

# New psychoactive substances: a review and updates

Abu Shafi, Alex J. Berry, Harry Sumnall, David M. Wood and Derek K. Tracy 

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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’.<sup>1,2</sup> 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.<sup>3–5</sup> 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’.<sup>6,7</sup>

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’.<sup>8</sup> 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.<sup>2,9,10</sup> 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.<sup>11</sup> 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

Correspondence to:

**Derek K. Tracy**  
Consultant Psychiatrist,  
Oxleas NHS Foundation  
Trust, London, UK

Department of Psychosis  
Studies, the Institute of  
Psychiatry, Psychology  
and Neuroscience,  
King’s College London,  
DeCrespigny Park,  
London, SE5 8AF, UK  
[Derek.tracy@nhs.net](mailto:Derek.tracy@nhs.net)

**Abu Shafi**  
East London Foundation  
Trust, London, UK

**Alex J. Berry**  
Division of Psychiatry,  
University College London,  
UK

**Harry Sumnall**  
Liverpool John Moores  
University, UK

**David M. Wood**  
Clinical Toxicology, Guy’s  
and St Thomas’ NHS  
Foundation Trust, London,  
UK

Clinical Toxicology, Faculty  
of Life Sciences and  
Medicine, King’s College  
London, London, UK

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.<sup>4,12,13</sup> 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.<sup>14</sup>

By 2018, a total of 892 individual NPS, reported by 119 countries, were being monitored by the UNODC early warning system,<sup>15</sup> and by the end of 2018, over 730 NPS had been notified to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).<sup>16</sup> The rapid proliferation at which new NPS have emerged on the global drugs market is unparalleled,<sup>17</sup> and it was estimated that at its peak in 2015, new NPS appeared at a rate of at least one new substance per week.<sup>18</sup> 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.<sup>16</sup> 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.<sup>19–21</sup>

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.<sup>22</sup> 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.<sup>23</sup> 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).<sup>23</sup>

Although research suggests that NPS are associated with harms in key populations such as people who are homeless or prisoners,<sup>24</sup> 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).<sup>25</sup> 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.<sup>26</sup>

The term new psychoactive substance is a legal definition and there is no universally agreed way to categorise NPS.<sup>27</sup> 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.<sup>27,28</sup>

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.<sup>29</sup> Currently, they represent the largest group of NPS that are monitored by the UNODC and EMCDDA.<sup>16,17</sup> They are designed to replicate the effects of traditional stimulant controlled drugs, such as cocaine, MDMA and amphetamines.<sup>30</sup> 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.<sup>31</sup> 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').<sup>32</sup> Synthetic stimulants act on the two neurotransmitter systems to different extents, accounting for their differing range of desired and unwanted effects.<sup>26,33</sup> 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.<sup>33,34</sup> 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.<sup>35–37</sup>

### 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 (methylo) and 3,4-methylenedioxypyrovalerone (MDPV) followed by a second generation consisting of 4-methyl-N-ethylcathinone (4-MEC), 4-fluoromethcathinone (fephedrone, 4-FMC), its positional isomer 3-fluoromethcathinone (3-FMC) and  $\alpha$ -PVP ( $\alpha$ -pyrrolidinopentiophenone). Synthetic cathinones are similar in structure to amphetamine type stimulants and are chemically referred to as  $\beta$ -ketone analogues because of the carbonyl (=O) group in  $\beta$  carbon.<sup>38,39</sup> The common pharmacophore group responsible for the psychoactive effect observed in synthetic stimulants is phenethylamine,<sup>32</sup> and its derivatives are reported to represent at least 37% of the NPS available on the illicit drug market.<sup>40</sup>

Synthetic stimulants structurally similar to pyrovalerone (a psychoactive drug once used in the treatment of chronic fatigue and lethargy) such as MDPV,<sup>41</sup> 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.<sup>42,43</sup> 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'.<sup>44</sup>

### 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.<sup>45</sup> 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.<sup>46</sup> 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.<sup>47–50</sup>

### 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.<sup>29,51</sup> 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.<sup>52,53</sup> 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.<sup>54</sup> 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.<sup>55</sup> 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.<sup>56</sup> 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.<sup>56–58</sup>

Case reports have shown synthetic stimulants can induce acute intra-parenchymal and subarachnoid haemorrhages as well as ischemic infarction,<sup>58</sup> and  $\alpha$ -PVP has been implicated in ST-elevation myocardial infarction (STEMI) with multiple intra-cardiac thrombi.<sup>59</sup> 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.<sup>60</sup>

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 as 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.<sup>61</sup> In Scotland, an increase in injection of NPS, including synthetic stimulants, was associated with contiguous increases in HCV infection.<sup>62</sup> Synthetic stimulants have been found in a number of products claiming to enhance 'brain health' and cognitive ability,<sup>63</sup> and those targeting athletes wanting to improve their performance.<sup>64</sup> 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.<sup>65,66</sup> 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.<sup>67</sup>

### 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.<sup>68</sup> They have since proliferated worldwide in many different structures, forms and potencies, and currently represent the largest and most structurally diverse class of NPS.<sup>69,70</sup> The UNODC have reported approximately 280 synthetic cannabinoids had been identified by the end of 2019.<sup>71</sup> 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.<sup>72</sup> Synthetic cannabinoids have been misused [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.<sup>73</sup>

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.<sup>74</sup> 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.<sup>75</sup>

However synthetic cannabinoids are associated with a wide range adverse effects, including cardiovascular and respiratory complications, haemodynamic embarrassment, renal injury and cerebrovascular accidents ('strokes').<sup>76–80</sup> 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.<sup>24,81–85</sup> In England and Wales, synthetic cannabinoids comprised the largest proportion of NPS-related poisoning deaths in 2018,<sup>85</sup> with large outbreaks of intoxications also being reported in Europe.<sup>86</sup>

### 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.<sup>22,87</sup> New synthetic cannabinoids are regularly developed by both legitimate and clandestine chemists, and these differ by the addition or removal of a substituent group,<sup>88</sup> making the pharmacological profiles of new compounds entering the market difficult to predict and monitor.<sup>89</sup> Synthetic cannabinoids demonstrate limited structural similarity to d9-THC, and are referred to as synthetic cannabinoids due to their pharmacological mechanisms.<sup>90</sup> Therefore, unless specifically included in reference databases they will typically not be detected in conventional drug screening procedures such as urine tests.<sup>91</sup>

### 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 neo-cortex, 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.<sup>92,93</sup> 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.<sup>94</sup> 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.<sup>95,96</sup>

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.<sup>96–99</sup> 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.<sup>79</sup>

### 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.<sup>100</sup> 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.<sup>101,102</sup> A wide range of serious physical health harms associated with synthetic

cannabinoid use has also been reported. These include convulsions and seizures,<sup>103</sup> rhabdomyolysis and hyperemesis syndrome,<sup>104,105</sup> supraventricular and ventricular arrhythmias,<sup>106,107</sup> pulmonary embolism,<sup>107,108</sup> intracranial hemorrhage,<sup>109</sup> delirium and multiple organ failure.<sup>104,110</sup> 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.<sup>98,111–114</sup>

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.<sup>115</sup> MRI brain changes associated with synthetic cannabinoid toxicity reveal diverse findings, including embolic stroke, global hypoxic-ischaemic brain injury, demyelinating injury, and leptomeningeal enhancement.<sup>116</sup> 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.<sup>70</sup> Synthetic cannabinoids have been implicated in executive-function impairment either after acute or repeated consumptions.<sup>117</sup> 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.<sup>118–120</sup>

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.<sup>121</sup> Termed EVALI (e-cigarette, or vaping, product-use-associated lung injury), recent reports have highlighted the increasing association with either lipid pneumonia, chemical pneumonitis or an organising pneumonia leading to respiratory complications including death.<sup>121,122</sup>

### 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.<sup>123</sup> Most hallucinogens share a common mechanism of 5-HT<sub>2A</sub> receptor modulation of serotonergic activity, although there is an increasing understanding of the role of the glutamatergic system, and some dissociative hallucinogens also have activity at  $\kappa$  opioid receptors.<sup>124</sup> Routes of use include inhalation, nasal insufflation, oral ingestion (pill or blotter paper), sublingual/buccal administration, and intravenous injection.<sup>125–127</sup>

