Legal highs: staying on top of the flood of novel psychoactive substances

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Abstract: There has been growing clinical, public, and media awareness and concern about the availability and potential harmfulness of so-called ‘legal highs’, which are more appropriately called new or novel psychoactive substances (NPS). A cat-and-mouse process has emerged wherein unknown chemists and laboratories are producing new, and as yet nonproscribed, compounds for human consumption; and as soon as they are banned, which they inevitably are, slightly modified analogues are produced to circumvent new laws. This rapidly changing environment, 81 new substances were identified in 2013 alone, has led to confusion for clinicians, psychopharmacologists, and the public at large. Our difficulties in keeping up with the process has had a two-fold negative effect: the danger of ignoring what is confusing; and the problem that some of the newer synthesized compounds appear ever more potent. This review aims to circumscribe a quick moving and growing field, and to categorize NPS into five major groups based upon their ‘parent’ compounds: stimulants similar to cocaine, amphetamines and ecstasy; cannabinoids; benzodiazepine based drugs; dissociatives similar to ketamine and phencyclidine (PCP); and those modelled after classic hallucinogens such as LSD and psilocybin. Pharmacodynamic actions, subjective and physical effects, harmfulness, risk of dependency and, where appropriate, putative clinical potentials are described for each class. Clinicians might encounter NPS in various ways: anecdotal reportage; acute intoxication; as part of a substance misuse profile; and as a precipitant or perpetuating factor for longer-term physical and psychological ill health. Current data are overall limited, and much of our knowledge and treatment strategies are based upon those of the ‘parent’ compound. There is a critical need for more research in this field, and for professionals to make themselves more aware of this growing issue and how it might affect those we see clinically and try to help: a brave new world of so-called ‘psychonauts’ consuming NPS will also need informed ‘psychotherapeutonauts’. The paper should serve as a primer for clinicians and interested readers, as well as provide a framework into which to place the new substances that will inevitably be synthesized in the future.

Keywords: legal highs, novel psychoactive substances

Introduction

‘Alas, poor man! You have enough necessary ills without increasing them by your invention’

(Montaigne, *Essays*, III, 5, On Some Verses of Virgil)

Recent years have seen a surge in the availability of new or novel psychoactive substances (NPS) sold variously as ‘legal highs’, ‘bath salts’ or ‘research chemicals’, with ambiguous names such as ‘K2’, ‘Spice’ or ‘NRG-1’. These are often pharmacological analogues of compounds prohibited

under current drug laws such as amphetamines and cannabis, and consumed as legal or quasi-legal alternatives available from online vendors or in so-called ‘head shops’. Very little is known about their psychopharmacological effects or acute and long-term risks, although typically governmental responses have been to ban them as soon as possible.

However, drug laboratories have responded to prohibition of one agent with the introduction of another, leaving lawmakers engulfed in largely

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futile, Sisyphean legislative efforts as new substances hit the market in rapid succession. This problem is exemplified by the synthetic cannabinoid JWH-018, which was identified as a main ingredient of 'Spice' in Germany in 2009 and subsequently banned. Only 4 weeks thereafter, another sample of 'Spice' was obtained, that, whilst not showing traces of JWH-018 anymore, now contained the unregulated homologue JWH-073 [Lindigkeit *et al.* 2009]. Not only does this back-and-forth lead to significant financial costs and wasted efforts, but it may lead to increased risks for substance users who are willing to try an increasing number of unknown and potentially harmful substances. Furthermore, nascent data indicate that some agents may be more harmful than their more established parent compound in terms of risk of dependency, overdose and long-term health impacts. The United Nations Office on Drugs and Crime (UNODC) implemented the Synthetics Monitoring: Analyses, Reporting and Trends (SMART) global collaborative programme in 2008 to assess, report and manage NPS; but the speed of their synthesis has meant it has proven difficult for professionals and services to keep abreast of new developments. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) operates the European Union's 'Early Warning System' (EWS) for NPS, monitoring over 350 NPS: their most recent report (see <http://www.emcdda.europa.eu>), published in May 2014, stated that 81 NPS were notified for the first time to the EWS in 2013, and that this system was 'coming under increasing pressure from the volume and variety of new drugs appearing on the market'.

This review aims to provide professionals and interested readers an overview in which to consider the most common current NPS, their pharmacodynamics, subjective and physiological effects, risks and impact, as well as a framework by which to categorize the novel compounds that will undoubtedly be synthesized in the future.

Categorizing 'legal highs'

Five major categories of NPS will be reviewed in this article, based on their 'parent' compound: those modelled after psychostimulants such as amphetamine, 3,4-methylenedioxy-N-methylamphetamine (MDMA) and cocaine; those that mimic the effects of cannabis; those based upon benzodiazepines; those that produce dissociate effects similar to ketamine or phencyclidine

(PCP); and those developed as analogues of 'classical' hallucinogens such as LSD or psilocybin. Pharmacodynamic mechanisms; associated psychological and physical effects; associated health risks as well as risks of dependency and addiction; and potential pharmacotherapeutic potential will be discussed for each class.

Several groups of legal agents that are not necessarily associated with the new wave of synthetic legal highs, and some that target other systems or emulate other drugs of abuse, are not included in this review. Most notably, several legally available substances target the opioid system, including analgesics available 'over the counter' (OTC) that contain codeine, and the leaves of the *Mitragyna speciosa*, which contain the μ -opioid receptor agonist kratom are not discussed. Very recently there have been reports of novel, and legally available, opioid-based analogues such as AH-791, but data are so sparse that they have been excluded from this paper. As well as OTC medications, there have been concerning reports of some legitimately prescribed nonopioid medications also being used, or having the potential to be used, as drugs of abuse (the issue of benzodiazepines being so used will be addressed later in this paper), including: pregabalin and gabapentin, posited due to their GABA-mimetic properties [Schifano, 2014; Carrus and Schifano, 2012]; bupropion, which may be perceived as a stimulant in those with a history of cocaine misuse [Vento *et al.* 2013], and the antimuscarinic tropicamide that when injected can induce quasi-psychotic phenomena [Bersani *et al.* 2013]. It should also be noted that several otherwise illegal classical hallucinogens are legally obtainable in their plant form, including psilocybin in sclerotia of the *psilocybe* genus, mescaline in the peyote cactus (*Lophophora williamsii*), and dimethyltryptamine (DMT) in a brew of *Banisteriopsis caapi* and *Psychotria viridis* commonly known as ayahuasca. Further, there are other legally available plant-based psychoactive substances such as the amphetamine-like stimulant cathinone contained in *Catha edulis* (or khat), the anticholinergic/antimuscarinic agent scopolamine or the κ -opioid and D₂ receptor agonist salvinorin A contained in *Salvia divinorum*. However, these aforementioned substances are not associated with the recent flood of research chemicals (and in the case of the latter two have generally undesirable effects and low addictive potential) and discussion of psychoactive plants, ethnopharmacology and abuse of prescription/OTC medications goes beyond the scope of the present review.

Psychostimulants

Pharmacodynamic mechanisms

Traditional psychostimulants such as amphetamine, cocaine or MDMA all primarily target monoaminergic systems, leading to increased extracellular levels of serotonin (5-HT), dopamine (DA), and/or noradrenaline (NA). They do this via two major mechanisms, by which they can be subcategorized. Under normal circumstances, monoamines that have been released into the synaptic cleft are recycled back into the cell via monoaminergic reuptake pumps, and then, via vesicular reuptake pumps, are stored in synaptic vesicles for future reuse. Some stimulants, most notably cocaine [Fleckenstein *et al.* 2000], increase extracellular monoamine levels by blocking the respective monoamine reuptake pumps of serotonin (SERT), dopamine (DAT) and noradrenaline reuptake transporters (NAT). Of note many antidepressants have similar effects on the SERT and NAT [Penn and Tracy, 2012], although their specific pharmacology and pharmacodynamics are such that the effects are clearly quite different. Another group of stimulants, including MDMA and methamphetamine, *reverse* activity of monoaminergic reuptake pumps, by permeating into the intracellular space and inhibiting vesicular reuptake of monoamines within the cell, leading to increased cytoplasmic monoamine efflux into the synaptic cleft [Fleckenstein *et al.* 2007]. Such agents, also called substrate releasers, are associated with greater risk of neurotoxicity than agents that act as pure inhibitors of monoamine transporters [Fleckenstein *et al.* 2000; Simmler *et al.* 2014a, 2014b]. As with most drugs of abuse, administration of stimulants typically leads to increased dopaminergic activity in the mesolimbic reward pathway, which is associated with reinforcing effects that mediate addictive behaviours [Koob and Volkow, 2010]. However, the serotonergic component should not be underestimated, as it has been demonstrated that the subjective rewarding properties of MDMA are primarily mediated by the serotonin system [Liechti and Vollenweider, 2001]. The release of noradrenaline may significantly contribute to increases in activity of the sympathetic nervous system, cardiovascular effects and risks, and hypervigilance [Liechti and Vollenweider, 2000; Hysek *et al.* 2011].

Psychostimulant NPS similarly differ, and can be subcategorized, by whether or not they are substrate releasers [Simmler *et al.* 2013]. The most common

NPS psychostimulant biochemical family are cathinones, which includes the most well-known, and perhaps infamous, agent mephedrone (4-methylcathinone), colloquially often referred to as “M-Cat” or “meow meow”, although there are other groups, such as aminoindanes and piperazines. In a most revealing series of *in vitro* studies, Simmler and colleagues [Simmler *et al.* 2013, 2014a, 2014b] recently evaluated and compared monoamine transporter and receptor profiles of established drugs of abuse as well as NPS psychostimulants that are sold as ‘MDMA/amphetamine-like’ under names such as ‘Ivory Wave’ or ‘Bath Salts’, including: cathinones such as mephedrone, ethcathinone and buphedrone; aminoindanes such as 5-iodoaminoindane (5-IAI) and 2-aminoindane (2-AI); piperazines such as trifluoromethylphenylpiperazine (TFMPP) and 1-benzylpiperazine (BZP); and pipradol derivatives such as desoxypipradol (2-DPMP) and diphenylprolinol (D2PM). While all agents modulated monoaminergic transporter function, marked differences were found in the differential ratios between the drugs. Interestingly, it appears that novel psychostimulants fall between MDMA-like agents associated with a high serotonin:dopamine release ratios, and more pure amphetamine-like agents, which have a higher ratio of dopamine:serotonin release (Table 1).

Further, they differ in their interactions with other receptor groups. Notably, cathinones, which have a ketone oxygen group, differ from noncathinone amphetamines (also called non- β -keto amphetamines) in that they do not activate the trace amine-associated receptor 1 (TAAR1) [Simmler *et al.* 2013]. This may contribute to stronger effects on dopaminergic and serotonergic systems as activation of TAAR1 is associated with dampening of activity in these systems, and is a mechanism that buffers effects of activating amphetamines, such as MDMA [Lindemann *et al.* 2008; Miller, 2011; Xie and Miller, 2009]. Simmler and colleagues further report activation of 5-HT_{2A} receptors by several psychostimulants, and, as discussed in more detail later, these effects may be associated with some of the subjective effects of classical hallucinogens, including altered meanings of perceptions and visual effects.

Neuropharmacology

Neuroimaging studies of acute effects of amphetamine-like stimulants have presented evidence for a strong activation of areas classically associated with reward sensitization and addiction. Völm

Table 1. Monoamine releasing effects of novel stimulants (based on Simmler *et al.* [2013, 2014a, b]).

