Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

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Inspiring Improvement

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Chapter 12

Hallucinogenic drugs

Drug group: Hallucinogen

Hallucinogens are drugs that distort the way a user perceives time, motion, colour, sounds and self. The varied perceptual distortions caused by such drugs do not strictly correspond to clinical definitions of 'hallucinations' (perceptions in the absence of external stimuli that are experienced as if they were real, as seen in psychoses and delirium).[1,2] Therefore, alternative terms, such as 'illusions' and 'pseudo-hallucinations' and 'perceptual distortions' have also been employed.[3]

Some authors have suggested that the term 'psychedelic' should replace terms like 'classical hallucinogen' to describe drugs such as LSD and psilocybin,[4] but it has also been argued that this term carries disadvantages because of its cultural connotations of a style of music and art associated with Western counter-culture in the 1960s. Other terms used include 'psychomimetic', a term previously used to emphasise effects that resemble the symptoms of psychosis, and the term 'entheogen', which emphasises the mystical-type experiences the drugs are said to promote. However, these terms have also been criticised, as they highlight only a single aspect of a much broader range of hallucinogenic effects.[5]

This chapter will use the term 'hallucinogen' to refer only to the serotonergic hallucinogens: drugs with a mechanism of action mediated primarily by agonism of the $5HT_{2A}$ serotonin receptor. LSD (N,N-diethyl-D-lysergamide) and psilocybin are the prototypical and most prevalent drugs of this class. In recent years, a number of hallucinogen novel psychoactive substances (NPS) have also been made available on the illicit market and as so-called 'legal highs' that act on $5\text{-}HT_{2A}$ serotonin receptors.

Two substances which have some 'hallucinogenic' properties but are not serotonergic hallucinogenic will also be considered briefly in this chapter:

- *Salvia divinorum*. This is considered here because it has been described as 'psychedelic-like'[6] and its use is widespread.
- Psychoactive mushrooms in the *Amanita* genus. These are considered here because they can be hallucinogenic and may be conflated by users or clinicians with the truly psychedelic 'magic' mushrooms of the *Psilocybe* genus.

There are a number of other substances and drug groups which can produce some hallucinogenic effects but cannot be classified as 'serotonergic '. These include drugs discussed elsewhere in this document: cannabis and other cannabinoid receptor agonists (Chapter 13), MDMA and other similar drugs (Chapter 10) and dissociative anaesthetics such as ketamine or PCP, which function as NMDA glutamate receptor antagonists (Chapter 4).[7]

Table 12.1. *Hallucinogenic drugs used for recreational purposes*

Chemical name	Abbreviation as used in this text.	Street products and names (these change over time; other names may be used locally)
Lysergamides		
(6a*R*,9*R*)-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-*fg*]quinoline-9-carboxamide *(N,N-diethyl-D-lysergamide)*	LSD	'Acid', 'A tab', 'Blotter' (LSD on blotting paper squares, ~1 cm^2), 'Geltabs', 'Windowpane' (LSD in gelatine squares/pieces), 'Microdots' (very small pills)[8]
(8β)-9,10-didehydro-6-methyl-ergoline-8-carboxamide	LSA (ergine)	'Morning Glory seeds' and 'Hawaiian Baby Wood rose seeds' (seeds containing LSA and other alkaloids)
(6a*R*,9*R*)-4-acetyl-*N*,*N*-diethyl-7-methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*] quinoline-9-carboxamide[9] (1-acetyl-*N*,N-diethyllysergamide)	ALD-52[9]	
(6a*R*,9*R*)-*N*,*N*-diethyl-7-ethyl-4,6,6a,7,8,9-hexahydroindolo-[4,3-*fg*]quinoline-9-carboxamide (6-ethyl-6-nor-lysergic acid diethylamide)	ETH-LAD[9]	
(8β)-*N*,*N*-Diethyl-6-propyl-9,10-didehydroergoline-8-carboxamide (6-propyl- 6-nor- Lysergic acid diethylamide)	PRO-LAD[9]	
6-allyl-6-nor-lysergic acid diethylamide	AL-LAD[9]	
(8β)-8-{[(2*S*,4*S*)-2,4-Dimethylazetidin-1-yl] carbonyl}-6-methyl-9,10-didehydroergoline *(lysergic acid 2,4-dimethylazetidide)*	LSZ[9]	
Tryptamines		
O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine 4-hydroxy-N,N-dimethyl-tryptamine	Psilocybin Psilocin	'Magic mushrooms', 'Mushies' or 'Shrooms' contain psilocybin and related tryptamines 'Liberty caps' or 'Libs' are the most common wild UK species of magic mushroom, *Psilocybe semilanceata*. Also occurring in the UK are *Panaeolus cinctulus* and 'Wavy caps', *Psilocybe cyanescens* 'Cubes' or 'Boomers' are the most commonly home-cultivated species, *Psilocybe cubensis* 'Truffles' or 'Philosopher's stones' are cultivated nodular growths (technically 'sclerotia') from other *Psilocybe* species. They are sold online
N,N-dimethyltryptamine	DMT	'Dimitri' and 'Spice' are terms sometimes used for the white, yellow or brown DMT crystals or powder, often used for smoking (technically vapourising). This should not be confused with 'spice' also commonly used for synthetic cannabinoids. 'Ayahuasca' and 'Yagé' are decoctions that include a DMT-containing plant and another plant containing a monoamine oxidase inhibitor, which allows DMT to be orally bioavailable
alpha-methyltryptamine	αMT	'AMT' [9]

N,N-diallyl-5-methoxytryptamine	5-MeO-DALT	
N,N-diisopropyltryptamine	DiPT	'Foxy'
5-methoxy-N,N-diisopropyl-tryptamine	5-MeO-DiPT	'Foxy Methoxy'
12-methoxyibogamine	Ibogaine	'Iboga' (*Tabernanthe iboga*) is the shrub that contains ibogaine and other iboga alkaloids
Phenethylamines		
3,4,5-trimethoxyphenethylamine	Mescaline	'Hallucinogenic cacti' contain psychoactive alkaloids, principally mescaline. 'Peyote', 'San Pedro' and 'Peruvian Torch' are the common names for the three predominant species
2C Series, and their derivatives	2C-B has various close analogues; bk-2C-B, and 25B-NBOMe The same selection of analogues may exist for the rest of the 2C series, e.g. 2C-E, 2C-I, 2C-T-7	'Bees' are tablets or capsules containing 2C-B. 'Nexus' is also 2C-B 'Tripstasy' was 2C-T-7, but could be used for any drug combining hallucinogenic effects with MDMA-like effects 'N-Bomb' drugs are the NBOMe analogues series, so 25I-NBOMe may also be called 'NBOMe 2C-I' and so on.
Hallucinogenic amphetamines, *DOx series and their derivatives*	*DOM, DOI, DOB, TMA-2*	'STP' (for 'serenity, tranquillity and peace') was the original name for pills of DOM
Tetrahydrodifranyl compounds[10]	2C-B-FLY, bromo-dragonfly	They are called 'FLY' because their molecular structure resembles the insect[11]

