Progress in Neuro-Psychopharmacology & Biological Psychiatry 64 (2016) 267–274

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

The potential utility of some legal highs in CNS disorders

Colin Davidson [a,*], Fabrizio Schifano [b]

[a] Institute of Medical and Biomedical Education, St George's University of London, London SW17 0RE, United Kingdom
[b] School of Life and Medical Sciences, University of Hertfordshire, Hatfield AL10 9AB, United Kingdom

ARTICLE INFO

Article history:
Received 17 June 2015
Received in revised form 24 July 2015
Accepted 26 July 2015
Available online 29 July 2015

Keywords:
Legal high
Novel psychoactive substance
Pharmacotherapy
Treatment

ABSTRACT

Over the last decade there has been an explosion of new drugs of abuse, so called legal highs or novel psychoactive substances (NPS). Many of these abused drugs have unknown pharmacology, but their biological effects can be anticipated from their molecular structure and possibly also from online user reports. When considered with the findings that some prescription medications are increasingly abused and that some abused drugs have been tested clinically one could argue that there has been a blurring of the line between drugs of abuse and clinically used drugs. In this review we examine these legal highs/NPS and consider whether, based on their known or predicted pharmacology, some might have the potential to be clinically useful in CNS disorders.

© 2015 Elsevier Inc. All rights reserved.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine; ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; DAT, dopamine transporter; EMCDDA, European Centre for Drugs and Drug Addiction; GHB, gamma hydroxybutyric acid; L-DOPA, L-3,4-dihydroxyphenylalanine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxy methamphetamine; MAOI, monoamine oxidase inhibitor; NET, norepinephrine/noradrenaline transporter; NPS, new psychoactive substances; NMDA, N-methyl-D-aspartate; PCP, phencyclidine; PTSD, post traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor; SERT, serotonin transporter; TBI, traumatic brain injury; TCA, tricyclic antidepressant.

* Corresponding author.
E-mail address: cdavidso@sgul.ac.uk (C. Davidson).

1. What are legal highs/NPS?

Legal highs can be defined as new narcotic or psychotropic drugs which are not controlled by the United Nations' 1961 Narcotic Drugs or 1971 Psychotropic Substances Conventions, but which may pose a public health threat (EMCDDA, 2013). They are typically legal psychoactive drugs, which are bought on the internet, in 'head shops' or at music festivals or nightclubs, and are sold 'not for human consumption' but which are clearly for human consumption. They are often sold as

http://dx.doi.org/10.1016/j.pnpbp.2015.07.010
0278-5846/© 2015 Elsevier Inc. All rights reserved.

'plant food', 'bath salts' or 'research chemicals' and are a cheap and convenient way to buy recreational drugs. The term 'legal high' has been superseded in the scientific community in Europe by the term 'New' or Novel Psychoactive Substances (NPS). This is because, in many cases, the term 'legal highs' was being used to describe drugs that were actually illegal, to describe drugs that were recently legal, but now illegal (e.g. mephedrone) or to describe drugs which are legal in one country, but illegal in another. Thus to avoid confusion about legality, NPS is used. However the 'novelty' of these NPS has recently been questioned. For example, α-methyltryptamine (AMT) is a drug, developed as an antidepressant but which was found for sale as a 'legal high'. In the USA the term 'bath salts' is quite common, but hardly descriptive. Other names include 'designer drugs' and 'club drugs'; none are adequate and we await a consensus on an accurate and useful name for these compounds (Goodair et al., 2014; King and Nutt, 2014). Given the above background and in the interests of simplicity we will use the term NPS throughout the rest of this manuscript.

2. Examples of clinically used drugs that are being abused and NPS originally developed for clinical conditions

It has long been known that some clinically used drugs are abused. Anaesthetics, benzodiazepines, painkillers and stimulants have a long history of abuse and have been reviewed elsewhere (Griffiths and Weerts, 1997; Kollins et al., 2001; Zacny et al., 2003). Here we highlight some clinically used drugs, which have within the last 5–10 years, been found to be abused. Of the more commonly prescribed drugs which are abused, we include pregabalin (Schifano, 2014), prescribed for neuropathic pain, anxiety and epilepsy. This drug is increasingly associated with drug-related deaths (Corkery et al., 2014). Other prescribed drugs which have recently been found to be abused include benzydamine (Anand et al., 2007), found in oral rinses for sore throats, and tropicamide (Bersani et al., 2013), which is used to dilate the pupil in diagnostic eye test. Another abused substance, dextromethorphan (Bryner et al., 2006; Chomchai and Manaboriboon, 2012), is an antitussive with some affinity at the mu-opioid and N-methyl-D-aspartate (NMDA) receptors and the 5-HT and noradrenaline transporters (Burns and Boyer, 2013; Codd et al., 1995). Other clinically used drugs which have been abused include phenazepam, olanzapine, quetiapine, venlafaxine and orphenadrine (Schifano et al., 2015). Some of these drugs have been found in NPS. Phenazepam, for example, is one of several designer benzodiazepines available online (Moosmann et al., 2015).

The re-emergence and abuse of older, clinically used or clinically tested drugs is not a new phenomenon, but appears to be gathering pace. There are increasing numbers of old disused clinical drugs being rebranded by Internet opportunists as NPS. For example, desoxypipradrol, tested for narcolepsy many decades ago, resurfaced in 2009 as 'Ivory Wave' and was associated with a number of psychotic episodes and drug related deaths (Corkery et al., 2012). The aforementioned α-methyltryptamine (AMT), once used as an antidepressant, is also now abused (Gibbons, 2012) and associated with drug-related deaths (Corkery et al., 2014). Both drugs have recently been banned in the UK. Tricyclic antidepressants (TCAs) have been used for about 50 years and their pharmacology is well known. Most TCAs inhibit reuptake of 5-hydroxytryptamine (5-HT), noradrenaline, and, to a lesser extent, dopamine. Some NPS, which might have a similar pharmacology to TCAs, include benzofurans (e.g. (5-(2-aminopropyl)benzofuran (5-APB); 5-(2-Aminopropyl)-2,3-dihydrobenzofuran (5-APDB)) and novel psychedelic phenethylamines (e.g. 2,5-dimethoxy-4-bromophenethylamine (2-CB)) (Schifano et al., 2015).

3. Examples of abused drugs being tested clinically

In the current issue, the utility of ketamine in the treatment of depression and anxiety is reviewed (Rasmussen, 2015). There are numerous clinical trials on the use of ketamine in treatment-resistant depression (Naughton et al., 2014; Pochwat et al., 2014). Indeed, ketamine appears to be helpful in many of these cases and also has a very fast therapeutic onset, unlike the regular antidepressants selective serotonin reuptake inhibitors (SSRIs), TCAs or monoamine oxidase inhibitors (MAOIs), which usually take 4–6 weeks to have a clinical effect. Amphetamine and methamphetamine have also been tested clinically in stroke and traumatic brain injury (TBI; reviewed in the current issue by Walker-Batson et al., 2015) and amphetamine (Janowsky, 2003) and other stimulants (Stotz et al., 1999) have been used to treat depression. More recently, 3,4-methylenedioxy-methamphetamine (MDMA) has been tested in post-traumatic stress disorder (PTSD; Mithoefer et al., 2013; Oehen et al., 2013) and other types of anxiety (Danforth et al., 2015) and hallucinogens such as LSD and magic mushrooms are being tested in PTSD (Check, 2014) and the treatment of addiction (Bogenschutz and Johnson, 2015). Thus, we can already see an overlap between clinically used drugs and drugs that are misused or abused (Fig. 1 and Table 1). As such, it is conceivable, and indeed likely, that some NPS have important clinical utility.

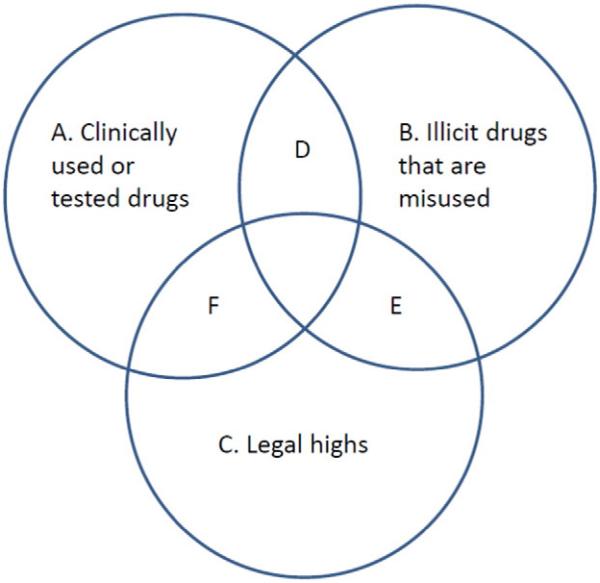

Fig. 1. The overlap between the different types of drugs. There is overlap between clinically used or clinically tested drugs, illicit drugs that are abused and the legal highs (NPS). Within section D one might find benzodiazepines and methylphenidate, clinically used drugs for anxiety and ADHD, which can be misused. Within section E one might find MDMA- and amphetamine-derivatives, which have been found in the legal high/NPS 'Nexus'/2-CB and 'el blanco'/ethylphenydate respectively. Within section F one might find α-methyltryptamine and desoxypipradrol, clinically tested for depression and narcolepsy respectively, but found in the legal highs 'AMT' and 'Ivory Wave'.

