

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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Part I: Introduction, background and overall principles

Introduction

1.1. This document

For the purposes of this document, 'club drugs' is a short-hand term used for convenience to refer to a group of psychoactive substances typically used in dance venues, house parties, music festivals and sometimes in a sexual context. The term therefore describes a diverse group of substances with different actions. They include substances with primarily stimulant effects, those with primarily hallucinogenic effects, as well as some central nervous system depressants and synthetic cannabinoids. Club drugs include substances well established in the UK such as MDMA (ecstasy), as well as the rapidly expanding range of novel psychoactive substances (NPS) such as synthetic cannabinoids, synthetic cathinones and a range of other amphetamine-type stimulants. Some club drugs are sold on the illicit market, whilst others are sold as so-called 'legal highs'.

This document provides guidance on the clinical management of harms resulting from acute intoxication and from the harmful and dependent use of club drugs and NPS. It categorises club drugs broadly according to their clinical effects:

- **depressant;**
- **stimulant;**
- **hallucinogenic.**

In addition, the **synthetic cannabinoids** are treated as a separate category, largely for reasons relating to their clinical management but also because they do not fit neatly into that threefold categorisation.

The guidance is based on available evidence and clinical consensus. It is a response to the current gap in knowledge and experience in the management of these drugs across the UK and beyond.

Guidance is aimed in particular at clinicians in a range of settings, specifically:

- specialist drug treatment services
- hospital emergency departments (EDs)
- general practice/ primary care
- sexual health clinics

This document provides **guidance**, *not* **guidelines**. Together with the recommendations of its reviews, technical appraisals and standards, national guidelines produced by the National Institute for Health and Care Excellence (NICE) determine the wider

principles within which treatment and care should be provided within drug services, EDs, primary care, sexual health and mental health services. However, these guidelines do not relate specifically to NPS. NEPTUNE guidance must be used within the wider principles of these national guidelines.

This guidance does not aim to replace the role and resources of the National Poisons Information Service (NPIS) and its online toxicology database and telephone enquiry service TOXBASE® for advice on the clinical assessment and management of acute toxicity within hospital EDs, primary care and other healthcare facilities (Box 1.1). Clinicians should consult TOXBASE®, and where necessary call the NPIS for up-to-date information. It is highly recommended that clinicians and departments be registered to be able to use these facilities. Readers should also consult TOXBASE® for information provided by the UK Teratology Information Service (UKTIS) on all aspects of the toxicity of drugs and chemicals in pregnancy.

Box 1.1. TOXBASE®

For up-to-date guidance on the management of acute toxicity, 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®.

The database (<http://www.toxbase.org>) contains information on approximately 17,000 products, together with generic advice on the management of poisoning. It is available free of charge to registered NHS users and it is highly recommended that clinicians and departments be registered to be able to use these facilities. By using TOXBASE®, clinical staff can obtain key clinical information rapidly, including advice on potentially hazardous doses and appropriate management.

The NPIS 24-hour telephone helpline (in the UK 0844 892 0111 and Ireland NPIC (01) 809 2566) is available for discussion of more complex cases. When appropriate, senior medical staff can discuss their cases directly with an NPIS consultant clinical toxicologist.

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

Non-UK readers of this document should contact their local, regional or national poisons information service for up-to-date advice and guidance on the management of acute club drug intoxication and withdrawal.

NEPTUNE guidance is **time-limited** (provisionally to end 2017), not least because new compounds continue to emerge and the evidence is continuing to grow.

1.2. Novel Psychoactive Treatment UK Network (NEPTUNE): project aims and guidance development

1.2.1. Objectives of the NEPTUNE Project

This guidance has been developed by NEPTUNE (Novel Psychoactive Treatment UK Network), a project funded by the Health Foundation's^{*} Shine Innovation Programme 2012[†] and led by Central and North West London NHS Foundation Trust.

The objectives of the NEPTUNE project were as follows:

- Convene a multidisciplinary group of UK experts in the treatment of harms resulting from the use of club drugs, including experts by experience (patients).[‡]
- Review the national and international evidence on club drugs, and most particularly the evidence on the harms and the management of harms linked to acute intoxication and acute poisoning, as well as those associated with long-term harmful use and/or dependence.
- Develop treatment guidance based on the best available research evidence. Where this is lacking, the guidance is based on the expert group's[‡] clinical consensus and patient experience.
- Develop guidance specifically for the following clinical settings:
 - (1) drug treatment services;
 - (2) emergency departments;
 - (3) general practice;
 - (4) sexual health clinics.

The group convened comprises UK experts in the management of acute and chronic problems associated with club drugs. It is a collaboration between individuals from a number of different NHS and voluntary organisations, with observers from relevant government departments (for the full list see pp. ii–iii). The expert group includes psychiatrists, psycho-pharmacologists, psychologists, clinical and analytical toxicologists, emergency physicians, genitourinary medicine (GUM) physicians and HIV physicians, general practitioners, urologists, nurses, senior managers and experts in club drugs among lesbian, gay, bisexual and transgender (LGBT) populations.

1.2.2. Aims of the NEPTUNE clinical guidance

The aim of the guidance is to improve confidence and competence, and increase the skills of clinicians in the detection, assessment and management of the harms

* The Health Foundation is an independent charity working to improve the quality of health care in the UK. <http://www.health.org.uk/>

† <http://www.health.org.uk/areas-of-work/programmes/shine-twelve/>

‡ Henceforth referred to as 'expert group'.

associated with the use of club drugs, across all target settings. Specific areas addressed include:

- **Detection/identification.** Recognising the significant psychological, physical and social risks which can be associated with club drugs, and equipping professionals to be able to recognise problematic use, associated harms and dependence, and to be able to use screening tools where indicated.
- **Assessment.** Assessment of the problems related to the use of club drugs, including the assessment of both direct and indirect harms.
- **Management.** Clinical management of acute and chronic harms related to the use of club drugs- in the target clinical settings, based on the best available evidence, or on clinical consensus where evidence is lacking.
- **Harm reduction.** Interventions aimed at preventing morbidity and mortality among individuals presenting to clinical settings, including measures to reduce the harms of club drugs for individuals and communities and to help patients achieve and sustain recovery and well-being.

The underlying principles of good clinical practice in relation to the users of club drugs are applicable to all problematic psychoactive drug use and form the basis of national UK guidelines aimed at the drug treatment and recovery field. However, good assessment and management of the harms of club drugs (including NPS) must also take into account the particular challenges posed by these drugs and address them directly. These include challenges posed by:

- new drugs (rapidly changing profile and ever increasing numbers of substances, with poorly understood harms);
- new populations in treatment (including new patterns of drug use and contexts of harm);
- new harms (some club drugs are associated with harms not previously linked to illicit drug use, for example ketamine-related ulcerative cystitis).

NEPTUNE therefore aims to improve clinicians' knowledge of the specific issues relating to club drugs and to support evidence-based practice at local levels. It also aims to help improve clinicians' confidence in working with patients who use club drugs, by providing the following:

- 'technical' knowledge (what the drugs are and how they work).
- 'cultural' knowledge (who is using them, and how).
- 'clinical' knowledge (how to clinical manage both acute and chronic presentations).

1.3. Target audience for the guidance

1.3.1. Primary audience

This guidance is aimed primarily at a clinical audience. The target clinical settings have been chosen because they offer specialist treatment for acute or chronic problems (EDs and specialist drug services) or because they provide an untapped access to populations at risk of drug-related harms (sexual health clinics and general practice, which are potentially clinical areas with a high prevalence of patients using club drugs).

The stepped care approach used in this guidance document, as well as the phased and layer framework of drug treatment (see Chapter 2), takes into account the different roles and competencies of clinicians in each of the target settings in delivering interventions aimed at those who use club drugs.

1.3.2. Other audiences

The guidance is also a resource for commissioners and policy-makers in developing local and national services. It also provides patients and carers with information on what interventions should be available.

1.4. The process of developing the guidance: method for the literature review

A comprehensive review of the English language literature on the harms and the clinical management of a range of club drugs was carried out, using systematic methods.

Studies, including case reports, were identified using electronic searches of Medline, Medline Plus, the Cochrane Library, CINAHL, Current Content, Embase, PUBMED, PsychINFO, Google Scholar and the Science Citation Index. In addition, bibliographies of articles were screened for additional relevant studies.

Box 1.2. Search terms included in combination with drug names

Addiction; Adverse effects; Subjective effects; Craving; Chronic; Clinical features; Cognitive; Detoxification; Dependence; Harms; Ingestion; Intoxication; Pharmacology; Poisoning; Psychological interventions; Psychological treatment; Brief interventions; Drug management; Clinical features; Harms; Toxicity; Motivational; Chronic use; Withdrawal; Craving; Cue exposure; Detoxification; Dependence; Addiction; Managed care; Pharmacotherapy; Intoxication; Prevention; Health outcomes; Clinical outcomes; Recreational use; Toxicology; Prescribing; Relapse prevention; Relapse management; Motivational interviewing; CBT; Behavioural therapies; Cue exposure treatment; Community reinforcement approach; Motivational enhancement therapy; Relapse prevention; Relapse management; Psycho-sexual counselling; Care plan; Gay men; Men who have sex with men; LGBT; Clubbers; Party circuit; Drug use in clubs; Drug-facilitated sex; Injecting; Insufflation; Clinical; Guidelines; A&E; Substance misuse treatment; General practice; Sexual health; Urology; Dentistry; Ophthalmology; Pregnancy; HIV; Hepatitis C.

Search terms included the drugs names alone, or in combination with the terms listed in Box 1.2. Terms specific to one of the substances reviewed were also included where relevant (e.g. ulcerative cystitis for ketamine).