Group	Substance	DA release	5-HT release	NA release
Cathinones	Mephedrone	+++	+++ *	+++ *
	4-MTA	++	+++ *	++ *
	PMA	+++ *	++ *	+++ *
	PMMA	+++ *	+++ *	+++ *
	N-Ethylamphetamine	++++ *	+++++ *	+++ *
	4-MEC	++	+++ *	++
	Pentylone	++	++ *	+
	Ethcathinone	+++	++++ *	+++ *
	3-FMC	+++++ *	+++ *	+++ *
	Buphedrone	++	+	+++ *
	Pentedrone	++	+	++
	N,N-Dimethylcathinone	+++	-	++
	Methcathinone	+++++ *	+++ *	X
	Cathinone	+++++ *	+	X
	Flephedrone	+++++ *	+++ *	X
	Methylone	++	+++ *	X
	Butylone	+	++++ *	X
	Naphyrone	++	+	X
	Ehtylone	+++	+++ *	X
	MDEA	+	++++ *	X
	MBDB	+	++++ *	X
	Pyrovalerone	++	+	X
	MDPV	+	+	X
Aminoindands	5-IAI	+++ *	+++ *	++
	MDAI	+++	+++ *	+++ *
	2-AI	+++++ *	-	+++++ *
Piperazines	m-CPP	+	++ *	++
	TFMPP	+	++	+
	BZP	++++ *	+	++
Pipradol derivatives	D2PM	++	+	+
	2-DPMP			
'Classic' agents	MDMA	++++ *	+++++ *	+++++ *
	Methamphetamine	+++++ *	+++++ *	+++ *
	Amphetamine	+++++ *	+++ *	X
	Cocaine	+	+	X
	Methylphenidate	++	+	+

4-MTA, 4-Methylthioamphetamine; PMA, para-Methoxyamphetamine; PMMA, para-Methoxymethamphetamine; 4-MEC, 4-Methylethcathinone; 3-FMC, 3-Fluoromethcathinone; MDEA, Methylenedioxyethylamphetamine; MBDB, N-methyl-1,3-benzodioxolylbutanamine; MDPV, Methylenedioxypropylamphetamine; 5-IAI, 5-Iodo-2-aminoindane; MDAI, 5,6-Methylenedioxy-2-aminoindane; 2-AI, 2-Aminoindan; m-CPP, meta-Chlorophenylpiperazine; TFMPP, Trifluoromethylphenylpiperazine; BZP, Benzylpiperazine; D2PM, Diphenylprolinol; 2-DPMP, 2-Diphenylmethylpiperidine; MDMA, 3,4-methylenedioxy-methamphetamine; + 10–20% increase in efflux; ++, 20–30% increase in efflux, etc.; *, substrate releaser. X, no data available.

and colleagues [Völm *et al.* 2004] administered single-blind methamphetamine infusions (0.15 mg/kg) to seven healthy volunteers in a functional magnetic resonance imaging (fMRI) study and showed that, compared with saline placebo, methamphetamine significantly increased activity in

the ventral striatum, a key region of the mesolimbic reward pathway, as well as medial orbitofrontal and anterior cingulate cortices, which correlated with subjective effects. More recent fMRI work by O'Daly and colleagues [O'Daly *et al.* 2014a, 2014b] has demonstrated in a

double-blind randomized controlled trial (RCT) of healthy participants that acute amphetamine administration sensitised and altered dopaminoreceptive brain regions in the striatum and amygdala during a rewarded gambling task, and increased blood-oxygen-level-dependent (BOLD) signal in the medial temporal lobe during learning tasks. Similarly, Vollenweider and colleagues [Vollenweider *et al.* 1998a] administered euphoric doses of d-amphetamine to 10 healthy volunteers in a positron emission tomography (PET) study and found increased glucose metabolism across the whole brain, with metabolic changes in frontal cortex, caudate nucleus and putamen correlating with mania-like symptoms.

The available literature on MDMA in neuroimaging studies is currently very small and the present review could identify only three such works [Gamma *et al.* 2000; Bedi *et al.* 2009; Carhart-Harris *et al.* 2014]. In healthy volunteers, a single oral dose of MDMA has been shown to attenuate left amygdalar activation and enhance that of the ventromedial prefrontal cortex (vmPFC) as measured by PET [Gamma *et al.* 2000]. Gamma and colleagues also reported bilateral increases in regional cerebral blood flow in the ventral anterior cingulate cortices, whilst decreases were observed bilaterally for the dorsal anterior cingulate, the posterior cingulate cortex (PCC), the superior temporal gyrus, the dorsomedial thalamus and the insula, as well as the right parahippocampal gyrus. Bedi and colleagues [Bedi *et al.* 2009] used fMRI in a double-blind design administering varying doses of MDMA (0.75 and 1.5 mg/kg) to nine healthy volunteers to investigate effects on neural response to social threat and reward. Evidence obtained suggests that at the higher dose MDMA attenuates the response of the left amygdala to angry but not fearful facial expressions, whereas at the lower dose an augmented response of the ventral striatum is observed in response to happy facial expressions. MDMA further increased self-reported sociability. Recently, Carhart-Harris and colleagues [Carhart-Harris *et al.* 2014] administered oral MDMA (100 mg) to 25 healthy individuals in a double-blind, placebo-controlled RCT using arterial spin labelling and BOLD signal imaging. Cerebral blood flow significantly decreased in the hippocampus, the right medial temporal lobe and the amygdala, as well as several areas related to sensory processing, and the authors suggest this effect to be mediated by 5-HT_{1A} receptors. Moreover, BOLD signal revealed decreased functional connectivity between

vmPFC and PCC (with a nonsignificant correlation to positive mood), as well as between the medial PFC (mPFC) and hippocampus.

Subjective effects

Amphetamine-like psychostimulants are typically associated with induction of a mania-like syndrome, which includes euphoria, talkativeness, disinhibition, agitation and increased locomotor activity [Greene *et al.* 2008; Vollenweider *et al.* 1998; White *et al.* 2006], and may induce increased impulsivity during acute intoxication [White *et al.* 2007]. Further, psychotic symptoms such as hallucinations, thought control, ideas of reference, paranoid ideation, derealization and depersonalization may be induced at higher doses [Vollenweider *et al.* 1998; Greene *et al.* 2008]. Indeed, it has long been recognized that amphetamines may induce psychosis: amphetamine sensitization has been used experimentally to model psychosis [O'Daly *et al.* 2014a], and this has been recognized in the diagnostic categorization of psychotic disorders [American Psychiatric Association, 2013].

MDMA-like substances are usually associated with subjective reports of consistently elated mood, self-confidence, extroversion, but also psychedelic experiences [Liechti *et al.* 2001] that may include altered perceptions, experience of unity and a blissful state, insightfulness and so-called oceanic boundlessness [Studerus *et al.* 2010]. Further they may decrease feelings of anxiety without having sedative effects [Greer and Tolbert, 1998], despite physiological increases in blood pressure, heart rate and body temperature [Liechti *et al.* 2001]. Nichols coined the term 'entactogen' [Nichols, 1986] for MDMA and MDMA-like substances, in that they instil feelings of trust and empathy. Interestingly, recent research has shown that these agents may affect aspects of empathy differentially: when asked to infer mental states from pictures of the eye region in a social cognition task, participants who had been administered MDMA showed an impaired processing of negative emotion such as anger but enhanced processing of positive emotion such as friendliness [Hysek *et al.* 2012]; and MDMA acutely increases explicit and implicit emotional empathy as well as prosocial behaviours, whilst impairing the recognition of negative emotions in fearful, angry and sad faces (with some gender-specific differences) [Hysek *et al.* 2013]. There is also evidence that MDMA acutely impairs aspects of memory performance [Kuypers and Ramaekers,

2007], which may relate to apparent adverse long-term effects reported by and observed in some chronic recreational users.

From a theoretical point of view, subjective effects of psychostimulant NPS should be somewhat predictable based on their pharmacological profiles: substances that have high serotonin:dopamine ratios being largely analogous with entactogenic substances such as MDMA; whereas high dopamine:serotonin ratios might predict more of a strong stimulant experience. Furthermore high or low affinity to modulation of noradrenergic systems might be anticipated to be associated with varying sympathetic nervous system activation, whereas activation of 5-HT_{2A/1A} receptors would more likely predict hallucinogen-like effects. Fitting with this, subjective effects of mephedrone appear to be both similar to those of MDMA [Carhartt-Harris *et al.* 2011] as well as cocaine [Winstock *et al.* 2011a, 2011b], which is congruent with its pharmacological profile. Users report increased energy and talkativeness, euphoria, restlessness, empathy and increased libido; yet also forgetfulness, anxiety, paranoia, panic, agitation, as well as visual and auditory hallucinations [Winstock *et al.* 2011a, 2011b]. Similar evidence has been obtained for other stimulant NPS by Jebadurai and colleagues [Jebadurai *et al.* 2013]: naphyrone, commonly sold under the name NRG-1 as a legal replacement for mephedrone, has been reported to have marked euphoric effects by recreational users, however with a high potency, protracted onset and prolonged duration of effects compared with mephedrone. It may also induce paranoia, prolonged hallucinations, depression and anxiety, as well as cognitive difficulties. Similarly, 6-APB, a phenethylamine sold under the name 'Benzo fury' (which, despite its name, is not pharmacologically related to benzodiazepines) with a high affinity for SERT and lower affinity for DAT and NAT [Iversen *et al.* 2013], has been associated with reports of anxiety, panic attacks, insomnia and paranoid ideation [Jebadurai *et al.* 2013].

These agents are also liable to cause acute withdrawal effects upon cessation of use: specifically mephedrone withdrawal includes tiredness, insomnia, flu-like symptoms, irritability, difficulties in concentration, cravings and symptoms of disordered mood including depression and anxiety, a pattern largely consistent with withdrawal effects induced by established stimulants [Winstock *et al.* 2011].

Physiological effects

Stimulants are associated with numerous physiological effects, some of which may have significant adverse consequences, particularly those associated with overactivity of the adrenergic system. Dangerous effects may include tachycardia, arrhythmias, vasospasm, hypertension, hyperthermia, seizures, intracerebral haemorrhage and coma [Greene *et al.* 2008]. More serotonergic agents may, at high doses, induce serotonin syndrome, which, as described later, consists of headache, agitation, mania, shivering, sweating, hyperthermia, tachycardia, nausea, diarrhoea, myoclonus and tremors, and is an acute medical emergency [Boyer and Shannon, 2005]. Owing to the significant degree of overlap of symptoms, the particular type of toxicity may not always be easily discerned in emergency situations. There is also evidence for hepatic toxicity from MDMA, in both human and animal research [Turillazzi *et al.* 2010].

MDMA can also significantly alter hormonal function: Harris and colleagues [Harris *et al.* 2002] administered oral MDMA in a double-blind crossover RCT in healthy volunteers and reported increased plasma cortisol, prolactin and dehydroepiandrosterone (DHEA) levels. Moreover, DHEA levels correlated with euphoric feelings, whilst cortisol increases correlated both with increased heart rate as well as drug-liking, a finding consistent with animal models that show that corticosteroids enhance rewarding effects of substances of abuse. Increases in cortisol have also been found by subsequent research [Hysek *et al.* 2012, 2013]. A double-blind crossover RCT in 15 healthy volunteers demonstrated that oral administration of 100 mg MDMA significantly augmented oxytocin release, as measured by serum concentrations, which was found to be associated with increased subjective prosocial feelings, more so than serum MDMA levels [Dumont *et al.* 2009]. It should be noted however that the strong subjective effects of MDMA make successful blinding very unlikely.

Early data suggest that psychostimulant NPS appear to carry similar physiological effects. Recreational users report that mephedrone can induce restlessness, nose bleeds, diaphoresis (excess sweating), loss of appetite, palpitations, bruxism (jaw clenching/teeth grinding), overheating, blurred vision, shortness of breath, chest pains and nausea [Dargan *et al.* 2010; Winstock *et al.* 2011]. Gee and colleagues [Gee *et al.* 2005]

reported clinical presentations due to use of the piperazine BZP, with common side-effects including anxious, agitated and confusional states; nausea and palpitations; as well as generalised seizures in some. Similarly, 6-APB users have reported tachycardia, hypertension, hyperthermia, diaphoresis, bruxism, insomnia, gastrointestinal problems, dry mouth and eyes, as well as a prolonged 'hangover' over the days ensuing consumption [Jebadurai *et al.* 2013]. Emergency presentations most frequently involve tachycardia, diaphoresis and hypertension, as well as acute psychiatric episodes including agitation, confusion, hallucinations, paranoia, dysphoria, insomnia and delirium [Miotto *et al.* 2013]. Whilst cases of mortality have been reported in relation to NPS stimulant use [Miotto *et al.* 2013] these may be skewed due to polysubstance use or pre-existing conditions, and the low overall numbers make it difficult to establish firm data on toxicity [Maskell *et al.* 2011; Murray *et al.* 2012; Young *et al.* 2012; Dickson *et al.* 2010; Krikkku *et al.* 2011]. Elliott and Evans [Elliott and Evans, 2014] report from specimens analysed for UK coroner and police forces for both fatalities and criminal cases: their data show that mephedrone was by far the most commonly detected NPS compound, particularly so when still legal, followed mostly by other stimulants including 4-methylcathinone, BZP, MDPV, TFMPP, 4-methylamphetamine and 4-FMC, but also the dissociative methoxetamine (discussed later). In 84% of samples, other drugs and alcohol were present, and indeed novel agents were present as the sole drug in only 7% of death cases. A total of 22% of deaths involving NPS were suicides, with 41% of those in individuals who had used cathinones, despite cathinones only being present in 0.1% of all death cases, suggesting potential particular suicide risk exerted by cathinones, although considerable caution is warranted in such a supposition at this time.

