has been termed 'ephedrone encephalopathy'. Persistent globi pallidi hyperintensities on T1-weighted MRI have also been reported in those with this rare syndrome, and M-CAT use for longer than 6 months correlated with significant disability that did not improve despite drug cessation.[60]

A number of public health concerns associated with synthetic stimulants have been highlighted. The growing practice of 'slamming' during ChemSex [sexual activity engaged with multiple partners and often without protection, while under the influence of stimulant drugs, often with co-use of drugs such gamma-hydroxybutyrate (GHB) and related analogues] in which mephedrone and/or other stimulants are injected to enhance sexual activity has raised concerns regarding substance use disorders, and increased risk of injection site injury, blood-borne virus transmission and sexually transmitted diseases.[61] In Scotland, an increase in injection of NPS, including synthetic stimulants, was associated with contiguous increases in HCV infection.[62] Synthetic stimulants have been found in a number of products claiming to enhance 'brain health' and cognitive ability,[63] and those targeting athletes wanting to improve their performance.[64] Those with a diagnosis of attention deficit hyperactivity disorder (ADHD) have increasingly turned to the internet to source synthetic stimulants to help with their symptoms.[65,66] The harmful interactions between synthetic stimulants and prescription drugs, increasing the risk of drug toxicity or reducing the therapeutic efficacy of the drugs has also been highlighted.[67]

Synthetic cannabinoids

Synthetic cannabinoids emerged in the mid-2000s and were first formally identified and reported to the EMCDDA in 2008, initially being used as alternatives to herbal cannabis, particularly to avoid detection in those settings with forensic drug testing regimes such as prisons, sports programmes and the military.[68] They have since proliferated worldwide in many different structures, forms and potencies, and currently represent the largest and most structurally diverse class of NPS.[69,70] The UNODC have reported approximately 280 synthetic cannabinoids had been identified by the end of 2019.[71] They are typically manufactured and transported from producer countries as bulk powders, and, after dissolving in solvents such as acetone or methanol, are most commonly sprayed onto inert plant material (resembling traditional cannabis) or paper (to minimise risk of detection and facilitate access to forensic settings such as prisons) and either mixed with tobacco or smoked directly – inhalation being the main route of use.[72] Synthetic cannabinoids have been missold [e.g. as delta-9-tetrahydrocannabinol (d9-THC) or cannabidiol (CBD)], and

have been detected in formulations such as powders and as liquids for use in vaping devices, or tablets and capsules resembling ecstasy.[73]

Synthetic cannabinoids interact with the endocannabinoid system, which is involved in various physiological functions, including cognition, motor control, pain sensation, appetite, cardiovascular and respiratory performance, gastrointestinal motility and immunoregulation.[74] Positive experiences from use include relaxation, euphoria and disinhibition, which are similar to the desired effects of d9-THC, the main psychoactive component of traditional cannabis.[75]

However synthetic cannabinoids are associated with a wide range adverse effects, including cardiovascular and respiratory complications, haemodynamic embarrassment, renal injury and cerebrovascular accidents ('strokes').[76–80] There have been numerous reports of severe morbidity and mortality from synthetic cannabinoids, especially from use in prisons and other secure settings and in people who are homeless.[24,81–85] In England and Wales, synthetic cannabinoids comprised the largest proportion of NPS-related poisoning deaths in 2018,[85] with large outbreaks of intoxications also being reported in Europe.[86]

Chemical structures

The main classes of synthetic cannabinoids can be divided into the following major chemical classes: classical cannabinoids, carbazoles, cyclohexyl-substituted phenols, naphthoylindoles, the URB-class and benzoylindoles.[22,87] New synthetic cannabinoids are regularly developed by both legitimate and clandestine chemists, and these differ by the addition or removal of a substituent group,[88] making the pharmacological profiles of new compounds entering the market difficult to predict and monitor.[89] Synthetic cannabinoids demonstrate limited structural similarity to d9-THC, and are referred to as synthetic cannabinoids due to their pharmacological mechanisms.[90] Therefore, unless specifically included in reference databases they will typically not be detected in conventional drug screening procedures such as urine tests.[91]