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.<sup>128</sup> Common adverse effects include complications associated with serotonergic and sympathomimetic toxicity,<sup>129</sup> and a broad range of mental health crises.<sup>130</sup>

**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.<sup>131</sup> 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.<sup>132</sup>

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-disopropyltryptamine (5-MeO-DIPT) 'foxy methoxy'. They possess an indole ring structure, a bicyclic combination of a benzene ring and a pyrrole ring, with an amino group attached to a 2-carbon side chain.<sup>133</sup>

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.<sup>134,135</sup>

**Mechanism of action.** Phenethylamine derivatives interact mainly with cortical serotonin receptors, with the highest affinity for 5-HT<sub>2A</sub> receptors.<sup>136</sup> NBOMe derivatives have higher affinity for 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors and lower affinity for 5-HT<sub>1A</sub> receptors compared with their 2C analogues. Tryptamine derivatives have an affinity for 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors, and can inhibit reuptake and increase the release of serotonin.<sup>133</sup> LSD analogues activate both 5-HT<sub>2A</sub> and 5-HT<sub>1A</sub> receptors.<sup>137</sup> Activation of 5-HT<sub>2A</sub> 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.<sup>138</sup>

**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.<sup>139–142</sup>

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.<sup>143–147</sup> More serious adverse effects associated with phenethylamine derivatives, include multi-organ failure, psychosis, seizures and serotonin syndrome.<sup>144</sup> Serious adverse effects of tryptamine derivatives include prolonged delusions,<sup>148</sup> rhabdomyolysis and renal failure and a number of reported fatalities.<sup>149,150</sup> LSD derivative adverse effects include impaired thermoregulation, cardiovascular instability, difficulty concentrating, imbalance and exhaustion.<sup>151</sup>

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,<sup>152</sup> hyperreflexia and clonus,<sup>130</sup> and acute pulmonary oedema and hyperthermia leading to death.<sup>153</sup>

## 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.<sup>154</sup> Both classes of dissociatives act as antagonists on the N-methyl-D-aspartate receptor (NMDAR).<sup>155</sup>

Routes of use include inhalation, nasal insufflation, oral ingestion and intravenous injection.<sup>156</sup> 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.<sup>129</sup>

**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.<sup>157</sup> 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.<sup>158</sup>

**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.<sup>159</sup> 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.<sup>160</sup>

**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.<sup>161,162</sup> 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.<sup>163</sup> Serious adverse effects include cerebellar toxicity, rhabdomyolysis, severe kidney and bladder damage and a number of fatal intoxications.<sup>164</sup>

*In vitro* studies have shown MXE to potentially inhibit neuronal activity and alter monoamine metabolism.<sup>165</sup> Repeated parenteral administration of mMXE stimulates the mesolimbic dopaminergic transmission in rats, and affects brain functions and behaviour.<sup>166</sup> A similar study found that repeated parenteral administrations of MXE induced anxiety-like states and interfered with memory.<sup>167</sup> 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.<sup>167</sup> MXE use by humans has been associated with acute neurological impairment including psychomotor agitation and altered motor coordination,<sup>168</sup> and chronic bladder and urinary tract toxicity reported in mice.<sup>169</sup>

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

### 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.<sup>24</sup> Furthermore, among high-risk opioid users, benzodiazepines, especially when injected, can prolong the intensity and duration of the opioid effects.<sup>177</sup>

#### 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’.<sup>178</sup> Reports on internet forums also suggest that users experience anticonvulsant, muscle relaxant and amnesic properties.<sup>179</sup>

**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).<sup>180</sup>

**Mechanism of action.** A contemporary hypothesis is that novel benzodiazepines mediate their effects through interactions at gamma-aminobutyric acid-A (GABA-A) receptors similar to prescription benzodiazepines.<sup>181</sup> 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,<sup>180,182</sup> 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.<sup>183</sup> 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.<sup>184</sup>

**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, anti-tuberculosis and antimicrobial actions.<sup>179,185</sup>



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,<sup>184</sup> and atypical symptoms such as agitation, hyperthermia and tachycardia.<sup>186</sup> Abrupt cessation may lead to withdrawal symptoms, such as anxiety, panic attacks, restlessness, insomnia and convulsions.<sup>187</sup> 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).<sup>188–191</sup> Bentazepam has been associated with chronic hepatitis.<sup>192</sup>

### *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.<sup>193</sup> Two of these, morphine and codeine, are two of the most common pain medications prescribed.<sup>194</sup> 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.<sup>195</sup>

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.<sup>195–198</sup> In Europe, 49 new synthetic opioids were detected between 2009 and 2018, 34 of which were fentanyl derivatives.<sup>16</sup> 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 risk of morbidity and mortality for the user, who is normally unaware of the addition of the synthetic opioid.<sup>199–201</sup>

**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.<sup>202</sup>

**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.<sup>203,204</sup> 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.<sup>205</sup> 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.<sup>203,206</sup>

**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).<sup>207,208</sup> Intoxication with synthetic opioids has been associated with non-cardiogenic pulmonary oedema, acute lung injury, diffuse alveolar haemorrhage and rhabdomyolysis.<sup>209,210</sup> Withdrawal from synthetic opioids may present with physiological and psychological distress.<sup>211</sup> 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.<sup>212,213</sup> 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.<sup>214,215</sup>

### **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.<sup>17</sup> 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,<sup>216,217</sup> and that NPS preparations themselves may be contaminated with other illicit drugs,<sup>218</sup> or dissolved in diluents.<sup>219</sup>

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.<sup>220</sup> 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.<sup>220</sup>

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.<sup>221</sup> 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.<sup>222</sup>

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,<sup>223</sup> saliva,<sup>224</sup> urban wastewater and dried blood samples.<sup>225,226</sup> 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.<sup>227,228</sup> 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.<sup>227</sup> 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.<sup>228,229</sup>

## 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.<sup>230–233</sup>

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.<sup>234</sup> 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.<sup>235</sup>

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### ORCID iD

Derek K Tracy  <https://orcid.org/0000-0002-3609-9407>

### References

1. Luethi D and Liechti ME. Designer drugs: mechanism of action and adverse effects. *Arch Toxicol* 2020; 94: 1085–1133.
2. Peacock A, Bruno R, Gisev N, *et al.* New psychoactive substances: challenges for drug surveillance, control, and public health responses. *Lancet* 2019; 394: 1668–1684.
3. Soussan C and Kjellgren A. The users of novel psychoactive substances: online survey about their characteristics, attitudes and motivations. *Int J Drug Policy* 2016; 32: 77–84.
4. O'Hagan A and McCormack S. To what extent has the United Kingdom law on psychoactive substances been successful? *Forensic Res Criminol* 2019; 7: 176–183.
5. Batisse A, Eiden C, Peyriere H, *et al.* Use of new psychoactive substances to mimic prescription drugs: the trend in France. *Neurotoxicology* 2020; 79: 20–24.
6. Griffiths P, Sedefov R, Gallegos A, *et al.* How globalization and market innovation challenge how we think about and respond to drug use: 'Spice' a case study. *Addiction* 2010; 105: 951–953.
7. Zawilska JB and Andrzejczak D. Next generation of novel psychoactive substances on the horizon – a complex problem to face. *Drug Alcohol Depend* 2015; 157: 1–17.
8. United Nations Office on Drugs and Crime. Global smart update 2016, <https://www.unodc.org/documents/scientific/Global-SMART-Update-2016-vol-16.pdf> (accessed 4 April 2020).
9. Hill RG. Understanding the UK Psychoactive Substances Act. *Br J Clin Pharmacol* 2020; 86: 499–504.
10. Corkery JM, Schifano F and Martinotti G. British Journal of Clinical Pharmacology themed issue on new psychoactive substances: pharmacology influencing practice, policy and the law. *Br J Clin Pharmacol* 2019; 86.
11. Legislation. Psychoactive substances act 2016, <http://www.legislation.gov.uk/ukpga/2016/2/contents/enacted> (accessed 4 April 2020).
12. Nutt D. New psychoactive substances: pharmacology influencing UK practice, policy