Longer-term effects

In a landmark study Nutt and colleagues [Nutt *et al.* 2010] calculated the various risks of 20 commonly abused substances, and found that some of the greatest risk to users was conveyed by strong dopaminergic stimulants such as methamphetamine, amphetamine and crack/cocaine, whereas the more serotonergic agents MDMA, and to some degree mephedrone, were associated with fewer risks. Amphetamines are associated with the acute risks elaborated above under physiological effects, but also side-effects associated with

ongoing use, most notably amphetamine-psychosis, depression and cognitive impairments [Shoptaw *et al.* 2009; Cruickshank and Dyer, 2009]. Moreover, chronic psychostimulant use may impair neurological and neurocognitive functioning. A meta-analysis on methamphetamine abuse reported neuropsychological deficits in several domains, including executive functions, episodic memory, information processing and working memory [Scott *et al.* 2007]. This might be related to evidence obtained in animal models and post-mortem studies that demonstrated neurotoxic effects from psychostimulants, particularly to monoaminergic neurons [McCann and Ricaurte, 2004; Berman *et al.* 2008]. Recent decades have seen extensive debate, especially concerning MDMA use, around potential neurotoxic damage and neuropsychological deficits in chronic users and the issue remains highly controversial in the public arena [Parrott, 2013; Doblin *et al.* 2014; Krebs and Johansen, 2012a; Mithoefer *et al.* 2003]. However, it should be noted that two meta-analyses on this topic reported on deficits in attention, verbal and non-verbal learning, psychomotor and executive function, as well as short-term and working memory [Kalechstein *et al.* 2007; Nulsen *et al.* 2010]. Moreover, there are apparent alterations of integrity of the serotonergic system associated with chronic recreational abuse, such as decreases in SERT density, as well as some reports of impaired sleep and increased risk of psychiatric disorders, most notably depression [Parrott, 2012, 2013]. However, there are considerable caveats when interpreting such epidemiological data. In controlled clinical settings, MDMA appears to be largely safe, though how closely this maps onto real-world use can be debated [Doblin *et al.* 2014; Krebs and Johansen, 2012; Mithoefer *et al.* 2011, 2012; Parrott, 2013].

Simmler and colleagues [Simmler *et al.* 2013] report high blood-brain barrier (BBB) permeability of several NPS, most notably mephedrone and MDPV. It has previously been argued that stimulant-induced alteration of BBB permeability may lead to exacerbation of neurotoxic effects of these agents, as well as greater vulnerability to peripheral toxins and pathogens, and may lead to neuroinflammation [Kousik *et al.* 2012]. Interestingly, recent evidence suggests that mephedrone itself is not directly neurotoxic to dopaminergic neurons; however, there is evidence that it can enhance the toxicity of both MDMA and amphetamines [Angoa-Pérez *et al.* 2012,

2014]. Perhaps consistent with the finding that chronic MDMA abuse may facilitate the onset of depressive disorders [Parrott, 2013], individual user reports for agents including 6-APB, naphyrone and mephedrone also suggest the onset of psychiatric illness, most notably depression, after prolonged recreational use or upon cessation of use [Jebadurai *et al.* 2013; Winstock *et al.* 2011]. Animal models have presented evidence for long-term changes to monoaminergic as well as cognitive function following chronic cathinone administration [den Hollander *et al.* 2013].

Dependency and addiction

In general, psychostimulants are considered to have high risks of abuse potential and addictive behaviour. Dopaminergic stimulants increase impulsivity and risk-taking both acutely during intoxication [White *et al.* 2007] as well as chronically in recreational users [Bornovalova *et al.* 2005]. Similarly, recreational MDMA users are more likely to show impulsivity and risk-taking [Butler and Montgomery, 2004]. Vulnerability to compulsive use of psychostimulants may be exacerbated in adolescence and early adulthood due to limited constraint and self-control of the developing brain [Romer, 2010]. As noted above, stimulant NPS have been associated with induction of withdrawal symptoms upon cessation of use, suggesting abuse potential similar to that of established stimulants. However, it has also been increasingly recognized that abuse liability may vary depending on several factors, most notably the individual drug's serotonin-dopamine release ratio. In animal models, agents that have increased relative potency as serotonin releasers are associated with lower self-administration [Rothman and Baumann, 2006], and thus whilst they all have addictive potential the risk is reduced as one moves towards the entactogen side of the spectrum.

An interesting demonstration that a strong serotonergic component alone is less likely to result in abuse liability comes from nascent work on mephedrone. Kehr and colleagues [Kehr *et al.* 2011] showed in a microdialysis study comparing 5-HT and DA release of mephedrone and MDMA that whilst mephedrone was slightly more potent at releasing 5-HT, it was about twice as potent as MDMA at releasing DA in the nucleus accumbens. Physiologically unsurprisingly, mephedrone is also associated with robust induction of self-administration patterns in

animal models [Aarde *et al.* 2013; Motbey *et al.* 2013], whereas MDMA has generally more mixed reinforcing effects in animal models [Schenk, 2009]. Indeed, these data are supported by subjective reports in a user survey, where participants rated intranasal administration of mephedrone more addictive than cocaine, as well as conferring greater subjective drug-liking [Winstock *et al.* 2011]. Moreover, a significant proportion of recreational users self-report dependence symptoms such as increased tolerance, difficulty controlling use, unsuccessfully reducing use and continued use despite psychological and physiological problems [Winstock *et al.* 2011]. Given this predictive effect of serotonin:dopamine ratios on abuse potential of individual agents, Table 1 may be helpful, with caution, in preliminary predictions about the addictive potential of individual agents. Further impacting on abuse liability is the issue as to whether or not agents are substrate releasers, as this is associated with greater potency, as well as wider receptor affinity profiles.

Pharmacotherapeutic potential

Given the risks associated with most of these agents, there seems to be little current pharmacotherapeutic potential of amphetamine-like NPS in the treatment of major mental illnesses. Nonetheless, there is interest as to whether, analogous to opioid treatments, compounds with relatively lower risk profiles might be utilised as part of harm reduction or substitutive interventions: however, to date no such analogue model has been identified for psychostimulant users. There is a small but increasing evidence base suggesting that MDMA, and therefore, perhaps, novel entactogenic analogues, carries potential in the treatment of treatment-resistant post-traumatic stress disorder (PTSD). Early evidence obtained in several RCTs of MDMA-assisted PTSD interventions has delivered a rationale for more research in this important area of psychopharmacotherapy [Mithoefer *et al.* 2011, 2012; Oehen *et al.* 2012] and more trials currently on their way, including in the UK (B. Sessa, Personal communication, 2014).

Synthetic cannabinoids

Pharmacodynamic mechanisms

Cannabis is the most widely used illicit recreational substance [EMCDDA, 2014a]. Unsurprisingly therefore, synthetic cannabinoids

(sometimes colloquially called ‘noids’), which offer similar effects without the same threat of legal prosecution, are, along with novel stimulants, amongst the most popular of NPS [UNODC, 2012]. Owing to a perceived notoriety in the mainstream press, they have received significant attention in the scientific literature, and several reviews have been published on the subject: these are referred to in this paper where relevant to guide the interested reader further. Synthetic cannabinoids modulate G-protein coupled receptors (GPCRs) of the endocannabinoid system, of which two have been identified: cannabinoid receptor 1 (CB₁), largely prevalent in neurons of the central nervous system; and cannabinoid receptor 2 (CB₂), which is primarily expressed on cells of the immune system, such as microglia, although there is some crossover in expression. The two most prominent identified endogenous cannabinoids are anandamide and 2-arachidonoylglycerol (2-AG), both of which are synthesized in response to increased post-synaptic intracellular calcium levels and can activate CB₁ and CB₂ receptors [Pertwee, 2008]. Receptor activation inhibits presynaptic neurotransmitter release and therein excessive synaptic activity, and one of the main functions of the endocannabinoid system appears to be maintenance of neuronal homeostasis. Presynaptic CB₁ receptors inhibit the efflux of many excitatory neurotransmitters from the neuron into the synaptic cleft, including serotonin, dopamine, noradrenaline, acetylcholine and glutamate. However, some CB₁ receptors are also found on inhibitory GABA-ergic neurons, and thus their activation and quiescence of these GABA-ergic neurons may have downstream excitatory effects [Pertwee, 2008]. CB₂ receptors modulate function of the immune system, although the precise nature of this and its physiological relevance has yet to be fully elucidated. Owing to this apparent subspecialization of receptor functioning, it is generally considered that subjective effects of cannabinoids are primarily mediated by CB₁ receptors.

Pharmacological activation of cannabinoid receptors by exogenous ligands such as delta-tetrahydrocannabinol (THC), the most prominent psychoactive component of cannabis and primary mediator of its subjective effects, may lead to patterns of neural signalling quite dissimilar from localized endocannabinoid activity. This is congruent with the finding that THC, as a partial agonist with similar affinity on both CB₁ and CB₂ receptors, appears to increase dopaminergic

signalling in ventral striatal regions, including the nucleus accumbens, a key site of the mesolimbic reward pathway [Kuepper *et al.* 2013; Gardner, 2005]. Increased activity in striatal dopaminergic signalling pathways is likely associated with the subjective rewarding, euphoric and reinforcing effects of cannabinoids, as well as its potential psychotomimetic effects [Koob and Volkow, 2010]. Moreover, as THC has only partial receptor agonism, it might stimulate activity of CB receptors in some target tissues, but decrease it in other areas where it competes against endocannabinoids. Such a competitive interplay may also explain why, as well as individual differences in pharmacokinetics, effects may differ widely between subjects and can often be opposing, demonstrated for example by the potential of cannabis to act in an anxiolytic but also anxiogenic manner [Brida *et al.* 2007; Schramm-Sapota *et al.* 2007].

Novel cannabinoids mimic THC insofar as they activate primarily CB₁, although there is also some evidence for CB₂ receptor binding, albeit with differing receptor affinities and efficacies [Gurney *et al.* 2014; Pertwee, 2008], and the neuropharmacological effects of novel agents may differ substantially: an example of this is that several novel cannabinoids acting as full agonists have been identified, such as JWH-018. The first synthesized cannabinoids were indole-derived, many of which are known as the JWH series named after their first synthesiser John W. Huffman, and subsequently the group was extended by pyrroles and indenes. There is now a wide range of synthetic cannabinoids that have been found sold as legal highs, with Presley and colleagues [Presley *et al.* 2014] listing 10 chemical subfamilies, although their psychopharmacological characteristics remain to be fully delineated. In general, it appears that synthetic cannabinoids act as would be expected from their affinity to CB₁ receptors. In a neuron model, it was demonstrated that JWH-018 decreases neurotransmitter release in a dose-dependent manner via activation of the CB₁ activation [Atwood *et al.* 2010]. However, for example, it has been found that halogenation of compounds has led to the development of new analogues with higher potency, such as AM-2201 which has a 10-fold stronger binding to the CB₁ receptor than its precursor JWH-018 [Gurney *et al.* 2014]. Moreover, whilst early agents were primarily produced by academic and pharmaceutical company research, increasingly agents have come seemingly out of DIY

laboratories. For example, whilst UR-144 was first produced by Abbott Laboratories, its more potent, halogenated analogue XLR-11, apparently named after rocket fuel, has an unknown source and was first found in legal high smoking blends [Gurney *et al.* 2014; Presley *et al.* 2014].

Subjective and physiological effects

Subjective effects of smoking a joint include feeling high, stoned, stimulated and sedated, but not anxious or restless, whilst increases in heart rate but decreases in diastolic blood pressure are typically observed [Schwope *et al.* 2012]. Moreover, participants report slowed or slurred speech, dry mouth, shakiness, as well as feeling thirsty and hungry (the infamous ‘munchies’). However, it should be noted that cannabis contains a wide range of over fifty psychoactive components that may have very different effects. A notable example is cannabidiol (CBD), which has a complex and distinct pharmacological profile to that of THC, which is without any intrinsic psychoactive effects of its own: it has a lower affinity for the CB receptors than THC, where it has been shown to be an indirect antagonist (blocking agonist activity) as well as, at different synaptic concentrations, an inverse agonist (producing the opposite effect of the agonist) [Pertwee, 2008]. The result of CBD binding appears to partially attenuate subjective, psychotomimetic and neuropharmacological effects of THC [Bhattacharyya *et al.* 2009, 2010]. Some of the self-limiting effects that strains of cannabis with a high CBD:THC ratio can have, may not be present in cannabinoid NPS that do not contain CBD.

A recent RCT investigated acute subjective effects in recreational users smoking cannabis with varying THC doses, found that THC dose was correlated with a ‘high’ feeling, dizziness, sedation, anxiety, dry mouth and palpitations, whilst decreasing alertness, contentment and calmness and impairing memory and concentration, with effects lasting for up to 8 hours [Hunault *et al.* 2014]. Similarly, acute administration of a single oral dose of THC in another RCT was associated with anxiety, dysphoria, psychotic symptoms and sedation, as well as increased heart rate [Martin-Santos *et al.* 2012]. Acutely, fMRI resting-state data have shown THC to cause increases in global cerebral blood flow, particularly in prefrontal, orbitofrontal and anterior cingulate cortices, as well as temporal, insular and cerebellar regions. Blood flow in these areas also increases during

experimental tasks requiring attentional processing, such as dichotic listening tasks; whereas during emotional processing of fearful and angry faces, THC has been shown to be associated with reduced amygdalar reactivity to threat-related stimuli [Bhattacharyya *et al.* 2009].