The outputs of searches were considered against sets of inclusion and exclusion criteria (see section 1.4.1). The citations produced by these searches were then screened via their abstract. Those considered relevant were identified and subjected to critical assessment by the core NEPTUNE team and other members of the NEPTUNE expert group.

The critical assessment of the evidence was based on the framework developed by the British Association for Psychopharmacology for the development of guidelines for the management of substance misuse.¹ This classifies the strength of evidence as follows:

- **Strong research evidence** (e.g. Cochrane reviews, meta-analyses, high-quality randomised controlled trials);
- **Research evidence** (e.g. controlled studies or semi-experimental studies);
- **Emerging research evidence** (e.g. descriptive or comparative studies, correlation studies, evaluations or surveys and non-analytic studies, for example case reports, case series);
- **Expert panel evidence/consensus;**
- **Expert by experience evidence** (service users/patients);
- **Lack of evidence** (no evidence, for or against);
- **Conflicting evidence.**

In order to assess the applicability and relevance of the international literature to a UK context, considerations of population, setting, intervention and outcomes have been taken into account for statements in the guidance.

It was clear from the onset of the literature review that the evidence base is relatively small. In particular, studies on the toxicity of NPS, and risks associated with long-term use and dependence liability, are few, partly because most NPS have limited or no medical use,² and partly because some of these substances have only recently emerged.

Overall, there is a lack of robust evidence, in particular from meta-analyses or high-quality randomised controlled trials, and even controlled and semi-experimental studies are few. The bulk of the research available provides what is referred to as **emerging research evidence**, as it is based principally on non-experimental descriptive studies, consisting mainly of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records.

The literature review also identified clinical questions that were not addressed by the research evidence. Where evidence was lacking, consensus was sought from the multidisciplinary NEPTUNE expert group, based on a process of open discussion, with a view to producing guidance that is of practical use to clinicians.

This document therefore does not give definitive answers on the clinical management of club drugs and NPS, but broad guidance based on the current best available evidence and clinical consensus.

1.4.1. General inclusions and exclusions in the guidance

- The guidance focuses on acute and chronic harms linked to the use of club drugs, and their management.
- The guidance is aimed at the management of adults (18 years and older). The development of similar guidance for children and adolescents is recommended.
- The guidance does not address interventions in non-clinical or pre-hospital settings, such as nightclubs, schools and universities, or festivals, some of which are discussed elsewhere.³
- Issues specifically pertaining to prisons and corrective facilities have also been excluded, although much of the clinical guidance is equally applicable to clinical management within the prison service. The 2013–14 annual report of HM Inspectorate of Prisons mentions the increased availability of NPS, and most particularly synthetic cannabinoids, in prisons and the association of these drugs with debt and bullying, as well as their effects on health.⁴

1.4.2. Substances and drug groups covered by this guidance

Cocaine is the most commonly used substance in the UK that can be described as a club drug, despite some reduction in its use since its peak in 2008/09 in England and Wales. However, this document does not address the management of long-term harms and dependence of cocaine specifically. This is because substance misuse treatment professionals already have access to an extensive and robust body of evidence on the **long-term** harmful and dependent use of cocaine, and Cochrane reviews have been published. There is also good clinical experience in drug treatment services in the UK in the management of cocaine-related harms and evidence that people with primary cocaine problems are accessing treatment and recovery services (for more details see Chapter 2). This document does, however, address briefly **acute** cocaine intoxication, which is a significant clinical problem in the UK. Studies from the UK have shown under-recognition of acute cocaine toxicity in patients presenting with chest pain. There are aspects of acute cocaine toxicity that are different to the toxicity associated with other stimulants, in particular myocardial ischaemia/chest pain (related to vasospasm) and arrhythmias (related to ion channel effects). These are discussed briefly in Chapter 6.

Not all NPS meet the loose definition of a 'club drug' and some NPS have been excluded from this guidance document, such as the newly developed opioids receptor agonists and benzodiazepines that have recently been on sale on the internet.

Because of the potentially very large number of club drugs and NPS that can currently be bought on the illicit and 'legal' markets and those that will emerge in the future, it

is not possible to cover them all in any detail within the confines of this work. In order to address this issue, a two-pronged approach has been adopted:

First, the structure of the guidance provided by this document – and within which individual drugs are discussed – is based on the following broad classifications:

- predominantly depressant drugs;
- predominantly stimulant drugs;
- hallucinogens drugs;
- synthetic cannabinoids.

Although these classifications provide a useful framework for this guidance, it is important to note that they are not rigid categories. In reality, many club drugs have a combination of effects, for example stimulant and hallucinogenic effects.⁵

The second part of our approach was to focus in more detail on the drugs (as well as their derivatives and related compounds) most used in the UK and those that cause most harm.

Where a particular drug is not discussed in this document (either because it was infrequently used in the UK or because it was not developed at the time of writing), clinicians can refer to the broad groups to which it belongs and can extrapolate information on the management of its acute and chronic harms, while taking into account potential differences in potency, toxicity, half-life, length of effect and so forth.

1.5. An overview of club drugs

1.5.1. Old drugs, new drugs and 'legal highs'

'Club drugs' include a wide range of substances. Some, such as ecstasy, are well established substances, that have been subject to legal control for many years. Others are new psychoactive substances (NPS), which are emerging at a fast pace on the drugs market, many supposedly as non-illicit alternatives to controlled drugs.² At the time of writing, many of these NPS were controlled, whilst others were sold as so-called 'legal highs'.

An increasing number of NPS can be found globally. The United Nations Office on Drugs and Crime has identified six main groups: synthetic cannabinoids, synthetic cathinones, ketamine, phenethylamines, piperazines and plant-based substances; there is also a seventh group, of miscellaneous substances – recently identified NPS which do not fit into the groups mentioned.²

The *World Drug Report 2014* indicated that the number of NPS on the global market more than doubled over the period 2009–13. By December 2013, the number of NPS reported to UNODC reached 348, up from 251 in July 2012 and 166 substances in 2009. This means that, now, the number of NPS exceeds the number of psychoactive

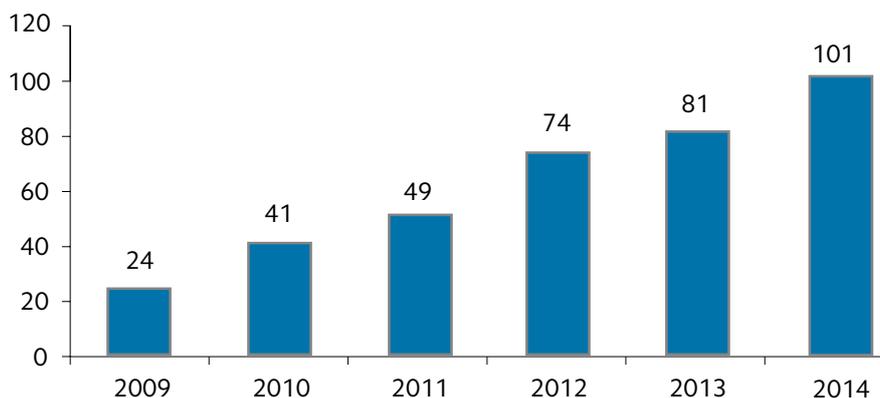


Figure 1.1. *Number of psychoactive substances with use reported for the first time within the European Union*

substances controlled at the international level (234 substances).⁶ The overall increase over the period August 2012–December 2013 was mostly due to new synthetic cannabinoids (50% of newly identified psychoactive substances), followed by new phenethylamines (17%), other substances (14%) and new synthetic cathinones (8%).

The use of NPS is thus emerging as a truly global phenomenon. NPS are now found in most of Europe and North America, as well as Oceania, Asia and South America, and in a number of African countries. To some extent, however, NPS are a North American and European phenomenon, with the UK accounting for 23% of the European total of NPS users.⁷

The number of NPS is increasing at a fast pace in Europe, as shown in Figure 1.1.⁸

In recent years, these newly emerging ‘legal highs’ in Europe have been dominated by new synthetic cannabinoid receptor agonists, with phenethylamines, tryptamines and cathinones reflecting other popular illicit drugs. Of the 81 new psychoactive substances reported for the first time within the EU in 2013, 29 were synthetic cannabinoids, 14 phenethylamines, 7 synthetic cathinones, 7 arylalkylamines, 5 opioids, 2 benzodiazepines, 1 tryptamine, 1 aminoindane, 1 arylcyclohexylamine, 1 piperidines/ pyrrolidine, 1 piperazine, and 12 were substances that do not conform to any of these groups. Of particular concern are new synthetic opioids – such as AH-7921, MT-45, carfentanil and ocfentanil – reported as emerging in the past two years but which are already controlled under the Misuse of Drugs Act.⁸ These are, however, outside the remit of this document, because they cannot be considered club drugs, as defined in section 1.1.

Most of these NPS are thought to be manufactured to mimic the effects of controlled drugs, usually in China or India, or in clandestine laboratories in Europe. There is no doubt that the producers of novel NPS and ‘legal highs’ are well aware of the legal framework surrounding illicit substances and are continuously replacing controlled compounds with an array of compounds which are modified to avoid legal control.