- and the law. *Br J Clin Pharmacol* 2020; 86: 445–451.
13. Reuter P and Pardo B. Can new psychoactive substances be regulated effectively? An assessment of the British Psychoactive Substances Bill. *Addiction* 2017; 112: 25–31.
14. Home Office. *Review of the Psychoactive Substances Act 2016*. London: Home Office, 2018.
15. United Nations Office on Drugs and Crime. Current NPS threats March 2019, [https://www.unodc.org/documents/scientific/Current\\_NPS\\_Threats\\_Volume\\_I.pdf](https://www.unodc.org/documents/scientific/Current_NPS_Threats_Volume_I.pdf) (accessed 4 April 2020).
16. European Monitoring Centre for Drugs and Drug Addiction. European drug report 2019: trends and developments, [http://www.emcdda.europa.eu/system/files/publications/11364/20191724\\_TDAT19001ENN\\_PDF.pdf](http://www.emcdda.europa.eu/system/files/publications/11364/20191724_TDAT19001ENN_PDF.pdf) (2019). (accessed 4 April 2020).
17. Chung H, Lee J and Kim E. Trends of novel psychoactive substances (NPSs) and their fatal cases. *Forensic Toxicol* 2016; 34: 1–11.
18. United Nations Office on Drugs and Crime. Understanding the synthetic drug market: the NPS factor, [https://www.unodc.org/documents/scientific/Global\\_Smart\\_Update\\_2018\\_Vol.19.pdf](https://www.unodc.org/documents/scientific/Global_Smart_Update_2018_Vol.19.pdf) (accessed 4 April 2020).
19. Al-Banaa I, Hawkins L, Hill SL, *et al.* Effect of the UK Psychoactive Substances Act 2016 on episodes of toxicity related to new psychoactive substances as reported to the National Poisons Information Service. A time series analysis. *Int J Drug Policy* 2020; 77: 102672.
20. Rinaldi R, Bersani G, Marinelli E, *et al.* The rise of new psychoactive substances and psychiatric implications: a wide-ranging, multifaceted challenge that needs far-reaching common legislative strategies. *Hum Psychopharmacol* 2020; 35: e2727.
21. Dinis-Oliveira RJ and Magalhães T. Abuse of licit and illicit psychoactive substances in the workplace: medical, toxicological, and forensic aspects. *J Clin Med* 2020; 9: 770.
22. Potts AJ, Cano C, Thomas SHL, *et al.* Synthetic cannabinoid receptor agonists: classification and nomenclature. *Clin Toxicol (Phila)* 2020; 58: 82–98.
23. Home Office. Drugs misuse: findings from the 2018/19 crime survey for England and Wales. *Statistical Bulletin*: 21/19, [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/832533/drug-misuse-2019-hosb2119.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832533/drug-misuse-2019-hosb2119.pdf) (accessed 19 September 2019).
24. Ralphs R, Williams L, Askew R, *et al.* Adding spice to the porridge: the development of a synthetic cannabinoid market in an English prison. *Int J Drug Policy* 2017; 40: 57–69.
25. Public Health England. *Adult substance misuse statistics 2018 to 2019: report*. London: Public Health England, 2019.
26. Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2018 registrations, <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/death-related-to-drug-poisoning-in-england-and-wales/2018-registrations> (accessed 11 April 2020).
27. Tracy DK, Wood DM and Baumeister D. Novel psychoactive substances: types, mechanisms of action, and effects. *BMJ* 2017; 356: i6848.
28. Miliano C, Serpelloni G, Rimondo C, *et al.* Neuropharmacology of new psychoactive substances (NPS): focus on the rewarding and reinforcing properties of cannabimimetics and amphetamine-like stimulants. *Front Neurosci* 2016; 10: 153.
29. Valente MJ, de Pinho PG, de Lourdes Bastos M, *et al.* Khat and synthetic cathinones: a review. *Arch Toxicol* 2014; 88: 15–45.
30. Prosser JM and Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol* 2012; 8: 33–42.
31. Karila L, Megarbane B, Cottencin O, *et al.* Synthetic cathinones: a new public health problem. *Curr Neuropsychopharmacol* 2015; 13: 12–20.
32. Banks ML, Worst TJ, Rusyniak DE, *et al.* Synthetic cathinones (“bath salts”). *J Emerg Med* 2014; 46: 632–642.
33. German CL, Fleckenstein AE and Hanson GR. Bath salts and synthetic cathinones: an emerging designer drug phenomenon. *Life Sci* 2014; 97: 2–8.
34. Coppola M and Mondola R. Synthetic cathinones: chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as “bath salts” or “plant food”. *Toxicol Lett* 2012; 211: 144–149.
35. Zawilska JB and Wojcieszak J. Novel psychoactive substances: classification and general information. In: Zawilska JB (ed.) *Synthetic cathinones*. Cham: Springer, 2018, pp.11–24.
35. Weinstein AM, Rosca P, Fattore L, *et al.* Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health. *Front Psychiatry* 2017; 8: 156.



37. Archer T and Kostrzewa RM. Synthetic cathinones: neurotoxic health hazards and potential for abuse. In: Zawilska JB (ed.) *Synthetic cathinones*. Cham: Springer, 2018, pp.1–10.
38. Angoa-Pérez M, Zagorac B, Winters AD, *et al.* Differential effects of synthetic psychoactive cathinones and amphetamine stimulants on the gut microbiome in mice. *PLoS One* 2020; 15: e0227774.
39. Wo niak MK, Banaszkiewicz L, Wierowski M, *et al.* Development and validation of a GC–MS/MS method for the determination of 11 amphetamines and 34 synthetic cathinones in whole blood. *Forensic Toxicol* 2020; 38: 42–58.
40. Mercieca G, Odoardi S, Cassar M, *et al.* Rapid and simple procedure for the determination of cathinones, amphetamine-like stimulants and other new psychoactive substances in blood and urine by GC–MS. *J Pharm Biomed Anal* 2018; 149: 494–501.
41. Baumann MH, Partilla JS and Lehner KR. Psychoactive “bath salts”: not so soothing. *Eur J Pharmacol* 2013; 698: 1–5.
42. Eastlack SC, Cornett EM and Kaye AD. Kratom—pharmacology, clinical implications, and outlook: a comprehensive review. *Pain Ther* 2020; 9: 55–69.
43. Nóbrega L and Dinis-Oliveira RJ. The synthetic cathinone  $\alpha$ -pyrrolidinovalerophenone ( $\alpha$ -PVP): pharmacokinetic and pharmacodynamic clinical and forensic aspects. *Drug Metab Rev* 2018; 50: 125–139.
44. Altun B and Çok . Psychoactive bath salts and neurotoxicity risk. *Turk J Pharm Sci* 2020; 17: 235–241.
45. Katz DP, Bhattacharya D, Bhattacharya S, *et al.* Synthetic cathinones: “a khat and mouse game”. *Toxicol Lett* 2014; 229: 349–356.
46. Cozzi NV, Sievert MK, Shulgin AT, *et al.* Inhibition of plasma membrane monoamine transporters by  $\beta$ -ketoamphetamines. *Eur J Pharmacol* 1999; 381: 63–69.
47. Marusich JA, Antonazzo KR, Wiley JL, *et al.* Pharmacology of novel synthetic stimulants structurally related to the “bath salts” constituent 3, 4-methylenedioxypyrovalerone (MDPV). *Neuropharmacology* 2014; 87: 206–213.
48. Baumann MH, Ayestas MA Jr, Partilla JS, *et al.* The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology* 2012; 37: 1192–1203.
49. Cameron K, Kolanos R, Verkariya R, *et al.* Mephedrone and methylenedioxypyrovalerone (MDPV), major constituents of “bath salts,” produce opposite effects at the human dopamine transporter. *Psychopharmacology* 2013; 227: 493–499.
50. Eshleman AJ, Wolfrum KM, Hatfield MG, *et al.* Substituted methcathinones differ in transporter and receptor interactions. *Biochem Pharmacol* 2013; 85: 1803–1815.
51. Dal Cason TA, Young R and Glennon RA. Cathinone: an investigation of several N-alkyl and methylenedioxy-substituted analogs. *Pharmacol Biochem Behav* 1997; 58: 1109–1116.
52. Hupli A. Cognitive enhancement with licit and illicit stimulants in the Netherlands and Finland: what is the evidence? *Drugs Alcohol Today* 2020; 20: 62–73.
53. Salahshour B, Sadeghi S, Nazari H, *et al.* Determining undeclared synthetic pharmaceuticals as adulterants in weight loss herbal medicines. *Int J Med Toxicol Forensic Med* 2020; 10: 26253.
54. Drug Enforcement Administration. *Drugs of abuse: a DEA resource guide*. Springfield, VA: Drug Enforcement Administration, US Department of Justice, 2017.
55. Franzén L, Bäckberg M, Beck O, *et al.* Acute intoxications involving  $\alpha$ -pyrrolidinobutylphenone ( $\alpha$ -PBP): results from the Swedish STRIDA project. *J Med Toxicol* 2018; 14: 265–271.
56. Colon-Perez LM, Tran K, Thompson K, *et al.* The psychoactive designer drug and bath salt constituent MDPV causes widespread disruption of brain functional connectivity. *Neuropsychopharmacology* 2016; 41: 2352–2365.
57. Luethi D, Walter M, Zhou X, *et al.* **Para**-halogenation affects monoamine transporter inhibition properties and hepatocellular toxicity of amphetamines and methcathinones. *Front Pharmacol* 2019; 10: 438.
58. Majchrzak M, Celiński R, Kowalska T, *et al.* Fatal case of poisoning with a new cathinone derivative:  $\alpha$ -propylaminopentylphenone (N-PP). *Forensic Toxicol* 2018; 36: 525–533.
59. Cherry SV and Rodriguez YF. Synthetic stimulant reaching epidemic proportions: flakka-induced ST-elevation myocardial infarction with intracardiac thrombi. *J Cardiothorac Vasc Anaesth* 2017; 31: e13–e14.
60. Okujava M, Todua F, Janelidze M, *et al.* Pattern of MRI findings in ephedronic encephalopathy.