Table 12.2. *Drugs considered in this chapter that are not true hallucinogens*

Drug	Plant	Street names
Salvia divinorum	*Salvia*	Salvia is the term used in the literature, on product labelling and by users. It is the genus name to which the psychoactive belongs, other 'Salvias' are not psychoactive. This species contains the diterpenoid Salvinorin A, which is responsible for the effects. 'Sally D', 'SkaMaríaPastora', 'Seer's Sage' are other names that may be used
Psychoactive *Amanita* mushrooms		
Amanita muscaria		
Amanita pantherina	Fly agaric (*Amanita muscaria)* Panther cap (*Amanita pantherina*) contains the psychoactive muscimol (5-(aminomethyl)-isoxazol-3-ol) and its prodrug, ibotenic acid	May be described and sold as so-called legal 'magic mushrooms', but should not be confused with the truly hallucinogenic psilocybin-containing 'magic mushrooms'

12.1. Street names

Hallucinogenic drugs can be roughly divided into tryptamines, phenethylamines and lysergamides (LSD-like structures).[7] Table 12.1 lists some of the hallucinogenic drugs that were available on the market for recreational use at the time of writing and/or that have been associated with harm; several of the substances listed will be rarely used.

The drugs listed in Table 12.2 are not true hallucinogens, but are nonetheless considered in this chapter.

12.2. Legal status

The most prevalent hallucinogenic drugs, LSD and magic mushrooms, are Class A controlled drugs in the UK under the Misuse of Drugs Act 1971 (MDA 1971). Some novel psychoactive hallucinogens have also been controlled as Class A drugs Schedule 1. These include the NBOMe series and others not explicitly named in the Misuse of Drugs Act 1971, but are controlled as close analogues of banned drugs in the tryptamine or phenethylamine family, and generic clauses in the MDA 1971 exist to cover most simple derivatives.[9] The compounds captured by the extended definition of tryptamines include the substances commonly known as AMT and 5-MeO-DALT. Also Class A drugs are the LSD-related compounds commonly known as ALD-52, AL-LAD, ETH-LAD, PRO-LAD and LSZ.

The legal status of unrefined natural products containing hallucinogenic drugs, such as dried pieces of mescaline-containing cacti and material from DMT-containing plants, is ambiguous, or could be seen as *de facto* legal[12] until they are prepared for use as drugs. The exception is *Psilocybe* mushrooms, fresh or dried, or any other fungus material containing psilocin and its esters (e.g. psilocybin), possession of which has been specifically controlled since 2005.

Some hallucinogens were uncontrolled at the time of writing. Legislation was, however, expected to be announced that would bring many currently used 'legal' novel psychoactive hallucinogens under the generic definitions of the MDA 1971, making them Class A Drugs.[13] On 10 June 2014 the Advisory Council on the Misuse of Drugs recommended that some of these drugs be scheduled as Class A drugs by updating the blanket ban clause on tryptamines. This would include both the tryptamine 5-MeO-DALT[13] and αMT,[13] which currently do not fall under the tryptamine clause. Similarly, soon due to be banned are bk-2C-B, a legal derivative of the phenethylamine 2C-B.ALD-52, and the lysergamides ETH-LAD, PRO-LAD, AL-LAD and LSZ.[13]

At the time of writing, the hallucinogenic-like Salvia is not controlled and is available as a 'legal high' online[14] and in 'head-shops'. Fly agaric (*Amanita muscaria*) and *Amanita pantherina* grow in the UK and since they do not contain psilocybin they are currently uncontrolled. Dried *Amanita muscaria* caps are sold as 'legal highs' online[14] and in 'head-shops'.

12.3. Quality of research evidence

The international evidence on the clinical management of the harms related to the use of hallucinogens remains limited. The bulk of it focuses on LSD and psilocybin, although research on the clinical management of harms of even these substances is limited.

Very little has been published about other hallucinogenic drugs, with evidence limited to case reports and series of patients with acute toxicity.

12.4. Brief summary of pharmacology

As stated above, structurally, most hallucinogens can be roughly divided into tryptamines, phenethylamines and lysergamides (LSD-like structures).[2,7] LSD and other lysergamides share a complex molecular structure with both tryptamine and phenethylamine backbones. However, lysergamide structures are sufficiently elaborated from these skeletons for them to be more usefully considered a distinct class of hallucinogenic.[2] Some hallucinogenic NPS, such as the 'Fly' series, are less easy to classify, because they are fairly distant structural analogues of their phenethylamine parent compound.[11]

The common denominator in the pharmacology of true hallucinogenic drugs is agonism or partial agonism of 5-HT_2 serotonin receptors,[2] particularly 5-HT_{2A} and/or other 5-HT_2 receptors.[15] This activity is of central importance to their characteristic hallucinogenic effects.[15] Hallucinogenic drugs interact with an array of other sites too, contributing to the psychopharmacological and behavioural effects.[15–17] A recent study looking at the hallucinogenic drug DMT, a tryptamine, suggests that it may be an endogenous ligand for the sigma-1 receptor in humans. This suggests the need to look beyond the serotonin system for a complete understanding of the pharmacology of tryptamines.[18]

The naturally occurring tryptamine ibogaine is an example of a hallucinogen with pharmacological effects beyond the 5-HT_{2A} receptor. In comparison with other hallucinogens, ibogaine interacts strongly the NMDA receptor, σ–receptors, μ-opioid receptors, and muscarinic receptors.[16] It also causes serotonin and dopamine reuptake inhibition at their transporters (SERT and DAT).[19] Ibogaine's tendency to cause a 'rough trip' with strong physical side-effects has been described.[20] It has also been shown to block the hERG potassium channel, which may be associated with the life-threatening QT interval elongation observed in several cases of ibogaine toxicity.[21]

The psychoactive *Amanita* species (*A. muscaria* and *A. pantherina*) contain muscimol and ibotenic acid. Muscimol is a potent $GABA_A$ receptor agonist with depressant, hypnotic and dissociative effects.[22] Ibotenic acid is a pro-drug for muscimol, but may also cause psychoactive effects in its own right as an NDMA glutamate receptor agonist.[23] It has been argued that the relative proportions of these pharmacologically distinct substances present in *Amanita* mushrooms could explain the sharply contrasting pharmacological effects reported, with descriptions ranging from alcohol-like to hallucinatory.[24] *Amanita muscaria* contains more excitatory ibotenic

acid and less depressant muscimol than *Amanita pantherina,* which has led some to refer to two subtypes of syndromes resulting acute *Amanita* toxicity.[25] It has been reported that some users deliberately modify the pharmacology through preparatory methods that decarboxylate the ibotenic acid into muscimol.[26]

Understanding of hallucinogen drugs is still very limited. It is assumed that qualitative differences in the subjective phenomenology of the drugs may relate to their individual affinity profiles.[16] In a recent study, psilocybin, the prototypical hallucinogenic tryptamine, has been shown to reduce apparent activity in hub regions, and to uncouple synchronised activity in the posterior cingulate cortex and the medial prefrontal cortex.[27] This suppression of orderly and regulated patterns of activity between different brain areas has been interpreted as allowing for the relatively unconstrained patterns of cognition, with abnormal integration of sensory information, that seem to characterise the 'psychedelic state'.[27] More research is needed.