Given the very numerous possibilities for altering the structure of chemicals, the list of substances produced is likely to grow continuously.²

New substances are produced very quickly to replace those that are placed under legal control by various states. A well known example is from Germany, where a second generation of synthetic cannabinoid products (JWH-073) were available on the market just four weeks following the ban of JWH-018.⁹ In the UK, and although JWH-018 continued to be found in 60% of 'spice' products after the ban, products containing JWH-073 increased from 6.5% to 70% of products tested.¹⁰ Similarly, it was noted that online discussions on MDAI in drug user fora became more frequent after May 2010, following the UK ban on methcathinones the previous month. MDAI was then advertised as a 'legal' alternative to mephedrone.¹¹

However, despite the fact that the manufacturers of so-called 'legal highs' often try to circumvent the law by developing compounds slightly different from those banned, there is evidence that some of these products sold online or in 'head shops' do contain classified compounds and are therefore illegal under UK law.¹⁰ Reports of the Forensic Early Warning System (FEWS) confirm that this continues to be the case: products advertised as legal alternatives to illicit substances are not always legal.^{12,13} In addition, the report showed that 81% of the approximately 2000 products that contained new psychoactive substances collected during 2012–13 were a mixture of two or three different active compounds.^{12,13} Products with the same name brands also sometimes contained different mixtures of active compounds, even those from the same supplier.¹²

In 2013–14, 19.2% of NPS samples collected by FEWS contained controlled drugs. There a difference by setting, whereby a low proportion of controlled drugs was detected in NPS samples from headshops (4.3%) and the internet (3.0%), but a high proportion of controlled drugs was detected in NPS samples from festivals (88.1%). In addition, approximately 91% of the samples analysed that contained NPS were identified as mixtures of either two (61%) or three (30%) different active components; 1% of samples were identified as containing six different active components. Furthermore, products with the same brand name, such as 'Black Mamba', 'Critical Haze' and 'Sparklee', including those from the same suppliers, were observed to contain mixtures of different components.¹³

UK and other research has also shown that there is significant variation in the content of 'legal high' products bought over the internet.^{14–19} One study found that six out of the seven products it analysed did not contain the advertised active ingredients but, rather, some controlled products.¹⁹ Moreover, the actual components of products sold as 'legal highs' are subject to variation even between batches, and change over time and in different places. For example, 'Ivory Wave' was identified in 2009 as a mixture of MDPV and lidocaine,²⁰ but further toxicological analyses of other 'Ivory Wave' batches also revealed the presence of 2-DPMP²¹ and D2PM.²² It has also been reported that caffeine has been detected in legal high products and some products tested were shown to contain caffeine only.¹⁴

Therefore, although the term 'legal high' is used for a number of NPS, it is a confusing and unhelpful one. It has been argued that these substances are not 'legal' but are

instead 'not prohibited'. Their 'legal' status does not reflect their safety but rather the lack of regulation over their production, distribution and use.^{23,24} Many are untested and have unknown psychological and toxicological effects.^{25,26}

Moreover, not all NPS are 'novel'. 'New' does not always mean a new invention but could refer to substances that have recently been made available for recreational use. For example, mephedrone was reportedly first synthesised in 1929, but emerged as a recreational substance of misuse as late as 2007.² Other 'new' substances were synthesised and patented in the 1970s or earlier, but recently their chemistry has been modified slightly to produce psychoactive effects similar to those of well established illicit substances, as is discussed in the chapters below.

It is also important to note that new drugs may appear on the illicit market and then disappear, usually as a result of little demand. NPS may be popular at first and then fall in and out of favour, as users try them and move away from them; for example, pipradrols such as D2PM, desoxypipradrol and bromo-dragonfly are currently used less than previously.

There is some evidence that the appeal of some NPS is sometimes linked to the poor quality of more established illicit substances available on the black market. In particular, a reduction in the purity of ecstasy and cocaine was linked to an increased use of mephedrone in the UK²⁷ and 2C-B in Spain.²⁸

1.5.2. New markets and user communication about drugs

Club drugs are sold through a variety of channels, including street-level drug dealers and through web sites; such outlets often sell controlled substances as well as 'legal highs' (see below for details). Some users will access a mixed economy; for example, there is anecdotal evidence from clinical practice that some GHB/GBL users will buy a small amount from street dealers as well as purchasing in bulk via the internet.

'Legal highs' are sold online, in 'head-shops' or sometimes alongside controlled substances on the illicit market. Anecdotal reports from the UK also suggest that some legal high products (such synthetic cannabinoid products) are being sold in a wide range of outlets,²⁹ including corner shops, pubs and petrol stations. Legal highs are marketed as 'plant food', 'bath salts', 'research chemicals', 'incense' or 'herbal highs' and are typically labelled as 'not for human consumption' in an apparent attempt to evade legal sanction.

One of the attractions of NPS to users is the inability of standard drug tests to identify them. There are currently no accurate field testing devices for most of the NPS, despite continued developments in the area of chemical standards, analytical capability and forensic detection of compounds.

The 'market' for club drugs and NPS appears to have gradually become more sophisticated. For example, a Spanish study of 2C-B has reported that whereas in 2006/07 the majority of 2C-B samples collected appeared to be in poorly elaborated forms such as powder or capsules, in 2008 and 2009 the most frequent form of presentation was tablets.²⁸

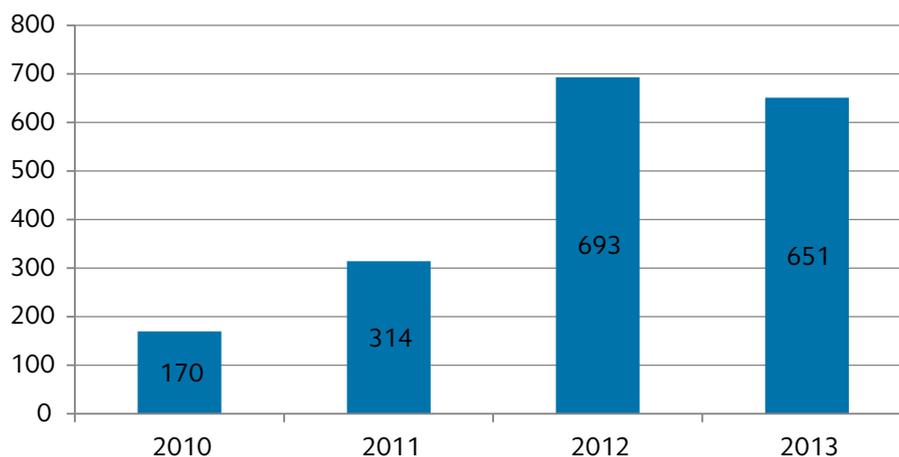


Figure 1.2. Number of internet NPS shopping sites in Europe per year identified by the EMCDDA's targeted internet study (snapshot)⁸

As compounds are controlled and substances banned, their new illegal status does not always deter use. Some drugs, like mephedrone, quickly made the cross-over in the UK from being a so-called 'legal high' to becoming a relatively commonly used Class B substance.³⁰ Most sales were then transferred to street dealers, with users reporting paying a higher price than they did before the substance was controlled, for what was perceived to be a lower-quality product.^{31,32}

The rise in the use of club drugs and NPS coincided with the ability to purchase drugs online. Although mostly bought through street-level dealers, illicit substances are also sometimes bought on the internet (some with next-day delivery to consumers⁸), specifically from websites operating from outside the UK, or on the 'dark web' – that part of the internet which is not indexed by standard search engines and is accessible only through anonymising browsers such as Tor. A number of websites sell a wide variety of so-called 'legal high' products, as well as controlled substances, using this method.⁶ Information about new psychoactive products is often now provided via 'alerts' in the form of text messages, instant messaging or emails ('email this product to a friend').^{33,34}

There has been a steep rise in the number of online 'shops' selling both 'legal' and illegal products to European customers. The targeted internet (snapshot) study carried out by the European Monitoring Centre for Drugs and Drug Abuse (EMCDDA) looked at the rise in the number of internet NPS 'shops' over the period 2010–13.³⁵ The results are shown in Figure 1.2.³⁶

The internet is also facilitating communication for people who use NPS and providing access to knowledge, expertise and logistics about these drugs. There are a number of sites and moderated discussion fora and blogs that are used to share information about newer compounds, feedback on the effects of drugs and harm reduction advice developed through experience.³⁶ User sites, such as Drugs Forum, Bluelight and Erowid, among others, have also provided researchers with some understanding of these drugs when scientific evidence was not available.

1.6. Club drug use in the UK

1.6.1. Overall drug use

Based on combined data from the Crime Survey of England and Wales (CSEW; formerly the British Crime Survey), with similar population data from Scotland and Northern Ireland for 2010/11, the UK Focal Point Report estimated that 35.6% of the adult population in the UK, between the ages of 16 and 59 years, had used drugs sometime in their lifetime.³⁷

The most complete time series data available come from England and Wales through the CSEW. In 2013/14, approximately 1 in 11 (8.8%) adults aged 16–59 had taken an illicit drug in the last year. This proportion more than doubles when looking at those aged 16–24 years (18.9%).³⁸ Overall, data from the CSEW show that cannabis continued to be the most commonly used drug in 2013/14, with 6.6% of all adults between the ages of 16 and 59 years using it in the past year, followed by cocaine powder (2.4%) and ecstasy (1.6%).³⁸

In the Scottish Crime and Justice Survey (SCJS) 2012/13,³⁹ 23% of respondents reported lifetime use of drugs, which was a statistically significant decrease from 2008/09, where 25.6% of adults reported drug use. Drug use in the last year also decreased, with 6.2% of adults reporting having used one or more illicit drugs in 2012/13, in comparison with 7.6% of adults in the 2008/09 SCJS.