4. Categories of NPS and their similarity to clinically used drugs in CNS disorders

Thus far we have made the case that some clinically developed drugs have become drugs of abuse or NPS, and that there are also some drugs, best known as drugs of abuse, presently being tested in clinical conditions. We now consider NPS, both those that were developed many years ago and those that have been synthesised very recently.

NPS can be split, broadly, into 9 main groups (Schifano et al., 2015): a) synthetic cannabinoids/cannabimimetics; b) cathinones/synthetic cathinones; c) MDMA-like entactogens; d) novel stimulants; e) synthetic opioids; f) novel tryptamine derivatives; g) GABAergic drugs; h) dissociatives; i) piperazines. Here, we examine each group and hypothesise about their possible clinical use.

Table 1
Can dangerous drugs be of clinical use? Data are taken from Nutt et al. (2010). Of the 20 most dangerous drugs, as determined by an expert group, at least 14 of them have, or are likely to have, a clinical use. TBI = traumatic brain injury; ADHD = attention deficit hyperactivity disorder; PTSD = post-traumatic stress disorder; GHB = gamma hydroxybutyric; LSD = lysergic acid diethylamide; HIV = Human Immunodeficiency Virus; IBD = Inflammatory Bowel Disease.

Misused drug	Examples of clinical use	Legal high/NPS with similar pharmacology
Alcohol	Mild sedative[a], antiseptic and disinfectant[b]	GHB; GBL; 1,4-BD
Heroin		AH-7921; MT-45
Methamphetamine	Narcolepsy[c] ADHD and obesity[4]	Mephedrone, 5-APB
Cocaine	Local anaesthetic	ethylphenidate
Tobacco	Nicotine for Parkinson's disease[d]	
Amphetamine	ADHD, tested for stroke[e]	Mephedrone, 5-APB
Cannabis	End of life[f], neuropathic pain[g], incontinence in multiple sclerosis[h], spasticity[i], nausea & vomiting[j], weight gain in HIV and IBD[k], sleep disorders[l], Tourette's syndrome[m]	Synthetic cannabinoids*
GHB		GBL; 1,4-BD
Benzodiazepines	Anxiety, pre-med, epilepsy	GHB, GBL, a range of designer benzodiazepines such as phenazepapm and pyrazolam
Ketamine	Anaesthetic, in clinical trials for depression[n]	Methoxetamine, diphenidine
Methadone	Opiate addiction, pain	AH-7921; MT-45
Mephedrone		Some 40 synthetic cathinones now available including ephedrone, naphyrone etc.
Butane		Nitrous oxide
Khat		Synthetic cathinones
Anabolic steroids	Cancer, AIDS	Selective androgen receptor modulators or SARMs
Ecstasy	In clinical trials for PTSD[o]	MDA, MDEA, MBDB
LSD	In clinical trials for PTSD[p]	mCPP
Buprenorphine	Pain, opiate addiction	Synthetic opiates/opioids
Mushrooms	In clinical trials for anxiety[q,r]	A range of novel psychedelics acting on the 5-HT_{2A} receptors such as AMT or 5-MeO-DALT.

[a] Roehrs et al. (1993).
[b] McDonnell and Russell (1999).
[c] Miller et al. (1993); [4]www.accessdata.fda.gov/drugsatfda_docs/label/2013/005378s028lbl.pdf.
[d] Quik et al. (2012).
[e] Schuster et al. (2011).
[f] Carter et al. (2011).
[g] Ellis et al. (2009).
[h] Freeman et al. (2006).
[i] Zajicek et al. (2012).
[j] Duran et al. (2010).
[k] Lahat et al. (2012).
[l] Whiting et al. (2015).
[m] Muller-Vahl (2013).
[n] Naughton et al. (2014).
[o] Oehen et al.,, 2013.
[p] Smith et al. (2014).
[q] Grob et al. (2011).
[r] Moreno et al. (2006).
* Those that have been tested appear to have increased potency at CB1 receptors (G Di Chiara personal communications).

4.1. Synthetic cannabinoids/cannabimimetics

This is the largest category of NPS. Compounds that fall within this category are typically a preparation of dried plant sprayed with the synthetic cannabinoid. Current synthetic cannabinoids have a much greater agonist activity at the cannabinoid CB1 receptor than tetrahydrocannabinol (THC; Brents and Prather, 2014; Fattore and Fratta, 2011). These drugs are often sold as 'Spice' or 'K2' and have been associated with an increased incidence of psychoses (Papanti et al., 2013). This may be due to the presence of an indole group in synthetic cannabinoids which may contribute to the increased incidence of psychoses via activation of 5-HT_{2A} receptors (Wells and Ott, 2011; Yip and Dart, 2014). At least one synthetic cannabinoid (WIN 55,212-2) was able to inhibit monoamine oxidase (MAO) activity (Fisar, 2010), which would suggest that some synthetic cannabinoids can increase monoamine levels, perhaps with antidepressant efficacy?

Given their known and suggested pharmacology, potent CB1 and CB2 agonists, potential agonists at 5-HT_{2A} and weak MAOI, a key question concerns whether any of these drugs have potential clinical use. Given that their effects on CB1 and CB2 receptors at much lower doses than those needed to see effects at 5-HT_{2A} or MAO, then, with the synthetic cannabinoids, we are really only looking for a clinical use for CB1 or CB2 receptor agonists. In the current issue, Mursaleen and Stamford (2015) review the utility of cannabinoids in Parkinson's disease. The evidence that they present clearly suggests that cannabinoids may be of some use, not only in treating the symptoms of Parkinson's disease, but also in reducing L-3,4-dihydroxyphenylalanine (L-DOPA)-induced dyskinesias (More and Choi, 2015). Sieradzan et al. (2001) examined the synthetic cannabinoid nabilone in Parkinson's disease and found reduced L-DOPA induced dyskinesias. Nabilone has been used in other conditions such as pain (Lynch and Ware, 2015; Wissel et al., 2006), chemotherapy induced nausea and vomiting (Cunningham et al., 1988) and fibromyalgia (Skrabek et al., 2008). Other synthetic cannabinoids such as WIN-55,212-2 and HU-210 (1,1-dimethylheptyl-11-hydroxytetrahydrocannabinol) have been found to be neuroprotective in preclinical models of Parkinson's disease (reviewed by More and Choi, 2015) and may also be useful in Alzheimer's disease (Ramirez et al., 2005) but this is not always the case (Chen et al., 2010). Also in the current issue, Arevalo-Martin et al. (2015) have highlighted the utility of cannabinoid agonists, including synthetic cannabinoids, in spinal cord injury. One could wonder whether some of the 700+ new, misused synthetic cannabinoids might have some clinical use or whether their putative increased activity at CB1 versus CB2 receptors, increasing their psychotomimetic profile, may preclude their clinical use. It may be possible that a synthetic cannabinoid is manufactured that has a better pharmacological profile clinically, but this can only be determined with increased preclinical testing of NPS.

4.2. Cathinones/synthetic cathinones

Mephedrone is perhaps the best-known NPS and was marketed under numerous names e.g. MCAT, meow meow (Schifano et al., 2015). It was banned in the UK in 2010 and in the USA in 2011. It has been shown to be a stimulant with amphetamine-like properties, increasing both dopamine and 5-HT levels (Green et al., 2014). It causes reverse transport of dopamine in much the same way as amphetamine (Opacka-Juffry et al., 2014). Although there have been drug-related deaths associated with mephedrone use (Corkery et al., 2014) others suggest that it has a relatively safe profile (Nutt et al., 2010; McElrath and O'Neill, 2011). Other NPS cathinones include methylone and butylone (Lopez-Arnau et al., 2012). More well-known cathinones include bupropion, developed as an antidepressant but now used mostly for smoking cessation (Wilkes, 2008) and diethylpropion, used for weight loss (Cercato et al., 2009). Ephedrone (methcathinone) was also used as an antidepressant (Foley and Cozzi, 2003). We speculate that some NPS cathinones might also have use in smoking cessation or weight loss, or in some of the conditions that stimulants have been found to be useful for (vide infra).