Initially, synthetic cannabinoids were developed and tested for their analgesic properties [Gurney *et al.* 2014]. Animal data on the effects of novel cannabinoids, which have been utilized to explore both pharmacotherapeutic and adverse effects, have shown that acute effects are reasonably congruent with those of THC. For example, JWH-018, UR-144 and HU-210 all have analgesic, cataleptic, hypothermic as well as demobilizing effects in rats, with chronic administration leading to lethargy and unresponsive states [Gurney *et al.* 2014]. Further suggesting similarity between subjective effects of cannabinoid NPS and THC, a recent drug discrimination study in rats showed that JWH-018, JWH-073 and JWH-210 substituted for THC, and that THC substituted for JWH-018 [Wiley *et al.* 2014]. Currently, subjective and physiological effects of cannabinoid NPS are primarily based on excerpts from user reports obtained online or in medical emergencies [Spaderna *et al.* 2013], and, as such, this will likely bias the literature towards negative effects. Moreover, as synthetic cannabinoids are typically sold in herbal mixtures under names such as ‘Spice’, it is even less clear what users actually consume. Online user reports typically detail subjective changes in sensation, induction of both positive and negative mood states, cognitive impairments and disorganized thought, anxious and paranoid reactions, hallucinations and dissociation, as well as nausea, palpitations and appetite stimulation [Spaderna *et al.* 2013; Harris and Brown, 2013]. A review of adverse effects in adolescents and young adults following synthetic cannabinoid consumption similarly detailed reports of anxiety, agitation, paranoia and hallucinations [Brewer and Collins, 2014]. Curiously, unlike prototypical cannabis effects, users also report that cannabinoid NPS can induce ‘hangover’-like states [Spaderna *et al.* 2013]. Whilst cannabis is generally regarded nonlethal due to the considerable amounts that would need to be consumed to risk an overdose, this has not been confirmed for its NPS counterpart, with evidence for more severe effects than THC.

A recent systematic review by Gurney and colleagues reported serious emergency presentations

including renal and pulmonary damage and seizures [Gurney *et al.* 2014]. It remains unclear how much such risks may vary between novel cannabinoids, a fact confounded by the aforementioned mixed potpourris typically sold. The available data from such analyses suggest that smoking mixtures consumed by individuals presenting to emergency services most commonly contain agents of the JWH series, including JWH-018, JWH-081, JWH-250, JWH-210 and JWH-122, as well as agents such as AM-2201, AM-694, UR-144, XLR-11 [Gurney *et al.* 2014]. However this group of compounds largely overlaps with findings from analyses of smoking mixtures [Presley *et al.* 2014; Seely *et al.* 2013], suggesting that their prevalence in emergency services may be due to their general availability rather than a particularly increased risk of individual agents. Overall emergency presentations appear to have a relatively low prevalence: a survey by Winstock and Barratt [Winstock and Barratt, 2013] indicated that 2.4% of 950 individuals who had used synthetic cannabinoids in the previous year had subsequently contacted emergency medical services, most commonly due to psychological problems including anxiety, panic and paranoia.

Longer-term effects

As well as reward reinforcing, modulation of the dopaminergic system may be central to the development of acute and sometimes long-term psychotic symptoms. There is now considerable evidence indicating that cannabis use in adolescence and early adulthood increases the risk for the development of psychotic disorders, particularly so in heavy users in a dose–response relationship [Moore *et al.* 2007]. THC increases dopamine synthesis whilst inhibiting its uptake, and increases activity in striatal dopaminergic regions. CBD's pharmacodynamics have meant that it has received attention as a potential antipsychotic agent [Bhattacharyya *et al.* 2010], with early evidence in psychosis samples suggesting safety and efficacy similar to that of established antipsychotics, but with improved side-effects profiles, though more data are required and further trials are currently progressing [Leweke *et al.* 2012; Englund A, 2014; Personal communication, 2014]. Interestingly, enhanced anandamide signalling due to inhibition of degradation enzymes has been shown to correlate with clinical improvements in CBD treatment [Leweke *et al.* 2012], further highlighting the buffering effects of CBD that may be lost in synthetic cannabinoids, and

the potential increased risk of psychosis development.

The endocannabinoid system heavily modulates immune activity, the adaptive purpose of which may be the induction of appropriate sickness behaviour in illness states, including lethargy, fragmented sleep, decreased appetite and psychomotor retardation. Recent years have seen a surge in interest in the inflammatory immune system and inflammatory dysregulation in the onset of psychiatric symptoms as well as evidence of elevated inflammation in absence of appropriate pathogens in a row of psychiatric disorders [Dantzer *et al.* 2008; Raison *et al.* 2005; Baumeister *et al.* 2014c; Ayorech *et al.* 2015]. Whilst cannabinoids have anti-inflammatory properties in the short term, it has been argued that this might lead to long-term immunological adaptations that confer risk for the development of psychopathology. For example, recent animal evidence showed that anti-inflammatory effects of chronic THC treatment, marked by decreases of IL-1b and TNF-a and decreases in IL-10, occur in both adolescent and adult mice: however, adults treated with THC during adolescence had cytokine production reversed to a pro-inflammatory phenotype with increased IL-1b and TNF-a, yet decreased IL-10 [Moretti *et al.* 2014]. Such changes in immunological function due to cannabis exposure have recently been hypothesised to be a further putative mediating factor in psychosis development [Suárez-Pinilla *et al.* 2014], and indeed IL-1b and TNF-a are amongst the most consistently implicated inflammatory cytokines in mental disorder, shown elevated by several meta-analyses spanning depression, bipolar disorder and schizophrenia [Baumeister *et al.* 2014c].

A further interesting finding has been that the endocannabinoid system modulates a wide variety of functions of the hypothalamic–pituitary–adrenal (HPA) axis, which is part of the neuroendocrine stress system [Hill and Tasker, 2012]. Acute antagonism of CB₁ receptors leads to increased HPA activity, and CB1 knockout mice show greater basal HPA activation. Interestingly, activation of CB₁ receptors external to the paraventricular nucleus of the hypothalamus attenuates release of corticotrophin-releasing factor (CRF) by inhibiting glutamatergic neurons, leading to decreased adrenocorticotrophic hormone (ACTH) efflux from the pituitary gland, which results in decreased cortisol secretion from the adrenal cortices [Hill and Tasker, 2012].

Subjectively, this may account for decreases in perceived stress, yet chronic changes in HPA function due to an adaptive downregulation of CB₁ receptors in response to chronic stimulation may putatively pose significant risks to appropriate stress function, and dysregulation of the HPA axis is heavily implicated in mental disorders [Baumeister *et al.* 2014b]. Consistent with this, a recent meta-analysis found a significant association between depressive illness and cannabis use, particularly so in heavy users. Moreover, there is evidence from some longitudinal studies for higher rates of depressive and affective illness, as well as suicidal ideation and attempts, in those using cannabis during adolescence [Chadwick *et al.* 2013]. However, it should be noted that this does not mean that pharmacologically induced decreases in cannabinoid activity consequentially confer protection or improvements to mental health, but rather homeostasis appears to be key. Demonstrating this, the CB₁ antagonist Rimonabant was available as an anorectic agent in obesity treatment, however was withdrawn from the markets as it also led to increases in suicidal ideation and behaviour [Silvestri and Di Marzo, 2012]. Indeed, there is some evidence that chronic treatment of adult rats with the synthetic cannabinoid HU-210 leads to decreases in anxious and depressive symptoms, mediated by HU-210 induced promotion of hippocampal neurogenesis [Jiang *et al.* 2005]. Conversely, animals that have been exposed to chronic unpredictable stress show an anxious response to both low and high doses of HU-210, whereas non-stressed animals have an anxiolytic response to low doses but an anxiogenic one to high doses [Hill and Gorzalka, 2004].

Most of the existing information on longer-term effects inevitably comes from data on cannabis and THC. However, the nascent data that do exist show that there are significant differences between cannabis/THC and synthetic cannabinoids. The novel compounds are typically full CB receptor agonists (in contrast to THC's partial agonism), some of which have considerably greater receptor affinity and require a lower receptor occupancy for receptor activation than THC, and work has shown that the administration of multiple synthetic cannabinoids can produce additive and even synergistic effects [Papanti *et al.* 2014]. Novel cannabinoids have also been shown, again unlike THC, to have active metabolites with a high affinity for both CB₁ and CB₂ [Fantegrossi *et al.* 2014]. The dangers therein are compounded

by the fact that these newer substances also typically lack the ameliorative effects of CBD, making the risks for harm appear considerably greater at this time. A case series reported on 10 young adults admitted to a psychiatry ward experiencing psychotic symptoms subsequent to repeated synthetic cannabinoid use, 7 of whom remitted within 14 days, although the other 3 continued to experience symptoms more than 5 months after initial presentation [Hurst *et al.* 2011]. As of yet there is not sufficient long-term data to extrapolate precisely how the risk of psychopathological consequences of chronic use from synthetic cannabinoids compares to cannabis, though a recent systematic review [Papanti *et al.* 2013] described mounting evidence for the occurrence of such problems with the novel compounds. As with cannabis, pregnant women in particular should avoid any exposure to novel cannabinoids, as optimal functioning of the endocannabinoid system is crucial for neural development of the embryo as well as progression of pregnancy [Jiang *et al.* 2005; Park *et al.* 2004; Sun and Dey, 2012; Psychoyos *et al.* 2012; Papanti *et al.* 2014].

Dependency and addiction

Cannabis does not have the potential to induce 'classical' addiction marked by significant physical withdrawal symptoms upon cessation of use [Kattimani and Bharadwaj, 2013]. However, chronic cannabis use can bring about psychological dependency and induce withdrawal that is marked by mood swings, irritability and cravings [Karila *et al.* 2013]. Currently, there is only limited evidence available to explore whether this issue translates to NPS counterparts; however, user reports do indeed suggest similarities to, if not exacerbations of, the addiction liability associated with cannabis. Users have reported the onset of craving and withdrawal symptoms following chronic use, which appear to subside after several weeks of abstinence [Zimmermann *et al.* 2009; Soussan and Kjellgren, 2014]. Interestingly, there are isolated reports where individuals dependent on cannabis substituted this for novel cannabinoids without experiencing particular withdrawal symptoms [Gunderson *et al.* 2012]. Whether the abuse liability of the novel cannabinoids exceeds that of cannabis cannot currently be established, although fitting with the pharmacological argument about side effects, the augmented potency of several of the cannabinoid NPS makes it reasonable to anticipate that they will produce an increased risk.

Pharmacotherapeutic potential

Modulation of the endocannabinoid system has been identified as a potential pharmacotherapeutic approach for the treatment of a wide range of disorders, including neurological disorders such as Parkinson's disease, Huntington's disease or multiple sclerosis; cardiovascular-related disorders such as hypertension, stroke or myocardial infarction; inflammatory disorder such as atherosclerosis; chronic pain conditions; as well as mood and anxiety disorders [Pacher *et al.* 2006]. The topic is somewhat controversial, and there is a need to establish which specific compounds of cannabis have pharmacotherapeutic potential, which are most appropriate for given conditions, and to which degree this potential is mediated by individual CB receptors. For chronic users unable or unwilling to commit to cessation of use, lower potency analogues may present a future useful method of harm reduction, although to date most novel synthesized compounds have a significantly higher potency, and lack the protective effects of CBD.

Benzodiazepines

Pharmacodynamic mechanisms

Benzodiazepines have been amongst the most controversial of psychopharmaceutical agents since the initial synthesis of chlordiazepoxide by Sternbach in 1956 (followed by the marketing of diazepam in 1963) [Dell'osso and Lader, 2013]. They bind to an allosteric modifying site on the pentameric ionotropic gamma-aminobutyric acid (GABA) receptor. The GABA receptor has a resting activity, meaning that small amounts of negatively charged Cl⁻ ions influx even when no ligand is bound, although GABA binding significantly augments this. Benzodiazepine binding, through allosteric change of the receptor, further facilitates normal physiological functioning of the receptor when GABA is bound through increased frequency of opening of the central receptor pore, though these drugs have no effect on the receptor without the copresence of the endogenous ligand. The net effect of GABA receptor activation is to decrease the ability of the cell to exert an action potential. Notably, the GABA receptor further has a site that binds ethanol, and this is a primary mediating mechanism of the subjective effects of alcohol: this common mechanism of action means that benzodiazepines and alcohol produce cross-tolerance, and, importantly, can potentiate each other's effects. Benzodiazepines, due to their potential for dependency, are prescription-only

medications licensed for short-duration interventions, though they are otherwise widely available. They are commonly misused and overused, in terms of clinical indication and duration of use in both prescribed and illicit markets. The role of the commonly used benzodiazepines, and their use outside of recommended guidelines, whatever the source, is a contentious topic and outwith the remit of this paper. We herein briefly discuss benzodiazepine actions and the available data on their NPS analogues: for a broader review and debate on the psychopharmacological use of benzodiazepines we refer the interested reader to the work of Dell'osso and Lader [Dell'osso and Lader, 2013].