1.6.2. Club drug and NPS use

As with drugs in general, subsequent CSEW data have consistently shown that adults between the ages of 16 and 24 years are more likely to use club drugs than adults in general. The data for 2013/14, for example, are shown in Table 1.1.³⁸

Table 1.1. *Percentage of adults using drugs in the last year (CSEW, 2013/14)*

Drugs used in past year by age group, 2013/14	Adults aged 16–24 years	All adults aged 16–59 years
Ecstasy	3.9%	1.6%
Mephedrone	1.9%	0.6%
Ketamine	1.8%	0.6%
LSD	0.9%	0.3%
Magic mushrooms	0.8%	0.4%
Methamphetamine	0.1%	0.1%
Salvia	1.8%	0.5%
Nitrous oxide	7.6%	2.3%

The 2012/13 Scottish Crime and Justice Survey also showed variations, with men, and young people, most likely to have used any of five drugs from a group of new drugs (benzylpiperazine, GBL, synthetic cannabinoids, khat or *Salvia divinorum*) as well as mephedrone.³⁹

Some club drugs and NPS can be injected. In England, the 2014 Public Health England (PHE) report on infections among people who inject drugs mentions a recent increase in the injecting of amphetamines and amphetamine-type substances, including mephedrone and methamphetamine. The injecting of these drugs is associated with high risks of infection and lower levels of intervention uptake.⁴⁰

Among people presenting for treatment of their drug misuse in England and who have used mephedrone, methamphetamine, ketamine and GHB/GBL, the proportion of those who reported injecting doubled, to 10%, between 2011/12 and 2012/13.⁴⁰ In Wales, the proportion of those using needle and syringe exchanges and reporting injection of amphetamine and/or other amphetamine-type substances (ATS) as their main drugs increased from 7% in 2011/12 to 10% in 2013/14.⁴¹ In Scotland, there is no evidence of an increase in presentations for treatment of people using amphetamines, ecstasy or mephedrone, and numbers remain small.⁴⁰

1.6.3. Drug-using repertoires and poly-drug use

There are also reports of indiscriminate use of substances by some, with users reporting taking unidentified synthetic white powders with no knowledge of their chemical content, as shown by a survey of participants in the night-time economy.⁴² This was supported by the results of the Global Drug Survey, which found that 15% of all respondents and a fifth of those aged between 18 and 25 years had in the past 12 months used an 'unknown white powder'.*

Thus, the users of club drugs will typically use a wide repertoire of substances. The co-ingestion of more than one substance (simultaneous use), including alcohol, is also relatively common and increases the risk of adverse effects, as is discussed in greater detail in the chapters within Parts II to V of this document.

1.6.4. Club drug users and contexts of use

There is evidence that levels of drug use are higher among particular populations and that club drugs are a popular aspect of socialisation.⁴³ These include the following:

1.6.4.1. Clubbers and night-time economy

There is evidence that people who use the night-time economy, and dance clubs or nightclubs in particular, are more likely to use club drugs than the general population.^{44,45} Data from the CSEW consistently show that the levels of drug use

* The Global Drug Survey is independent research organisation. See <http://globaldrugsurvey.com/about>. The results of a 2012 survey sponsored by the *Guardian* were reported in that newspaper: see <http://www.guardian.co.uk/society/2012/mar/15/guardian-mixmag-drug-survey-drugs> and <http://www.guardian.co.uk/society/datablog/2012/mar/15/global-drug-survey-us-uk>.

increase with frequency of visits to nightclubs and pubs. For example, the 2013/14 CSEW reported that 10.9% of respondents who had been to a nightclub four or more times in the last month were frequent users of drugs, in comparison with 2.3% of users who had not visited a nightclub in the past month. Similarly, 9.2% of adults who had visited a pub nine or more times in the last month had taken any drug in the last year, compared with 2.4% of those who had not visited a pub.³⁸

Other targeted surveys have also shown variations by user of different types of venues in the night-time economy, for example with those attending nightclubs reporting significantly higher levels of drug use than bar/pub attenders.⁴⁴ Drug use is also higher in certain music or stylistic 'scenes', such as among club-goers attending dance events playing 'hard dance' music compared with the same venues when playing other genres of dance music.⁴⁴ There are reports of particularly high levels of lifetime use among 'clubbers' who attend electronic dance music clubs, ranging from 79% to 94%.^{46,47} Clubbing and club drug use, as part of a socially active lifestyle, has been associated with elevated sexual health risks.⁴⁸

1.6.4.2. Lesbian, gay, bisexual and transgender populations

There is UK and international evidence that levels of club drug use among LGBT people, and men who have sex with men (MSM) in particular, is higher than in the general population. The European Men-Who-Have-Sex-With-Men Internet Survey, carried out in 38 countries in 2013,⁴⁹ showed, for example, that UK has higher levels of the use of some drugs than do other parts of Europe.

Robust UK prevalence data on drug use among LGBT populations, and comparisons with the heterosexual population, are limited. The 2013/14 CSEW and its predecessor, the British Crime Survey (BCS), have provided data over a number of years, but these must be treated with caution because of the small numbers in the survey. In 2011/12 and 2013/14, respondents who identified themselves as lesbian, gay and bisexual (LGB) were approximately three times more likely to have reported taking any illicit substances in the last year in comparison with heterosexual respondents (28.4% versus 8.1%), with differences remaining when age-standardised data were analysed. LGB respondents were also much more more likely to report the use of stimulant drugs* (14.4% versus 2.9%). A higher level of use was reported by LGB respondents for most individual substances, including powder cocaine, ecstasy, hallucinogenic drugs, amphetamine, cannabis, tranquillisers, ketamine and amyl nitrite.³⁸

There are increasing concerns over associations between club drug use and high-risk sexual behaviours among a minority of MSM. This includes concern over 'chemsex', a term used to describe sex between men that occurs under the influence of drugs immediately preceding and/or during the sexual session,⁵⁰ with methamphetamine, GHB/GBL and mephedrone the drugs most often used. A combination of factors, including high-risk sexual practices and injection, have been described as 'a perfect storm for transmission of both HIV and HCV, as well as a catalogue of ensuing mental health problems'.⁵¹

* The stimulant drugs surveyed were powder cocaine, crack cocaine, ecstasy, amphetamines and amyl nitrite.

1.6.4.3. 'Psychonauts'

'Psychonauts' is a term given to a group of people who explore their own psyche, especially by taking psychedelic or hallucinogenic substances. The emphasis of use is on seeking novelty and extremes of experience. Psychonauts may experiment with newly emerging psychoactive substances, including obscure hallucinogens, and may experiment with drug combinations or push boundaries in terms of dose, for example. The internet plays an important role and provides a platform for sharing experience and information.⁵²

1.7. Overview of the effects and harms of club drugs

1.7.1. How drugs work

Drugs can be classified in various ways – according to chemical structure, pharmacological activity or psychological effects.^{53,54} One approach is to consider a drug's primary effects along the dimensions of sedation–stimulation, although account needs to be taken of the fact that in some people sedatives can be disinhibiting in the early rising phase of drug entry into the brain, or at low doses, and so can mimic the effects of stimulants. For example, although GHB/GBL is a sedative, it has, at low doses, a stimulant effect.

A separate axis is in terms of alterations of perceptions and feelings. For example, MDMA, as well as being a moderate stimulant, is also an empathogen (empathy-enhancing), whereas magic mushrooms and LSD alter consciousness to cause novel phenomena such as hallucinations and a disordered sense of time and being (hallucinogens or psychedelics). Ketamine and related drugs are dissociative anaesthetics, producing a state of altered consciousness. Opioids dampen pain but also promote sleep and visions during it, and produce a profound sense of pleasure. Stimulants tend to activate a person.

The proximal mechanisms of most of these effects (as far as they are known) are shown in Table 1.2. Most NPS are designed to provide legal alternatives to controlled substances, and have harms similar to those associated with the controlled drugs they have been manufactured to mimic.

1.7.2. Toxicity and other harms

Club drugs and NPS are associated with a range of harms.⁵⁵ The harm associated with any drug of potential misuse may include: the physical harm to the individual user caused by the drug; the dependence-inducing potential of the drug; and the effects of drug use on families, communities and society.⁵⁶ All three aspects need to be considered when assessing the impact of a drug.

'Toxicity' generally refers to the extent to which a substance causes functional or anatomical damage to a living organism.^{57,58} There are wide variations in the toxicity

Table 1.2. *The proximal mechanisms of drug effects*

Drug	Primary (proximal) target	Brain effects
Alcohol	Agonist at GABA and antagonist at glutamate receptors	Increases GABA Blocks NMDA glutamate receptors
Benzodiazepines	Agonists at benzodiazepine site on GABA-A receptor	Increase GABA
GHB	GHB and GABA-B receptor agonist	Mimics GABA Inhibits dopamine release
Ketamine	NMDA glutamate receptor antagonist	Blocks glutamate
Caffeine	Antagonist at adenosine A2 receptor	Reduces sedation Increases noradrenaline
Khat	Releases ephedrine, a dopamine releaser	Mild increase in noradrenaline and dopamine
Cannabis	Cannabis CB1 receptor agonist	Stimulates endo-cannabinoid signalling, leading to a change in cortical and memory functions
Cocaine	Blocks dopamine reuptake site	Greatly increases dopamine
Amphetamines (dexamphetamine and methyl)	Release dopamine and block reuptake	Greatly increase dopamine and noradrenaline
Nicotine	Agonist at (nicotinic) acetylcholine receptors	Slightly increases dopamine
MDMA	Blocks serotonin and dopamine reuptake	Increases serotonin and dopamine function
Mephedrone	Release dopamine and block reuptake	Increase dopamine, and serotonin
Hallucinogens	Agonists at serotonin 5-HT _{2A} receptors	Change across-cortex signalling
Heroin and other opioids	Agonists at endorphin receptors	Produce euphoria, reduce pain

Agonist = drug that activates or stimulates a receptor; Antagonist = drug that blocks a receptor.

of the various club drugs and NPS, including their single-dose lethal toxicity.⁵⁷ In addition, individuals vary greatly with respect to metabolism and psycho-physical vulnerability.

A number of other factors are also linked to acute toxicity:

- The co-use of more than one substance will increase the chances of acute toxicity, particularly when drugs with similar physiological effects are combined (e.g. sedatives such as GHB and alcohol or stimulants such as cocaine and amphetamine)
- The risk of overdose is increased by repeated administration of the drug.
- The safety ratio of drugs does not reflect the metabolic or functional tolerance that a user may have developed.
- Non-drug variables can alter toxic reactions significantly (e.g. the psychological effects of the environment, diet, stress, expectation etc.).⁵⁸

- The mode of administration, with injecting not only exposing the user to the risk of bacterial infections but also increasing the risk of overdose and dependence.⁵⁵
- Drug purity and adulterants can affect toxicity.