4.3. MDMA-like entactogens

MDMA, 'Ecstasy' or 'molly' has been a popular party drug since the late 1980's. It increases both 5-HT and dopamine levels in

rodent studies (Kehr et al., 2011). More recently it has been tested in clinical trials in PTSD. It is hypothesised that the feelings of empathy for which MDMA is famous may be useful in improving the patient–clinician relationship, thus increasing the efficacy of psychotherapy (Mithoefer et al., 2013; Oehen et al., 2013). The use of MDMA in PTSD has been reviewed and is suggested to be useful in treatment resistant patients (White, 2014; and see Danforth et al., in current issue). NPS that have been suggested to be ecstasy-like include 3,4-methylenedioxyamphetamine (MDA); 3,4-methylenedioxy-*N*-ethylamphetamine (MDEA); 1,3-benzodioxolyl-*N*-methylbutanamine (MBDB) (Schifano et al., 2006). Some phenethylamine-like NPS include 2-CB (nexus), 2-CI and 2-CE. They show affinity for the 5-HT_{2A} receptor and inhibit dopamine, noradrenaline and 5-HT reuptake. Others include 25C-NBOMe (2-(4-chloro-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine), 3C-bromo-Dragonfly and the benzofurans (Dawson et al., 2014; Iversen et al., 2013). It is possible that one of these MDMA-like NPS might be a useful adjunct to psychotherapy in some types of anxiety.

The use of MDMA itself in clinical trials of various CNS disorders is problematic due to legal and political issues, as well as suggested neurotoxicity (Parrott, 2014). To circumvent these issues Johnston et al. (2012) examined UWA-101 (2-(1,3-benzodioxol-5-yl)-1-cyclopropyl-N-methylethanamine), an analog of MDMA, and found it to enhance L-DOPA effects in a primate model of Parkinson's disease. The use of MDMA in Parkinson's disease is reviewed in this issue by Mursaleen and Stamford (2015).

4.4. Novel stimulants

The pharmacological effect of stimulants would be primarily to increase dopamine levels via dopamine transporter (DAT) blockade or reverse transport. They might also increase noradrenaline levels. Some well known stimulant NPS, which block the DAT include 4,4′-DMAR ((±)-cis-para-methyl-4-4-methylaminorex; Brandt et al., 2014), methiopropamine (Iversen et al., 2013) and desoxypipradrol (Davidson and Ramsey, 2012). These drugs have been sold as cocaine or amphetamine substitutes. Some are like amphetamine, causing reverse transport of dopamine (Opacka-Juffry et al., 2014; Sulzer et al., 2005). Amphetamine is clinically used in attention deficit hyperactivity disorder (ADHD) and has been tested in some types of depression (with anergia), stroke (Crisostomo et al., 1988; Walker-Batson et al., in the current issue) and Parkinson's disease (Huot et al., 2015; Parkes et al., 1975). Methylphenidate is another stimulant, used clinically in ADHD, tested in post-stroke depression with promising results (Lazarus et al., 1992) and which has also been tested in stroke, with positive effects (Grade et al., 1998; Lokk et al., 2011). Lokk et al. (2011) also tested L-DOPA in stroke. L-DOPA is converted to dopamine in the brain, but dopamine is also converted to noradrenaline by the enzyme dopamine B-hydroxylase. Thus, drugs which enhance dopamine levels may actually be having their clinical effect by enhancing the precursor molecule for noradrenaline production. L-DOPA has also been shown to have beneficial effects in stroke (Scheidtmann et al., 2001). The mechanism underlying the use of these drugs in depression and stroke are likely their stimulant properties, providing the depressed patient with more energy and allowing the stroke patient to undertake their essential physiotherapy. In addition to functional/behavioural improvements, pre-clinical studies have found amphetamine to increase nerve growth and synapse formation in rodents after brain injury (Ramic et al., 2006; Stroemer et al., 1998). Some in vitro studies have found amphetamines to be neuroprotective against oxygen–glucose deprivation in slice cultures (Rau et al., 2011). This positive effect of a stimulant cannot be attributed to providing the animal or patient with more energy, encouraging movement and nerve regeneration, as this experiment was wholly done in vitro.

Amantadine is another drug that increases dopamine efflux and is used clinically. It is commonly used in Parkinson's disease (Pedrosa and Timmermann, 2013) and has been shown to speed up the recovery from TBI (Giacino et al., 2012). The utility of dopamine uptake inhibitors in Parkinson's disease has been recently reviewed (Huot et al., 2015).

It has long been known that drugs that enhance noradrenaline levels may be useful clinically in brain damaged patients (Kochanek et al., 2015). It is likely that some drugs that increase both dopamine and noradrenaline levels may also be useful (Grade et al., 1998). Examination of stimulant NPS reveals similar pharmacology to these older drugs which show some efficacy in brain damage, at least in clinical trials and pre-clinical studies. Table 2 shows the affinity of a number of more established drugs at the dopamine (DAT), noradrenaline (NET) and serotonin (SERT) transporters and the pharmacology of some stimulant NPS, where it is evident that there is a good degree of overlap in their pharmacology at the amine transporters. In particular, they tend to have effects at the DAT and NET, but less so at the SERT.

Another area where stimulant-like drugs might be of use is in obesity. Obesity is often a result of over-eating or 'addiction' to food, and thus can be considered a psychiatric condition in many cases (Meule and Gearhardt, 2014). Stimulant drugs have powerful anorectic effects and this is very noticeable in cocaine or methamphetamine addicts. Stimulant drugs, which have been approved for weight loss, include methamphetamine, fenfluramine, diethylpropion and bupropion (amfebutamone) (Bray, 1993; Weintraub et al., 1984). Of the legal highs thus far examined, a number have been shown to evoked weight loss in rodents (Martínez-Clemente et al., 2014). User reports from mephedrone abusers also suggest that this drug is anorectic as is methiopropamine (Winstock et al., 2010).

As a caveat, we would highlight the sympathomimetic properties of most stimulants, leading to increased heart rate and blood pressure, if taken at a large enough dosages. The doses of amphetamine (~10 mg; Long and Young, 2003) and methylphenidate (5–20 mg; Grade et al., 1998; Lokk et al., 2011) tested in stroke and brain damage are lower than those which might be abused (~100 mg and 5–40 mg respectively), and lead to cardiovascular issues. The route of administration would also be a critical variable, where abused drugs tend to be taken via the intravenous route or insufflation, whereas in clinical use the same drugs might be taken orally, slowing down the pharmacodynamics.

Table 2
Similar effects of some clinically used and novel psychoactive compounds at amine transporters. These data show that the top five drugs, which are clinically used, have good affinity at the dopamine and noradrenaline transporters, but not the 5-HT transporter. The bottom 5 drugs, which are legal highs/NPS, have a similar pharmacological profile to the clinically used drugs. Data are pKi, *kDs or IC50s and are taken from Iversen et al., 2013. NT = not tested. DAT, NET and SERT = dopamine, noradrenaline and 5-HT transporters respectively.

	DAT	NET	SERT
Amphetamine	6.54	6.20	4.78
Methylphenidate	24[a]	27[a]	>10,000[a]
Bupropion	520[a]	940[a]	9100[a]
Nomifensine	6.90	7.04	5.56
Amantadine	122[b]	41[b]	NT[b]
Desoxypipradrol	7.30	6.26	4.27
Mephedrone	6.08	5.88	4.99
Methiopropamine (MPA)	6.05	6.09	4.14
6-APB	6.25	6.24	5.39
Naphyrone	7.28	6.70	6.63

[a] Huot et al., 2015.
[b] Sommerauer et al., 2012.

4.5. Synthetic opioids

These include drugs such as AH-7921 (3,4-dichloro-N-[(1-dimethylamino)cyclohexylmethyl]benzamide), MT-45 (1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine), nortilidine, W15, W18, 4-fluoro-butyrfentanyl, acetylfentanyl and methiodone (http://www.guidechem.com/trade/pdetail3063084.html). AH-7921 and MT-45 were developed

many decades ago (Natsuka et al., 1975), but did not reach the clinic. It is unclear if the other drugs were developed specifically for the NPS market (Helander et al., 2014; Vorce et al., 2014) but, as far as it is known, these drugs share much of the pharmacology of morphine, specifically they are mu-opioid receptor agonists, and have similar potency (Schifano et al., 2015). Therefore, it is possible that some of these drugs might be useful analgesics or sedatives.