In recent years internet purchasing has meant that some benzodiazepines, notably phenazepam [7-bromo-5-(2-chlorophenyl)-1, 3-dihydro-2H-1,4-benzodiazepine-2-one] and the thienotriazolobenzodiazepine derivative etizolam, that are not licensed in most Western nations, but which remain available in some (predominantly Russia and ex-Soviet) states, began to appear more widely [Maskell *et al.* 2012]. Following trends in other NPS, these two compounds were generally proscribed, although phenazepam remains sometimes available under the name 'bonsai' or 'bonsai supersleep' [Corkery *et al.* 2012a], only to be followed by several more recently synthesized NPS benzodiazepines, such as pyrazolam, flubromazepam ((7-bromo-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one) and iso-flubromazepam (5-(2-bromophenyl)-7-fluoro-1,3-dihydro-2H-1,4-benzodiazepin-2-one). Pyrazolam was the first novel benzodiazepine to appear as an NPS [Moosmann *et al.* 2013a], having originally been a research trial drug whose development did not proceed to clinical use [Hester and Von Voigtlander, 1979]; although flubromazepam was actually initially synthesized in the 1960s [Sternbach *et al.* 1962]. Currently NPS benzodiazepines remain amongst the least-well-categorized and elucidated of the novel psychoactive substances. Their pharmacokinetics and dynamics, and how similar they are to established agents, are not currently well understood, and data on their prevalence are similarly nebulous at this time. As commonly occurs in the field of substance misuse these difficulties are compounded by various drugs intentionally or inadvertently being mixed and, for example, phenazepam has been discovered in assays of batches of LSD and the synthetic cannabinoid kronic [Maskell *et al.* 2012]. The lack of data on

this class is exemplified by recent work [Moosmann *et al.* 2013b] wherein one of the authors consumed 4 mg of flubromazepam so as that its pharmacokinetic properties might begin to be defined: the compound, in this paper, appeared to have a very long half-life of more than 100 hours, and one metabolite was detectable in urine 28 days post-ingestion. Early animal studies indicated that flubromazepam might be more potent than other common benzodiazepines, as measured by dosed effects on mouse aggression, although circumspection is required in interpreting these data that are almost half a century old.

Subjective and physiological effects

Benzodiazepines have four major effects: anxiolytic, hypnotic, muscle-relaxant and anticonvulsive. Intoxication is very similar to that of alcohol, with individuals variously disinhibited, cognitively impaired, with slurred speech and impaired motor control. Further, benzodiazepines act as respiratory depressants, which, at high doses, may lead to fatal overdoses, particularly when combined with other substances that share this property, such as alcohol and/or opiates. Moreover, their anticonvulsive properties, and adaptive changes of GABA:glutamatergic receptor ratios when they are taken excessively, confer a risk of seizures following sudden cessation of use.

Dependency and addiction

Benzodiazepines in general have a very well-recognized high propensity to addiction. In broad terms tolerance is associated with downregulation and functional uncoupling of the GABA_A receptor through changes to subunit composition [Follesa *et al.* 2001]. Overall the risks from individual compounds are related to their half-lives (shorter having greater risks than longer); and whether they are pharmacodynamically tonically or phasically active (phasic having greater risks). How closely NPS will map onto the parent class addiction risk has yet to be evaluated, but at this time it appears reasonable to consider that individual drug half-lives will be an important factor. Moosmann and colleagues [Moosmann *et al.* 2013b] noted that the apparent very long half-life of flubromazepam, as well as the fact that some consumers might be naïve to the effects of this class of drug, means that repeated dosing risks accumulated toxic concentrations, particularly if combined with alcohol. As well as such direct toxicity, this might also confer considerable indirect

risks such as through driving or the use of machinery. There is a stark lack of scientific data on actual toxic effects, although a case report [Dargan *et al.* 2012] gave an account of a 42-year-old man who presented with an acute confusional and disorientated state that lasted approximately 60 hours, with phenazepam the only analytically identified compound.

Pharmacotherapeutic potential

Benzodiazepines have several clinical indications, including for acute anxiety attacks and agitation, alcohol detoxification and catatonia in mental health; and as anxiolytic sedatives in medical and surgical interventions where keeping an individual awake and conscious is preferable to general anaesthesia. As they belong to the same biochemical class NPS benzodiazepines are likely to have similar clinical potential, though the lack of understanding of their individual pharmacodynamics and their lack of license currently prohibits this.

Dissociatives

Pharmacodynamic mechanisms

Dissociative drugs, such as ketamine ('Special K', 'K' or 'Ket') and phencyclidine ((1-(1-phenylcyclohexyl)piperidine, or PCP, but often referred to as 'angel dust') act mainly as uncompetitive antagonists, through open channel blockade, of the glutamate ionotropic NMDA receptor (NMDAR) [Herrling, 1997]. The NMDAR, whose activation requires the two coagonists glutamate and glycine, has distinguishable pharmacological and functional properties from the glutamatergic AMPA and kainate ionotropic receptors, particularly its high permeability to Ca²⁺, which is thought to have roles in higher cognition such as learning and memory [Traynelis *et al.* 2010] through activation of intracellular secondary messenger systems affecting processes such as synaptogenesis [Li *et al.* 2010]. Despite this class-defining specificity of NMDAR antagonism, dissociatives affect numerous other receptors and ionic channels, leading to their occasional informal description of being neurochemically 'dirty' drugs [Morgan and Curran, 2006]. They have been found to variously interact with opioid [Hustveit *et al.* 1995], dopaminergic [Becker *et al.* 2003]; serotonergic [Lindfors *et al.* 1997; Roth *et al.* 2013]; adrenergic [Roth *et al.* 2013]) nicotinic [Furuya *et al.* 1999], muscarinic [Durieux,

1995], and adenosine [Loix *et al.* 2011] receptors.

Ketamine was initially widely used in medical practice as a replacement anaesthetic for PCP. Despite both having a safe cardiovascular and respiratory profile, it was found that ketamine had a shorter half-life with fewer psychotomimetic effects, making it a preferable option [Domino *et al.* 1965]. Regardless, its strong dissociative effects on post-operative patients remained cause for concern and it was soon removed from mainstream anaesthetic use in humans, although it retains niche roles as a paediatric anaesthetic, and in veterinary practice (where it acquired the pejorative nickname ‘horse tranquilizer’). Both ketamine and PCP are arylcyclohexylamines, with an aryl group attached to a cyclohexane ring and a basic amine function. The first amine of this class, 1-(1-Phenylcyclohexyl)amine (PCA), was reported in 1907 [Kursanov, 1907], although the class exemplars of PCP and ketamine were first commercialized by Parke Davis 50 and 60 years after this, respectively. PCP became a class A drug in the UK and schedule II in the USA in the late 1970s; ketamine, which had been considered to have lower abuse potential, was widely available until the late 1990s when it was classified as a schedule III drug in the US. In the UK, ketamine was first classified as a class C in 2005, although this was recently changed in June 2014 to a class B controlled drug. Other historical first-generation arylcyclohexylamine analogues include 1-[1-(Thiophen-2-yl)cyclohexyl]piperidine (TCP, Tenocyclidine), 1-(1-Phenylcyclohexyl)pyrrolidine (PCPy, Rolicyclidine), N-Ethyl-1-phenylcyclohexylamine (PCE, Eticyclidine). These were first synthesized by Parke Davis [Levy *et al.* 1960; Kalir *et al.* 1969], and were later controlled by the Misuse of Drugs act in the UK in 1984, soon after PCP, as class A drugs, and never became widely available.

A resurging interest in dissociative analogues arose in part through the online forum ‘*The Hive*’ from the late 1990s onwards, with users collaboratively synthesizing and testing different arylcyclohexylamines [Morris and Wallach, 2014]. These included both previously tested analogues, such as 1-[1-(3-Methoxyphenyl)cyclohexyl]-piperidine (3-MeO-PCP) [Geneste *et al.* 1979], which was synthesized in 1979, although the first reports of illicit use did not emerge until the late 1990s, and which has been shown to be one of the strongest NMDAR antagonists [Roth *et al.* 2013]; and new

ones that would go on to become NPS dissociatives, such as 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexane (3-MeO-PCE). The first arylcyclohexylamine NPS sold online was methoxydine (4-MeO-PCP1-[1-(4-Methoxyphenyl)cyclohexyl]-piperidine), a low-potency PCP analogue, in 2008; followed shortly thereafter by one of the most popular dissociative NPS, methoxetamine (2-(3-Methoxyphenyl)-2-(ethylamino)cyclohexan-1-one) in 2010. To date, to the best of the authors’ knowledge, there have been only two studies looking into the pharmacokinetic properties of methoxetamine [Menzies *et al.* 2014; Meyer *et al.* 2013]. Structurally, it is similar to ketamine, with a 3-methox substituent on the phenyl ring and no 2-chloro group; and with an N-ethyl rather than an N-methyl substitute. Owing to the 3-methox substituent, there seems to be a higher affinity for the serotonin transporter protein (SERT) [Roth *et al.* 2013], which could be responsible for its euphoric effects. The N-ethyl group has been argued to be responsible for its increased duration and potency in comparison with ketamine [Coppola and Mondola, 2012]. Since methoxetamine, other dissociative research chemicals have been synthesised, including 3-MeO-PCE, 3-MeO-PCP, 3-MeO-PCPy, 3-MeO-PCPr and, more recently, N-EK (N-ethylnorketamine) and 2-MK (2-MeO-ketamine).

On February 2013, the UK government classified methoxetamine as a class B drug along with most arylcyclohexylamines through a so-called ‘catch all’ clause, to cover other dissociative NPS in the market as well as potential future compounds of this class. However, most (if not all) of these ketamine- and PCP-derived research chemicals are still readily available, and, in keeping with the broader field of NPS, novel analogues have since been synthesised. Diarylethylamines were originally synthesized in the early 20th century and initially patented by Gray and Cheng [Gray and Cheng, 1989] as treatments for neurotoxic injury. However, they have since been recognized for their similar pharmacodynamic structures to other dissociatives, also acting as antagonists at the NMDA receptor: diphenidine (1-(1,2-diphenylethyl)piperidine) and 2-MeO-diphenidine have been the first of this class to come into the market

Subjective and physiological effects

Most available data on the subjective and physiological side-effects of dissociatives have focused on ketamine and PCP, with, to the best of the

authors' knowledge, virtually no scientific information available on any of the currently marketed dissociative NPS. The most recent report from the EMCDDA [EMCDDA, 2014] on methoxetamine indicates that there are currently no data assessing the behavioural or psychological effects of the drug, and it makes no reference to any other arylcyclohexylamines. Despite this, most anecdotal reports from consumers note comparable effects to those experienced from ketamine, albeit at different degrees of intensity and length [EMCDDA, 2014; Hofer *et al.* 2012]. In 2003, Dillon and colleagues published a seminal study on subjective and physiological patterns among 100 recreational users of ketamine [Dillon *et al.* 2003]. The most commonly reported physiological effects (>25%) were increased heart rate, nausea, vomiting, pyrexia, blurred vision, impaired speech and analgesia, whereas subjective effects (>25%) included dizziness, dissociation from the environment, dissociation from the body, auditory and visual hallucinations, confusion, excitement, loosening of associations, unusual thought content, impaired memory, euphoria, visual distortions, novel bodily sensations, weightlessness and other altered body perceptions, and a sense of an absence of time. Of these, most psychological experiences (13 out of 16) were considered by the majority of participants to have been positive experiences; although the most frequent physiological symptoms were not as pleasant, with only three of the seven being reported as positive. Muetzelfeldt and colleagues [Muetzelfeldt *et al.* 2008] delineated 90 ketamine users into three distinct groups, frequent users, infrequent 'recreational' users, and exusers (>3 months abstinence), and found that overall 88% had a positive initiation experience with the drug. The most positive effects at initiation included the feelings of dissociation, contentedness, intense merriment and enjoyment of the sense of intensity; such feelings extended to current use, added with enjoying the experience of being high and relaxed. On the other hand, unpleasant subjective experiences included, for frequent users, impaired sociability, blunted affect, low mood, dissociation and paranoia. For users during initiation, the negative side effects also included feelings of nausea and vomiting and a sense of loss of control. At higher doses consumers sometimes experience the infamous 'k-hole', described by one user as 'tunnel vision then rising above the body like a near death experience' [Critchlow, 2006, p. 1212]. Risk of death from an acute dose of ketamine is considered quite rare: between 1993 and 2006

there were four deaths identified, in the UK, where ketamine was the only drug detected [Schifano *et al.* 2008]. In medical settings, inadvertent administration of single very high doses of ketamine, up to 100 times higher than recommended, has been reported in children with no adverse outcomes [Green *et al.* 1999]. However, intoxication with dissociative drugs could potentially lead to risky and careless behaviour, and the highest mortality risk was found to be accidental death while intoxicated [Jansen, 2000; Stewart, 2001], namely motor vehicle accidents [Cheng *et al.* 2005].