Club drugs and NPS pose a particular challenge to clinicians and may constitute a public health challenge, for the following reasons:³³

- these substances are not approved for human consumption;
- they are possibly associated with a number of unknown adverse effects;
- insufficient information on them is available in peer-reviewed scientific journals;
- they appear in increasingly sophisticated (i.e. non-powder) forms and remain unregulated for long periods of time;
- they are often synthesised in underground laboratories by modifying the molecular structure of controlled drugs, raising concerns over the presence of contaminating agents;
- they are largely available online to everyone, 'just a click away';
- they are increasingly accepted as part of a 'trendy' lifestyle.

Whereas, all users of club drugs face the risk of acute toxicity, the harms caused by club drugs encompass a wide range of different patterns. Club drugs are associated with harmful use, defined by the World Health Organization (WHO) as a pattern of psychoactive substance use that is causing damage to health, which can be physical (e.g. ketamine can lead to bladder damage and ulcerative cystitis) or mental (e.g. psychosis associated with synthetic cannabinoids).⁵⁹ Some club drugs have also been shown to have a liability to produce dependence and some have been associated with a withdrawal syndrome, which can be severe, for example in the case of GHB/GBL.

1.7.3. Mortality related to the use of club drugs

Data on drug-related mortalities have been provided for a number of years by the National Programme for Substance Abuse Death (NPSAD). Deaths involving NPS (including 'legal highs') have increased in recent years,⁶⁰ although the rates remain much lower than deaths from heroin/morphine.

Overall, the limitations of data on drug-related mortality must be used with caution and as indicative, rather than robust.⁶¹ The Office for National Statistics' report *Deaths Related to Drug Poisoning in England and Wales 2012* indicates a sharp increase in the number of deaths involving NPS, from 29 in 2011 to 52 in 2012.⁶² This rose to 60 in 2013. There were 26 deaths in 2013 involving cathinones (including mephedrone). This was a rise of 44% from the 18 deaths in 2012, and was over four times greater than the 6 deaths in 2011.⁶³ Deaths in 2013 where other NPS were implicated include those listed in Table 1.3.

Table 1.3. Number of deaths related to drug poisoning with a mention of a novel psychoactive substance, by specific substance, England and Wales, 2013

Substance	Sole drug mentioned in coroner's report	Any drug mentioned in coroner's report
1-(benzofuran-6-yl)-propan-2-amine	0	2
2-(1H-indol-5-yl)-1-methylethylamine	0	1
4-fluoroephedrine	0	0
4-fluoromethcathinone	1	1
4-methylamphetamine	0	1
4-methylethcathinone	1	3
Alpha-methyltryptamine	4	7
BZP	0	1
Cathinone ^a	0	1
Desoxyipradrol	0	0
Fluoromethcathinone	0	0
Gamma-hydroxybutyrate (GHB)/ gamma-butyrolactone (GBL)	10	18
Khat	0	0
Legal high	0	0
Mephedrone	1	18
Methiopropamine	1	4
Methoxetamine	1	2
Methylenedioxypropylone	1	2
Methylone	1	4
Synthetic cannabinoid	0	0
TFMPP	0	0
1-(benzofuran-5-yl)-propan-2-amine	0	3
1-(benzofuran-5-yl)-N-methylpropan-2-amine	0	1
APB	2	3
2-diphenylmethylpyrrolidine	0	1
4-Methoxymethcathinone	0	1
N-Methyl-3-phenyl-norbornan-2-amine	1	1
Fluoromethamphetamine	0	1
MDDA	0	1

^a Where cathinone was found in the text of the coroner's report and no further derivative breakdown was available. This does not represent the total number of deaths relating to the group 'cathinones'.

Source: Deaths related to drug poisoning with a mention of NPS in the coroner's report, by specific substance, England and Wales, deaths registered in 2013.⁶³

1.8. Response to club drug use

1.8.1. Policy response to club drug and NPS use

The question of how to respond to the challenges posed by the emergence of new drugs has now become a major concern within the EU and at the international level.⁸ In the UK, the need to tackle the problematic use of NPS and club drugs and actions to do so featured prominently in the government's 2010 drug strategy⁶⁴ and the subsequent reviews of that strategy.⁶⁵ The issue of NPS was also addressed by devolved administrations in Scotland, Northern Ireland and in Wales, which supported the expansion of the WEDINOS (Welsh Emergency Doctor Illicit Novel Substances).

In December 2013, the Home Office convened an expert panel to look at NPS⁶⁶ and provide recommendations.⁶⁷ The government in its response endorsed the dissemination of effective practice and specifically highlighted the role of the NEPTUNE project in doing so.⁶⁸ NPS and club drugs continue to be a government priority.

To date, the government has banned more than 500 new drugs, created the Forensic Early Warning System to identify NPS in the UK and supported law enforcement action with the latest intelligence on new substances. It is also taking forward a comprehensive action plan to further enhance the response to prevention, treatment and information sharing regarding NPS, for example providing a toolkit for commissioners which gives a broad overview of the challenges and which provides them with resources and advice to inform a suitable local response. A guidance document has also been issued to informal educators of young people (e.g. youth workers), with basic information on NPS and which provides signposting information for further advice and support.

1.8.2. NPS and drug-related presentations to hospitals and treatment

Accurate data on emergency hospital admissions resulting from club drug use in the UK are difficult to obtain, for a variety of reasons, not least because ICD-10 codes do not include specific codes for NPS and because coding is generally based on clinical condition at presentation. In order to address this current paucity of reliable data, the European Drug Emergencies Network (Euro-Den) established in 2014 as a network of 16 sentinel centres in 10 EU and neighbouring countries. The project was set up to provide data on the clinical, demographic and geographical patterns of acute recreational use and NPS toxicity, and to act as a stimulus to ensure best practice in the management of acute toxicity from recreational drug and NPS in pre-hospital recreational settings.⁶⁹

A useful indicator is provided by activity data of the NPIS, although it needs to be borne in mind that these do not record hospital admissions. The NPIS received 1561 telephone enquiries and 58,469 TOXBASE® accesses related to 61 drugs of misuse monitored by the NPIS during 2013/14. When adjusted for overall increases in all NPIS enquiries, telephone enquiries for these drugs of misuse increased by 24.9% and TOXBASE® accesses by 0.6% compared with 2012/13.⁷⁰

Data are available on patient access to substance misuse recovery services. There is evidence that some individuals regularly using club drugs are developing on-going problems, including dependence. Data on club drug use among populations in treatment in England has been collected by the National Drug Treatment Monitoring System (NDTMS) for England since 2005/06.^{71,72} A 'club drug user' was defined as a person citing any of the following five substances, as either a primary or an adjunctive drug: GHB/GBL, ketamine, ecstasy, methamphetamine or mephedrone. The number of clients presenting for drug treatment in England for a club drug reported by NDTMS increased from 2675 in 2011/12 to 3543 in 2013/14. Increases in numbers presenting to treatment were observed for all five substances: the most significant was an 82% increase in mephedrone presentations, from 900 in 2011/12, to 1641 in 2013/14. Numbers presenting to treatment citing methamphetamine use increased by 107%, from 116 in 2011/12 to 240 in 2013/14, but still made up just 0.3% of all presentations to drug treatment and recovery services.⁷³ The PHE report on drug treatment in England in 2012/13 suggested that recovery rates for the users of club drugs and NPS remained good.⁷²

1.8.3. Principles underlying the assessment and management in target settings of the harms associated with the use of club drugs and NPS

1.8.3.1. Emergency departments

Emergency medicine physicians and other clinicians should seek advice on the diagnosis, treatment and care of patients who have been – or may have been – poisoned with a club drug, primarily from the National Poisons Information Service (NPIS) through its telephone service and TOXBASE® database. This will assist in ensuring optimal and up-to-date information on care for patients in cases of serious poisoning and, where toxicity is low, offering advice to minimise unnecessary hospital attendances and admissions.

The use of psychoactive substances in pregnancy can lead to multiple health and social harms to mother and child. The NPIS provides the UK Teratology Information Service (UKTIS), which is the national source of information and advice about exposures to drugs and chemicals during pregnancy. Information is provided to health professionals via a telephone information service and online through TOXBASE®, which holds the full pregnancy review documents produced by UKTIS on maternal exposures to drugs and chemicals. Other guidelines on the identification and management of substance misuse in pregnancy are available, including recent guidelines from the WHO.⁷⁴

1.8.3.2. Sexual health services

The association between substance misuse and high-risk sexual behaviours is well established and there is evidence of a high prevalence of drug use among patients attending sexual health clinics. For example, one study of patients at a London sexual health clinic reported significantly higher rates of past month drug use, than in the general adult population in England and Wales. This was particularly so among

MSM.⁷⁵ Sexual health services may therefore provide opportunistic encounters to identify patterns of recreational drug use, explore motivations for use and implement strategies to reduce harms related to drug use.⁷⁵

MSM and people who have alcohol and drug problems have also been identified as higher-risk groups for poor sexual health outcomes.^{76,77} As a result, targeted work has been suggested. For example, the Royal College of Physicians and the British Association for Sexual Health and HIV recommend that sexual health settings distribute information on alcohol-related harms and facilitate brief alcohol interventions to reduce consumption and related sexual ill-health.^{78,79}

NICE public health guidance (PH24)⁸⁰ identifies sexual health services as a specific setting where alcohol use should be assessed and interventions provided and/or referral made. Given the clear proven association (if not causation) between substance misuse and high risk sexual behaviour and consequent sexual ill health, along with some of the emerging harms associated with specific substances (e.g. ketamine bladder) there has been increasing recognition within the specialty for a need to identify those potentially at risk, and to provide either simple interventions or clear pathways into specialised services. Recent data⁸¹ suggest there is a low level of screening for either alcohol and or substance misuse within sexual health services. However, screening for some risk behaviour is common (e.g. injecting drug use), as it forms part of the risk assessment for the acquisition of blood-borne viruses (BBV).