Mechanism of action

Synthetic cannabinoids interact primarily with the endocannabinoid system, and its two specific G protein-coupled receptors: predominantly with the cannabinoid receptor type-1 (CB1) and, less frequently, with the cannabinoid receptor type-2 (CB2). The CB1 receptor is widespread throughout the brain, with particular concentration in the neocortex, basal ganglia and hippocampus, where they modulate pre-synaptic neurotransmitter release, and participate in a variety of brain function modulations, including executive, emotional, reward and memory.[92,93] The CB2 receptor, initially thought to be confined to immune cells and peripheral tissues, has recently also been found in cerebellum and brain stem neurons, where their roles remain an issue of active research.[94] Research into how synthetic cannabinoids modulate their effects *via* these receptors and the difference between the observed clinical effects of traditional cannabis and synthetic cannabinoids is ongoing, but current hypotheses include biased signalling at cannabinoid receptors or the disruption of mitochondrial homeostasis. Synthetic cannabinoids do not contain cannabidiol (the main neuro-protective compound found in natural cannabis which predominantly acts on CB2 receptors) and this may also be related to the increased toxicity observed with these compounds compared with natural cannabis.[95,96]

Synthetic cannabinoids have a greater potency and binding affinity than d9-THC at the cannabinoid receptors. They are full agonists compared with the partial agonist properties of d9-THC, with potency of 10–200 times greater than that of d9-THC. These differences likely underpin the emerging greater incidence of major psychiatric complications and other adverse effects compared with traditional cannabis.[96–99] A self-reported survey of 80,000 illicit substance users revealed that those who used synthetic cannabinoids were 30 times more likely to end up in an emergency department than users of traditional cannabis.[79]

Harms and adverse effects

There is currently no evidence for any therapeutic potential of synthetic cannabinoids with overwhelming reports of mild to severe adverse effects.[100] Most common mild-to-moderate adverse effects include nausea, protracted vomiting, agitation, drowsiness, dizziness, confusion, hypertension, tachycardia and chest pain, which typically have a limited duration and require only supportive treatment. There is growing evidence that renal injury is associated with a direct toxic effect upon the kidneys rather than an indirect effect due to dehydration (caused by vomiting) as was previously thought.[101,102] A wide range of serious physical health harms associated with synthetic

cannabinoid use has also been reported. These include convulsions and seizures,[103] rhabdomyolysis and hyperemesis syndrome,[104,105] supraventricular and ventricular arrhythmias,[106,107] pulmonary embolism,[107,108] intracranial hemorrhage,[109] delirium and multiple organ failure.[104,110] Serious mental health harms include paranoia, psychosis, aggression and violence towards others, self-harm and suicide. A trend of synthetic cannabinoid related toxicity has also been observed, with first generation compounds predominantly presenting with cannabis-like unwanted effects, second generation compounds with cardiovascular/stimulant toxicity and third generation compounds with neurological toxicity associated with central nervous system depression. [98,111–114]

Synthetic cannabinoid use has been associated with white matter abnormalities in adolescents and young adults, which may lead to cognitive impairment and vulnerability to psychosis.[115] MRI brain changes associated with synthetic cannabinoid toxicity reveal diverse findings, including embolic stroke, global hypoxic-ischaemic brain injury, demyelinating injury, and leptomeningeal enhancement.[116] These varied imaging findings may reflect the diverse actions of the endocannabinoid system, including its role in the regulation of cerebral perfusion, inflammatory responses and mitochondrial function.[70] Synthetic cannabinoids have been implicated in executive-function impairment either after acute or repeated consumptions.[117] Intense psychological withdrawal syndromes after use have also been described leading to a high addictive potential for synthetic cannabinoids, where users have been reported to use synthetic cannabinoids every 30 min to avoid feeling unwell.[118–120]

Public health concerns have been raised around the use of synthetic cannabinoids in vaping devices or water pipes and the subsequent development of serious lung injuries including acute respiratory distress syndrome and the diffuse alveolar haemorrhage.[121] Termed EVALI (e-cigarette, or vaping, product-use-associated lung injury), recent reports have highlighted the increasing association with either lipoid pneumonia, chemical pneumonitis or an organising pneumonia leading to respiratory complications including death.[121,122]

Synthetic hallucinogens

Synthetic hallucinogens (SH) include two main subcategories: hallucinogens and dissociatives.