4.6. Novel tryptamine derivatives

These drugs typically have agonist activity at 5-HT_{2A} receptors, for which there are no obvious clinical use. These compounds include N-diallyl-5-methoxy-tryptamine (5-MeO-DALT), 5-(2-aminopropyl)indole (5-IT) and α-methyltryptamine (AMT). In addition to agonist activity at the 5-HT_{2A} receptor, these drugs have affinity at 5-HT_{2B} receptors (Arunotayanun et al., 2013). Their pharmacological profile suggests that they will have lysergic acid diethylamide-(LSD) like hallucinogenic properties. There is an old, but resurgent literature on the use of LSD in anxiety during end of life, PTSD or cancer (reviewed by Emerson et al., 2014; Smith et al., 2014). Small clinical studies suggest that LSD might be useful in some end of life scenarios (Smith et al., 2014) and headache (McGeeney, 2012) . There is a larger literature on the use of hallucinogens, such as LSD, in the treatment of addictions, and this has been reviewed by Bogenschutz and Johnson, 2015. Briefly, LSD and psilocybin tend to have positive effects in alcohol and nicotine dependence (Bogenschutz et al., 2015; Garcia-Romeu et al., 2015; Krebs and Johansen, 2012). It should be noted that relative to other misused drugs, LSD and psilocybin have a good safety profile(Nutt et al., 2010).

4.7. GABAergic drugs

The most common GABAergic NPS are gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL). GHB was developed as an anaesthetic many years ago (Brennan and van Hout, 2014; Labroit, 1964), while GBL is an industrial chemical that is quickly metabolised into GHB (Corkery et al., 2015; Meyer et al., 2014). Both drugs are agonists at $GABA_{A/B}$ receptors (Brennan and van Hout, 2014) and as such share a similar pharmacology with the anxiolytic benzodiazepines. GHB (sodium oxybate), used clinically for narcolepsy and alcoholism, not only binds to $GABA_{A/B}$ receptors, but appears to have a specific GHB binding site (Andriamampandry et al., 2003, 2007; Bay et al., 2014). The reported psychological effects of GHB and GBL, at low to moderate doses, include euphoria and calmness, and also increased libido (Corkery et al., 2015). These properties might be useful in treating some anxiety disorders, including those associated with sexual dysfunction. Other effects of these drugs include short-term memory loss (Teter and Guthrie, 2001), which might be useful in an anaesthetic premed. A further use of GABA receptor agonists is in treating drug withdrawal symptoms. The use of GABAergic drugs in alcohol (Liang and Olsen, 2014), nicotine (Franklin et al., 2009) and cocaine (Haney et al., 2006; Shoptaw et al., 2003) withdrawal is well documented. Unfortunately, both GBL and GHB are highly addictive and have been associated with many fatalities (Corkery et al., 2015). Nevertheless, it is possible that a GABAergic NPS may yet be synthesised that could be a useful anxiolytic.

4.8. Dissociatives

Dissociative anaesthetics such as ketamine and phencyclidine (PCP) were developed in the 1950s (Morris and Wallach, 2014). They produce a dissociative, detached or dream-like state as well as analgesia and amnesia, important for anaesthetics. Their main pharmacological mechanism is NMDA receptor antagonism although there are other pharmacological effects (Kavalali and Monteggia, 2012). Ketamine has also been shown to increase dopamine levels in the accumbens (Hancock and Stamford, 1999; Nishimura and Sato, 1999).

Ketamine has been misused for many years and is one of the most popular 'party' drugs, certainly within the UK and Europe. However, over the last few years it has been shown that ketamine causes bladder problems, starting with increased frequency of urination through loss of elasticity in the bladder and bladder shrinkage (Gu et al., 2013; Tsai et al., 2009). This bladder wall fibrosis can necessitate surgery for a colostomy bag. Methoxetamine (Corazza et al., 2013) appeared on the legal high market around 2010 as a 'bladder-friendly' alternative to ketamine, although there was no evidence to back up this claim. Methoxetamine is also an NMDA receptor antagonist (Roth et al., 2013) and seems to be associated with worse side effects than ketamine, ranging from mood disturbances and suicide attempts to acute cerebellar toxicity (Corazza et al., 2013). This drug was banned in the UK in 2012. More recently 2 NPS, diphenidine and methoxphenidine, have appeared to replace methoxetamine. Although there is very little pharmacological data, it is likely (from user reports and their chemical structures) that these drugs are also NMDA receptor antagonists. NMDA receptor antagonists have long been tested as potential neuroprotective agents. They have been tested in numerous cell culture models of toxicity and in animal models of stroke (Gerriets et al., 2003) Parkinson's disease (Finlay and Duty, 2014) and Alzheimer's disease (Malinow, 2012). They have also been tested in clinical trials for stroke (Parsons et al., 1999). Although these drugs have generally not succeeded in clinical trials this does not mean that a new NMDA receptor antagonist would not succeed. Memantine is an NMDA receptor antagonist (Parsons et al., 1999) used for the treatment of moderate to severe Alzheimer's disease (Olivares et al., 2012). At higher doses, it is also a dissociative and can partially substitute for PCP in drug discrimination studies (Swedberg et al., 2014). Thus, another indication for which this class of NPS/legal highs might be considered is Alzheimer's disease.

Aside from having potential in neurodegenerative diseases, NMDA receptor antagonists might also be useful anaesthetics, like ketamine and PCP or may be useful in depression. Ketamine has recently been found to be useful in refractory depression (Naughton et al., 2014; Pochwat et al., 2014) and methoxetamine has been hypothesised to be useful in depression (Coppola and Mondola, 2012).

4.9. Piperazines

Benzylpiperazine (BZP) was tested as an antidepressant in the 1970s (Montiero et al., 2013). It is a 5-HT_{2A} receptor agonist, but may also block the dopamine transporter (Schifano et al., 2015). At low doses the user will experience stimulant effects and at higher doses hallucinations may also be reported (Schifano et al., 2015). mCPP (*meta*-Chlorophenylpiperazine) is another NPS piperazine (Schifano et al., 2015) which might be useful in some types of obesity (Yan et al., 2015) and is a metabolite of trazodone, used in depression and anxiety.

5. Using NPS to treat drug abuse

Abused drugs have been tested to reduce the use of other abused drugs. Perhaps the best-known example is methadone, used to treat heroin addicts. Buprenorphine is also used to treat opiate abusers. It has partial agonist effects at the mu opioid receptor, and so both methadone and buprenorphine can both be considered agonist therapies (Mattick et al., 2014). Maintenance therapy or agonist therapy has been tried with cocaine abusers, who have been treated with oral cocaine (Llosa, 1994) and other milder stimulants (Carroll et al., 2006; Peng et al., 2010), the underlying theory being that it is better to substitute a less 'dangerous' drug for a more dangerous drug and the less dangerous drugs tend to have longer half-lives. Nutt et al. (2010) have recently ranked drugs of abuse, with the 3 most dangerous *illicit* drugs being heroin, crack cocaine, and methamphetamine. It is possible that an NPS might be a useful substitution therapy for one of these more dangerous drugs. For example, an oral preparation of a new stimulant

might be useful in cocaine dependence. Similarly some of the new synthetic opiates, for example AH-7921 or MT-45, might be useful in the treatment of heroin addiction.

Aside from maintenance or agonist therapy, drugs of abuse can be used to treat the abuse of drugs from a different pharmacological class. The hallucinogens LSD and psilocybin have been tested for alcohol abuse and nicotine dependence (Bogenschutz, 2013; Krebs and Johansen, 2012) and there are NPS which, like these classic hallucinogens, are agonists at the 5-HT_{2A} receptor, for example 5-APB and mCPP. In addition to classical hallucinogens, some less well-known hallucinogens such as the South American traditional brew ayahuasca, have been tested with positive results in alcohol, nicotine and cocaine dependence (Thomas et al., 2013). Although ayahuasca has been used for many centuries it is novel to the Western world. Other abused serotonergic agents that might be useful in treating other drugs of abuse include MDMA, especially when coupled with psychotherapy. Thus MDMA might be useful in alcohol abuse, not by any direct effect, but by reducing the anxiety that may underlie some alcohol dependencies (Jerome et al., 2013). There are numerous MDMA-like NPS such as MDA, MDEA and MBDB. It has been suggested from preclinical studies that NMDA receptor antagonists might be useful in treating the acute and chronic effects of a variety of types of drugs of abuse (Bisaga and Popik, 2000) and we can speculate that the ketamine-like NPSs methoxetamine and diphenidine might be similarly useful.