The British Association for Sexual Health and HIV (BASHH) provides recommendations on screening for alcohol and recreational drug use in several of its specialty guidance documents. The '2013 UK national guideline for consultations requiring sexual history taking'⁸² recommends that all patients are asked about their alcohol intake and suggests that a recreational drug history is considered for specific at-risk groups, such as MSM and young people. The '2012 UK National Guidelines on safer sex advice'⁸³ highlighted the need to identify those who may be at risk of sexual ill health and thus may be good candidates for advice on safer sex and other brief interventions, including those individuals with a history of alcohol or substance misuse.

The BASHH statement on 'club' (recreational) drug use⁸⁴ identifies MSM, young people, students and 'clubbers' as possible target groups for screening, so as to identify potentially problematic use, and provides some proposed screening questions. It recommends that clinicians give simple safety advice and information on possible harm, including other sources of information, and that services have agreed referral pathways into appropriate local services.

The British HIV Association (BHIVA), in its *Standards of Care for People Living with HIV in 2013*,⁷⁹ recommends screening for drug and alcohol misuse within three months of diagnosis, and annually thereafter, and that services have appropriate referral pathways in place.

Currently, there is no systematic capture and reporting of alcohol and substance use by individuals accessing sexual health services in the UK. However, there are proposed changes to the national GUM clinical activity dataset (GUMCAD) which will include both alcohol and drug use data fields. If approved, this should, for the first time, permit some estimate of the scale of the problem within this patient group.

1.8.3.3. Substance misuse treatment services

Guidelines for substance misuse treatment in the UK in general is defined by the *Drug Misuse and Dependence: UK Guidelines on Clinical Management*⁸⁵ (a 2007 document that was due to be updated in 2015). These provide the standards and quality of care for the appropriate treatment of drug misusers, if the performance of any clinical area is to be assessed.

Guidelines for standards of care are also defined by range of relevant NICE clinical guidance and technology appraisals, although none currently focuses on club drugs and NPS. In order to deliver high-quality treatment, including for the users of club drugs and NPS, drug treatment services should be able to demonstrate their adherence to the NICE quality standards for drug use disorders (NICE Quality Standard 23)⁸⁶ and alcohol (NICE Quality Standard 11).⁸⁷ Such guidance should contribute to improving the effectiveness, safety and positive experience of care for people with substance misuse disorders. There should also be adherence to NICE psychological interventions guidelines on the management of drug misuse.⁸⁸ NICE Clinical Guidance 52, on opiate detoxification,⁸⁹ states that 'all interventions for people who misuse drugs should be delivered by staff who are competent in delivering the intervention and who receive appropriate supervision'.

To increase the prospects of recovery from drug misuse, PHE recommends that treatment needs to be dynamic, phased and layered.⁹⁰ Its publication *Medications in Recovery* suggests an approach to phasing and layering treatment which includes the following steps:⁹⁰

- engagement and stabilisation;
- preparation for change;
- active change;
- completion.

1.8.4. Overview of the interventions for the screening, identification and management of drug harms in the target settings

The different target organisations (treatment settings) of the NEPTUNE guidance have different roles in the detection, identification and management of chronic harms and/or dependence resulting from the use of club drugs. This is determined by the competence of clinicians to deliver substance misuse treatment and particular pharmacological or psychosocial and recovery interventions.

Table 1.4 provides a summary of the role of each of the target settings and the aims of the interventions provided in terms of the screening, identification, assessment and management of the harms linked to the use of club drugs. Further information on the level of intervention needed is also presented in Chapter 2.

Table 1.4. The role of particular settings and the aims of interventions provided

	Detection	Assessment	Brief intervention	Complex intervention (acute)	Complex intervention (chronic)
Primary care	✓	✓	✓	✗	✗
Emergency department	✓	✓	✓	✓	✗
Sexual health	✓	✓	✓	✗	✗
Substance misuse treatment	✓	✓	✓	✗✓	✓

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Chapter 2

Psychosocial interventions for club drugs and novel psychoactive substances

There is a large body of evidence on the effectiveness of psychosocial interventions (PSIs) for the management of substance misuse problems, as well as national guidelines. It is therefore possible to make specific and robust recommendations.

Effective treatment for all substance misuse problems includes PSIs. These in fact are the primary form of treatment intervention for the misuse of, and dependence on, the majority of substances, as few types of substance misuse have recognised pharmacological interventions.¹ Where pharmacological interventions do have a role, for instance in opioid dependence, PSIs are generally believed to enhance treatment outcomes.² PSIs are important in helping people prepare for planned, medically assisted detoxification and are essential following detoxification, to sustain changes.

Psychological interventions for substance misuse problems focus on supporting behaviour change to achieve desired outcomes. PSIs may aim to support people to achieve abstinence from use of specific or multiple substances, or a reduction in use to a less harmful level or using substances in a less harmful manner. Psychological interventions are also used to help with co-occurring psychological, social or physical problems, again with the aim of contributing to sustained change in substance misuse.

The evidence for the effectiveness of PSIs for a range of substance use problems is very positive. However, in what Orford terms the 'outcome equivalence paradox', no single approach is regarded as universally superior.³ In the UK, several specific psychosocial approaches reach the standard of evidence to be recommended by the National Institute for Health and Care Excellence (NICE; formerly the National Institute for Health and Clinical Excellence) and meta-analyses such as Cochrane reviews (see Table 2.1). Very limited research has so far been published relating specifically to PSIs for the treatment of NPS. Where this exists, it has been summarised in the relevant chapters in this publication. Given the growing use of NPS and the concerns about direct and associated harms, the expert group sees this as an area to be prioritised for high-quality research.

In the UK, the evidence for the effectiveness of PSIs for drug misuse is described in the NICE guideline *Drug Misuse: Psychosocial Interventions*⁴ and further elaborated in the document *Drug Misuse and Dependence: UK Guidelines on Clinical Management*.⁵ However, these publications largely relate to opioid and (crack) cocaine treatment.

This chapter makes important recommendations on initial and lower-intensity responses for individuals who identify use of club drugs and NPS but focuses mostly on the psychosocial treatment options for their problematic use (including

Table 2.1. Summary of evidence for the effectiveness of PSIs for substance misuse

Document	Content and conclusions
NICE recommendations (CG51, 2007) on drug misuse ^{4,8}	Brief interventions (motivational interviewing) Information on self-help groups Behavioural couples therapy Contingency management Evidence-based PSI for co-occurring psychological problems
Government clinical guidelines (2007) on drug misuse ⁵	<i>NICE 51 plus:</i> CBT-based relapse prevention Community reinforcement approaches Social behaviour network therapy Family therapy Psychodynamic therapy
NICE recommendations (CG 115, 2011 and 2013) on alcohol misuse ⁷	Motivational interviewing Information on self-help groups CBT-based relapse prevention Behavioural therapies Social network and environmental therapies Behavioural couples therapy Evidence-based psychosocial interventions for co-occurring psychological problems
<i>Cochrane reviews:</i> Smedslund et al. (2011) ⁹ Knapp et al. (2007) ¹⁰ on cocaine and psycho-stimulants	Motivational interviewing Contingency management CBT Community reinforcement approach
National Treatment Agency (2005) ¹¹	CBT – coping skills Motivational interviewing Relapse prevention Community reinforcement Contingency management Supportive expressive psychotherapy Family therapy Social behaviour network therapy
NICE (PH 49, 2014) ⁶	Proven behaviour change techniques: goal setting and planning feedback and monitoring social support

dependence). Many NPS are stimulant in nature and this chapter therefore draws heavily on research for the treatment for stimulant misuse. However, it also draws on the broader literature on PSIs for health behaviour change in general, for which the evidence base is described in NICE's public health guidance *Behaviour Change: Individual Approaches*.⁶ Reference is also made to commonly accepted good practice for effective psychological interventions in general.

Patterns of NPS use show a close parallel to recognised patterns of alcohol use: the most common pattern is infrequent, non-dependent use, with lower risk of severity and likelihood of harm; through to a much smaller proportion of entrenched dependent use with the potential for more significant associated harm. The chapter therefore also draws on the much more extensive literature on PSIs for alcohol problems. These are described in NICE guidance (number 115, originally published in 2011 and updated in 2013) on the diagnosis, assessment and management of harmful drinking and alcohol dependence.⁷

2.1. Stepped care

Psychosocial interventions for substance use are commonly provided following a stepped care model (Figure 2.1).^{12,13}

Within stepped care models, psychosocial and psychological interventions are grouped according to the level of specific psychological treatment competences required to deliver them effectively. It is therefore common to refer to 'lower-intensity PSIs' and 'higher-intensity PSIs'.

The main principles of a stepped care approach are as follows:

- The least intrusive intervention needed to achieve a required outcome is delivered first.
- If an intervention does not achieve the desired outcome, service users should be offered the option of being 'stepped up' to a more intensive intervention.
- Where a higher level of intensity of treatment is no longer required, 'stepping down' to a less intensive option should be offered.
- Service users should have access to all levels of treatment within a treatment system.
- Service users should have direct access to the intensity of intervention likely to be required to achieve their desired outcomes, and not unnecessarily proceed through lower levels in a stepwise order.