Hallucinogens

Hallucinogens are typically further sub-divided into three classes: tryptamines, lysergamines and phenethylamines.[123] Most hallucinogens share a common mechanism of 5-HT2A receptor modulation of serotoninergic activity, although there is an increasing understanding of the role of the glutamatergic system, and some dissociative hallucinogens also have activity at κ opioid receptors.[124] Routes of use include inhalation, nasal insufflation, oral ingestion (pill or blotter paper), sublingual/buccal administration, and intravenous injection.[125–127]

Distributed throughout the brain and spinal cord, serotonin is involved in the control of a wide range of behavioural, perceptual, and regulatory systems, including mood, hunger, body temperature, sexual behaviour, muscle control, and sensory perception. Common sought after experiences include euphoria and joy, alterations in time/space perception, increased creativity and insight, accelerating and broadening thought processes and content, promoting novel thought associations, and providing psychedelic, spiritual and mystical experiences.[128] Common adverse effects include complications associated with serotonergic and sympathomimetic toxicity,[129] and a broad range of mental health crises.[130]

Chemical structure. The largest group of synthetic hallucinogens are the phenethylamine derivatives which are 2,5-dimethoxyphenethylamines, and contain a small lipophilic substituent at the 4-position, known as the 2C series because they possess two carbon atoms between the benzene ring and amino group.[131] Further derivatives are mostly but not exclusively chemically modified at the phenyl ring. The introduction of an N-benzylmethoxy ('NBOMe') group has resulted in an increase the potency of derivatives.[132]

Tryptamines are a group of monoamine alkaloids that are synthesised through decarboxylation of the amino acid tryptophan, and include compounds such as alpha-methyltryptamine (AMT), N,N-dimethyltryptamine (DMT), N,N-diallyl-5-methoxytryptamine (5-MeO-DALT) and 5-methoxy-N,N-disopropyltyptamine (5-MeO-DIPT) 'foxy methoxy'. They possess an indole ring structure, a bicyclical combination of a benzene ring and a pyrrole ring, with an amino group attached to a 2-carbon side chain.[133]

Synthetic derivatives of the ergot alkaloid derivative lysergic acid diethylamide (LSD) such as

1-acetyl-LSD (ALD-52), 1-propionyl-LSD (1P-LSD) and 1-butyryl-LSD (1B-LSD) have been shown to have very different pharmacological profiles and may differ significantly in their effects.[134,135]

Mechanism of action. Phenethylamine derivatives interact mainly with cortical serotonin receptors, with the highest affinity for 5-HT2A receptors.[136] NBOMe derivatives have higher affinity for 5-HT2A and 5-HT2C receptors and lower affinity for 5-HT1A receptors compared with their 2C analogues. Tryptamine derivatives have an affinity for 5-HT1A, 5-HT2A and 5-HT2C receptors, and can inhibit reuptake and increase the release of serotonin.[133] LSD analogues activate both 5-HT2A and 5-HT1A receptors.[137] Activation of 5-HT2A receptors causes glutamate release and activation of alpha-amino-3-hydroxy-methyl-5-4-isoxazolpropionic (AMPA) glutamatergic receptors, thus increasing cortical activity and information processing.[138]

Harms and adverse effects. Over the last 50 years, there has been ongoing interest and research into the use of the hallucinogen base compounds and their synthetic derivatives in the treatment of anxiety, depression and substance misuse disorders, and as an adjunct in psychotherapy. Data are currently encouraging, but lacking adequate evidence for use outside of scientific trials at this time.[139–142]

Common adverse effects primarily reported in studies of non-clinical use, shared across all three classes include tachycardia, hypertension, mydriasis, hyperthermia, agitation, aggression, hallucinations, drowsiness and confusion.[143–147] More serious adverse effects associated with phenethylamine derivatives, include multi-organ failure, psychosis, seizures and serotonin syndrome.[144] Serious adverse effects of tryptamine derivatives include prolonged delusions,[148] rhabdomyolysis and renal failure and a number of reported fatalities.[149,150] LSD derivative adverse effects include impaired thermoregulation, cardiovascular instability, difficulty concentrating, imbalance and exhaustion.[151]