The structure–activity relationships of hallucinogens are complex, and differ between the various drugs. This means that hallucinogen NPS appearing on the market may be structurally similar to other NPS, or to other well known hallucinogenic drugs, but may have different levels of potency, effects, duration of effects and risks.

For example, the phenethylamines 2C-B and bk-2C-B[28] differ only by the addition of a ketone group, but some reports suggest that the latter drug has a significantly longer duration of effect.[29] The duration of the effects of 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DiPT, foxy methoxy) is seven times greater than that for N,N-diisopropyltryptamine (DiPT or 'Foxy').[30] Bromo-dragonfly is a distant derivative from the core phenethylamine structure, with a potency similar to that of LSD, but has a far longer duration of effect (1–3 days) and apparently has greater toxicity.[11] In terms of acute toxicity, within the 2C family, 2-CB has not been associated with any fatalities, whereas there are reports from the US of deaths in which 2C-T-7 has been implicated.[31]

Some hallucinogens have strong stimulant effects. For example, αMT is a tryptamine, with a methyl group in the alpha position, just like an amphetamine, and has marked stimulant effects, seen in clinical observations.[32] On the other hand, some phenethylamines, which are amphetamine-type substances, are also hallucinogenic drugs. These include ring-substituted substances, such as the '2C series' and the 'D series' (e.g. DOI, DOC), and benzodifurans (e.g. bromo-dragonfly, 2C-B-Fly). Similarly, the phenethylamines DOB(2,5-dimethoxy-4-bromoamphetamine) and MEM are highly selective for 5-HT_2 receptors.[16]

12.5. Clinical uses

There are currently no hallucinogenic drugs that are licensed for clinical use, and many of the compounds, including LSD and psilocybin, are restricted as Schedule 1 substances.

Some research on the clinical use of hallucinogens was carried out in the 1950s, 1960s and 1970s. A recent meta-analysis of early randomised controlled trials of

LSD for alcoholism showed that a single application of LSD in a variety of treatment modalities reduced alcohol intake or maintained abstinence at rates which compare favourably to mainstream treatment with naltrexone and acamprosate.[33] Ibogaine, a natural hallucinogen from the iboga shrub, has been used as a controversial addiction treatment to facilitate withdrawal from opiates and other drugs.[34] One evaluation began into this clinical use, but a death during the small study may have brought an end to clinical research.[35]

Some clinical research involving the administration of classical hallucinogens is currently taking place again.[36–39] This includes small pilot studies looking at the utility of LSD[40] and psilocybin[41] for treating anxiety associated with life-threatening diseases. Psilocybin has also been trialled in nine people with obsessive-compulsive disorder, all of whom experienced improvement in symptoms, mostly short-lived, but with one experiencing full, lasting remission.[42] Another trial has been approved for testing psilocybin in treatment-resistant depression, and is due to begin.[43]

12.6. Prevalence and patterns of use

LSD and magic mushrooms have been firmly established and widely available in the UK for a number of decades. At a population level, the last-year use LSD and magic mushrooms in the UK and Europe in general is relatively low, as shown in Table 12.3. Use has fallen since comparable records began in 1996, but has been stable for the past 10 years.

The Crime Survey for England and Wales (CSEW) shows that general 'hallucinogen' use in the past year and LSD use in past year were significantly higher in 2013/14 than they were in 2012/13.[44] The use of magic mushrooms, though, did not change significantly during that period. Lifetime use of hallucinogens is comparable to the lifetime use of ecstasy or cocaine in adults (aged 16–59 years) (9.1%, 9.3% and 9.5% respectively). Among 16–24-year-olds, lifetime use was lower, at 5.1%, and less common than the use of drugs such as ecstasy, cocaine and amphetamines.

The Global Drug Survey (GDS) shows higher levels of use than those reported in the CSEW, reflecting the greater experience of the GDS respondents with illicit substances and a possible sample bias. In the 2014 Global Drugs Survey, UK respondents reported: last-year LSD use of 12.2% (lifetime use 39.6%) and magic mushrooms last-year use of 13.7% (lifetime use 53.1%).[45]

Much less is known about the prevalence of use of hallucinogenic NPS, especially at a population level, as these data are not collected by the CSEW or the Scottish Crime and Justice Survey. Some information is provided by the Global Drug Survey 2014 for use in the last 12 months; in the UK, 7.7% of respondents had used 2CB.[46] No information at all is available on the use of other NPS, although there is clear evidence that they are available on the market. For example, Avon and Somerset police reported in March 2014 that αMT was on sale at most 'legal high' shops.[9]

Hallucinogenic drugs tend to be used relatively infrequently. Among respondents to the CSEW who had used hallucinogens in the last year, few had taken them more than

Table 12.3. *Figures from the 2013/2014 Crime Survey for England and Wales (CSEW) on the use of LSD in the last year and other hallicunogens*

Age group	Percentage reporting use in last year
16–59-year-olds reporting LSD use	0.3% in 2013/14, a statistically significant increase from 0.2 in 2012/13. Use had been relatively stable over the previous decade.
16–24-year-olds reporting LSD use	0.9% in 2013/14, showing no significant difference from use in 2012/13
16–59-year-olds reporting magic mushroom use	0.4% in 2013/14, showing no significant difference from use in 2012/13. Use had fallen significantly over the previous decade, from 0.8 in 2003/04
16–24-year-olds reporting magic mushroom use	0.8% in 2013/14, showing no significant difference from use in 2012/13. Use had fallen significantly over the previous decade, from 2.7 in 2003/04
16–59-year-olds reporting *Salvia* use	0.5% in 2013/14, significantly up from 0.3 in 2012/13
16–24-year-olds reporting *Salvia* use	1.8% in 2013/140, not significantly different from 2012/13

once a month. In fact, hallucinogens were the least likely kind of substance to be used frequently.[44]

Hallucinogenic drugs are typically used by people who also use other drugs. As with other drugs, the CSEW 2013/14 reported higher prevalence rates of use of these drugs among those who also used other illicit drugs. Among users, 4% had used magic mushrooms and 4% had used LSD in the last year.

Users of hallucinogens are typically young and use a wide repertoire of other drugs. The higher levels of use by 'clubbers', in comparison to non-clubbers, has been reported by the CSEW (2013/14), where use of hallucinogens was highest among those who had visited a club four or more time in the past month. Similar findings were produced in the Global Drug Survey 2012 (Figure 12.1).[46]