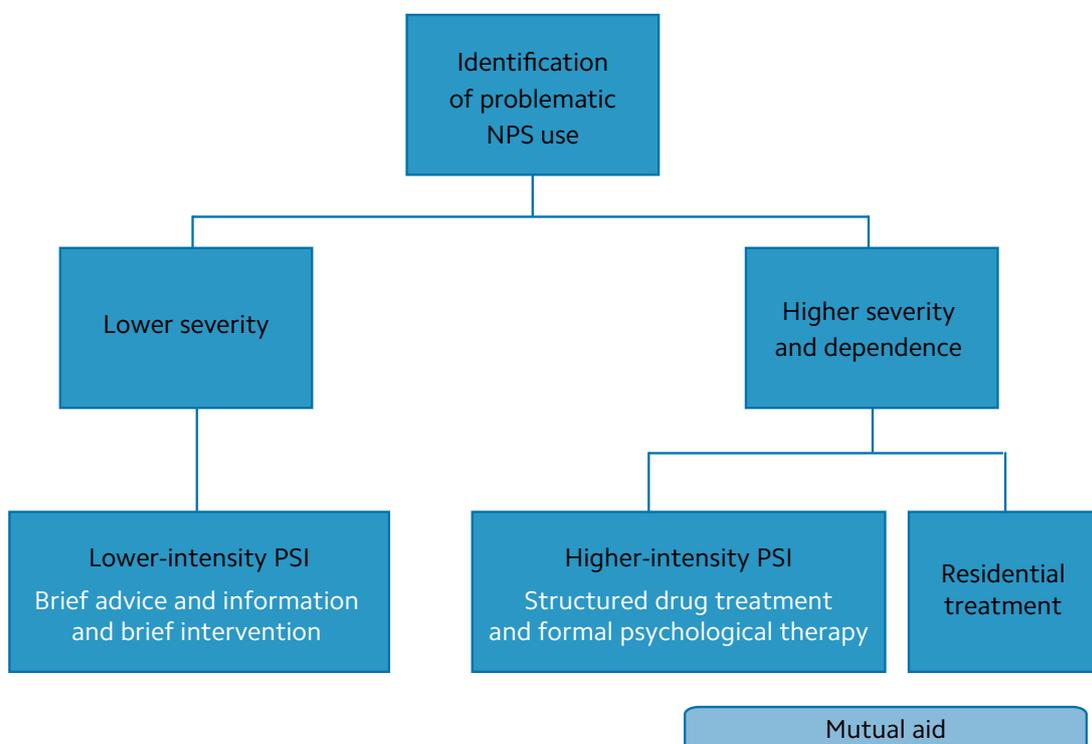


Figure 2.1. Stepped care PSI for problematic NPS use

2.2. Identification of NPS use and its severity

The clinical identification of individuals experiencing NPS harmful use, misuse or dependence, particularly those less severely affected, is not always easy when regular use may be linked to a clubbing-related lifestyle. Determining the need for specific psychosocial interventions to address behaviour change will also be influenced by a wide range of factors. Many people make substantial changes to their substance misuse without formal treatment.³

Substance use or intoxication is not in itself an indication for treatment. Unlike the several robust screening tools for alcohol use, there are no recognised screening tools for NPS use and routine screening for NPS use in general health care settings has not been recommended. However, any contact with a health professional where NPS use is identified can be an opportunity to offer non-judgemental health advice on safety and, potentially, change.

Self-report, incidental or opportunistic enquiry may reveal NPS use and risk but no evidence of harm or need for a treatment intervention. This provides a potentially useful opportunity to offer information and brief advice or to signpost to sources of other information. Other individuals will provide clearer evidence of at least some degree of problematic use. Many such problematic users may well be able to change their risky behaviour without assistance and not require professional help. Some of these problematic users will benefit from the offer of information and brief advice (and/or signposting). Brief advice and information should also be considered (in addition to the offer of referral to formal treatment services) where higher-severity NPS use and dependence are identified. This would amount to an opportunistic intervention for anyone who does wish to, or does not go on to, access treatment at that time. When information and brief advice is used in this way to help address problem use, it forms part of the stepped care 'treatment' pathway shown in Figure 2.1.

Contemporary thinking emphasises approaches based on strengths and needs, for example a 'recovery capital' model, rather than a deficits-based approach (see Marsden et al.¹⁴). A recovery capital model looks at the strengths and needs a service user has over a range of domains beyond substance use. More resources across the domains would suggest greater likelihood of positive outcomes, and fewer resources suggest an indication for broader and more intensive interventions. Four types of recovery capital are identified:¹⁵

- human capital – e.g. skills, employment, mental and physical health;
- physical capital – e.g. tangible resources, housing, money;
- cultural capital – e.g. values, beliefs;
- social capital – e.g. relationships with others.

Those who have more strengths and resources (recovery capital) may be more likely to achieve their desired outcomes with little or no professional input.¹⁶ Indicators for more intensive interventions include: longer problem duration, injecting drug use, substance dependence, unsuccessful independent attempts to change, multiple

substance misuse problems, multiple co-occurring problems, fewer individual strengths and less access to resources. An additional consideration is that people may have substantial substance misuse problems but at the present time are only ready or able to access and engage with less intensive interventions (e.g. needle exchange interventions for injecting drug use).

The intensity of the PSI should be more directly related to the severity of the substance misuse problem than to the severity of the health and other consequences of the substance use. For example, someone experiencing an extreme medical consequence of one-off use of a substance may be able to make desired changes without formal treatment.

It seems likely that most NPS use is infrequent, largely remains within the control of the individual and is associated with a low risk of harm.¹⁷ Nonetheless, some NPS are injected and the majority of NPS have reported incidents of serious associated acute and chronic harms. The repeated use of some NPS can lead to dependence and for some, such as GHB/ GBL, acute withdrawal can be a medical emergency.

Box 2.1 lists the recommended as pragmatic indicators for a referral to drug treatment services, which will include PSIs.

Box 2.1. Indicators for a referral to drug treatment services and PSIs

- Current injecting of any substance;
- Self-report of inability to make changes to NPS use when attempted;
- Repeated presentation(s) with drug-related harm (psychological, social or physical);
- Self-identification of needing specialist help or request for referral to drug treatment services.

2.3. Settings for the delivery of PSIs

The intensity of the PSI delivered will vary across the settings in which they are offered. Some PSIs require additional or specialist competences to deliver them, whereas mutual aid, for instance, is a peer-led intervention and so is not dependent on particular settings for its delivery (and therefore is not discussed further in this sub-section).

2.3.1. Settings for lower-intensity PSIs

In non-drug treatment settings, where NPS use, or problematic use, has been identified during a clinical interaction with a service user, the offer of brief advice and information may be helpful. Such non-drug treatment settings include general practice, emergency departments, primary and secondary care mental health services, sexual health clinics and HIV services, in addition to other services where people may present with acute problems related to NPS use.

There is evidence that NPS use has a higher prevalence in people attending sexual health services¹⁸ and HIV treatment services.¹⁹ These services (and others with service users with known higher prevalence rates of NPS use) have an appropriate opportunity actively to ask about NPS use as part of their normal clinical assessment process. These non-drug treatment services that work with service user groups with a higher prevalence of NPS use, as an additional level of opportunistic intervention beyond offering brief advice and information, should also develop the relevant skills and competences and should offer brief interventions (BIs), referring individuals on for additional support, if needed.

Numerous studies report people living with HIV have a higher prevalence of NPS use (as will be discussed below) and there are concerns about the additional health and viral transmission risks NPS use may pose. People living with diagnosed HIV typically have frequent medical review appointments at HIV treatment services. These service contacts provide a valuable opportunity for similar appropriate questions on NPS use, asked routinely or targeted as appropriate; and the offer of brief advice and information and, if suitable, brief interventions.

Because of high levels of presentations related to substance use, some EDs have staff with skills to provide a brief intervention. Similarly, because there are high levels of substance misuse among people accessing mental health services,²⁰ these services often have staff with additional competences ('dual-diagnosis workers') to provide higher-intensity drug interventions in combination with mental health interventions.

2.3.2. Settings for higher-intensity PSIs

Higher-intensity PSIs, structured drug treatment and formal psychological therapy are likely to be delivered in community or residential drug treatment services.

There may be benefits in locating the delivery of higher-intensity PSIs in specific non-drug services where presentation with problematic NPS use is frequent and associated with other health or social problems. This may encourage engagement in drug treatment, by minimising any perceived stigma involved in attending drug treatment services. There may also be merit in developing specialist hybrid services for specific populations with co-occurring needs. For example, innovative services where drug treatment and psychological therapy are provided in settings such as sexual health services with a high level of presentation of co-occurring sexual health problems, problematic NPS use and in some cases psychological problems.

These differing levels of intensity of interventions will be reflected in the increasing specialised competences that the health professionals delivering them will have. All levels of intervention must be delivered within an appropriate governance framework with more intensive PSIs requiring specific supervision.⁸

Recommendation A stepped care model of interventions for NPS use should be available to service users across a treatment system, with referral pathways between the various services where service users are likely to present. It is recommended that the settings listed in Table 2.2 offer a *minimum* level of PSI. Each intervention is described in greater detail below.

Table 2.2. Minimum recommended levels of PSI in settings dealing with NPS use

Setting	Minimum level of PSI
General practice	Availability of brief advice and information
Emergency department	Availability of brief advice and information
Sexual health services	Availability of brief advice and information plus brief intervention
HIV services	Availability of brief advice and information plus brief intervention
Mental health services (including primary and secondary care psychological therapy services)	Availability of brief advice and information plus brief intervention (<i>Some services may have 'dual diagnosis workers' with additional competences to provide structured drug treatment</i>)
Drug treatment services	Availability of brief advice and information, brief intervention, structured drug treatment, formal psychological therapy, facilitated access to mutual aid. Access to assessment for residential drug treatment

All non-drug treatment services should offer referral to drug treatment services, as indicated in Box 2.1.