Case reports have highlighted serious but relatively uncommon complications associated with toxicity of synthetic hallucinogens including an 'excited delirium' picture with severe agitation, aggression, and violence,[152] hyperreflexia and clonus,[130] and acute pulmonary oedema and hyperthermia leading to death.[153]

Dissociatives

The two main classes of dissociatives are arylcyclohexylamine [to which ketamine, phencyclidine (PCP) and methoxetamine (MXE) belong] and diarylethylamine. PCP was first synthesised in 1956 as an anaesthetic but largely withdrawn from frontline use because of its unfavourable side effects and abuse potential. Ketamine remains an important medicine in both specialist anaesthesia and aspects of pain management and is currently being studied as a rapid-acting antidepressant.[154] Both classes of dissociatives act as antagonists on the N-methyl-d-aspartate receptor (NMDAR).[155]

Routes of use include inhalation, nasal insufflation, oral ingestion and intravenous injection.[156] The sought after experiences include the sense of a disconnection between thoughts, identity, memory and consciousness, as well as sensory and tactile distortions, euphoria and depersonalisation. Common serious adverse effects include neurological impairment, renal and bladder injury.[129]

Chemical structure. All first-generation dissociatives are simple derivatives of PCP. The arylcyclohexylamine structure contains three distinct regions: an aromatic ring, a substituted cyclohexane ring, and a basic amine function. The first-generation dissociatives involved an aryl or amino substitution, without alteration of the cyclohexane ring. Retention of the cyclohexane ring provides for NMDAR affinity and therefore potency.[157] The latest generation of dissociatives, diarylethylamines, include 1-(1,2-diphenethyl) piperidine (diphenidine) and 1-[1-(2-methoxyphenyl)-2-phenylethyl] piperidine (2-MeO-diphenidine), and are also similar in structure to PCP.[158]

Mechanism of action. Similar to ketamine and PCP, dissociative arylcyclohexylamine and diarylethylamine drugs act as relatively selective non-competitive antagonists at the ionotropic glutamatergic NMDAR. Their NMDAR affinity is strongly correlated with their clinical potency in producing dissociative effects The NMDAR channels play an important role in synaptic plasticity and synapse formation underlying memory, learning and formation of neural networks during development in the central nervous system.[159] Ketamine has a predominant action at the NMDA receptors whereas PCP, methoxetamine, 3-MeO-PCP, 4-MeO-PCP and 3-MeO-PCE have actions at serotonin receptors which may explain some of their additional toxicity.[160]

Harms and adverse effects. Current research into the use of dissociatives in the treatment of a number of conditions is ongoing, including depression, pain management and palliative care.[161,162] Common adverse effects shared across both classes include nausea, diaphoresis, hypertension, tachycardia, renal impairment, agitation, disorientation, confusion, nystagmus, slurred speech, hallucinations, amnesia, ataxia and muscle rigidity.[163] Serious adverse effects include cerebellar toxicity, rhabdomyolysis, severe kidney and bladder damage and a number of fatal intoxications.[164]

In vitro studies have shown MXE to potently inhibit neuronal activity and alter monoamine metabolism.[165] Repeated parenteral administration of mMXE stimulates the mesolimbic dopaminergic transmission in rats, and affects brain functions and behaviour.[166] A similar study found that repeated parenteral administrations of MXE induced anxiety-like states and interfered with memory.[167] The same investigation also demonstrated that MXE induced persistent damage of dopaminergic neurons in the nigrostriatal and mesocorticolimbic systems, as well of serotonergic neurons in the nucleus accumbens core.[167] MXE use by humans has been associated with acute neurological impairment including psychomotor agitation and altered motor coordination,[168] and chronic bladder and urinary tract toxicity reported in mice.[169]

Case reports have reported serious adverse effects including seizures, hyponatremia, and sinus bradycardia,[170] neurological impairment with significant cerebellar toxicity and a number of fatalities associated with intoxication.[171–176]