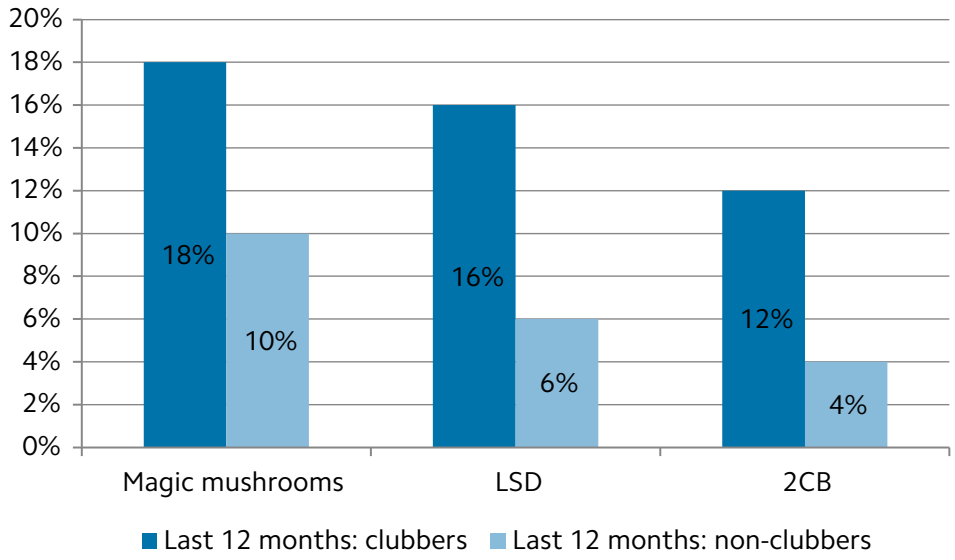

Figure 12.1. *Drug use by frequency of visits to 'clubs' (Global Drug Survey 2012)*

Other than 'clubbers', there is anecdotal evidence from users and online discussion groups, that a particular type of drug user, sometimes referred to as 'psychonauts', may be more likely to use hallucinogens, more likely to use them more frequently and more likely to experiment with a wider range of drugs, perhaps especially NPS.

12.7. Routes of ingestion and frequency of dosing

There are very marked differences between the various hallucinogenic drugs in terms of potency, and type, onset and duration of effects.

12.7.1. Potency

The potency of a hallucinogenic substance appears to be broadly, but not entirely, a function of its affinity to the 5-HT_{2A} receptor.[2,15] Substances with lower affinity for the receptor, and lower potency, include mescaline[2] (typical oral dose approximately 0.25 g). LSD has a high affinity, and is the most commonly used potent hallucinogenic substance (a typical dose may be 75–150 µg[47]).

In recent years, very potent new hallucinogenic substances have emerged on the recreational market, such as the NBOMe series and bromo-dragonfly.[48] The latter, for example, has been described by users (on drug user websites) as 'just too powerful', due to its duration as well as potency.[11] This may have contributed to the fact that some new drugs, such as bromo-dragonfly, appeared on the market but then disappeared quickly.[11] Salvinorin A products and commercially available salvia leaf preparations prepared for smoking can also be very potent.

12.7.2. Onset of effects and duration

There are significant differences between substances in the speed of onset of effects after ingestion, ranging from a few moments to hours. For example, DMT has an almost immediate effect, while the effects of LSD appear approximately 60 minutes after oral ingestion. Users' reports suggest that maximal effects following ingestion of bromo-dragonfly may not be reached for up to 6 hours after ingestion,[49] posing a risk that users re-dose because of mistaken belief that the first dose has had no effect.

Similarly, the duration of action of hallucinogenic drugs ranges between minutes and days, depending on the substance used. The hallucinogenic-like salvia and vaporised DMT are examples of very short-acting drugs with rapid onset. DMT's effects appear in under a minute and may peak within 5 minutes, with minimal adverse after-effects (come-down).[50] Hallucinogens of intermediate duration include 2C-B,[51] with effects lasting 2–3 hours. LSD and mescaline are longer-acting hallucinogenics and a duration of 8–12 hours is expected.[52] Very long-acting hallucinogens include DOM and others in the DOx series, ibogaine, 2C-P and bromo-dragonfly, the effects of which have been reported to last a day or longer, and in some cases can lead to exhaustion.[11,52,53]

The purity and quantity of the active compounds in a single tablet or' tab' and the reliability of hallucinogenic drugs (in terms of being the drug users think they are buying) varies between product and batches, contributing risk to dose estimation. As with other drugs, users will not know the strength of the tablet they are taking, or may not be ingesting the substance they intended to use, or think they are taking. Hallucinogenic NPS have, on some occasions, been sold as LSD.[54] For example, three samples purchased as LSD and tested by the WEDINOS scheme in Wales in 2014 were revealed to contain the phenethylamine derivatives 25I-NBOMe, 25C-NBOMe and DOB.*

Some drugs can be more 'reliable' than others at particular times and in different locations. For example, in a Spanish study, 99% of samples purporting to be 2C-B actually contained 2C-B (average for the four-year study period), a high reliability compared with 66.8% for MDMA, 86.3% for amphetamines, 87.4% for cocaine, 92.2% for ketamine.[51] Similarly, there are differences between different batches for the same product; for example, bromo-dragonfly appears to come in batches of different potency.[11]

Changes in the drugs' strength and potency over time have also been documented. LSD 'tabs' in 2003 contained significantly less LSD on average than in the early years of use, in the 1960s and 1970s; doses of above 100 µg/tab were then typical, but, by 2003, 30-40 µg/tab was more usual.[55]

12.7.3. Modes of ingestion

Hallucinogens are typically ingested orally, or sublingually/buccally, often through small blotter paper portions or 'tabs', which are held in the mouth to allow absorption through the oral mucosa.

Other routes of administration are used by a minority, including insufflation, smoking, rectally and injection. For example, among 59 enquiries about AMT to the UK National Poisons Information Service, 55 were about oral ingestions, and 4 insufflations.[32]

The route of administration for 25I-NBOMe is typically sublingual and buccal, but nasal (insufflation and absorption of liquid solutions), oral, injection (intravenous and intramuscular), rectal and smoking have also been reported.[56,57] Salvia extracts are exceptions, as they are usually smoked; DMT, too, can be 'smoked' (technically, 'vaporised' is the appropriate term).

As with other drugs, the route of administration of hallucinogens may have an impact on effects, their onset and duration. User reports suggest, for example, that the effects of 25I-NBOMe last 6–8 hours when the drug is taken sublingually or buccally, but only 4–6 hours when it is insufflated.

* Wedinos (2014) Keyword search; LSD. See Sample 000030322, Sample 000030324, Sample W002197. Retrieved July 17, 2014, from WEDINOS; Welsh Emerging Drugs and Identification of Novel Psychoactive Substances: http://www.wedinos.org/db/samples/search.

12.7.4. Frequency of use

Overall, bingeing is not reported with hallucinogenic drugs, partly because once the effects begin to fade, subsequent doses usually do not produce further psychoactive effects (tachyphylaxis)[2] (see section 12.13.1 on dependence).