PCP presents similar subjective effects, although with a much wider and unstable range of symptoms and with a much higher propensity for toxicity. Pradhan [Pradhan, 1984] reviewed the acute effects of PCP on human behaviour and physiology: at subanaesthetic doses it has several similar effects to ketamine, as it induces (1) sensory changes, with dissociative, out-of-body feelings and distorted visual and auditory perceptions; (2) cognitive changes, such as memory impairments, altered perception of time, slowness; (3) affective changes, although quite labile, varying between euphoric, anxious, apathetic and irritable; (4) unpredictable behavioural changes, potentially including aggression; and (5) changes in consciousness. Physical symptoms depend largely on the level of intoxication. At higher doses, usually administered through injection or oral ingestion (although these are not as common as nasal insufflation), the consumer can go into a comatose state that can be either responsive to pain or not. There are considerable risks associated with use, including pulmonary oedema, cerebrovascular accidents, and cardiac arrest. Presenting a relatively similar pattern to ketamine deaths, a (now considerably dated) work describing 19 PCP-related deaths [Noguchi and Nakamura, 1976], noted that only 3 were due to intoxication and 13 were due to acute behavioural effects and acts.

With regards to NPS dissociatives, reports available on 120 non-fatal cases of methoxetamine-associated intoxication from the EMCDDA report [EMCDDA, 2014] show a similar adverse symptom profile including: gastrointestinal problems such as nausea, vomiting and diarrhoea; cardiorespiratory problems including arrhythmias, blackouts, dyspnoea; neurological problems such as distorted vision, headaches, seizures, tremor, and disorientation and confusion; and

neuropsychological sequelae including post-use depression, a sense of mental slowing, anxiety, difficulty speaking, catatonia, agitation, aggression, hallucinations, paranoia and psychosis. Clearly however, such work faces the usual research bias in this field of not focusing on or reporting pleasant experiences. Deaths associated with methoxetamine [EMCDDA, 2014] need judicious interpretation, and the presence of the drug in post-mortem samples does not necessarily indicate causality; on the other hand, many deaths might have been neglected due to inadequate post-mortem toxicological analyses. One case study [Wikström *et al.* 2013] reported an accidental fatal intoxication with methoxetamine, though three NPS cannabinoids were also present in the post-mortem results.

Longer-term effects

The present review failed to identify any human data with regard to longer-term risks from dissociative NPS: most potential guidance coming from ketamine research, the applicability of which remains to be determined. Four main risks domains of ketamine are commonly identified: gastrointestinal complications, urinary tract complications, cognitive impairments (particularly memory decline) and psychopathological sequelae. One of the most frequently noted longer-term complications is damage to the urinary tract, particularly ulcerative cystitis of the bladder (sometimes known as 'Bristol bladder'), although renal damage is also possible: symptoms can include haematuria, dysuria, discomfort, and increased frequency and urgency of urinating [Shahani *et al.* 2007; Chu *et al.* 2008]. Whilst cessation of use appears to resolve the condition for most affected users, cases of severe damage and irreversible change have been reported in heavy users [Winstock *et al.* 2012]. A survey by Winstock and colleagues [Winstock *et al.* 2012] found that urinary symptoms were significantly related to frequency and dose of ketamine use, and were present in over a quarter of regular users. Suggesting that this is similar to at least methoxetamine, rodent data shows that the estimated equivalence to human dosing delivered over three months results in damage to the kidneys and bladders of mice [Dargan *et al.* 2014]. Gastrointestinal complications, the so-called 'K-cramps', are common, especially in more frequent ketamine users [Muetzelfeldt *et al.* 2008]. A total of 21% of patients admitted to A&E with ketamine reported abdominal pain [Ng *et al.*

2010], and nascent data suggest a correlation with abnormal liver function [Wong *et al.* 2009].

Prolonged use of ketamine has been found to affect several cognitive domains, perhaps unsurprising given the involvement of the NMDA receptor in learning and memory processes through neuronal long-term potentiation and long-term depression. Differential impairments appear to occur with problems in encoding (but not retrieval) of episodic memory, semantic memory, manipulation (but not maintenance) of working memory and procedural learning [Morgan and Curran, 2006].

Ketamine is psychotomimetic at higher doses, and has been frequently used to model schizophrenia in both human and animal paradigms. Krystal and colleagues [Krystal *et al.* 1994] first reported this potential of NMDA antagonists, demonstrating both negative and, particularly, positive symptoms domains in healthy volunteers administered with a low dose of the drug. Patients with schizophrenia have been shown to have their symptoms triggered by both ketamine [Malhotra *et al.* 1997] and PCP [Steinpreis, 1996], and neuroimaging studies have shown overlap of brain activation patterns between acute effects of ketamine and patients with psychosis [Vollenweider *et al.* 2000]. Frequent drug users have been shown to exhibit psychopathological symptoms similar to a psychosis prodrome [Larson *et al.* 2010], with higher scores on schizotypal, dissociative and affective symptoms as well as cognitive impairments [Morgan *et al.* 2009]. These schizotypal symptoms remained largely stable throughout the 1-year observation period in the frequent users group, although abstinent exusers showed marked decreases in most parameters, except depressive symptoms. As of yet, no clear causal relationship between ketamine consumption and the development or incidence of psychotic disorders has been established with the degree of certainty ascribed to cannabis, though such a link cannot be ruled out, and while drug cessation has been shown to lead to a decrease in psychopathology in most affected drug users, symptoms have been reported to persist in some [Morgan *et al.* 2004].

Dependency and addiction

Ketamine acts as a dopamine agonist in the rat striatum and prefrontal cortex [Moghaddam *et al.* 1997] and PET studies in humans show that ketamine increases dopaminergic firing in the

striatum [Vitkun *et al.* 1998; Vollenweider *et al.* 2000]. As with many other drugs of abuse it is considered that it is this dopaminergic activation that confers much of its addictive potential [Robinson and Berridge, 1993; Koob and Volkow, 2010]. Although ketamine has a low affinity for opioid receptors, other novel dissociatives such as methoxetamine have been found to have a higher affinity, which could hypothetically contribute to an addictive potential [Morris and Wallach, 2014]. However despite this a neurochemical potential and anecdotal reports by frequent users, only limited data are available on the prevalence of ketamine dependence and virtually none on dissociative NPS. A large survey by Winstock and colleagues [Winstock *et al.* 2012] reported that out of 1285 self-selected ketamine users 17% met criteria for dependence. In a study by Muetzelfeldt and colleagues [Muetzelfeldt *et al.* 2008], 28% of participants highlighted their concerns over compulsive use of ketamine, and more than half of the participants (46 out of 90) indicated binge-like compulsive behaviours such as 'us[ing] K without stopping, until it is all gone'; and only 2 out of 90 in that sample agreed with the statement that they would 'use some K, then stop'. Data on withdrawal symptoms from ketamine and dissociative NPS are inconsistent, with no clear syndrome being described in the literature [Critchlow, 2006; Lim, 2003]. Again more data currently come from anecdotal reports, where frequent users have indicated 'cravings' as one of the main reasons for not being able to discontinue: Morgan and colleagues [Morgan *et al.* 2008] described 28 out of 30 chronic ketamine users failing when trying to quit due to an emotionally driven craving to take the drug. The degree to which this translates to novel dissociatives remains unclear.

Pharmacotherapeutic potential

Ketamine has been found to have fast-acting antidepressant effects on patients with treatment-resistant depression at a subanaesthetic dose. At a dose of 0.4 mg/kg intravenously infused over forty minutes, it has been shown to reduce depressive symptoms in some refractory patients within a time period as low as 2 hours, which can last for as long as 2 or 3 weeks [Zarate *et al.* 2006; Ibrahim *et al.* 2012]. Trials on the efficacy of ketamine as a fast-acting antidepressant have been run both clinically, with psychiatric patients, and preclinically, with animals. Preclinical studies have found this phenomenon to be potentially related to: an increase in synaptogenesis through glutamatergic

signalling and subsequent activation of the mTOR pathway [Li *et al.* 2010]; regulation of the neurotrophic brain-derived neurotrophic factor (BDNF) [Garcia *et al.* 2008]; reduction in pro-inflammatory cytokines [Loix *et al.* 2011]; amelioration of circadian patterns [Pompili *et al.* 2013]; and alterations to intracellular $\sigma 1$ receptors [Hayashi *et al.* 2011]. We refer the interested reader to our recent meta-analysis on the efficacy of ketamine as an antidepressant [Caddy *et al.* 2014]. Understandably attention has been raised about whether or not novel dissociatives might have a similar clinical role [Coppola and Mondola, 2012; Pochwat *et al.* 2014], although no such trials have yet been conducted.

Hallucinogens

Pharmacodynamic mechanisms

Hallucinogens may be divided into three subgroups: phenethylamines (e.g. mescaline or Bromo-DragonFLY); tryptamines (e.g. psilocybin or 5-MeO-DALT); and lysergamines (e.g. LSD or AL-LAD). However, despite this biochemical delineation there is extensive evidence that most of these so-called classical hallucinogens produce cross-tolerance [Nichols, 2004]. Current evidence strongly suggests that the common mechanism of action of these agents is agonism or partial agonism of the 5-HT_{2A} receptor [Presti and Nichols, 2004]. Supporting this, the selective 5-HT_{2A} antagonist ketanserin, as well as the partial antagonist risperidone, have been shown to block psychedelic effects of psilocybin [Vollenweider *et al.* 1998]. However, classical hallucinogens generally display a similar potency as agonists for 5-HT_{2C} and 5-HT_{1A} receptors as well as some degree of action on most other serotonin receptor classes [Nichols, 2004]. Indeed, there is some evidence suggesting that psychedelic effects of DMT are partially mediated by 5-HT_{1A}, although with curiously paradox effects, in that the 5-HT_{1A} antagonist pindolol blocks psychedelic effects of DMT in animals but potentiates them in humans [Strassman, 1995].

Psilocybin has been shown to decrease metabolic activity of parts of the thalamus in human subjects [Gouzoulis-Mayfrank *et al.* 1999; Carhart-Harris *et al.* 2014], and this may underlie some of the sensory alterations associated with hallucinogens. It appears plausible that the infamous 'doors of perception' [Huxley, 1954] open wider as thalamic filtering of sensory input to the cortices

decreases, and with a shift towards sensory awareness, self-referential processes may decrease. Moreover, psilocybin significantly decreases cerebral blood flow in the thalamus, hypothalamus, the anterior and posterior cingulate cortices and large parts of the prefrontal cortex (PFC) including the medial PFC, lateral orbitofrontal cortex and the frontal gyri [Carhart-Harris *et al.* 2012a]; increases functional connectivity of the so-called default-mode network (DMN), composed of the posterior cingulate cortex, medial PFC and lateral inferior parietal cortex, and the task-positive network (TPN), composed of prefrontal and parietal structures [Carhart-Harris *et al.* 2012b]. These anticorrelated networks are associated with non-goal-orientated introspection and goal-directed attentional tasks respectively [Tracy and Shergill, 2013]. We refer the interested reader to our recent detailed review of the pharmacodynamics of classical hallucinogens [Baumeister *et al.* 2014a].