- In: *Movement disorders*. Vol. 32. Hoboken, NJ: Wiley, 2017, pp.805–949.
61. Trouiller P, Velter A, Saboni L, *et al*. Injecting drug use during sex (known as “slamming”) among men who have sex with men: results from a time-location sampling survey conducted in five cities, France. *Int J Drug Policy* 2020; 79: 102703.
62. McAuley A, Yeung A, Goldberg DJ, *et al*. Emergence of novel psychoactive substance injecting associated with rapid rise in the population prevalence of hepatitis C virus. *Int J Drug Policy* 2019; 66: 30–37.
63. Crawford C, Boyd C, Avula B, *et al*. A public health issue: dietary supplements promoted for brain health and cognitive performance. *J Altern Complement Med* 2020; 26: 265–272.
64. Zahnow R, McVeigh J, Bates G, *et al*. Motives and correlates of anabolic-androgenic steroid use with stimulant polypharmacy. *Contemp Drug Probl* 2020; 47: 118–135.
65. Hinshaw SP and Scheffler RM. *The ADHD explosion: myths, medication, money, and today’s push for performance*. New York, NY: Oxford University Press, 2014.
66. Avellaneda-Ojeda A, Murtaza S, Shah AA, *et al*. Stimulant use disorders. *Psychiatr Ann* 2018; 48: 372–378.
67. Contrucci RR, Brunt TM, Inan F, *et al*. Synthetic cathinones and their potential interactions with prescription drugs. *Ther Drug Monit* 2020; 42: 75–82.
68. Fattore L. Synthetic cannabinoids—further evidence supporting the relationship between cannabinoids and psychosis. *Biol Psychiatry* 2016; 79: 539–548.
69. Tait RJ, Caldicott D, Mountain D, *et al*. A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. *Clin Toxicol (Phila)* 2016; 54: 1–13.
70. Pacher P, Steffens S, Haskó G, *et al*. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* 2018; 15: 151–166.
71. United Nations Office on Drugs and Crime. Current NPS threats. Volume II. January 2020, [https://www.unodc.org/documents/scientific/Current\\_NPS\\_Threats\\_Volume\\_II\\_Web.pdf](https://www.unodc.org/documents/scientific/Current_NPS_Threats_Volume_II_Web.pdf) (accessed 18 April 2020).
72. Banister SD and Connor M. The chemistry and pharmacology of synthetic cannabinoid receptor agonists as new psychoactive substances: origins. In: *New psychoactive substances*. Cham: Springer, 2018, pp.165–190.
73. Lefever TW, Marusich JA, Thomas BF, *et al*. Vaping synthetic cannabinoids: a novel preclinical model of e-cigarette use in mice. *Subst Abuse* 2017; 11: 1178221817701739.
74. Murray RM, Quigley H, Quattrone D, *et al*. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry* 2016; 15: 195–204.
75. Le Boisselier R, Alexandre J, Lelong-Boulouard V, *et al*. Focus on cannabinoids and synthetic cannabinoids. *Clin Pharmacol Ther* 2017; 101: 220–229.
76. Zimmer DI, McCauley R, Konanki V, *et al*. Emergency department and radiological cost of delayed diagnosis of cannabinoid hyperemesis. *J Addict* 2019; 2019: 1307345.
77. Vandrey R, Dunn KE, Fry JA, *et al*. A survey study to characterize use of spice products (synthetic cannabinoids). *Drug Alcohol Depend* 2012; 120: 238–241.
78. Berkowitz EA, Henry TS, Gal AA, *et al*. Pulmonary effects of synthetic marijuana: chest radiography and CT findings. *AJR Am J Roentgenol*. Epub ahead of print 26 December 2014. DOI: 10.2214/AJR.14.13138.
79. Winstock A, Lynskey M, Borschmann R, *et al*. Risk of emergency medical treatment following consumption of cannabis or synthetic cannabinoids in a large global sample. *J Psychopharmacol* 2015; 29: 698–703.
80. Winstock AR and Barratt MJ. Synthetic cannabis: a comparison of patterns of use and effect profile with natural cannabis in a large global sample. *Drug Alcohol Depend* 2013; 131: 106–111.
81. Ford LT and Berg JD. Analytical evidence to show letters impregnated with novel psychoactive substances are a means of getting drugs to inmates within the UK prison service. *Ann Clin Biochem* 2018; 55: 673–678.
82. Hvozdvovich JA, Chronister CW, Logan BK, *et al*. Case report: synthetic cannabinoid deaths in state of Florida prisoners. *J Anal Toxicol* 2020; 44: 298–300.
83. Springer YP, Gerona R, Scheunemann E, *et al*. Increase in adverse reactions associated with use of synthetic cannabinoids—Anchorage, Alaska, 2015–2016. *MMWR Morb Mortal Wkly Rep* 2016; 65: 1108–1111.
84. Joseph A, Lekas H-M, Manseau M, *et al*. A polydrug and psychosocial profile of synthetic