12.7.5. Poly-drug use

Hallucinogens are sometimes combined with other drugs, in poly-drug repertoires, particularly with stimulant drugs.[58] In a Spanish study of 52 users of 2C-B, 83% reported that they had taken it simultaneously with other drugs, with most commonly with MDMA (69%), alcohol (43%) or cannabis (40%).[51] Reported combinations with bromo-dragonfly include: alcohol; prescribed drugs such as alprazolam; illicit substances such cannabis, cocaine, amphetamine or LSD; and legal highs, including salvia and kratom.[11,59]

Some combinations have their own user names; for instance, LSD or magic mushrooms taken with ecstasy are called *candyflipping* and *hippyflipping* respectively.[60] It has even been suggested that the popularity of these combinations may have contributed to a resurgence of LSD use, following the increasing popularity and use of MDMA.[61]

12.8. Desired effects of recreational use

Hallucinogens are a diverse group of drugs that alter and distort perception, producing sensory distortions, most notably visual, and also modify thought and mood.[62] DiPT is atypical because (at least according to anecdotal reports) it produces predominately auditory perceptual changes.[20]

Desired effects include euphoria, mild stimulation, enhanced appreciation of music and lights, visually appealing distortions, intensification of sensual or sexual feelings, altered sense of time and place, and a sense of shared and heightened significance of the situation. In the 2014 Net Pleasure Index of the Global Drugs Survey, in which 22,000 people in different parts of the world ranked drugs in terms of pleasure and pain, users placed LSD and magic mushrooms as the second and third most pleasurable drugs, following MDMA.[63]

Reports from users and the work of researchers, such as the Shulgins, strongly suggest that each drug has distinct characteristics, and that there are qualitative differences between the different drugs, with variability in multiple sensory and emotional dimensions.[20,53] The chemical and pharmacological properties of the various groups of hallucinogens will partially determine differences in effects; for example, some hallucinogen NPS also have pronounced stimulant effects.

The substances also differ in how pronounced the characteristic visual distortions are. This may be linked to the context in which they are used. For example, 2C-B has been described as inducing 'perceptual enhancement' and euphoria, but these are milder than those of classical hallucinogens such as LSD and the drug lacks the potent hallucinogenic effects of LSD.[64] This has contributed to its association with 'clubbing'. 2C-B

has proved popular as a dance drug, and has sometimes appeared in tablets sold as ecstasy.[65] In the Spanish study of 52 users of 2C-B, 60% reported that typical settings of 2C-B use were recreational environments (clubs, parties raves), followed by home use with friends (54%), at home with partner (37%) or in the countryside (20%).[51]

Other seek more potent experiences. Self-described 'psychonauts' use a wide range of hallucinogens and may experiment with newly emerging psychoactive substances, potent substances and with drug combinations. The emphasis of use is on seeking novelty and extremes of experience and sometimes a spiritual experience. Users may push boundaries in terms of potency of the substance and dose. The internet plays an important role in providing a platform for sharing experience and information.

However, as with other substances, the effects of hallucinogens are dose-dependent. For example, at lower doses 2CB is described by users on discussion fora as an energetic experience similar to that produced by ecstasy. At higher doses the experience is more similar to that of LSD. In addition, and even when the same substance is used at similar doses, any two experiences by the same individual user may be strikingly dissimilar qualitatively.[66] Unlike most other drugs, the effects of hallucinogens are highly variable, producing different effects in different people at different times. Non-pharmacological variables such as expectations, personality, environment and emotional state appear to have a much greater influence on the effects of hallucinogens than with other drugs.[67] Compared with the more predictable and replicable effects of stimulants and depressants, the desired and actual effects of hallucinogenic drugs are highly context-dependent and user-specific.[17,66]

Hallucinogenic drugs have also had 'entheogenic' or religious or spiritual uses in many cultures and over many centuries. Emphasis is on ritual, producing introspective and meditative states, and access to mystical experiences.

There is also evidence that some hallucinogenic drugs are used for self-medication. LSD and psilocybin are both reportedly used by some sufferers of cluster headaches,[68] and are anecdotally effective in aborting clusters and also reducing headache frequency in the long term.[69] A non-hallucinogenic analogue of LSD has been tested on a small number of people with apparent success, although the trial was neither blinded nor randomised.[70]

12.9. Unwanted effects

The hallucinogenic experience, even when positive, is often experienced as emotionally and physically draining.[71] Unwanted psychological effects are common to many hallucinogens and include what is referred to as a 'bad trip', characterised by anxiety, fear/panic, dysphoria and/or paranoia. Distressing effects can be sensory (e.g. frightening perceptions), somatic (e.g. distressing awareness of physiological processes), personal (e.g. troubling thoughts or feelings) or even metaphysical (e.g. feelings about evil forces).[5,72,73,74,75] In very rare cases, this may escalate to dangerous behaviour; for example, fear and paranoid delusions may lead to erratic behaviour and potential aggression against self and others.[5,74] This is discussed further below.

Even when a user is not experiencing a 'bad trip', unwanted effects can include confusion, disorientation, anxiety and unwanted thoughts, emotions and memories.[76] Other unwanted physical effects can include nausea, diarrhoea or non-specific gastric discomfort,[66] heaviness or tingling, feelings of heat and cold, trembling and weakness.[20,53,76] They also include dizziness, weakness, tremors, drowsiness, paraesthesia, blurred vision, dilated pupils and increased tendon reflexes.[5] Sub-acute effects may include headache, which for psilocybin has been shown by an experimental study to be dose-dependent.[77] Hallucinogens can also moderately increase pulse rate and systolic and diastolic blood pressure.[5] However, it has been noted that physical effects vary and are '*unimpressive even at doses yielding powerful psychological effects*'.[5]

Salvia has been described as frequently dysphoric.[78] However, among a self-selecting sample who predominantly reported positive effects, the most common adverse effects were that the drug experience was unexpected or excessively intense.[79]

12.10. Mortality

UK deaths directly attributed to acute toxicity linked to the use of the most prevalent drugs (LSD and magic mushrooms) are uncommon, but some have reported.[74,80] There are also several reports of suicides during or following LSD intoxication, although studies have not necessarily imply causality.[74,81] There are also reports of fatalities following ingestion of ibogaine, or products containing mixed iboga alkaloids.[34]

Hallucinogenic NPS have also been associated with a small number of recent deaths. In the UK, αMT is the drug most frequently linked to reported tryptamine-related deaths, with three deaths in 2013 and four deaths in 2012.[9] 5-MeO-DALT was mentioned in the coroner's report on one death in 2010 (hit by a lorry, while under the influence of the drug[82]) and one in 2012. DOC was the cause of one death in 2011.[83]

All hallucinogen drugs have been implicated with accidents secondary to intoxication, such as traffic accidents and falls.[84]

12.11. Acute harms

It is common to see psychological effects of hallucinogens without marked physiological symptoms, especially from the use of LSD and magic mushrooms, which are of low intrinsic toxicity, unless a very large dose is ingested.[85] LSD has a safety ratio (the ratio of the typical effective dose to the lethal dose) of around 1:1000, making accidental overdoses rare.[86]

However, some hallucinogenic NPS, such as bromo-dragonfly and other 'Fly' drugs, the DOx family, the NBOMe series and AMT have much narrower therapeutic ratios and a very different safety ratio, and so carry greater risk of acute toxicity and death.[54,87]

Among hallucinogenic NPS, the patterns of systemic toxicity varies across the drug class and type. Some hallucinogens will have a potential to cause toxicity with stimulant features (e.g. αMT[88]); others drugs may more typically evoke symptoms of serotonin syndrome (e.g 5-MeO-DiPT[30]).