Whilst plant-based hallucinogens have been used entheogenically for millennia, the first synthetic, and perhaps most infamous, hallucinogen lysergic acid diethylamide (LSD) was created in 1938 by Swiss chemist Albert Hofmann. Ever since, several chemists, notably David E. Nichols and Alexander Shulgin, have developed a series of analogues and similar compounds that operate through fundamentally the same primary mechanism of actions as classical hallucinogens. Notable agents that are currently hold a legal or semilegal status are listed in Table 2. At present the full pharmacological profiles of most hallucinogenic NPS remain incomplete, and their grouping is based on subjective description of user experiences. It should also be noted that several agents that are primarily psychostimulants, including MDMA, mephedrone and methcathinone, also act as agonists upon the 5-HT_{2A} receptor either through direct agonism or that of metabolites, leading to a degree of co-activation of more psychedelic pathways. Demonstrating this, Liechti and colleagues [Liechti *et al.* 2000] administered ketanserin, a selective 5-HT_{2A} antagonist, as pretreatment to MDMA to healthy volunteers, and this was associated with a significant attenuation of perceptual changes, emotional excitation, body temperature and adverse response, but not positive mood, extroversion and wellbeing. Although few pharmacological data are currently available, the popular 2-C series as well as the NBOMe series may fall in-between the hallucinogen and psychostimulant categories, showing subjective effects congruent with either group, as detailed below.

Subjective effects

Perhaps the best data available on the subjective acute effects of hallucinogens at moderate doses has been obtained in experimental research utilising psilocybin. Studerus and colleagues [Studerus *et al.* 2010] reported on acute and long-term psychological effects of psilocybin in 110 healthy volunteers who received one to four oral doses of very low to high doses of psilocybin (45–315 µg/kg of body weight). Psilocybin had a significant effect on all dimensions of the Altered States of Consciousness Rating Scale, which comprises of several dimensions including oceanic boundlessness (a measure combining insightfulness, religious experience, experience of unity and blissful state), anxious ego dissolution (referring to a combination of anxiety, impaired control and disembodiment), visionary restructuralization (referring to a combination of elementary visual alterations, audio-visual synaesthesia, vivid imagery and changed meaning of perceptions) as well as alterations of auditory perceptions and cognitive vigilance. However, much smaller effects were recorded for anxious ego dissolution component of the scale. Adverse psychological effects were only observed in a minority of participants, who were all calmed down verbally rather than through the use of medication. Noteworthy, these adverse effects occurred only among those who were administered high doses, which may be relevant to the use of NPS where ‘appropriate’ doses are unknown. Follow-up questionnaires provided no evidence of any mental impairment or distress resulting from psilocybin exposure. However, as the authors excluded any participants with a personal or family history of schizophrenia, major depression, bipolar disorder, borderline personality disorder, neurological disorders or alcohol or substance abuse, the significance of these findings may not be easily transferred to broader populations and to the set and setting, which are known to hallucinogen consumers to have significance, in which recreational users may decide to ingest these substances. Anecdotally, the ‘horror trip’ is a culturally well-known phenomenon, and the limited substance-user literature and online reportage indicates that this may be equally associated with hallucinogenic NPS. Despite the noted common shared pharmacological mechanisms, individual agents vary in their exact pharmacodynamic activities regarding both receptor affinity as well as the degree of subsequent activation of intracellular signalling pathways, commonly termed the drugs’ functional selectivity [Nichols, 2004; Wacker *et al.* 2013]: the importance of these variations is incompletely understood, although

Table 2. Groups of substances ordered by their primary mechanism of action, and exemplar agents and effects (not comprehensive).

Target systems	Binding sites	Drug class	'Classic' agents	'Novel' agents	'Desired' effects	Adverse effects
Monoamine Reuptake Pumps	SERT DAT NAT	Stimulants	MDMA Cocaine Amphetamine Methamphetamine	Mephedrone 5-IAI 2-AI BZP 6-APB Naphyrone NBOMe-series 2C-series	Euphoria Social disinhibition Extroversion 'High'	Serotonergic syndrome Psychotic symptoms Paranoid ideation Agitation Impulsivity Mania Cardiovascular symptoms Hyperthermia Anxiety
Metabotropic G protein-coupled receptors	5-HT _{2A} 5-HT _{1A} 5-HT _{2C}	Psychedelics	Psilocybin LSD DMT Mescaline	Bromo-DragonFLY AL-LAD 5-MeO-Dalt NBOMe-series 2C-series	Psychedelic effects including: Perceptual restructuralisation Oceanic boundlessness	Paranoid ideation Anxiety Psychotic symptoms Cognitive impairment Seizures (novel agents only)
	CB ₁ CB ₂	Cannabimimetics	THC	JWH-018 JWH-081 JWH-122 AM-2201 UR-144 XLR-11	Relaxation Analgesia 'High' Sedation Euphoria Anxiolysis	Paranoid ideation Anxiety Psychotic symptoms Cognitive impairment Seizures (novel agents only)
Ionotropic ligand-gated ion channels	GABA	Benzodiazepines	Diazepam Aprazolam Lorazepam	Pyrazolam Flubromazepam Phenazepam	Anxiolysis Muscle-relaxation Sedation	Respiratory depression Seizure upon withdrawal Addiction
	NMDA	Dissociatives	Ketamine PCP	Methoxetamine Diphenidine 2-MeO-diphenidine 4-MeO-PCP 3-MeO-PCP N-EK 2-MK	Dissociation Analgesia 'High' Euphoria Weightlessness	Headache Psychotic symptoms Nausea Dizziness Paranoia Anxiety Cognitive impairments
MDMA, 3,4-methylenedioxy-methamphetamine; LSD, Lysergic acid diethylamine; DMT, N,N-Dimethyltryptamine; THC, Tetrahydrocannabinol; PCP, Phencyclidine; 5-IAI, 5-Iodo-2-aminoindane; 2-AI, 2-Aminoindan; BZP, Benzylpiperazine; 6-APB, 6-(2-aminopropyl)benzofuran; AL-LAD, 6-allyl-6-nor-LSD; 5-MeO-Dalt, N,N-diallyl-5-methoxytryptamine; JWH-018, 1-pentyl-3-(1-naphthoyl)indole; JWH-081, 4-methoxynaphthalen-1-yl- (1-pentylindol-3-yl)methanone; JWH-122, [4-methyl-1-naphthyl]-[1-pentylindol-3-yl)methanone; AM-2201, [1-(5-fluoropentyl)-3-(1-naphthoyl)indole]; UR-144, [1-pentylindol-3-yl]-(2,2,3,3-tetramethylcyclopropyl)methanone; XLR-11, 5"-fluoro-UR-144; 4-MeO-PCP, 4-Methoxyphencyclidine; 3-MeO-PCP, 3-Methoxyphencyclidine; N-EK, N-ethylketamine; 2-MK, Methoxyketamine.						

drug consumers have long anecdotally recognized and reported differences in their effects. Further, the half-life of the substances also differ, with, for example, psilocybin staying psychoactive for about 8 hours in human participants, whereas LSD can last for up to 12 hours [Nichols, 2004].

Subjective effects of novel hallucinogens have not yet been examined in experimental research,

however user reports indicate that they are generally similar to classical hallucinogens. This has been reported for NBOMe agents [Lawn *et al.* 2014], of which the most prominent is 25C-I-NBOMe (a potentiated derivative of 2C-I) with demonstrated increased 5-HT_{2A} affinity [Halberstadt and Geyer, 2014]. The best current knowledge has been obtained by reports following the so-called 'Heffter method', namely

self-experimentation (named after the German chemist Arthur Heffter who isolated mescaline from the peyote cactus and consumed it); or through clinical emergency presentation data. Most notable here are the books of Alexander 'Sasha' Shulgin who developed and tested hundreds of agents, many reported in his seminal work PIHKAL (Phenethylamines I have known and loved) [Shulgin and Shulgin, 1997]; as well as the increasing amount of self-reports (or 'trip reports') on online forums such as Erowid (see <http://www.erowid.org>), UK Chemical Research (see <http://www.ukchemicalresearch.org>) or Bluelight (see <http://www.bluelight.org>). In general these sources describe effects similar to classical hallucinogens, including changes in perceptual, cognitive and emotional domains marked by a strong visual component. For example, 5-MeO-DALT, an agent that is only very poorly understood in pharmacological terms, has been reported to induce entheogenic as well euphoric and stimulating effects, as well as visual distortions; but there are also clinical case reports of delirious reactions and severe agitation [Jovel *et al.* 2013; Corkery *et al.* 2012]. As mentioned previously, it has been recognized that there are several agents that chemically overlap with psychostimulants: agents such as 25C-I-NBOMe not only have classical hallucinogens effects such as visual and auditory perceptual distortions and spatial and temporal disorientation, but also have a marked component of MDMA-like subjective effects, including bright mood and euphoria, energetic arousal and increases in subjective empathy [Zuba *et al.* 2013; Nikolaou *et al.* 2014], as well as congruent physiological effects detailed below.

Physiological effects

In experimental setups the onset of symptoms is about 20–30 minutes after oral administration for psilocybin, but may occur within up to 2 minutes of intravenous administration [Hasler *et al.* 1997, 2004]. Data collected by Lawn and colleagues [Lawn *et al.* 2014] confirm this pattern for oral/sublingual/buccal administration of NBOMe-type NPS with a peak of effect at about 2 hours. However they also report that users may administer the drugs via nasal insufflation, in which case the onset of effects is within 5–10 minutes and peaks at around 45 minutes, albeit with lesser intensity than when orally administered and this method is less common amongst users. Hallucinogens are generally associated with few physiological effects: these most consistently include pupil dilation, and to some

degree mild and variable changes in heart rate and blood pressure, vasoconstriction, diaphoresis and hypersalivation and, depending on the agent, some nausea [Jerome, 2007, 2008; Passie *et al.* 2002; Hasler *et al.* 1997, 2004]. Interestingly, Hasler and colleagues [Hasler *et al.* 2004] found that during peak effects of psilocybin plasma concentrations of several hormones increased, including thyroid-stimulating hormone, cortisol, adrenocorticotrophic hormone as well as prolactin, with some dose-dependent variations. However, whilst mean arterial blood pressure increased moderately in response to high doses, they found no significant changes during a 24 hour electrocardiogram (ECG) or effects on body temperature, regardless of the dose.

Risks and side effects

Owing to the relatively low clinical relevance of hallucinogens to healthcare professionals and services for substance use disorders, and their apparent low prevalence of use in the general population, even agents that have been known for millennia or at least decades have received little attention in scientific research, an effect that may carry over to novel hallucinogens. Data obtained in research with healthy as well as clinical participants indicates that classical hallucinogens appear to have a relatively modest side-effect profile [Baumeister *et al.* 2014], and there have been no reported fatalities directly due to psilocybin [Jerome, 2007]. Nevertheless, existing study sample sizes are generally small, and hallucinogens have been demonstrated to produce psychosis-like symptoms, indeed serving as a serotonergic model of psychosis [Vollenweider *et al.* 1998; Halberstadt and Geyer, 2013; Murray *et al.* 2013], with questions remaining about how this may impact mental health in the longer term. Another potential side effect is hallucinogen perception persisting disorder (more commonly known under the term 'flashbacks'), in which the user re-experiences some of the subjective effects of hallucinogens a considerable time after consumption: however, in the scientific literature this effect has proven to be of very elusive prevalence, its erratic nature potentially making it difficult to 'capture and quantify', and it has not been demonstrated to be strongly associated with the amount or frequency of drug ingested, though it may cause significant morbidity in those chronically affected (Halpern and Pope, 2003; Kilpatrick and Bard Ermentrout, 2012]. Anecdotally it appears mostly associated with LSD, and it has been successfully treated, in the limited and primarily case-report

literature, with neuroleptics and benzodiazepines [Hapler and Pope, 2003]. There is some survey evidence that hallucinogen use in recreational users is associated with greater levels of anxiety, particularly at high doses [Nichols, 2004; Studerus *et al.* 2010], and panic attacks, although other users have also reported perceiving them as beneficial to their mental health and of low potential for harm [van Amsterdam *et al.* 2011]. The importance of so-called 'set and setting' has long been recognized by recreational users, and therefore experimental research has tried to create 'ideal' conditions for their participants [Griffiths *et al.* 2006; Johnson *et al.* 2008], and thus subjective effects may drastically alter when in exposed to adverse environmental stimuli.

Bouso and colleagues [Bouso *et al.* 2012] provided interesting evidence regarding long-term use of hallucinogens by studying religious groups using ayahuasca, a brew containing DMT, as well as a monoamine oxidase inhibitor (MAOI), which allows it to be orally ingested. The study compared 127 regular ayahuasca users with 115 actively religious controls. Regular hallucinogen users showed lower scores on all psychopathology scales as assessed by the Symptom Check-List-90-Revised, as well as on measures of harm-avoidance and self-directedness. However, they scored higher on a measure of psychosocial well-being, and performed better on the Stroop test (an indicator of resistance to emotional interference) as well as the Wisconsin Card Sorting Task (a measure of working memory). This data was reconfirmed at a 1-year follow up, demonstrating that there was no deterioration of mental health in regular users. Fitting with this finding was a population-based analysis by Krebs and Johansen [Krebs and Johansen, 2013] of a nationwide Norwegian drug-use survey ($n = 21,967$). Whilst causality cannot be assigned from such data, it was noteworthy that 13.4% of respondents reported lifetime use of hallucinogens, and no correlation was demonstrated between lifetime/past-year use of any psychedelic substance and any mental health outcome. Evaluation of the relationship between classic hallucinogen use and psychological functioning from five years of data in the United States ($N=190,000$) showed these drugs to be associated with reduced psychological distress and suicidality [Hendricks *et al.*, 2015]. Undoubtedly circumspection is required when interpreting surveys.