- cannabinoid use in a New York City community sample, 2016–2017. *Subst Use Misuse* 2019; 54: 282–287.
85. Ellsworth JT. Spice, vulnerability, and victimization: synthetic cannabinoids and interpersonal crime victimization among homeless adults. *Subst Abuse*. Epub ahead of print 7 November 2019. DOI: 10.1080/08897077.2019.1686725.
  86. Adamowicz P. Fatal intoxication with synthetic cannabinoid MDMB-CHMICA. *Forensic Sci Int* 2016; 261: e5–e10.
  87. Fantegrossi WE, Moran JH, Radomska-Pandya A, *et al.* Distinct pharmacology and metabolism of K2 synthetic cannabinoids compared to  $\Delta^9$ -THC: mechanism underlying greater toxicity? *Life Sci* 2014; 97: 45–54.
  88. ElSohly MA, Gul W, Wanas AS, *et al.* Synthetic cannabinoids: analysis and metabolites. *Life Sci* 2014; 97: 78–90.
  89. Shevyrin V, Melkozerov V, Endres GW, *et al.* On a new cannabinoid classification system: a sight on the illegal market of novel psychoactive substances. *Cannabis Cannabinoid Res* 2016; 1: 186–194.
  90. Chung H, Choi H, Heo S, *et al.* Synthetic cannabinoids abused in South Korea: drug identifications by the National Forensic Service from 2009 to June 2013. *Forensic Toxicol* 2014; 32: 82–88.
  91. Sobolevsky T, Prasolov I and Rodchenkov G. Detection of urinary metabolites of AM-2201 and UR-144, two novel synthetic cannabinoids. *Drug Test Anal* 2012; 4: 745–753.
  92. Banister SD, Moir M, Stuart J, *et al.* Pharmacology of indole and indazole synthetic cannabinoid designer drugs AB-FUBINACA, ADB-FUBINACA, AB-PINACA, ADB-PINACA, 5F-AB-PINACA, 5F-ADB-PINACA, ADBICA, and 5F-ADBICA. *ACS Chem Neurosci* 2015; 6: 1546–1559.
  93. Banister SD, Stuart J, Kevin RC, *et al.* Effects of bioisosteric fluorine in synthetic cannabinoid designer drugs JWH-018, AM-2201, UR-144, XLR-11, PB-22, 5F-PB-22, APICA, and STS-135. *ACS Chem Neurosci* 2015; 6: 1445–1458.
  94. Banister SD, Adams A, Kevin RC, *et al.* Synthesis and pharmacology of new psychoactive substance 5F-CUMYL-P7AICA, a scaffold-hopping analog of synthetic cannabinoid receptor agonists 5F-CUMYL-PICA and 5F-CUMYL-PINACA. *Drug Test Anal* 2019; 11: 279–291.
  95. Banister SD, Kevin RC, Martin L, *et al.* The chemistry and pharmacology of putative synthetic cannabinoid receptor agonist (SCRA) new psychoactive substances (NPS) 5F-PY-PICA, 5F-PY-PINACA, and their analogs. *Drug Test Anal* 2019; 11: 976–989.
  96. Finlay DB, Manning JJ, Ibsen MS, *et al.* Do toxic synthetic cannabinoid receptor agonists have signature in vitro activity profiles? A case study of AMB-FUBINACA. *ACS Chem Neurosci* 2019; 10: 4350–4360.
  97. Baumann MH, Garibay N, Partilla JS, *et al.* Structure-activity relationships for Cumyl-containing synthetic cannabinoids to induce hypothermic, cataleptic and analgesic effects in mice. *FASEB J* 2020; 34(Suppl. 1): 1.
  98. Darke S, Duflou J, Farrell M, *et al.* Characteristics and circumstances of synthetic cannabinoid-related death. *Clin Toxicol (Phila)* 2020; 58: 368–374.
  99. Takeda A, Doi T, Asada A, *et al.* Evaluation of carboxamide-type synthetic cannabinoids on the functional activities at cannabinoid receptors and biological effects via inhalation exposure test. *Forensic Toxicol* 2020; 38: 455–464.
  100. De Luca MA and Fattore L. Therapeutic use of synthetic cannabinoids: still an open issue? *Clin Ther* 2018; 40: 1457–1466.
  101. Law R, Schier J, Martin C, *et al.* Increase in reported adverse health effects related to synthetic cannabinoid use—United States, January–May 2015. *MMWR Morb Mortal Wkly Rep* 2015; 64: 618–619.
  102. Hoyte CO, Jacob J, Monte AA, *et al.* A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. *Ann Emerg Med* 2012; 60: 435–438.
  103. Bäckberg M, Tworek L, Beck O, *et al.* Analytically confirmed intoxications involving MDMB-CHMICA from the STRIDA project. *J Med Toxicol* 2017; 13: 52–60.
  104. Armstrong F, McCurdy MT and Heavner MS. Synthetic cannabinoid-associated multiple organ failure: case series and literature review. *Pharmacotherapy* 2019; 39: 508–513.
  105. Argamany JR, Reveles KR and Duhon B. Synthetic cannabinoid hyperemesis resulting in rhabdomyolysis and acute renal failure. *Am J Emerg Med* 2016; 34: 765.e1–2.
  106. Davis C and Boddington D. Teenage cardiac arrest following abuse of synthetic cannabis. *Heart Lung Circ* 2015; 24: e162–e163.
  107. Ozturk HM, Yetkin E and Ozturk S. Synthetic cannabinoids and cardiac arrhythmia risk: review

- of the literature. *Cardiovasc Toxicol* 2019; 19: 191–197.
108. Yirgin G, Ateşİ, Katipoğlu B, *et al.* Pulmonary embolism due to synthetic cannabinoid use: case report. *Turk Kardiyol Dern Ars* 2018; 46: 411–413.
109. Aydin G and Bakar B. Delayed intracerebral hemorrhage after synthetic cannabis (Bonsai) abuse; case report and literature review. *Bull Emerg Trauma* 2019; 7: 330–334.
110. Armenian P, Darracq M, Gevorkyan J, *et al.* Intoxication from the novel synthetic cannabinoids AB-PINACA and ADB-PINACA: a case series and review of the literature. *Neuropharmacology* 2018; 134: 82–91.
111. Akram H, Mokrysz C and Curran HV. What are the psychological effects of using synthetic cannabinoids? A systematic review. *J Psychopharmacology* 2019; 33: 271–283.
112. Nia AB, Mann CL, Spriggs S, *et al.* The relevance of sex in the association of synthetic cannabinoid use with psychosis and agitation in an inpatient population. *J Clin Psychiatry* 2019; 80:18m12539.
113. Kraemer M, Fels H, Dame T, *et al.* Mono-/polyintoxication with 5F-ADB: a case series. *Forensic Sci Int* 2019; 301: e29–e37.
114. Mensen VT, Vreeker A, Nordgren J, *et al.* Psychopathological symptoms associated with synthetic cannabinoid use: a comparison with natural cannabis. *Psychopharmacology* 2019; 236: 2677–2685.
115. Hoffman AF, Hwang EK and Lupica CR. Impairment of synaptic plasticity by cannabis,  $\Delta^9$ -THC, and synthetic cannabinoids. *Cold Spring Harb Perspect Med*. Epub ahead of print 27 May 2020. DOI: 10.1101/cshperspect.a039743.
116. Creagh S, Warden D, Latif MA, *et al.* The new classes of synthetic illicit drugs can significantly harm the brain: a neuro imaging perspective with full review of MRI findings. *Clin Radiol Imaging J* 2018; 2: 000116.
117. Cohen K, Kapitány-Fövény M, Mama Y, *et al.* The effects of synthetic cannabinoids on executive function. *Psychopharmacology* 2017; 234: 1121–1134.
118. Cooper ZD. Adverse effects of synthetic cannabinoids: management of acute toxicity and withdrawal. *Curr Psychiatry Rep* 2016; 18: 52.
119. Van Hout MC and Hearne E. User experiences of development of dependence on the synthetic cannabinoids, 5f-AKB48 and 5F-PB-22, and subsequent withdrawal syndromes. *Int J Ment Health Addict* 2017; 15: 565–579.
120. White CM. The pharmacologic and clinical effects of illicit synthetic cannabinoids. *J Clin Pharmacol* 2017; 57: 297–304.
121. March R, Guentert P, Kloska-Kearney E, *et al.* Utilization of extracorporeal membrane oxygenation for pulmonary toxicity caused by inhaled synthetic cannabinoid. A harbinger of future complications associated with inhaled cannabinoid products. *Int J Clin Med* 2020; 11: 53–61.
122. Duffy B, Li L, Lu S, *et al.* Analysis of cannabinoid-containing fluids in illicit vaping cartridges recovered from pulmonary injury patients: identification of vitamin E acetate as a major diluent. *Toxics* 2020; 8: 8.
123. Baumeister D, Barnes G, Giaroli G, *et al.* Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. *Ther Adv Psychopharmacol* 2014; 4: 156–169.
124. Mohr AL, Friscia M, Yeakel JK, *et al.* Use of synthetic stimulants and hallucinogens in a cohort of electronic dance music festival attendees. *Forensic Sci Int* 2018; 282: 168–178.
125. Lawn W, Hallak JE, Crippa JA, *et al.* Well-being, problematic alcohol consumption and acute subjective drug effects in past-year ayahuasca users: a large, international, self-selecting online survey. *Sci Rep* 2017; 7: 15201.
126. Hill SL, Doris T, Gurung S, *et al.* Severe clinical toxicity associated with analytically confirmed recreational use of 25I-NBOMe: case series. *Clin Toxicol (Phila)* 2013; 51: 487–492.
127. Stellpflug SJ, Kealey SE, Hegarty CB, *et al.* 2-(4-Iodo-2, 5-dimethoxyphenyl)-N-[(2-methoxyphenyl) methyl] ethanamine (25I-NBOMe): clinical case with unique confirmatory testing. *J Med Toxicol* 2014; 10: 45–50.
128. Weaver MF and Schnoll SH. Hallucinogens and club drugs. In: Kleber H and Galanter M (eds) *The American psychiatric publishing textbook of substance abuse treatment*. Washington, DC: American Psychiatric Publishing, 2008, pp.191–200.
129. Whitmore CA and Hopfer C. Youth club, prescription, and over-the-counter drug use. In: Kaminer Y and Winters KC (eds) *Clinical manual of youth addictive disorders*. Washington, DC: The American Psychiatric Association Publishing, 2019, p.229.
130. Nisavic M and Lai-Becker MW. Management of acute substance use disorders: hallucinogens