6. Caveats and conclusions

All drugs have inherent dangers, dependent upon dose and route of administration, and we do not suggest that any NPS should be misused. However we do advocate examining these drugs for potential useful effects. It is possible that by using some NPS at a low dose and through appropriate routes, these drugs could be used relatively safely, not for psychoactive effects, but for psychiatric or neurological conditions.

Obvious dangers from these drugs include: 1) sympathomimetic cardiovascular effects such as increased blood pressure and heart rate, even arrhythmias, with stimulants and cathinones; 2) heart valve problems from MDMA, fenfluramine and other drugs which activate 5-HT_{2B} receptors (Cosyns et al., 2013); 3) neurotoxicity from amphetamines, and to a lesser extent MDMA, which have been shown to be neurotoxic (Davidson et al., 2001; Halpin et al., 2014) and recent data shows that amphetamine abusers have increased likelihood to exhibit early onset Parkinson's disease (Callaghan et al., 2012). However, neurotoxic effects are likely due to high dose bingeing (Schwendt et al., 2009); 4) psychoses from cannabinoids, hallucinogens and high dose stimulants which might evoke psychotic events, leading the user to undertake dangerous activities; 5) bladder fibrosis from ketamine-like drugs; 6) other organ damage e.g. kidney, liver or lungs (from smoking drugs) (Pateria et al., 2013; Riezzo et al., 2012).

Despite these caveats, it is possible, indeed likely, that a new stimulant will appear that has some clinical use in conditions such as ADHD, stroke, narcolepsy, anergic depression or other conditions. We conclude that some NPS might actually be useful if, as with all drugs, they are used at correct dose via the correct route.

Acknowledgements

The European Commission-funded EU-MADNESS project (2014–2016; contract no: JUST2013/DPIP/AG/4823) resources were used to assist with the preparation of this research document. The views expressed here are those of the Authors only and do not necessarily represent those of the EU Commission.

References

Arevalo-Martin, A., Molina-Holgado, E., Garcia-Ovejero, D., 2015. Cannabinoids to treat spinal cord injury. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 190–199.

Anand, J.S., Glebocka, M.L., Korolkiewicz, R.P., 2007. Recreational abuse with benzydamine hydrochloride (tantum rosa). Clin. Toxicol. 45, 198–199.

Andriamampandry, C., Taleb, O., Viry, S., Muller, C., Humbert, J.P., Gobaille, S., et al., 2003. Cloning and characterization of a rat brain receptor that binds the endogenous neuromodulator g-hydroxybutyrate (GHB). FASEB J. 17, 1691–1693.

Andriamampandry, C., Taleb, O., Kemmel, V., Humbert, J.P., Aunis, D., Maitre, M., 2007. Cloning and functional characterization of a g-hydroxybutyrate receptor identified in the human brain. FASEB J. 21, 885–895.

Arunotayanun, W., Gibbons, S., Dalley, J.W., Huang, X.P., Setola, V., Roth, B.L., Treble, R., Iversen, L., 2013. An analysis of the synthetic tryptamines AMT and 5-MeO-DALT: Emerging 'Novel Psychoactive Drugs'. Bioorganic. Med. Chem. Lett. 23, 3411–3415.

Bay, T., Eghorn, L.F., Klein, A.B., Wellendorph, P., 2014. GHB targets in the CNS: focus on high affinity binding sites. Biochem. Pharmacol. 87, 220–228.

Bersani, F.S., Corazza, O., Simonato, P., Mylokosta, A., Levari, E., Lovaste, R., Schifano, F., 2013. Drops of madness? Recreational misuse of tropicamide collyrium; early warning alerts from Russia and Italy. Gen. Hosp. Psychiatry 35, 571–573.

Bisaga, A., Popik, P., 2000. In search of a new pharmacological treatment for drug and alcohol addiction: N-methyl-D-aspartate (NMDA) antagonists. Drug Alcohol Depend. 59, 1–15.

Bogenschutz, M.P., 2013. Studying the effects of classic hallucinogens in the treatment of alcoholism: rationale, methodology, and current research with psilocybin. Curr. Drug Abuse Rev. 6, 17–29.

Bogenschutz, M., Johnson, M.W., 2015. Classic hallucinogens in the treatment of addictions. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 250–258.

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wicox, C.E., Barbosa, P., Strassman, R.J., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof of concept study. J. Psychopharmacol. 29, 289–299.

Brandt, S.D., Baumann, M.H., Partilla, J.S., Kavanagh, P.V., Power, J.D., Talbot, B., et al., 2014. Characterization of a novel and potentially lethal designer drug (±)-cis-para-methyl-4-4-methylaminorex (4,4′-DMAR, or 'Serotoni'). Drug Test. Anal. 6, 684–695.

Bray, G.A., 1993. Use and abuse of appetite-suppressant drugs in the treatment of obesity. Ann. Intern. Med. 119, 707–713.

Brennan, R., Van Hout, M.C., 2014. Gamma-hydroxybutyrate (GHB): a scoping review of pharmacology, toxicology, motives for use, and user groups. J. Psychoactive Drugs 46, 243–251.

Brents, L.K., Prather, P.L., 2014. The K2/spice phenomenon: emergence, identification, legislation and metabolic characterization of synthetic cannabinoids in herbal incence products. Drug Metab. Rev. 46, 72–85.

Bryner, J.K., Wang, U.K., Hui, J.W., Bedodo, M., MacDougall, C., Anderson, I.B., 2006. Dextromethorphan abuse in adolescence and increasing trend: 1999–2004. JAMA Pediatr. 160, 1217–1222.

Burns, J.M., Boyer, E.W., 2013. Antitussives and substance abuse. Subst. Abuse Rehabil. 4, 75–82.

Callaghan, R.C., Cunningham, J.K., Sykes, J., Kish, S.J., 2012. Increased risk of Parkinson's disease in individuals hospitalized with conditions related to the use of methamphetamine or other amphetamine-type drugs. Drug Alcohol Depend. 120, 35–40.

Carroll, F.I., Howard, J.L., Howell, L.L., Fox, B.S., Kuhar, M.J., 2006. Development of the dopamine transporter selective RTI-336 as a pharmacotherapy for cocaine abuse. AAPS J. 8, E196–E2003.

Carter, G.T., Flanagan, A.M., Earleywine, M., Abrams, D.I., Aggarwal, S.K., Grinspoon, L., 2011. Cannabis in palliative medicine: improving care and reducing opioid-related morbidity. Am. J. Hosp. Palliat. Med. 28, 297–303.

Cercato, C., Roizenblatt, V.A., Leanca, C.C., Segal, A., Lopes Filho, A.P., Mancini, M.C., Halpern, A., 2009. A randomized double-blind controlled study of the long-term efficacy and safety of diethylpropion in the treatment of obese subjects. Int. J. Obes. 33, 857–865.

Check, E., 2014. The ups and downs of ecstasy. Nature 429, 126–128.

Chen, B., Bromley-Brits, K., He, G., Cai, F., Zhang, X., Song, W., 2010. Effect of synthetic cannabinoid HU210 on memory deficits and neuropathology in Alzheimer's disease mouse model. Curr. Alzheimer Res. 7, 255–261.

Chomchai, C., Manaboriboon, B., 2012. Stimulant methamphetamine and dextromethorphan use among Thai adolescents: implications for health of women and children. J. Med. Toxicol. 8, 291–294.

Codd, E.E., Shank, R.P., Schupsky, J.J., Raffa, R.B., 1995. Serotonin and norepinephrine uptake inhibiting activity of centrally acting analgesics: Structural determinants and role in antinociception. JPET 274, 1263–1270.

Coppola, M., Mondola, R., 2012. Methoxetamine: from drug of abuse to rapid-acting antidepressant. Med. Hypotheses 79, 504–507.

Corazza, O., Assi, S., Schifano, F., 2013. From "Special K" to "Special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci. Ther. 19, 454–460.

Corkery, J.M., Elliot, S., Schifano, F., Corazza, O., Ghodse, A.H., 2012. 2-DPMP (desoxypipradrol, 2-benzhydrylpiperidine, 2-phenylmethylpiperidine) and D2PM (diphenyl-2-pyrrolidin-2-yl-methanol, diphenylprolinol): A preliminary review. Prog. Neuropsychopharmacol. Biol. Psychiatry 39, 253–258.