Box 12.1. *Reported features of acute toxicity include are listed in*

CNS, neurobehavioural and psychiatric
Dilated pupils, mydriasis (common, psilocybin[89])
Sensory distortions, visual, auditory illusions, synaesthesia[8,90]
Tactile hallucinations, e.g. formication[91]
Affect lability
Euphoria[92]
Dysphoria[74]
Acute panic[8]
Paranoia, ideas of reference[8,90]
Depersonalisation[8,90,93]
Anxiety[8,90]
Disorientation[94]
Dissociation[94]
Agitation[30,33]
Aggression, combativeness[30]
Delirium
Depression, suicidal ideation, attempted suicide[95]
Psychosis, delusions, hallucinations[96,97]
Seizures[32]
Confusion[33,98]
Ataxia[8,90]
'Bizarre behaviour'[33]
Lightheadedness[8,93]
Headaches[8]
Paraethesias,[94] abnormal sensations of heat and cold, chills[8]
Restlessness, excitement[30,98]

Cardiovascular
Tachycardia[8,30]
Hypertension[8]
Musculoskeletal
Myalgias[8]
Twitching[93]
Muscle tension and jaw clenching[30]
Shaking[88]
Respiratory
Tachypnoea[30,93]
Metabolic
Metabolic acidosis[30]

Gastrointestinal/urological
Gastrointestinal symptoms may be more common after consumption of unrefined products containing hallucinogens such as *Ayahuasca*,[66] mushrooms and cacti, in comparison with refined chemical substances such as LSD
Nausea, vomiting[33,94] (psilocybin common)[89]
Diarrhoea[66,94]
Rhabdomyolysis[30]

Renal
Acute kidney injury/acute kidney failure[8]

Other symptoms
Hyperthermia[8,30]
Pyrexia[94]
Hypoglycaemia
Flushing[93]
Sweating[88]

12.11.1. Features of toxicity

Reported features of acute toxicity are listed in Box 12.1.

12.11.2. Psychological and psychiatric effects

These are the most common cause of hospital presentations related to hallucinogens[8,99] and are sometimes referred to by users as a 'bad trip'.[8] Adverse psychological reactions can occur at typical doses, and may feature feelings of loss of control, disturbing perceptions and attacks of anxiety, agitation and panic, which can be severe.[62] A patient's mental state may switch rapidly between severe anxiety and relative normality and back again.[100]

A typical distressing hallucinogenic experience is distinct from delirious or dissociative states. On typical recreational doses, it is usual for people to maintain insight into the cause of their experiences, but the dread of permanent madness or of death is not unusual.[101] Hallucinogenic drugs may provoke distressing thoughts and reflection on personal problems and past experiences and traumas.[5] They can profoundly exaggerate existing or underlying negative moods.[99] Some studies have identified the factors that may have contributed to the onset of paranoid delusions and psychosis, which include depressed emotional state at the time of taking the drug and doing so among strangers.[97]

12.11.2.1. Psychosis

As mentioned above, the term 'psychosis' has been used in the literature to describe typical hallucinogenic intoxications.[102]

A study using data from the large representative sample of the US National Survey on Drug Use and Health found that the use of hallucinogenic drugs appears not to be causally linked to the *de novo* development of chronic disorders of mental health such as schizophrenia or depression.[103]

Hallucinogens are rarely a cause of substance-induced psychosis, where the drug triggers a psychotic episode that may persist hours, days or even weeks after the acute intoxication should have run its course.[104] Nonetheless, psychotic symptoms in the context of LSD use have been reported, as well as in the context of hallucinogenic NPS, for example 2C-T-4.[105] It has been suggested that salvia[106] can trigger psychosis in people with existing psychotic illnesses or predispositions,[17] although there are also reports of the appearance of psychosis *de novo*.[107] There are a few case reports of psilocybin mushrooms causing an exacerbation of psychosis.[108] Similarly, it was also reported that there was greater psychotic response to LSD in persons with a genetic predisposition to schizophrenia.[109]

Overall, the evidence suggests that individuals who suffer from prolonged hallucinogen-induced psychosis may have pre-morbid mental illness. It is not known whether the onset of psychosis in these individuals represents a psychotic reaction that would not have occurred in the absence of use of hallucinogens, or whether it represents an earlier onset of psychosis that would have occurred anyway.[5,74]

Psychoses, apparently triggered by hallucinogens, have been reported in a small number of cases associated with violence and homicide. However, these have also been reported in subjects with pre-existing psychiatric conditions.[97,107]

12.11.2.2. Excited delirium

LSD has been involved in a small number of fatalities attributed to 'excited delirium', more commonly associated with cocaine.[110] Excited delirium has also been associated with 5-MeO-DALT [111] and αMT.[88] It has been argued that, in some instances, fatalities attributed to excited delirium may reflect underlying serotonergic and/or sympathomimetic toxicity.[112]

Excited delirium is often associated with the use of force and restraint, including cases where hallucinogens were implicated; the mechanism of death can be positional asphyxia or sudden cardiac arrest.[110,113]

12.11.3. Trauma and self-injury

Intoxication with hallucinogenic drugs can lead to accidental injury, and deaths, including from traffic accidents, falls or hypothermia.[110,114] There are a few case reports of self-injury associated with the use of hallucinogenic NPS and a case report of a fatality following AMT consumption.[88] Unusual self-injurious acts have also been recorded following hallucinogen use with or without co-intoxicants.[115] These include at least two cases of severe ocular self-injury,[115] a case of self-castration after LSD consumption,[116] and two cases of self-inflicted stab wounds following consumption of magic mushrooms.[117]

12.11.4. Physiological adverse effects

Overdose with LSD is rare, but may cause collapse, coma, vomiting, respiratory arrest and hyperthermia. Platelet dysfunction may occur causing mild, generalised bleeding tendency and polymorph leukocytosis.[75,81] Rhabdomyolysis has been reported.[118]

Tachycardia, tachypnoea, agitation, hyperpyrexia and hypertension have been reported following ingestion of bromo-dragonfly, a drug with a potency similar to LSD, but a far longer duration (1–3 days) and apparently greater toxicity.[11] The vasoconstriction that has been observed in cases of bromo-dragonfly toxicity has appeared resistant to treatment with ACE inhibitors, nitroprusside, prostacyclin analogues, glyceryltrinitrate or calcium channel blockers.[48]

Sympathomimetic toxicity has been reported after ingestion of several hallucinogenic agents, including ayahuasca,[119] LSD,[120] mescaline[121] and 2C-series drugs.[112] Severe and life-threatening effects have been associated with the ingestion of NBOMes[122,123] and bromo-dragonfly.[11]

Hallucinogens, particularly when taken in combination with other serotonergic drugs such as MDMA and SSRI antidepressants, may contribute to serotonin syndrome, which may be life-threatening (see section 7.7.2). Drugs with the potential to cause serotonin toxicity, for example 5-MeO-DiPT, may mimic the toxicity profile of MDMA.[30]

Other substances used for recreational purposes can also pose a risk of monoamine oxidase inhibition and toxicity. The Ayahuasca and Yage 'brews' contain a plant source of DMT and also a plant containing natural MAOIs (harmala alkaloids[124]). This combination produces hallucinogenic effects that typically last 4–6 hours,[76] whereas oral DMT without the MAOI is rapidly metabolised and inactivated, producing no hallucinogenic effects in doses of up to 1 g.[94]

Ayahuasca and various imitations are now concocted worldwide, using plant materials purchased online containing DMT and MAOIs. Plant sources of MAOIs such as Syrian rue seeds (*Peganum harmala*, which contains harmine and harmaline) are also used to potentiate the effects of other drugs such as 5-MeO-DMT, sometimes to harmful or even fatal[125]effect.[126,127] Furthermore, the plant material may be abandoned altogether, by using pharmaceutical MAOIs with DMT.[128]

12.12. Clinical management of acute toxicity

The management of acute toxicity resulting from the use of hallucinogens will in part depend on the hallucinogenic substance consumed. It has been suggested that monitoring and supportive treatment is all that is required for the majority of patients,[62] including airway management. TOXBASE® recommends that all patients be observed for at least four hours after exposure. Asymptomatic patients can then be discharged with advice to return if symptoms develop.