- and associated compounds. In: Donovan AL and Bird SA (eds) *Substance use and the acute psychiatric patient*. Cham: Humana, 2019, pp.83–91.
131. Shulgin A and Shulgin A. *PIHKAL: phenethylamines I have known and loved*. Berkeley, CA: Transform Press, 1995.
  132. Eshleman AJ, Wolfrum KM, Reed JF, *et al.* Neurochemical pharmacology of psychoactive substituted N-benzylphenethylamines: high potency agonists at 5-HT<sub>2A</sub> receptors. *Biochem Pharmacol* 2018; 158: 27–34.
  133. Tittarelli R, Mannocchi G, Pantano F, *et al.* Recreational use, analysis and toxicity of tryptamines. *Curr Neuropharmacol* 2015; 13: 26–46.
  134. Brandt SD, Kavanagh PV, Westphal F, *et al.* Return of the lysergamides. Part V: analytical and behavioural characterization of 1-butanoyl-d-lysergic acid diethylamide (1B-LSD). *Drug Test Anal* 2019; 11: 1122–1133.
  135. Wagmann L, Richter LHJ, Kehl T, *et al.* In vitro metabolic fate of nine LSD-based new psychoactive substances and their analytical detectability in different urinary screening procedures. *Anal Bioanal Chem* 2019; 411: 4751–4763.
  136. Kolaczynska KE, Luethi D, Trachsel D, *et al.* Receptor interaction profiles of 4-alkoxy-substituted 2, 5-dimethoxyphenethylamines and related amphetamines. *Front Pharmacol* 2019; 10: 1423.
  137. Luethi D, Widmer R, Trachsel D, *et al.* Monoamine receptor interaction profiles of 4-aryl-substituted 2, 5-dimethoxyphenethylamines (2C-BI derivatives). *Eur J Pharmacol* 2019; 855: 103–111.
  138. Uthaug MV, Van Oorsouw K, Kuypers KP, *et al.* Sub-acute and long-term effects of ayahuasca on affect and cognitive thinking style and their association with ego dissolution. *Psychopharmacology* 2018; 235: 2979–2989.
  139. Dos Santos RG and Hallak JEC. Therapeutic use of serotonergic hallucinogens: a review of the evidence and of the biological and psychological mechanisms. *Neurosci Biobehav Rev* 2020; 108: 423–434.
  140. Ross S. Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. *Int Rev Psychiatry* 2018; 30: 317–330.
  141. Nielson EM, May DG, Forchimes AA, *et al.* The psychedelic debriefing in alcohol dependence treatment: illustrating key change phenomena through qualitative content analysis of clinical sessions. *Front Pharmacol* 2018; 9: 132.
  142. Bogenschutz MP, Podrebarac SK, Duane JH, *et al.* Clinical interpretations of patient experience in a trial of psilocybin-assisted psychotherapy for alcohol use disorder. *Front Pharmacol* 2018; 9: 100.
  143. Iwersen-Bergmann S, Lehmann S, Heinemann A, *et al.* Mass poisoning with NPS: 2C-E and Bromo-DragonFly. *Int J Legal Med* 2019; 133: 123–129.
  144. Srisuma S, Bronstein AC and Hoyte CO. NBOMe and 2C substitute phenylethylamine exposures reported to the National Poison Data System. *Clin Toxicol (Phila)* 2015; 53: 624–628.
  145. Stoller A, Dolder PC, Bodmer M, *et al.* Mistaking 2C-P for 2C-B: what a difference a letter makes. *J Anal Toxicol* 2017; 41: 77–79.
  146. Wood DM, Sedefov R, Cunningham A, *et al.* Prevalence of use and acute toxicity associated with the use of NBOMe drugs. *Clin Toxicol (Phila)* 2015; 53: 85–92.
  147. Kamour A, James D, Spears R, *et al.* Patterns of presentation and clinical toxicity after reported use of alpha methyltryptamine in the United Kingdom. A report from the UK National Poisons Information Service. *Clin Toxicol (Phila)* 2014; 52: 192–197.
  148. Ikeda A, Sekiguchi K, Fujita K, *et al.* 5-methoxy-N, N-diisopropyltryptamine-induced flashbacks. *American Journal of Psychiatry*. 2005 Apr 1;162(4): 815–815.
  149. Jovel A, Felthous A and Bhattacharyya A. Delirium due to intoxication from the novel synthetic tryptamine 5-MeO-DALT. *J Forensic Sci* 2014; 59: 844–846.
  150. Boland DM, Andollo W, Hime GW, *et al.* Fatality due to acute  $\alpha$ -methyltryptamine intoxication. *J Anal Toxicol* 2005; 29: 394–397.
  151. Dolder PC, Schmid Y, Müller F, *et al.* LSD acutely impairs fear recognition and enhances emotional empathy and sociality. *Neuropsychopharmacology* 2016; 41: 2638–2646.
  152. Dean BV, Stellpflug SJ, Burnett AM, *et al.* 2C or not 2C: phenethylamine designer drug review. *J Med Toxicol* 2013; 9: 172–178.
  153. Walterscheid JP, Phillips GT, Lopez AE, *et al.* Pathological findings in 2 cases of fatal 25I-NBOMe toxicity. *Am J Forensic Med Pathol* 2014; 35: 20–25.
  154. Li L and Vlisides PE. Ketamine: 50 years of modulating the mind. *Front Hum Neurosci* 2016; 10: 612.