Corkery, J., Claridge, H., Loi, B., Goodair, C., Schifano, F., 2014. Drug Related Deaths in the UK; Annual Report 2013. International Centre for Drug Policy, St George's, University of London (UK) (ISBN: 978-1-897778-9-2).

Corkery, J.M., Loi, B., Claridge, H., Goodair, C., Corazza, O., Elliott, S., Schifano, F., 2015. Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD; BDO): a literature review with a focus on UK fatalities related to non-medical use. Neurosci. Biobehav. Rev. 53, 52–78.

Cosyns, B., Droogmans, S., Rosenhek, R., Lancellotti, P., 2013. Drug-induced valvular heart disease. Heart 99, 7–12.

Crisostomo, E.A., Duncan, P.W., Probst, M., Dawson, D.V., Davis, J.N., 1988. Evidence that amphetamine with physical therapy promotes recovery of function in stroke patients. Ann. Neurol. 23, 94–97.

Cunningham, D., Bradley, C.J., Forrest, G.J., Hutcheon, A.W., Adams, L., Sneddon, M., Harding, M., Kerr, D.J., Soukop, M., Kaye, S.B., 1988. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. Eur. J. Cancer Clin. Oncol. 24, 685–689.

Danforth, A.L., Struble, C.M., Yazar-Klosinski, B., Grob, C.S., 2015. MDMA-assisted therapy: a new treatment model for social anxiety in autistic adults. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 64, 237–249.

Davidson, C., Ramsey, J., 2012. Desoxypipradrol is more potent than cocaine on dopamine efflux in the nucleus accumbens. J. Psychopharmacol. 26, 1036–1041.

Davidson, C., Gow, A.J., Lee, T.H., Ellinwood, E.H., 2001. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. Brain Res. Rev. 36, 1–22.

Dawson, P., Opacka-Juffry, J., Moffatt, J.D., Daniju, N., Ramsey, J., Davidson, C., 2014. The effects of benzofury (5-APB) on the dopamine transporter and 5-HT2-dependent vasoconstriction in the rat. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 48, 57–63.

Duran, M., Perez, E., Abanades, S., Vidal, X., Saura, C., Majem, M., et al., 2010. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br. J. Clin. Pharmacol. 70, 656–663.

Ellis, R.J., Toperoff, W., Vaida, F., van den Brande, G., Gonzales, J., Gouaux, B., et al., 2009. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 34, 672–680.

EMCDDA, 2013. EMCDDA-Europol 2013 Annual Report on the Implementation of Council Decision 2005/387/JHA Available at: www.emcdda.europa.eu/attachements.cfm/att_229598_EN_TDAN14001ENN.pdf.

Emerson, A., Ponte, L., Jerome, L., Doblin, R., 2014. History and future of the multidisciplinary association for psychedelic studies (MAPS). J. Psychoactive Drugs 46, 27–36.

Fattore, L., Fratta, W., 2011. Beyond THC: the new generation of cannabinoid designer drugs. Front. Behav. Neurosci. 21, 1–11.

Finlay, C., Duty, S., 2014. Therapeutic potential of targeting glutamate receptors in Parkinson's disease. J. Neural Transm. 121, 861–880.

Fisar, Z., 2010. Inhibition of monoamine oxidase activity by cannabinoids. Naunyn Schmiedebergs Arch. Pharmacol. 381, 563–572.

Foley, K.F., Cozzi, N.V., 2003. Novel aminopropiophenones as potential antidepressants. Drug Dev. Res. 60, 252–260.

Franklin, T.R., Harper, D., Kampman, K., Kildea-McCrea, S., Jens, W., Lynch, K.G., O'Brien, C.P., Childress, A.R., 2009. The GABAB agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. Drug Alcohol Depend. 103, 30–36.

Freeman, R.M., Adekanmi, O., Waterfield, M.R., Waterfield, A.E., Wright, D., Zajicek, J., 2006. The effect of cannabis on urge-incontinence in patients with multiple sclerosis: a multicenter, randomized placebo-controlled trial (CAMS-LUTS). Int. Urogynecol. J. Pelvic Floor Dysfunct. 17, 636–641.

Garcia-Romeu, A., Griffiths, R.R., Johnson, M.W., 2015. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr. Drug Abuse Rev. 7, 157–164.

Gerriets, T., Stolz, E., Walberer, M., Kaps, M., Bachmann, G., Fisher, M., 2003. Neuroprotective effects of MK-801 in different rat stroke models for permanent middle cerebral artery occlusion: adverse effects of hypothalamic damage and strategies for its avoidance. Stroke 34, 2234–2239.

Giacino, J.T., Whyte, J., Bagiella, E., Kalmar, K., Childs, N., Khademi, A., et al., 2012. Placebo-controlled trial of amantadine for severe traumatic brain injury. N. Engl. J. Med. 366, 819–826.

Gibbons, S., 2012. 'Legal highs' — novel and emerging psychoactive drugs: a chemical overview for the toxicologist. Clin. Toxicol. 50, 15–24.

Goodair, C.M., Corkery, J., Claridge, H., 2014. Legal Highs: a problem of definitions? Lancet 383, 1715.

Grade, C., Redford, B., Chrostowski, J., Toussaint, L., Blackwell, B., 1998. Methylphenidate in early poststroke recovery: a double-blind, placebo-controlled study. Arch. Phys. Med. Rehabil. 79, 1047–1050.

Green, A.R., King, M.V., Shortall, S.E., Fone, K.C.F., 2014. The preclinical pharmacology of mephedrone; not just MDMA by another name. Br. J. Pharmacol. 171, 2251–2268.

Griffiths, R.R., Weerts, E.M., 1997. Benzodiazepine self-administration in humans and laboratory animals: implications for problems of long-term use and abuse. Psychopharmacology 134, 1–37.

Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., Halberstadt, A.L., Greer, G.R., 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch. Gen. Psychiatry 68, 71–78.

Gu, D., Huang, J., Shan, Z., Yin, Y., Zheng, S., Wu, P., 2013. Effects of long-term ketamine administration on rat bladder protein levels: a proteomic investigation using two-dimensional difference gel electrophoresis system. Int. J. Urol. 20, 1024–1031.

Halpin, L.E., Collins, S.A., Yamamoto, B.K., 2014. Neurotoxicity of methamphetamine and 3,4-methylenedioxymethamphetamine. Life Sci. 97, 37–44.

Hancock, P.J., Stamford, J.A., 1999. Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. Br. J. Anaesth. 82, 603–608.

Haney, M., Hart, C.L., Foltin, R.W., 2006. Effects of baclofen on cocaine self-administration: opioid and non-opioid-dependent volunteers. Neuropsychopharmacology 31, 1814–1821.

Helander, A., Backberg, M., Beck, O., 2014. MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. Clin. Toxicol. 52, 901–904.

Huot, P., Fox, S.H., Brotchie, J.M., 2015. Monoamine reuptake inhibitors in Parkinson's disease. Parkinson's Disease 2015 http://dx.doi.org/10.1155/2015/609428.

Iversen, L., Gibbons, S., Treble, R., Setola, V., Huang, X.-P., Roth, B., 2013. Neurochemical profiles of some novel psychoactive substances. Eur. J. Pharmacol. 700, 147–151.

Janowsky, D.S., 2003. Depression and dysphoria effects on the interpersonal perception of negative and positive moods and caring relationships: effects of antidepressants, amphetamine, and methylphenidate. Curr. Psychiatry Rep. 5, 451–459.

Jerome, L., Schuster, S., Yazar-Klosinski, B.B., 2013. Can MDMA play a role in the treatment of substance abuse? Curr. Drug Abuse Rev. 6, 54–62.

Johnston, T.H., Millar, Z., Huot, P., Wagg, K., Thiele, S., Salomonczyk, D., et al., 2012. A novel MDMA analogue, UWA-101, that lacks psychoactivity and cytotoxicity, enhances L-DOPA benefit in parkinsonian primates. FASEB J. 26, 2154–2163.

Kavalali, E.T., Monteggia, L.M., 2012. Synaptic mechanisms underlying antidepressant action of ketamine. Am. J. Psychiatry 169, 1150–1156.

Kehr, J., Ichinose, F., Yoshitake, S., Goiny, M., Sievertsson, T., Nyberg, F., Yoshitake, T., 2011. Mephedrone, compared with MDMA (ecstasy) and amphetamine, rapidly increases both dopamine and 5-HT levels in nucleus accumbens of awake rats. Br. J. Pharmacol. 164, 1949–1958.

King, L.A., Nutt, D.J., 2014. Deaths from "legal highs": a problem of definitions. Lancet 383, 952.