Synthetic depressants

Synthetic depressants are broadly classified into two sub-categories: synthetic benzodiazepines and synthetic opiates. Their acute emergency presentations can appear similar – though treatments are different – but they differ in their impact on mental health.[24] Furthermore, among high-risk opioid users, benzodiazepines, especially when injected, can prolong the intensity and duration of the opioid effects.[177]

Synthetic benzodiazepines

Synthetic benzodiazepines are commonly consumed for non-medical purposes. Primary motivations for use overlap with clinical utility, such as hypnotic and anxiolytic effects, and to manage the acute effects of stimulants or to self-treat withdrawal symptoms, but they also produce a subjective 'high'.[178] Reports on internet forums also suggest that users experience anticonvulsant, muscle relaxant and amnesic properties.[179]

Chemical structure. The base structure is the fusion of a benzene ring and a diazepine ring, individual compounds varying widely according to additions to the base structure, for example, 2-keto compounds (diazepam), 3-hydroxy compounds (temazepam), 7-nitro compounds (clonazepam), Triazolo compounds (alprazolam) and Imidazo compounds (midazolam).[180]

Mechanism of action. A contemporary hypothesis is that novel benzodiazpeines mediate their effects through interactions at gamma-aminobutyric acid-A (GABA-A) receptors similar to prescription benzodiazepines.[181] GABA-A receptors are ion channels that consist of different subunit compositions, responding to the inhibitory neurotransmitter GABA. Synthetic benzodiazepines may enhance the effects of GABA as positive allosteric modulators by binding to a receptor site that is different from the binding site of GABA,[180,182] resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. Another mechanism of action reported includes activation of the mitochondrial translocator protein (TSPO) 18 kDa, which stimulates synthesis of neuroactive steroids, including allopregnanolone. 4-chlorodiazepam (Ro 5-4864) binds to this protein instead of GABA-A receptor, leading to anxiogenesis and an increased risk of seizures.[183] Some synthetic benzodiazepines have also been found to activate the AMPA glutamate receptor, leading to the rapid opening and closing of an ion channel that is permeable to cations (sodium, calcium and potassium); if inhibited, this results in an inhibition of central nervous system fast excitatory synaptic transmission. Tofisopam is a competitive antagonist at this receptor (and doesn't have GABA-A activity) and may cause anxiolytic actions without the sedative effects seen with other benzodiazepines.[184]

Harms and adverse effects. Data on the effects and harms of new synthetic benzodiazepines remains somewhat limited at this time, but early studies have shown anxiolytic, anticancer, anticonvulsant, antipsychotic, muscle relaxant, antituberculosis and antimicrobial actions.[179,185]

Adverse effects include a sedative-hypnotic toxidrome and can include confusion, dizziness, drowsiness fatigue, as well as auditory and visual hallucinations, delirium, seizures, deep sleep and coma,[184] and atypical symptoms such as agitation, hyperthermia and tachycardia.[186] Abrupt cessation may lead to withdrawal symptoms, such as anxiety, panic attacks, restlessness, insomnia and convulsions.[187] A number of fatalities have been reported, as well as the added risk in relation to toxicity due to the slower onset of action and longer half-life of some of the synthetic benzodiazepines (slower onset users take more doses than required; longer half-life toxicity is more prolonged).[188–191] Bentazepam has been associated with chronic hepatitis.[192]

Synthetic opioids

Opioids include opiates, semi-synthetic opioids and synthetic opioids. Opiates are natural substances that originate from *Papaver somniferum* (opium poppy), which contain more than 20 different subtypes.[193] Two of these, morphine and codeine, are two of the most common pain medications prescribed.[194] Synthetic opioids are created to bind to the same receptors in the brain as opiates, and produce similar effects such as euphoria, anxiolysis, feelings of relaxation and drowsiness. Undesirable side effects include nausea, dizziness, constipation, vomiting, tolerance and respiratory depression.[195]