155. Newcomer JW, Farber NB and Olney JW. NMDA receptor function, memory, and brain aging. *Dialogues Clin Neurosci* 2000; 2: 219–232.
156. Morris H and Wallach J. From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. *Drug Test Anal* 2014; 6: 614–632.
157. Wallach J, Kang H, Colestock T, *et al.* Pharmacological investigations of the dissociative ‘legal highs’ diphenidine, methoxphenidine and analogues. *PLoS One* 2016; 11: e0157021.
158. Katselou M, Papoutsis I, Nikolaou P, *et al.* Diphenidine: a dissociative NPS makes an entrance on the drug scene. *Forensic Toxicol* 2018; 36: 233–242.
159. Abiero A, Botanas CJ, Custodio RJ, *et al.* 4-MeO-PCP and 3-MeO-PCMo, new dissociative drugs, produce rewarding and reinforcing effects through activation of mesolimbic dopamine pathway and alteration of accumbal CREB, deltaFosB, and BDNF levels. *Psychopharmacology (Berl)* 2020; 237: 757–772.
160. Roth BL, Gibbons S, Arunotayanun W, *et al.* The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. *PLoS One* 2013; 8: e59334.
161. Botanas CJ, de la, Peña JB, Kim HJ, *et al.* Methoxetamine: a foe or friend? *Neurochem Int* 2019; 122: 1–7.
162. Guirguis A. New psychoactive substances: a public health issue. *Int J Pharm Pract* 2017; 25: 323–325.
163. Hutton F. (ed.). Cultures of intoxication: ‘new’ psychoactive substances. In: *Cultures of intoxication*. Cham: Palgrave Macmillan, 2020, pp.87–110.
164. Hearne E and Van Hout MC. “Trip-sitting” in the black hole: a netnographic study of dissociation and indigenous harm reduction. *J Psychoactive Drugs* 2016; 48: 233–242.
165. Hondebrink L, Zwartsen A and Westerink RHS. Effect fingerprinting of new psychoactive substances (NPS): what can we learn from in vitro data? *Pharmacol Ther* 2018; 182: 193–224.
166. Zanda MT, Fadda P, Antinori S, *et al.* Methoxetamine affects brain processing involved in emotional response in rats. *Br J Pharmacol* 2017; 174: 3333–3345.
167. Costa G, Porceddu PF, Serra M, *et al.* Lack of Rhes increases MDMA-induced neuroinflammation and dopamine neuron degeneration: role of gender and age. *Int J Mol Sci* 2019; 20: 1556.
168. Fassette T and Martinez A. An impaired driver found to be under the influence of methoxetamine. *J Anal Toxicol* 2016; 40: 700–702.
169. Imbert L, Boucher A, Delhome G, *et al.* Analytical findings of an acute intoxication after inhalation of methoxetamine. *J Anal Toxicol* 2014; 38: 410–415.
170. Dargan PI, Tang HC, Liang W, *et al.* Three months of methoxetamine administration is associated with significant bladder and renal toxicity in mice. *Clin Toxicol (Phila)* 2014; 52: 176–180.
171. Shields JE, Dargan PI, Wood DM, *et al.* Methoxetamine associated reversible cerebellar toxicity: three cases with analytical confirmation. *Clin Toxicol (Phila)* 2012; 50: 438–440.
172. Johansson A, Lindstedt D, Roman M, *et al.* A non-fatal intoxication and seven deaths involving the dissociative drug 3-MeO-PCP. *Forensic Sci Int* 2017; 275: 76–82.
173. Krotulski AJ, Papsun DM, Friscia M, *et al.* Fatality following ingestion of tetrahydrofuranylfentanyl, U-49900 and methoxy-phencyclidine. *J Anal Toxicol* 2018; 42: e27–e32.
174. Kusano M, Zaitse K, Taki K, *et al.* Fatal intoxication by 5F-ADB and diphenidine: detection, quantification, and investigation of their main metabolic pathways in humans by LC/MS/MS and LC/Q-TOFMS. *Drug Test Anal* 2018; 10: 284–293.
175. Hill SL, Harbon SC, Coulson J, *et al.* Methoxetamine toxicity reported to the National Poisons Information Service: clinical characteristics and patterns of enquiries (including the period of the introduction of the UK’s first Temporary Class Drug Order). *Emerg Med J* 2014; 31: 45–47.
176. Wood DM, Davies S, Puchnarewicz M, *et al.* Acute toxicity associated with the recreational use of the ketamine derivative methoxetamine. *Eur J Clin Pharmacol* 2012; 68: 853–856.
177. EMCDDA Perspectives on Drugs. The misuse of benzodiazepines among high-risk opioid users in Europe, [http://www.emcdda.europa.eu/topics/pods/benzodiazepines\\_en](http://www.emcdda.europa.eu/topics/pods/benzodiazepines_en) (2018). (accessed 25 April 2020).
178. Zawilska JB and Wojcieszak J. An expanding world of new psychoactive substances—designer benzodiazepines. *Neurotoxicology* 2019; 73: 8–16.

179. El Balkhi S, Monchaud C, Herault F, *et al.* Designer benzodiazepines' pharmacological effects and potencies: how to find the information. *J Psychopharmacol* 2020; 34: 1021–1029.
180. Moosmann B and Auwärter V. Designer benzodiazepines: another class of new psychoactive substances. In: *New psychoactive substances*. Cham: Springer, 2018, pp.383–410.
181. Waters L, Manchester KR, Maskell PD, *et al.* The use of a quantitative structure-activity relationship (QSAR) model to predict GABA-A receptor binding of newly emerging benzodiazepines. *Sci Justice* 2018; 58: 219–225.
182. Manchester KR, Lomas EC, Waters L, *et al.* The emergence of new psychoactive substance (NPS) benzodiazepines: a review. *Drug Test Anal* 2018; 10: 37–53.
183. Shoshan-Barmatz V, Pittala S and Mizrahi D. VDAC1 and the TSPO: expression, interactions, and associated functions in health and disease states. *Int J Mol Sci* 2019; 20: 3348.
184. Qneibi M, Jaradat N, Hawash M, *et al.* Ortho versus meta chlorophenyl-2, 3-benzodiazepine analogues: synthesis, molecular modeling, and biological activity as AMPAR antagonists. *ACS Omega* 2020; 5: 3588–3595.
185. Verma S, Kumar S and Kumar S. Design, synthesis, computational and biological evaluation of new benzodiazepines as CNS agents. *Arab J Chem* 2020; 13: 863–874.
186. Carpenter JE, Murray BP, Dunkley C, *et al.* Designer benzodiazepines: a report of exposures recorded in the National Poison Data System, 2014–2017. *Clin Toxicol (Phila)* 2019; 57: 282–286.
187. Andersson M and Kjellgren A. The slippery slope of flubromazolam: experiences of a novel psychoactive benzodiazepine as discussed on a Swedish online forum. *Nordisk Alkohol Nark* 2017; 34: 217–229.
188. Koch K, Auwärter V, Hermanns-Clausen M, *et al.* Mixed intoxication by the synthetic opioid U-47700 and the benzodiazepine flubromazepam with lethal outcome: pharmacokinetic data. *Drug Test Anal*. Epub ahead of print 10 April 2018. DOI: 10.1002/dta.2391.
189. Domingo O, Roeder G, Stöver A, *et al.* Mitragynine concentrations in two fatalities. *Forensic Sci Int* 2017; 271: e1–e7.
190. Partridge E, Trobbiani S, Stockham P, *et al.* A case study involving U-47700, diclazepam and flubromazepam—application of retrospective analysis of HRMS data. *J Anal Toxicol* 2018; 42: 655–660.
191. Shearer K, Bryce C, Parsons M, *et al.* Phenazepam: a review of medico-legal deaths in South Scotland between 2010 and 2014. *Forensic Sci Int* 2015; 254: 197–204.
192. Ren B, Suriawinata AA and Iwai M. Drug-induced liver injury. In: Hashimoto E, Kwo PY, Suriawinata AA, *et al.* (eds) *Diagnosis of liver disease*. Singapore: Springer, 2019, pp.85–96.
193. Labonville S. *Opiate, opioid, narcotic-what's the difference*. Winnipeg, MB: The Patient Advocate Pharmacy, 2017.
194. Bodnar RJ. Endogenous opiates and behavior: 2017. *Peptides* 2020; 124: 170223.
195. Suzuki J and El-Haddad S. A review: fentanyl and non-pharmaceutical fentanyls. *Drug Alcohol Depend* 2017; 171: 107–116.
196. Bucerius SM and Haggerty KD. Fentanyl behind bars: the implications of synthetic opiates on prisoners and correctional officers. *Int J Drug Policy* 2019; 71: 133–138.
197. Solimini R, Pichini S, Pacifici R, *et al.* Pharmacotoxicology of non-fentanyl derived new synthetic opioids. *Front Pharmacol* 2018; 9: 654.
198. Toll L, Standifer KM and Massotte D. Current topics in opioid research. *Front Psychiatry* 2019; 10: 586.
199. Drewes AM, Jensen RD, Nielsen LM, *et al.* Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol* 2013; 75: 60–78.
200. Armenian P, Vo KT, Barr-Walker J, *et al.* Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review. *Neuropharmacology* 2018; 134: 121–132.
201. Baumann MH, Majumdar S, Le Rouzic V, *et al.* Pharmacological characterization of novel synthetic opioids (NSO) found in the recreational drug marketplace. *Neuropharmacology* 2018; 134: 101–107.
202. Charbogne P, Kieffer BL and Befort K. 15 years of genetic approaches in vivo for addiction research: opioid receptor and peptide gene knockout in mouse models of drug abuse. *Neuropharmacology* 2014; 76: 204–217.
203. Concheiro M, Chessier R, Pardi J, *et al.* Postmortem toxicology of new synthetic opioids. *Front Pharmacol* 2018; 9: 1210.
204. Müller D, Neurath H, Neukamm MA, *et al.* New synthetic opioid cyclopropylfentanyl