Kochanek, P.M., Jackson, T.C., Ferguson, N.M., Carlson, S.W., Simon, D.W., Brockman, E.C., et al., 2015. Emerging therapies in traumatic brain injury. Semin. Neurol. 35, 83–100.

Kollins, S.H., MacDonald, E.K., Rush, C.R., 2001. Assessing the abuse potential of methyphenidate in nonhuman and human subjects: a review. Pharmacol. Biochem. Behav. 68, 611–627.

Krebs, T.S., Johansen, P.O., 2012. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J. Psychopharmacol. 26, 994–1002.

Labroit, H., 1964. Sodium 4-hydroxybutyrate. Int. J. Neuropharmacol. 3, 433–452.

Lahat, A., Lang, A., Ben-Horin, S., 2012. Impact of cannabis treatment on the quality of life, weight and clinical disease activity in inflammatory bowel disease patients: a pilot prospective study. Digestion 85, 1–8.

Lazarus, L.W., Winemiller, D.R., Lingam, V.R., Neyman, I., Hartman, C., Abassian, M., Kartan, U., et al., 1992. Efficacy and side effects of methylphenidate for poststroke depression. J. Clin. Psychiatry 53, 447–449.

Liang, J., Olsen, R.W., 2014. Alcohol use disorders and current pharmacological therapies: the role of $GABA_A$ receptors. Acta Pharmacol. Sin. 35, 981–993.

Llosa, T., 1994. The standard low dose of oral cocaine: used for treatment of cocaine dependence. Subst. Abus. 15, 215–220.

Lokk, J., Roghani, R.S., Delbari, A., 2011. Effect of methylphenidate and/or levodopa coupled with physiotherapy on functional and motor recovery after stroke — a randomized, double-blind, placebo-controlled trial. Acta Neurol. Scand. 123, 266–273.

Long, D., Young, J., 2003. Dexamphetamine treatment in stroke. Q. J. Med. 96, 673–685.

Lopez-Arnau, R., Martinez-Clemente, J., Pubill, D., Escubedo, E., Camarasa, J., 2012. Comparative neuropharmacology of three psychostimulant cathinone derivatives: butylone, mephedrone and methylone. Br. J. Pharmacol. 167, 407–420.

Lynch, M.E., Ware, M.A., 2015. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J. Neuroimmune Pharmacol. 72, 735–744.

Malinow, R., 2012. New developments on the role of NMDA receptors in Alzheimer's disease. Curr. Opin. Neurobiol. 22, 559–563.

Martínez-Clemente, J., López-Arnau, R., Abad, S., Pubill, D., Escubedo, E., Dose, Camarasa J., 2014. Time-dependent selective neurotoxicity induced by mephedrone in mice. PLoS One 9, e99002.

Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone for opioid dependence. Cochrane Database Syst. Rev. CD002207.

McDonnell, G., Russell, A.D., 1999. Antiseptics and disinfectants: activity, action and resistance. Clin. Microbiol. Rev. 12, 147–179.

McElrath, K., O'Neill, C., 2011. Experiences with mephedrone pre- and post-legislative controls: perceptions of safety and sources of supply. Int. J. Drug Policy 22, 120–127.

McGeeney, B.E., 2012. Hallucinogens and cannabinoids for headache. Headache 52 (S2), 94–97.

Meule, A., Gearhardt, A.N., 2014. Food addiction in the light of DSM-5. Nutrients 6, 3653–3671.

Meyer, R., Jenewein, J., Boettger, S., 2014. Severe gamma-hydroxy-butyric acid (GHB) dependence with repeated withdrawal syndrome and induced delirium. J. Alcohol. Drug Depend. 2, 156–157.

Miller, M.M., Hajdukovic, R., Erman, M.K., 1993. Treatment of narcolepsy with methamphetamine. Sleep 16, 306–317.

Mithoefer, M.C., Wagner, M.T., Mithoefer, A.T., Jerome, L., Martin, S.F., Yazar-Klosinski, B., Michel, Y., Brewerton, T.D., Doblin, R., 2013. Durability of improvement in PTSD symptoms and absence of harmful effects or drug dependency after MDMA-assisted psychotherapy: a prospective long-term follow-up study. J. Psychopharmacol. 27, 28–39.

Montiero, M.S., Bastos, M.L., Guedes de Pinho, P., Carvalho, M., 2013. Update on 1-benzylpiperazine (BZP) part pills. Arch. Toxicol. 87, 929–947.

Moosmann, B., King, L.A., Auwärter, V., 2015. Designer benzodiazepines: a new challenge. World Psychiatry 14, 248.

More, S.V., Choi, D.-K., 2015. Promising cannabinoid-based therapies for Parkinson's disease: motor symptoms to neuroprotection. Mol. Neurodegener. 10, 17.

Moreno, F.A., Wiegand, C.B., Taitano, E.K., Delgado, P.L., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J. Clin. Psychiatry 67, 1735–1740.

Morris, H., Wallach, J., 2014. From PCP to MXE: a comprehensive review f the non-medical use of dissociative drugs. Drug Test. Anal. 6, 614–632.