Some products sold as LSD may in fact contain potent hallucinogens with far narrower therapeutic ratios,[54] such as NBOMes, with a greater potential to cause acute toxicity. It has therefore been suggested that emergency room staff monitor patients presenting following ingestion of 'LSD' with the greater intensity and supportive care necessary for the management of NBOMe intoxications.[129]

The management of phenethylamine derivatives, such as 2-CB, which acts as a serotonin agonist, will need to consider the effects and harms relating to the use of amphetamine-type substances as well as the potential risks of serotonin syndrome. As with other stimulants, TOXBASE® says that in the event of cardiac arrest, CPR should be continued for at least 1 hour and stopped only after discussion with a

For up-to-date guidance on the management of acute toxicity relating to hallucinogens, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Poisons-Index-A-Z/L-Products/LSD/

http://www.toxbase.org/Poisons-Index-A-Z/2-Products/2C-B/

http://www.toxbase.org/Poisons-Index-A-Z/2-Products/2C-B-NBOMe/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

senior clinician. Prolonged resuscitation for cardiac arrest is recommended following poisoning, as recovery with good neurological outcome may occur.

12.12.1. Management of adverse psychological effects, agitation and drug-induced psychosis

A number of studies have looked at the management of adverse reactions and the following have been shown to be beneficial:

- Attempts to 'talk the patient down'. Sympathetic[8] non-judgemental[130] reassurance, support and observation were often sufficient.[5] Where possible, the patient should be placed in a well lit room with minimal disturbance.[8,17] Patients may be prone to mistrust and paranoid ideation, and early efforts in empathising, expressing understanding of their fears and establishing confidence have been shown to be beneficial. [8,100] Finding a more peaceful corner or room may prove worthwhile,[62] as the typical clinical environment (with medical equipment and white coats) has been shown to be a predictor of adverse anxious reactions in participants in psychedelic research.[67]
- Benzodiazepines, particularly diazepam or lorazepam,[8,62] have been reported by some studies to be first-line choice if pharmacological interventions are needed and in cases of agitation.[5,17] Doses described in the literature include the following: 10 mg oral doses of diazepam[131] (0.1–0.3 mg/kg body weight). Doses of 15–30 mg per hour or as needed have been suggested for cases of 'bad trips' that do not respond to reassurance in an emergency department setting.[5] TOXBASE® (accessed 17 December 2014) suggests an initial dose of oral or intdravenous diazepam (0.1–0.3 mg/kg body weight). Larger doses may be required.
- Antipsychotics should be considered as a second line if benzodiazepines do not produce adequate sedation.[130]
- In cases of severe agitation or 'excited delirium', physical restraint should be avoided, as this is associated with sudden cardiovascular collapse.[132]
- In cases of drug-induced psychosis, TOXBASE® (accessed 17 December 2014) recommends that children over 12 years be sedated with a benzodiazepine (e.g. oral or intravenous diazepam, 0.1–0.3 mg/kg body weight), or if that is ineffective, an antipsychotic such as haloperidol or olanzapine.

12.13. Harms associated with chronic use

There is no evidence that 'classical' hallucinogens such as LSD or psilocybin have potential neurotoxic effects, as MDMA does in high doses.[5] For example, a brain imaging study comparing hallucinogen users with ecstasy users found evidence for serotonergic neurotoxicity only among the latter.[133]

A study has shown that people of a certain personality type – those who score highly in the domain of absorption, characterised by propensity to daydreams and

mystical experiences – seem more likely to enjoy and find value in hallucinogenic intoxication.[134] Those who ingest hallucinogens regularly may be fairly atypical[135] and research from the 1970s suggested that, in some cases, alienation, rejection of normative values, emotional disturbances and desire for self-change may pre-date the use of hallucinogens, and mediate any relationship between use and higher rates of psychopathology.[136]

12.13.1. Dependence

The use of LSD or other classic hallucinogens does not appear to lead to dependence. Typically there is no persistent and compulsive pattern of use[17,137] and the use of hallucinogens is not associated with any recognised withdrawal syndrome.[38,131,138]

Hallucinogens do not appear to show classic patterns of tolerance,[138] but, on the contrary, are associated with tachyphylaxis.[2] This means that sensitivity to the effects of LSD and other hallucinogens appears to be strongly attenuated for a period after use. It may therefore prove difficult for a user to achieve desired effects from LSD if taken two days in a row, or indeed to get a desired effect from other hallucinogens.[1,2]

DMT consumed by vaporisation (usually called 'smoking' by users) appears to be an exception to this rule, having both an unusually brief duration of action and a proportionately brief duration of tachyphylaxis.[139] Anecdotal evidence confirms that this enables users to have the desired effects multiple times a day if they want to.[140] According to the authors of one survey, this, added to DMT's fewer unwanted effects and less of a 'come-down' than LSD or mushrooms, gives it a higher potential for misuse.[50] However, the same survey did not find an increased desire to use.[50]

12.13.2. Hallucinogen persisting perceptual disorder (HPPD)

Hallucinogen persisting perception disorder (HPPD) and 'flashbacks' have been associated with use of classic hallucinogens in particular, although these concepts remain somewhat contested. HPPD as a diagnosis has been embraced by a group of people experiencing longer-term symptoms resulting from hallucinogen use. Hundreds of individuals discuss online their symptoms, including in dedicated fora.* Although knowledge of HPPD remains very limited, this disorder can persist for months or years after the use of hallucinogens.[141] For some, this long-term change to vision and hearing is much less problematic than for others,[142,143] for whom it can cause substantial morbidity.[141]

The concept of HPPD was first introduced in DSM-III, based on the work of Abraham on habitual LSD users.[144] The diagnostic criteria of HPPD as defined by DSM-V (292.89 F16.983) are as follows:

A Following cessation of use of a hallucinogen, the re-experiencing of one or more of the perceptual symptoms that were experienced while intoxicated with the hallucinogen (e.g. geometric hallucinations, false perceptions of movement in

* An example of such a forum is HPPD Online, http://hppdonline.com/ (accessed 18 September 2014).

the peripheral visual fields, flashes of colours, intensified colours, trails of images of moving objects, positive afterimages, halos around objects, macropsia, and micropsia).

B The symptoms in Criterion A cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C The symptoms are not due to a general medical condition (e.g. anatomical lesions and infections of the brain, visual epilepsies) and are not better accounted for by another mental disorder (e.g. delirium, dementia, schizophrenia) or hypnopompic hallucinations.