- together with other novel synthetic opioids in respiratory insufficient comatose patients detected by toxicological analysis. *Clin Toxicol (Phila)* 2019; 57: 806–812.
205. Wilde M, Sommer MJ, Auwärter V, *et al.* Acute severe intoxication with cyclopropylfentanyl, a novel synthetic opioid. *Toxicol Lett* 2020; 320: 109–112.
206. Cole JB, Dunbar JF, McIntire SA, *et al.* Butyrfentanyl overdose resulting in diffuse alveolar hemorrhage. *Pediatrics* 2015; 135: e740–e743.
207. Helander A, Bäckberg M, Signell P, *et al.* Intoxications involving acrylfentanyl and other novel designer fentanyls—results from the Swedish STRIDA project. *Clin Toxicol (Phila)* 2017; 55: 589–599.
208. Siddiqi S, Verney C, Dargan P, *et al.* Understanding the availability, prevalence of use, desired effects, *et al.* *Clin Toxicol (Phila)* 2015; 53: 54–59.
209. Fels H, Lottner-Nau S, Sax T, *et al.* Postmortem concentrations of the synthetic opioid U-47700 in 26 fatalities associated with the drug. *Forensic Sci Int* 2019; 301: e20–e28.
210. Nash C, Butzbach D, Stockham P, *et al.* A fatality involving furanylfentanyl and MMMP, with presumptive identification of three MMMP metabolites in urine. *J Anal Toxicol* 2019; 43: 291–298.
211. Kriikku P, Pelander A, Rasanen I, *et al.* Toxic lifespan of the synthetic opioid U-47,700 in Finland verified by re-analysis of UPLC-TOF-MS data. *Forensic Sci Int* 2019; 300: 85–88.
212. Richeval C, Gaulier J-M, Romeuf L, *et al.* Case report: relevance of metabolite identification to detect new synthetic opioid intoxications illustrated by U-47700. *Int J Legal Med* 2019; 133: 133–142.
213. Belackova V, Vacek J, Janikova B, *et al.* “Just another drug” for marginalized users: the risks of using synthetic cathinones among NSP clients in the Czech Republic. *J Subst Use* 2017; 22: 567–573.
214. Helander A, Bäckberg M and Beck O. Drug trends and harm related to new psychoactive substances (NPS) in Sweden from 2010 to 2016: experiences from the STRIDA project. *PLoS One* 2020; 15: e0232038.
215. Jannetto PJ, Helander A, Garg U, *et al.* The fentanyl epidemic and evolution of fentanyl analogs in the United States and the European Union. *Clin Chem* 2019; 65: 242–253.
216. Abdulrahim D, Whiteley C, Moncrieff M, *et al.* *Club drug use among lesbian, gay, bisexual and trans (LGBT) people.* London: Novel Psychoactive Treatment UK Network (NEPTUNE), 2016.
217. Graziano S, Anzillotti L, Mannocchi G, *et al.* Screening methods for rapid determination of new psychoactive substances (NPS) in conventional and non-conventional biological matrices. *J Pharmaceut Biomed Anal* 2019; 163: 170–179.
218. Peiper NC, Clarke SD, Vincent LB, *et al.* Fentanyl test strips as an opioid overdose prevention strategy: findings from a syringe services program in the Southeastern United States. *Int J Drug Policy* 2019; 63: 122–128.
219. Regester LE, Chmiel JD, Holler JM, *et al.* Determination of designer drug cross-reactivity on five commercial immunoassay screening kits. *J Anal Toxicol* 2015; 39: 144–151.
220. Salomone A, Gazzilli G, Di Corcia D, *et al.* Determination of cathinones and other stimulant, psychedelic, and dissociative designer drugs in real hair samples. *Anal Bioanal Chem* 2016; 408: 2035–2042.
221. Ares AM, Fernández P, Regenjo M, *et al.* A fast bioanalytical method based on microextraction by packed sorbent and UPLC–MS/MS for determining new psychoactive substances in oral fluid. *Talanta* 2017; 174: 454–461.
222. Sulej-Suchomska AM, Klupczynska A, Derezi ski P, *et al.* Urban wastewater analysis as an effective tool for monitoring illegal drugs, including new psychoactive substances, in the Eastern European region. *Sci Rep* 2020; 10: 4885.
223. Ambach L, Hernández Redondo A, König S, *et al.* Rapid and simple LC-MS/MS screening of 64 novel psychoactive substances using dried blood spots. *Drug Test Anal* 2014; 6: 367–375.
224. Grapp M, Kaufmann C, Streit F, *et al.* Systematic forensic toxicological analysis by liquid-chromatography-quadrupole-time-of-flight mass spectrometry in serum and comparison to gas chromatography-mass spectrometry. *Forensic Sci Int* 2018; 287: 63–73.
225. Kimble AN and DeCaprio AP. Systematic analysis of novel psychoactive substances. II. Development of a screening/confirmatory LC-QqQ-MS/MS method for 800+ compounds and metabolites in urine. *Forensic Chem* 2019; 16: 100189.
226. Seither JZ, Hindle R, Arroyo-Mora LE, *et al.* Systematic analysis of novel psychoactive substances. I. Development of a compound



- database and HRMS spectral library. *Forensic Chem* 2018; 9: 12–20.
227. Boileau I, Mansouri E, Williams B, *et al.* Fatty acid amide hydrolase binding in brain of cannabis users: imaging with the novel radiotracer [ $^{11}\text{C}$ ] CURB. *Biol Psychiatry* 2016; 80: 691–701.
  228. Yamasaki T, Mori W, Zhang Y, *et al.* First demonstration of in vivo mapping for regional brain monoacylglycerol lipase using PET with [ $^{11}\text{C}$ ] SAR127303. *Neuroimage* 2018; 176: 313–320.
  229. Sanabria-Bohórquez SM, Hamill TG, Goffin K, *et al.* Kinetic analysis of the cannabinoid-1 receptor PET tracer [ $^{18}\text{F}$ ] MK-9470 in human brain. *Eur J Nucl Med Mol Imaging* 2010; 37: 920–933.
  230. European Monitoring Centre for Drugs and Drug Addiction. Hospital emergency presentations and acute drug toxicity in Europe — update from the Euro-DEN Plus research group and the EMCDDA, Lisbon, [https://www.emcdda.europa.eu/publications/rapid-communications/2016/hospital-emergencies\\_en](https://www.emcdda.europa.eu/publications/rapid-communications/2016/hospital-emergencies_en) (accessed August 2016).
  231. European Monitoring Centre for Drugs and Drug Addiction. Drug-related hospital emergency presentations in Europe: update from the Euro-DEN Plus expert network EMCDDA, Lisbon, <https://www.emcdda.europa.eu/publications/technical-reports/drug-related-hospital-emergency-presentations-in-europe> (accessed February 2020).
  232. Wood DM, Heyerdahl F, Yates CB, *et al.* The European drug emergencies network (euro-DEN). *Clin Toxicol (Phila)* 2014; 52: 239–241.
  233. Dines AM, Wood DM, Yates C, *et al.* Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). *Clin Toxicol (Phila)* 2015; 53: 893–900.
  234. Wood DM, Ceronie B and Dargan PI. Healthcare professionals are less confident in managing acute toxicity related to the use of new psychoactive substances (NPS) compared with classical recreational drugs. *QJM* 2016; 109: 527–529.
  235. Gomes PM, Silva AMS and Silva VLM. Pyrazoles as key scaffolds for the development of fluorine-18-labeled radiotracers for Positron Emission Tomography (PET). *Molecules* 2020; 25: 1722.

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