Muller-Vahl, K.R., 2013. Treatment of Tourette's syndrome with cannabinoids. Behav. Neurol. 27, 119–124.
Mursaleen, L.R., Stamford, J.A., 2015. Drugs of abuse and Parkinson's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 209–217.
Natsuka, K., Nakamura, H., Uno, H., Umemoto, S., 1975. Studies on 1-substituted 4-(1,2-diphenylethyl)piperazine derivatives and their analgesic activities. J. Med. Chem. 18, 1240–1244.
Naughton, M., Clark, G., O'Leary, O.F., Cryan, J.F., Dinan, T.G., 2014. A review of ketamine in affective disorders: current evidence of clinical efficacy, limitations of use and pre-clinical evidence on proposed mechanisms of action. J. Affect. Disord. 156, 24–35.
Nishimura, M., Sato, K., 1999. Ketamine stereoselectively inhibits rat dopamine transporter. Neurosci. Lett. 274, 131–134.
Nutt, D.J., King, L.A., Phillips, L.D., 2010. Drug harms in the UK: a multicriteria decision analysis. Lancet 376, 1558–1565.
Oehen, P., Traber, R., Widmer, V., Schnyder, U., 2013. A randomized, controlled pilot study of MDMA (± 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). J. Psychopharmacol. 27, 40–52.
Olivares, D., Deshpande, V.K., Shi, Y., Lahiri, D.K., Greig, N.H., Rogers, J.T., Huang, X., 2012. N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. Curr. Alzheimer Res. 9, 746–758.
Opacka-Juffry, J., Pinnell, T., Patel, N., Bevan, M., Meintel, M., Davidson, C., 2014. Stimulant mechanisms of cathinones — effects of mephedrone and other cathinones on basal and electrically evoked dopamine efflux in rat accumbens brain slices. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 54, 122–130.
Papanti, D., Schifano, F., Botteon, G., Bertossi, G., Mannix, J., Vidoni, D., Impagnatiello, M., Pascolo-Fabrici, E., Bonavigo, T., 2013. 'Spiceophrenia': a systematic overview of 'Spice-related psychopathological issues and a case report. Hum. Psychopharmacol. 28, 379–389.
Parkes, J.D., Tarsy, D., Marsden, C.D., Bovill, K.T., Phipps, J.A., Rose, P., Asselman, P., 1975. Amphetamines in the treatment of Parkinson's disease. J. Neurol. Neurosurg. Psychiatry 38, 232–237.
Parrott, A.C., 2014. The potential dangers of using MDMA for psychotherapy. J. Psychoactive Drugs 46, 37–43.
Parsons, C.G., Danysz, W., Quack, G., 1999. Memantine is a clinically well tolerated N-methyl-D-aspartate (NMDA) receptor antagonist — a review of preclinical data. Neuropharmacology 38, 735–767.
Pateria, P., de Boer, B., MacQuillan, G., 2013. Liver abnormalities in drug and substance abusers. Best Pract. Res. Clin. Gastroenterol. 27, 577–596.
Pedrosa, D.J., Timmermann, L., 2013. Review: management of Parkinson's disease. Neuropsychiatr. Dis. Treat. 9, 321–340.
Peng, X.Q., Xi, Z.X., Li, X., Spiller, K., Li, J., Chun, L., et al., 2010. Is slow-onset long-acting monoamine transport blockade to cocaine as methadone is to heroin? Implications for anti-addiction medications. Neuropsychopharmacology 35, 2564–2578.
Pochwat, B., Palucha-Poniewiera, A., Szewczyk, B., Pilc, A., Nowak, G., 2014. NMDA antagonists under investigation for the treatment of major depressive disorder. Expert Opin. Investig. Drugs 23, 1181–1192.
Quik, M., Perez, X.A., Bordia, T., 2012. Nicotine as a potential neuroprotective agent for Parkinson's disease. Mov. Disord. 27, 947–957.
Ramic, M., Emerick, A.J., Bollnow, M.R., O'Brien, T.E., Tsai, S.Y., Kartje, G.L., 2006. Axonal plasticity is associated with motor recovery following amphetamine treatment combined with rehabilitation after brain injury in the adult rat. Brain Res. 1111, 176–186.
Ramirez, B.G., Blázquez, C., Gomez del Pulgar, T., Guzmán, M., de Ceballos, M.L., 2005. Prevention of Alzheimer's Disease Pathology by Cannabinoids: Neuroprotection Mediated by Blockade of Microglial Activation. 25, 1904–1913.
Rasmussen, K.G., 2015. Has psychiatry tamed the "ketamine tiger?" Considerations on its use for depression and anxiety. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 64, 218–224.
Rau, T.F., Kothiwal, A., Zhang, L., Ulatowski, S., Jaconson, S., Brooks, D.M., Cardozo-Pelaez, F., et al., 2011. Low dose methamphetamine mediates neuroprotection through a PI3K-AKT pathway. Neuropharmacology 61, 677–686.
Riezzo, L., Fiore, C., De Carlo, D., Pascale, N., Neri, M., Turillazzi, E., Fineschi, V., 2012. Side effects of cocaine abuse: multiorgan toxicity and pathological consequences. Curr. Med. Chem. 19, 5624–5646.
Roehrs, T., Zwyghuizen-Doorenbos, A., Roth, T., 1993. Sedative effects and plasma concentrations following single doses of triazolam, diphenhydramine, ethanol and placebo. Sleep 16, 301–305.
Roth, B.L., Gibbons, S., Arunotayanun, W., Huang, X.P., Setola, V., Treble, R., Iversen, L., 2013. The ketamine analogue methoxetamine and 3- and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PLoS One e59334.
Scheidtmann, K., Fries, W., Muller, F., Koenig, E., 2001. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomized, double-blind study. Lancet 358, 787–790.
Schifano, F., 2014. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs 28, 491–496.
Schifano, F., Corkery, J., Deluca, P., Oyefeso, A., Ghodse, A.H., 2006. Ecstasy (MDMA, MDA, MDEA, MBDB) consumption, seizures, related offences, prices, dosage levels and deaths in the UK (1994–2003). J. Psychopharmacol. 20, 456–463.
Schifano, F., Orsolini, L., Papanti, G.D., Corkery, J.M., 2015. Novel psychoactive substances of interest for psychiatry. World Psychiatry 14, 15–26.
Schuster, C., Maunz, G., Lutz, K., Kischka, U., Sturzenegger, R., Ettlin, T., 2011. Dexamphetamine improves upper extremity outcome during rehabilitation after stroke: a pilot study randomized controlled trial. Neurorehabil. Neural Repair 25, 749–755.
Schwendt, M., Rocha, A., See, R.E., Pacchioni, A.M., McGinty, J.F., Kalivas, P.W., 2009. Extended methamphetamine self-administration in rats results in a selective reduction of dopamine transporter levels in the prefrontal cortex and dorsal striatum not accompanied by marked monoaminergic depletion. JPET 331, 555–562.
Shoptaw, S., Yang, X., Rotheram-Fuller, E.J., 2003. Randomized placebo-controlled trial of baclofen for cocaine dependence: preliminary effects for individuals with chronic patterns of cocaine use. J. Clin. Psychiatry 64, 1440–1448.
Sieradzan, K.A., Fox, S.H., Hill, M., Dick, J.P., Crossman, A.R., Brotchie, J.M., 2001. Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: a pilot study. Neurology 57, 2108–2111.
Skrabek, R.Q., Galimova, L., Ethans, K., Perry, D., 2008. Nabilone for the treatment of pain in fibromyalgia. J. Pain 9, 164–173.
Smith, D.E., Raswyck, G.E., Davidson, L.D., 2014. From Hoffman to the Haight Ashbury, and into the future: the past and potential of lysergic acid diethylamide. J. Psychoactive Drugs 46, 3–10.
Sommerauer, C., Rebernik, P., Reither, H., Nanoff, C., Pifl, C., 2012. The noradrenaline transporter as a site of action for the anti-Parkinson drug amantadine. Neuropharmacology 62, 1708–1716.
Stotz, G., Woggon, B., Angst, J., 1999. Psychostimulants in the therapy of treatment-resistant depression. Dialogues Clin. Neurosci. 1, 165–174.
Stroemer, R.P., Kent, T.A., Hulsebosch, C.E., 1998. Enhanced neocortical neural sprouting, synaptogenesis, and behavioral recovery with D-amphetamine therapy after neocortical infarction in rats. Stroke 29, 2381–2393.
Sulzer, D., Sonders, M.S., Poulsen, N.W., Galli, A., 2005. Mechanisms of neurotransmitter release by amphetamines: a review. Prog. Neurobiol. 75, 406–433.
Swedberg, M.D.B., Ellgren, M., Raboisson, P., 2014. mGluR5 antagonist-induced psychoactive properties: MTEP drug discrimination, a pharmacologically selective non-NMDA effect with apparent lack of reinforcing properties. JPET 349, 155–164.
Teter, C.J., Guthrie, S.K., 2001. A comprehensive review of MDMA and GHB: two common club drugs. Pharmacotherapy 21, 1486–1513.
Thomas, G., Lucas, P., Capler, N.R., Tupper, K.W., Martin, G., 2013. Ayahuasca-assisted therapy for addiction: results from a preliminary observational study in Canada. Curr. Drug Abuse Rev. 6, 30–42.
Tsai, T.H., Cha, T.L., Lin, C.M., Tsao, C.W., Tang, S.H., Chuang, F.P., et al., 2009. Ketamine-associated bladder dysfunction. Int. J. Urol. 16, 826–829.
Vorce, S.P., Knittel, J.L., Holler, J.M., Magluilo Jr., J., Levine, B., Berran, P., Bosy, T.Z., 2014. A fatality involving AH-7921. J. Anal. Toxicol. 38, 226–230.
Walker-Batson, D., Mehta, J., Smith, P., Johnson, M., 2015. Amphetamine and other pharmacological agents in human and animal studies of recovery from stroke. Prog. Neuropsychopharmacol. Biol. Psychiatry 64, 225–230.
Weintraub, M., Hasday, J.D., Mushlin, A.I., Lockwood, D.H., 1984. A double-blind clinical trial in weight control. Use of fenfluramine and phentermine alone and in combination. Arch. Intern. Med. 144, 1143–1148.
Wells, D.L., Ott, C.A., 2011. The new marijuana. Ann. Pharmacother. 45, 414–417.
White, C.M., 2014. 3,4-methylenedioxymethamphetamine's (MDMA's) impact on post-traumatic stress disorder. Ann. Pharmacother. 48, 908–915.
Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., et al., 2015. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 313, 23–30.
Wilkes, S., 2008. The use of bupropion SR in cigarette smoking cessation. Int. J. COPD 3, 45–53.
Winstock, A.R., Mitcheson, L.R., Deluca, P., Davey, Z., Corazza, O., Schifano, F., 2010. Mephedrone, new kid for the chop. Addiction 106, 154–161.
Wissel, J., Hatdn, T., Muller, J., Brenneis, C., Berger, T., Poewe, W., Schelosky, L.D., 2006. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain: a double-blind placebo-controlled crossover trial. J. Neurol. 253, 1337–1341.
Yan, C., Yang, Y., Saito, K., Xu, P., Wang, C., Hinton Jr., A.O., Yan, X., Wu, Q., Elmquist JK, Tong Q., Fukuda, M., Xu, Y., 2015. Meta-chlorophenylpiperazine enhances leptin sensitivity in diet-induced obese mice. Br. J. Pharmacol. http://dx.doi.org/10.1111/bph.13141 (Epub ahead of print).
Yip, L., Dart, C.R., 2014. Is there something more about synthetic cannabinoids? Forensic Toxicol. 32, 340–341.
Zacny, J., Bigelow, G., Compton, P., Foley, K., Iguchi, M., Sannerud, C., 2003. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend. 69, 215–232.
Zajicek, J.P., Hobart, J.C., Slade, A., Barnes, D., Mittison, P.G., MUSEC Research Group, 2012. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J. Neurol. Neurosurg. Psychiatry 83, 1125–1132.