In contrast, ICD-10 views this disorder within the wider paradigm of a psychotic disorder (F1x.5) and specifically considers 'flashbacks' (F1x.70) within the context of 'residual and late-onset psychotic disorder' (F1x.7). ICD-10 also specifies that 'flashbacks' 'may be distinguished from psychotic disorders partly by their episodic nature, frequently of very short duration (seconds or minutes) and by their duplication (sometimes exact) of previous drug-related experiences'. The forthcoming ICD-11 may present a revised definition of this disorder.

In contrast with genuine psychosis, there is no paranoid misinterpretation of the perceptions in people who suffer from HPPD.[145] Studies on HPPD have recommended that other conditions be ruled out before a diagnosis of HPPD is made, including post-traumatic stress disorder (PTSD), depersonalisation and derealisation associated with severe anxiety and depression, as well as other hallucinogen-induced disorders recognised by DSM, such as hallucinogen-induced psychosis and mood or anxiety disorders.[141]

The symptoms of HPPD can include any perceptual disturbances but visual ones tend to be more prominent. They may be episodic or nearly continuous and must cause significant distress or impairment as specified in DSM-V criterion B above. There seems to be no strong correlation between HPPD and frequency of use of hallucinogens, with reported instances of HPPD in individuals with minimal exposure to hallucinogens.[146] Common visual features include geometrical hallucinations, flashes or intensification of colour, movements, particularly in the peripheral vision, afterimages, trails and haloes.[147]

A number of people have challenged the value of the concept of 'flashbacks'.[141] Indeed, it has been argued that the distinction between 'flashback' and HPPD remains unclear and requires further investigation. Some have even argued that the concept of 'flashback' is not a useful diagnostic entity, has been defined in very many different ways and is 'essentially valueless'.[141] In the literature, there is sometimes a distinction between the two, with 'flashbacks' generally used to describe intermittent, infrequent experiences, in contrast to the more persistent experiences of HPPD.[143] 'Flashbacks' are generally transient and often pleasant, in contrast to HPPD, which is chronic and can be highly debilitating.[145]

Transient 'flashback' phenomena appear largely absent from the more recent clinical literature, in which the chronic visual distortions critical for a diagnosis of HPPD

predominate. These are commonly associated with co-morbid psychiatric symptoms, particularly anxiety, somatisation, panic and affective disorders.[103,141,145]

HPPD is both rare and unpredictable.[143] Estimates of the proportion of users who have experienced flashbacks on one or more occasions after hallucinogen use vary widely, from 5% to 50%.[148,149] However, many of these studies were conducted before the development of the DSM-III diagnostic criteria for HPPD and are therefore difficult to interpret.[141] More recently, a 2003 review of the literature concluded that 'it seems inescapable that at least some individuals who have used LSD, in particular, experience persistent perceptual abnormalities reminiscent of acute intoxication, not better attributable to another medical or psychiatric condition, and persisting for weeks or months after last hallucinogen exposure'.[141] Current prevalence estimates are unknown, but DSM-V suggests 4.2% (292.89 F16.983).

Despite these findings, the existence of HPPD and flashbacks remains contested. Analysis of US data from 2001 to 2004 from the National Survey on Drug Use and Health does not support the idea of 'flashbacks' (described in extreme cases as recurrent psychotic episodes, hallucinations, or panic attacks) or HPPD (described as persistent visual phenomena with accompanying anxiety and distress). [103]

The exact causes of HPPD are not known. The condition is more often seen in individuals with a history of psychological problems but can arise in anyone, even after a single exposure.[150] HPPD is mainly associated with LSD use, but it has also been reported after use of other psychedelic drugs, including mushrooms,[151] mescaline[141] and 5-MeO-DIPT.[152] Other substances may trigger HPPD, including cannabis,[153] alcohol and MDMA.[154] HPPD or flashbacks have also been reported in people who have taken pharmaceutical drugs such as risperidone,[155] topimarate,[156] trazodone, mirtazapine, nefazodone[145] and SSRIs[157] and it has been suggested recently that hallucinogen use is not actually a necessary condition for this multifactorial syndrome.[145]

It has, however, been suggested that there may not be a common aetiology to the diverse phenomena described as HPPD and 'flashbacks' in the literature,[141,158] with diverse interpretations having been made. It has been suggested that some cases may be explained in terms of a heightened awareness of and concern about ordinary visual phenomena,[141] which is supported by the high rates of anxiety, obsessive-compulsive disorder, somatisation, hypochondria and paranoia seen in many such patients. Visual symptoms like 'visual snow', 'floaters', palinopsia (after-images) and trails are all common in the healthy general population,[103,141] or may be symptoms of psychosis, seizure disorders, persistent migraine aura without headache, or stroke.[143]

Explanatory models for HPPD and its association with hallucinogenic drugs have been contested because it has been associated with other substances (e.g. cannabis) and because of high co-morbidities with anxiety, attention problems and derealisation symptoms among people with HPPD.[154] Existing models range from purely incidental (i.e. no association between the drug use and symptoms) to 'an increased vulnerability to dissociative phenomena in susceptible individuals'.[159]

Others attribute a directly causal effect through neurotoxicity caused by the drug (e.g. 'destruction of inhibitory serotonergic interneurons'[157]). Some have argued

that serotonergic neurological damage underlies HPPD, resulting in imbalances of excitation and inhibition in brain regions responsible for early visual processing.[154] However, these models based on neurological disorders have also been questioned in light of reports of HPPD involving a single use of a typical dose of a psychedelic, while many users with a much higher frequency and dose of use do not present with these symptoms.[141]

12.13.2.1. Treatment of HPPD

A survey using a web-based questionnaire reported that although symptoms of HPPD were common, only a few found them distressing enough or impairing enough to consider treatment, with constant symptoms increasing the likelihood of seeking treatment. Even when these symptoms were constant, they were not always considered problematic.[143]

There is no established treatment for HPPD and research is very limited. Some cases of HPPD are reported to have improved with the use of sunglasses,[144] psychotherapy[144] and behaviour modification.[160]

Promising treatment outcomes have been reported from a number of pharmacological interventions, but the multifactorial nature of the disorder, and the prominence of co-morbidities, suggest the need for highly individualised treatment, with stress reduction, reduction of or abstinence from substance use (including alcohol and perhaps caffeine)and treatment of co-morbid disorders.[145]

Pharmacological interventions for HPPD have been used but many of the studies (especially older ones) had methodological limitations. These interventions have included several classes of antidepressants, anxiolytics and antipsychotics, a COMT inhibitor, naltrexone, levodopa, clonidine, lamotrigine[145] and citalopram.[161] Over the years, there have been reports of treatment using haloperidol,[162] diphenylhydantoin,[163] trifluoperazine,[164] barbiturates,[144] benzodiazepines,[144,165] carbamazepine,[166] sertraline,[167] naltrexone,[168] clonidine,[169,170] and a combination of olanzapine and fluoxetine.[171] Hermle et al. have suggested that the anti-epileptic lamotrigine may be a promising new medication for HPPD.[145] There are also reports of worsening of HPPD in patients receiving phenothiazines,[144] the atypical antipsychotic risperidone[172,173] or serotonin-selective reuptake inhibitors.[174]

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