The international opioid drug deaths epidemic is a source of much research and debate, but an examination of this is outside the scope of this review, and will be covered in a linked paper.[195–198] In Europe, 49 new synthetic opioids were detected between 2009 and 2018, 34 of which were fentanyl derivatives.[16] Whilst fentanyl itself is subject to international control, only some derivatives (e.g. carfentanil) are subject to international control at the time of writing. Recent evidence points to a problematic surge in the availability of heroin mixed with fentanyl (cheaper and easier to obtain than pure heroin) leading to an increased risked of morbidity and mortality for the user, who is normally unaware of the addition of the synthetic opioid.[199–201]

Chemical structure. The chemical structure of opioids is subdivided into those based the 4,5-epoxymorphinan ring (e.g. morphine), the phenylpiperidines (e.g. fentanyl) and the diphenylheptylamines (e.g. methadone). Synthetic opioids are modifications of each of these base compounds.[202]

Mechanism of action. Synthetic opioids analogues interact with G protein-coupled opioid receptors in the brain and spinal cord as partial to full agonists at mu, delta and kappa opioid receptor subtypes, with selectivity for the mu opioid receptor.[203,204] Agonism at mu opioid receptors is responsible for the main pharmacological effects of opioids, including euphoria, analgesia and respiratory depression, as well as the development of dependence.[205] Many synthetic opioids are considerably more potent than traditional opioids. The potency of fentanyl (acting on the mu opioid receptor) is 50- to 200-fold higher than morphine, and that of carfentanil (also on the mu opioid receptor) approximately 10,000 times higher than morphine.[203,206]

Harms and adverse effects. Synthetic opioid adverse effects range from mild (pruritus, nausea, vomiting, constipation, dizziness) to severe (respiratory depression, apnoea and central nervous system depression).[207,208] Intoxication with synthetic opioids has been associated with non-cardiogenic pulmonary oedema, acute lung injury, diffuse alveolar haemorrhage and rhabdomyolysis.[209,210] Withdrawal from synthetic opioids may present with physiological and psychological distress.[211] Statistics on morbidity and mortality may not reflect the real-life situation as users may recover, for example, from a mixed heroin/synthetic opioid overdose when naloxone is administered and the illicit drug documented will then be heroin and not a synthetic one.[212,213] In the STRIDA project from Sweden, it was reported that there were a number of cases of toxicity related to the use of MT-45 (a synthetic opioid) that, in addition to typical opioid-like toxicity, was also associated with hearing loss and/or deafness.[214,215]

Laboratory testing

Testing for NPS in clinical and forensic settings can be a complex task, as routine testing of such compounds in individuals who present with recreational drug toxicity is not typically undertaken, and the validity and reliability of test kits varies considerably in detecting these many new agents. Furthermore, in clinical practice, patients are typically treated on the basis of the pattern of toxicity they present with, and the turn-around time for a standard and comprehensive NPS screen would

often mean that the results are not available in a time-frame that would alter the clinical management of the patient.[17] Test designs also need to take into account that users of NPS will be likely to use additional over-the-counter medication, other illicit drugs,[216,217] and that NPS preparations themselves may be contaminated with other illicit drugs,[218] or dissolved in diluents.[219]

The Novel Psychoactive Treatment UK Network (NEPTUNE) recognise the current limitations in the availability of timely clinical testing available during acute presentations of NPS toxicity, and currently recommend toxicity diagnoses are made primarily on clinical features rather than by testing. However, NPS toxidromes may be highly non-specific (such as synthetic stimulant and synthetic cannabinoid toxicity) and, as noted, users may have taken multiple NPS or other substances simultaneously, making identification of a likely causative NPS class(es) from clinical features alone difficult. As such, reliable and clinically validated testing for NPS from human samples are clearly of value. Colorimetric tests, immunoassays and mass spectrometry-based techniques have been employed in the detection of NPS. A recent systematic review reported that relatively few tests are able to detect more than 50 NPS types.[220] Colorimetric methods are based on a target compound reacting with a reagent to produce a detectable colour change. They are easy to use, portable, point-of-use tests, with limited need for sample pre-preparation. The disadvantages include user variability in detecting colour-changes, cross-reactivity (associated with false-positive results), in addition to the limited range of individual NPS compounds that may be tested for in a single sample.[220]