However, novel agents may not necessarily have the same risk profile. For example, the partial 5-HT_{2A}

agonist ibogaine, derived from the iboga shrub, has a much more promiscuous pharmacological profile that includes affinity for opioid sigma and NMDA receptors. Whilst this drug has been associated with anti-addictive properties and opiate detoxification, it may also cause cardiac arrhythmias and prolongation of QT intervals [Koenig *et al.* 2014], highlighting that the actual risk of individual agents ultimately depends on their distinct pharmacological profile. Moreover, agents that share properties with high-serotonergic psychostimulants such as MDMA are more likely to also carry the risk associated with these, including isolated clinical reports of fatalities [Nikolaou *et al.* 2014]. For example, 2C-I is a partial agonist on 5-HT_{2A}, has a high affinity for 5-HT_{2C}, and acts as an inhibitor on serotonergic, dopaminergic and noradrenergic reuptake pumps [Acuña-Castillo *et al.* 2002; Nagai *et al.* 2007]. As might be expected from such a profile, reports of unwanted side-effects include paranoid ideation, aggression, confusion, tachycardia, and hypertension, and in some cases emergency presentations including renal failure, seizures, cardiac and respiratory arrest [Nikolaou *et al.* 2014; Drees *et al.* 2009]. Several case studies of such emergency presentations including marked sympathetic nervous system arousal involving the 2C and NBOMe series have now been published [Tang *et al.* 2014; Nikolaou *et al.* 2014; Hill *et al.* 2013; Bosak *et al.* 2013], but methodologically more robust data is yet to be obtained.

Dependency and addiction

It is largely accepted that classical hallucinogens are not physically or psychologically addictive [Lüscher and Ungless, 2006], however the extent to which this applies to novel agents remains unknown. Classical hallucinogens are associated with a rapid induction of tolerance upon repeated administration that is hypothesised to be a result of 5-HT_{2A} receptor downregulation, a pharmacodynamic property argued to make dependence and frequent use less likely than many other recreational drugs, with, for example, the psychoactive effects of LSD abolished after 4 days of daily administration [Nichols, 2004]. Moreover, hallucinogens exert inhibitory effects on dopaminergic neurons in the ventral tegmental area [Baumeister *et al.* 2014a], meaning they actually induce effects opposing those of classical drugs of addiction, and indeed, there is some debate as to whether or not hallucinogens might therein carry potential in the treatment of addictive disorders [Krebs & Johansen, 2012].

Pharmacotherapeutic potential

There are nascent data indicating potential usage of classical hallucinogens in the treatment of mood disorders, and in reducing recidivism amongst substance-involved offenders under community corrections supervision (Hendricks *et al.* 2014); for a full review of this issue, we refer the interested reader to our recent review [Baumeister *et al.* 2014a], although further work is required to better elucidate the putative therapeutic effects these compounds or their NPS derivatives might provide.

Practical steps for clinicians and drug consumers

What should we do about NPS? Pragmatically we must accept that these drugs are not yet fully understood, and whilst this is not a comfortable position in which to find ourselves, it is the status quo. Drug consumers may know more than many clinicians, particularly about the drugs' subjective effects, yet they might be similarly uncertain about what they are consuming (as well as its purity), and we are somewhat together in the dark about any longer-term risks. However, there are dangers of consciously or otherwise ignoring this ever more important topic and it is our opinion that it behoves professionals involved in the care of those taking NPS to at least understand the principal workings of these groups of compounds. As is usually the case in substance misuse work, there is a need for joint working with consumers, learning from them, but also offering a reciprocal educative and supportive role.

Clinicians might encounter those consuming NPS in various ways: unrelated anecdotal reportage during an assessment for a different matter; as a potential precipitant or perpetuating factor for physical or psychological difficulties; as part of an individual's concerns about illicit drug use; or in instances of acute intoxication. Whilst there are insufficient data to draw firm conclusions about rates or likelihood of NPS causing, exacerbating or perpetuating psychological or physical ill health, even a cursory comparison with known effects of the 'parent' drug class would indicate that this is a reasonable possibility, and one we are ever more likely to see in the future. The specifics of this, and any between- and within-group variations are yet to be fully elucidated, inevitably confounded by the common issues of polysubstance use and drug impurity, but at this time, treatment guidelines and recommendations are likely to be based around those for established parent compounds.

These will fall variously under general physical health, general psychiatric, and specialist substance misuse teams. Psychological, psychiatric, nursing and pharmacological interventions might all have valid and appropriate roles. There are no pharmacological compounds established specifically for replacement stabilisation and detoxification from NPS (or indeed their parent compounds) although work continues in this field and there are, for example, nascent trials on compounds such as the cannabis extract nabiximols to help detoxify individuals classified as cannabis dependent [Allsop *et al.* 2014]. At this time individual and group psychological and psychoeducative support and the involvement of substance misuse services is appropriate for those displaying dependency. The need for specialist NPS services or sub-services has yet to be established and local provision or willingness to assist those using NPS may vary.

In the case of acute intoxication, supportive care and reassurance is usually sufficient. However, in severe intoxication, particularly where the consumed compound(s) is/are unknown, combined and/or taken with sedatives (including alcohol), or where an individual's physical status and physiological markers (such as, but not limited to, pulse and respiratory rate and level of consciousness) appear compromised, higher levels of input might be necessary, including acute hospital admission for intensive medical support. There are no specific antidotes for any NPS, and Olives and colleagues [Olives *et al.* 2012] have argued that the varying and incompletely understood nature of cathinones makes it difficult to provide specific emergency advice for their acute toxic presentation beyond appropriate supportive care and being aware of their sympathomimetic properties, including tachycardia, hypertension and hyperthermia. The drugs' pharmacodynamics mean that professionals need to be vigilant for the emergence of the serotonin syndrome, with varying cognitive (including agitation, confusion and delirium), neuromuscular (including akathisia, ataxia, myoclonus and hyperreflexia) and autonomic (including dizziness, nausea and vomiting, tachycardia and sweating) symptoms. The identification and management of this disorder is beyond the remit of this paper, and we refer the reader to specific literature such as Boyer and Shannon [Boyer and Shannon, 2005]. Evidence regarding the onset of psychotic symptoms, both during acute intoxication as well as following prolonged use of agents such as cannabinoid NPS, have generally been found to respond to antipsychotic

treatment, and similarly panic or agitation seem to respond to benzodiazepine treatment, although this currently rests weakly upon case reports [Papanti *et al.* 2013; Spaderna *et al.* 2013].

Specific NPS investigative tests, such as urine drug screens, are not available, and existing routine drug tests have been shown to be variable in their detection, with high rates of false-positive (from cross-reactivity with currently tested analogues) and false-negative results [Jebadurai *et al.* 2013]. Indeed the logistics and costs of examining for potentially hundreds of NPS chemicals has been questioned [Schifano *et al.* 2006], and at this time self-report, with all of the inherent difficulties that can flow from this, remains the primary investigative tool for the clinician. This is likely to change in the future as better data on interpreting immunochemical screening assays of NPS accrues [Beck *et al.* 2014].

From an information viewpoint UNODC's SMART programme is a welcome initiative, but it is unclear how well this has breached the consciousness of healthcare professionals, and there is a need to have local resources and educational work within teams on this topic. It has yet to be properly established if, like many other drugs of abuse, there are locally specific endemic patterns of consumption and associated problems. It has, for example, been argued that amongst cathinones, 4-methylmethcathinone (mephedrone) is more prevalent in the United Kingdom, whilst methylenedioxypyrovalerone (MDPV) is more popular in the United States [Gregg and Rawls, 2014], through the relatively new phenomenon of internet purchasing, which appears to account for the vast majority of NPS sales [Dick and Torrance, 2010] may be levelling the issue and patterns globally. There is a need for clinicians, particularly those working in the arena of substance misuse, or with populations with high exposure rates to such substances, to make themselves aware of both the general issue of NPS (and we hope that this article might assist such a process) as well as local patterns of consumption and problems. Broader team-level discussions and on-going educative sessions are also to be encouraged. Emergency clinicians not working directly with the issues of drug dependency or psychological sequelae might nevertheless encounter NPS through acute intoxication, and there is a need to be mindful of this group of compounds in such instances, albeit accurate testing is not currently available. If clinicians are faced with so-called

psychonauts boldly going and exploring brave new worlds of inner-space, then we need 'psychotherapeutonauts' willing to support them.

To those individuals consuming NPS who may have sought out this article for information or guidance we urge caution in NPS usage. No compound or dose can be regarded as 'safe': we do not know enough at this time to state with confidence the relative differences in toxicity or other risks between NPS classes, whilst drug purities may vary considerably and individuals' tolerance and drug responses might be widely different. An evaluation of 39 unique UK-based websites selling NPS found that about 40% of products did not list their ingredients; over 90% did not cite potential side effects; and information that was provided was of questionable quality [Schmidt *et al.* 2011]. Such information failures and the common inclusion of product messages on the theme that the compounds are 'not for human consumption' may be surreptitious and invidious attempts by sellers attempting to abrogate responsibility for any subsequent adverse outcomes in drug consumers, although Schmidt and colleagues argued that the lack of information might be seen to (falsely) infer an implicit 'safety' upon NPS.

We cannot recommend NPS use, but if they are tried, this should be done with trusted support immediately available in case acute problems arise. The interactions between various NPS, or NPS and other drugs (including prescribed medication, OTC compounds, illicit drugs and alcohol) are not well understood, and any drug combinations should be considered potentially dangerous. Contact should be established with healthcare professionals upon development of any psychological or physical difficulties, or if concerned about the development of dependency: whilst scientific knowledge of these compounds is incomplete, professional support might nevertheless be of enormous value.

Conclusions

The growth in NPSs over the past few years has been enormous, with a parallel surge in media attention, and it is evident that the science has not yet caught up with these drugs. Most clinicians will be aware of NPS from the popular press, but many will likely feel an understandable sense of confusion about their legality, prevalence, effects on consumers, and their potential for physical and psychological harm and toxicity. This paper is intended to provide a framework to consider the

broad pharmacological domains and effects of the current major NPS classes, and act as a guide with which to help assign and categorise the compounds that will undoubtedly be synthesized in the future. The overall toxicity and harmfulness of NPS has been difficult to accurately gauge: in part this is an inherent issue in drug work; and in part the science, as noted, is incomplete. At present much of the data, particularly of deaths that were apparently NPS-induced are based upon case reports [e.g. Olives *et al.* 2012], the generalizability of which remains unclear. Undoubtedly there are also issues about the accuracy of terms such as 'legal highs', and more careful unpicking of drug poisoning data tempers more sensationalist media reports [King and Nutt, 2014].

The perennial call of all papers for 'more science' is duly made, although this is particularly pertinent in this poorly understood field, and there are several clear areas that need immediate work. It would be helpful and appropriate to seek the opinions of those consuming the drugs to get their subjective but uniquely informed thoughts on the effects of these compounds: how they compare with existing and better established drugs of abuse, problems they might have caused, and perspectives on their needs from clinical services. There is always a danger in the field of substance misuse that tackling questions only from a scientific viewpoint will alienate the people most important in these debates, and will limit our perspectives on the issues that are important to explore.

Nevertheless there is also a significant need to better understand various compounds' pharmacology: their pharmacodynamics and kinetics, toxicity profile, risk of dependency, and short- and longer-term risks to physical and mental health. A side, but still important, question is whether any of these new mind-manifesting drugs might have therapeutic potential, and the nascent data on ketamine (Caddy *et al.* 2014) and classical hallucinogens [Baumeister *et al.* 2014a] is instructive in this regard.

The politics of NPS look unlikely to change in the near future, with continuing proscription of agents as they are identified. One can of course make reasoned arguments about unknown risks of harmfulness and a need for societal protections, particularly of younger and vulnerable individuals many of whom will have limited knowledge of the compounds and who may face coercive pressures to consume. The authors wish to

acknowledge that these novel substances can indeed carry substantial risk to recreational users. However the understandable confusion currently felt by many clinicians that flows from the complexity of the growth in number of current banned agents, and the fact that many of the subsequently synthesized substances appear to be potentiated analogues of those they modelled highlight the pressing need for further scientific research into these biochemically fascinating compounds, with clinical strategies based on empirical evidence and open collaboration and engagement with recreational users. They might be new, but NPS are here to stay.

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