Immunoassays for NPS allow for potentially rapid testing, and are suitable for testing non-invasively obtained samples (typically urine samples, or dissolved drugs). Lateral flow immune-chromatographic assays have been used in harm-reduction trials where opiate users were encouraged to self-test drugs for the presence of fentanyl.[221] Commercially available immunoassays are limited to testing for relatively small selections of NPS. The sensitivity of commercially available immunoassay testing may also be limited, with a study of cross-reactivity amongst five commercially-available immunoassay kits reported to have failed to detect 13 of 94 (14%) NPS samples tested.[222]

Gas and liquid chromatographic mass spectrometry-based methods offer more sensitive and specific identification of individual NPS, and allow for quantification of NPS within biological samples. These techniques can allow for sampling across a range of biological samples, including blood, urine, hair,[223] saliva,[224] urban wastewater and dried blood samples.[225,226] Samples for analysis require laboratory pre-preparation before being used for these techniques, though so-called 'dilute and shoot' techniques are being validated to allow for more rapid preparation of biological samples for liquid chromatography mass spectrometry.[227,228] Liquid chromatography with quadrupole time of flight mass spectrometry (LC-QTOF MS) has demonstrated some superiority to gas chromatography mass spectroscopy (GC MS) in detecting most forms of NPS within serum samples.[227] Databases of spectral information from known NPS chemical structures are currently being built and validated, to allow for identification of known (and potentially unknown) substances based on the technique used.[228,229]

Conclusion

NPS comprise a diverse and ever-growing group of substances. There is much we still do not know, especially about the newest agents, and they can vary considerably in their desired effects and harms, even within drug classes. The classification system that has been used for this review has arisen for reasons of practicality and clinical utility, though this means that it inevitably has some limitations. The currently used four separate classification system groups together compounds with highly varied chemical structures (such as the synthetic cannabinoids), or mechanistically heterogeneous compounds (such as the hallucinogens and depressants) in a practical workable system for clinicians, scientists, law enforcement agencies and other interested parties.

Even with this broad classification system there remains considerable overlap between some groups of NPS (such as the 2-C series, 5-MeO DALT, and NBOMe- series), which may have characteristics in terms of their pharmacology, desired effects and/or unwanted effects that fit within more than one of the classification groups.

Much of the literature on health effects of NPS is derived from self-reports, and small case series, which are very likely to be subject to a variety of selection and recall biases. Given the nature of NPS and their use, the reliance on small case series and self-reports is unsurprising. In the UK,

national advisory bodies such as NEPTUNE and UK National Poisons Information Service (NPIS) are likely to be able to monitor trends of NPS use in a more rigorous and prospective manner. A network of emergency departments in Europe have collaborated to form the European Drug Emergencies Network Plus (EuroDEN-Plus) project, to better understand the pattern of toxicity associated with NPS clinical presentations.[230–233]

Clearly there is a need for healthcare and emergency professionals who are likely to encounter NPS use to remain up-to-date with clinical features of NPS use, and evidence-based approaches to harm-minimisation and treatment of dependence syndromes need to be developed. These should ideally be developed in conjunction with the experiences of NPS users themselves. Whether the current popularity of NPS use will continue remains uncertain, and there is comparatively little evidence regarding NPS use in lower- or middle-income countries, where NPS use may be particularly likely to be associated with societal harm.

Clinicians treating individuals who present with harms related to the use of NPS may feel less confident in managing those patients compared with patients who present following the use of classical recreational drugs.[234] However, since the management of both groups of individuals is typically based on the presenting clinical features rather than the specific drug(s) involved, clinicians should feel more confident in utilising the knowledge, skills and experience in managing classical recreational drugs to any individual who presents with acute recreational drug/NPS toxicity.

Further research is needed on the neuropsychological consequences of NPS use, given the apparent neurotoxic effects associated with NPS use. Recently developed novel radiotracers for use in positron emission tomography (PET) for CB1 and CB2 receptors, as well as hydrolytic enzymes of the endocannabinoid system, may be of use in identifying changes *in vivo* in those with sustained and acute synthetic cannabinoid (and other NPS) use.[235]

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