2.4. Lower-intensity PSIs

Lower-intensity PSIs can be divided into two main interventions: provision of brief advice and information; and provision of brief interventions. The published evidence that underlies this for drug users mainly relates to the provision of brief interventions. However, recommending the provision of brief advice and information is a considered and pragmatic approach that takes account of wider evidence on brief advice and is based on what is considered a minimum approach to addressing the basic health needs of NPS users attending non-drug treatment services. Brief interventions, derived mainly from the principles of motivational interviewing, are NICE recommended. They are also opportunistic interventions used in non-drug treatment settings with people who have little or no contact with drug treatment services. Winstock and Mitcheson recommend brief interventions for the majority of NPS users, whose use would be in the lower severity range. Provision of brief advice and information and brief interventions is also commonly recommended for risky drinking and alcohol use problems.^{7,8,21}

Lower-intensity PSIs (brief advice and information, and brief interventions) may be carried out by health professionals outside of the substance misuse treatment field who have identified problematic substance use in the course of a consultation for another problem or after routine or opportunistic screening. Lower-intensity PSIs may take no longer than a few minutes, perhaps forming part of a wider conversation about a health problem. Typically, lower-intensity PSIs for substance use involve:

- identification of substance use (and any related problems);
- personalised feedback;
- the offer of information on how changes might be made if the service user decides to take up the advice.

The information may include a short information leaflet or reference to reliable internet resources. Lower-intensity PSIs can be effective at reducing the risks and harms associated with substance use.⁴ The user's desired outcome is more likely to be a reduction in drug-related harms than abstinence. Lower-intensity PSIs are more likely to be effective when users perceive they have a problem (or reason to change) and believe that they can make a change.

All health professionals should already have the competences required to deliver brief advice and information. Clinicians could adopt a key element of motivational interviewing, which has a very strong evidence base for its effectiveness as substance use intervention, known as the 'elicit, provide, elicit' strategy (see Figure 2.2).²²

Identification of NPS use (and any related problems) followed by:

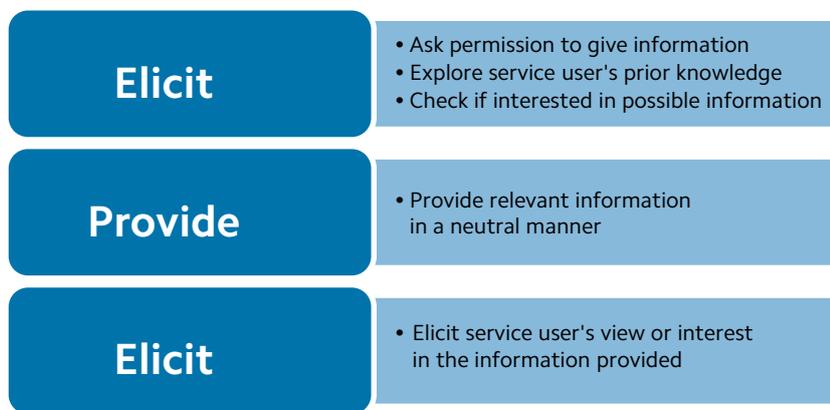


Figure 2.2. A framework for brief advice and information

Brief interventions offer structured advice on behaviour change in the context of a warm, reflective, empathic and collaborative approach by the practitioner. While this, too, is likely to require no more than the competences expected of any healthcare professional, a commonly used structure for BI across the substance misuse field is FRAMES (Box 2.2).²³

Box 2.2. FRAMES: a framework for brief interventions

Identification of NPS use (and any related problems) followed by:

- F** Feedback on personal risk – from screening, medical tests or clinical interview give personalised feedback on the person's current and likely substance-related problems
- R** Responsibility and choice – emphasise the service user's responsibility for and choice in making any changes
- A** Advice to change – give clear advice to change substance use
- M** Menu of options – offer a variety of strategies or options
- E** Empathy – a warm, reflective and understanding style of delivering brief intervention is more effective
- S** Self-efficacy and optimism – build confidence by affirming what the service user has already done or some aspect of strength

Box 2.3. Example of a brief intervention based on the FRAMES model

Health worker (HW): All the tests we've run are fine and I'm happy for you to go now. I've got a few minutes; before you go, would you want to know some more about how to perhaps avoid something like this in the future? **(Asking permission)**

Service user (SU): Yes, okay, if you like.

HW: You mentioned to me earlier you were using G [GBL] pretty much every weekend of late? Did I get that right? **(Brief history)**

SU: Yeah, every weekend for a couple of months now, more often than it used to be.

HW: What would a typical weekend be like? **(Open-ended question/brief history)**

SU: Can vary. Depends who I'm with and what we are doing.

HW: This weekend – tell me, if you will, about this weekend. **(Open-ended question)**

SU: This weekend was a pretty big one: it was my friend's birthday. We were partying then clubbing, then we hooked up with a few other guys and went on to another club.

HW: So you came here to A&E early this morning, Sunday. When did you start?

SU: Early Saturday night, at a friend's place. We had a few drinks then started with a couple of cap-fulls, then just before we all left for the club we had a few more. I guess before we left I'd had about four or five cap-fulls and a few vodkas, not so much by that stage as I knew it was going to be a long night.

HW: You were thinking ahead, pacing yourself. Good for you. **(Affirmation)**

SU: Then at the club we were having a cap-full in water every so often; we were there till about 3am so probably I'd have had another four. We left there and went on to another club with these other three guys we met. There was a lot of it going around between us there; I don't know really how much I had. We started taking their stuff as we'd run out. Then five or six of us went to this guy's flat. I think the idea was ... was, it would be a, you know, party. There was other stuff too like crystal meth, these guys were taking but I wasn't keen – I've had a couple of bad times with that before.

HW: So you've had a bad time with crystal meth before; now you're keeping away from it. That's good to hear. **(Affirmation)**

SU: That's where we had some more G and some more vodka. And then, I don't really know, then I was with the ambulance crew.

HW: So from what you've said it sounds like your use of G has been pretty regular over the last few months and maybe increasing. This weekend was a big one, as you say. It's likely the increasing amount and the combination with alcohol led to you being unconscious. It's good your friends called an ambulance to get you here. **(Feedback)**

You mentioned you are staying away from crystal meth because of some problems you'd had. Would you be interested to hear about the kinds of problems we see with G use like you've described? **(Asking permission)**

SU: Well I thought I was pretty clued up, but maybe I should.

HW: With G one of the big problems, even for experienced users, is that it can only need a very small amount, one or two more mls, before someone is overdosed. Even more of an issue if you're not entirely sure how strong the stuff you're taking is. Overdose is linked to vomiting, seizures, disorientation, memory loss, agitation, mood swings and collapse – at more severe levels being unconscious and coma. The other feature of G is its potential for dependence, when taking it regularly turns into not being able to go without, taking it daily even throughout the day. Once dependent, stopping can be pretty difficult and in some cases stopping suddenly can lead to serious medical emergencies. **(Feedback)**

It's of course up to you what you do with this kind of information, I'm just letting you know how your current pattern of G use might be linked to some health risks or problems that could develop. **(Responsibility)**

SU: I knew a fair bit of that, but some of it, like getting dependent, would concern me. I don't think I'm getting there yet though.

HW: No, you're right, it sounds like you can still keep your use to the weekends. The best way you can avoid something like getting dependent and some of the other problems would be to cut down or stop your use. **(Advice)**

In terms of being safer, stopping using G would be the safest option. If that doesn't feel like something you could do just now, not mixing with alcohol would make problems like the ones that brought you here less likely. If you do use, using less and knowing how much you're using would help. Some guys use something to measure their G, like a pipet. It's good that you use with friends and you take care of each other if needed. **(Menu of options)**

SU: I'm not sure stopping is what I want right now, but I'd already been a bit concerned about using so often.

HW: You could try having some weekends not using? It sounds like that's something you've managed before. Plus you said how you'd made previous changes like with crystal meth. **(Self-efficacy)**

SU: Yes and I've got friends who don't use G and stuff and I've not been spending much time with them lately, which isn't what I want.

HW: Is there anything more you'd like me to help with? I have the details of a website that has the information I just spoke about if you'd like it? I'll leave you this card with the details of a local service just in case you want some more expert help. I've heard good things about them and helping guys with problems with G.

Recommendations from alcohol treatment suggest that simple BI can be enhanced by including goal-setting (e.g. start date and daily or weekly limits of use), written self-help materials for the service user to take away (this may contain more detailed information on consequences of substance use and tips on cutting down) and arrangements for follow-up monitoring.²⁴

The World Health Organization has developed a manual on brief interventions in substance misuse for primary care.²⁵ The manual draws on components of motivational interviewing and the FRAMES model. Although the manual was not developed for, or tested with, NPS specifically, it does cover a range of substances, including amphetamine-type stimulants. The manual provides clear information on how to deliver brief interventions.

An example of a brief intervention based on the FRAMES model is given in Box 2.3.

Recommendation It is recommended that health professionals who, in the course of contact with service users, identify 'lower severity' NPS use, offer brief advice and information or a brief intervention, following a recognised format, focusing on making changes to substance use with the aim of improving health outcomes.

2.5. Higher-intensity PSIs

2.5.1. Structured drug treatment

Structured drug treatment comprises two or more treatment sessions, each lasting half an hour or longer, applying a single or range of psychosocial approaches, commonly including motivational interviewing. Structured drug treatment may range from an extended form of brief intervention, sometimes known as extended brief intervention,²¹ to a more ongoing regular set of treatment sessions. Structured drug treatment of any duration includes the setting and evaluation of specific goal(s) relating to a change in substance use.

Structured drug treatment should follow from a more comprehensive assessment of needs and resources that has led to intervention based on a care plan.²⁴ More advanced competences, of accreditation standard, in these approaches will be required for effective delivery, along with supervision and an appropriate governance framework.⁸ Structured drug treatment may be delivered as individual psychological therapy or as group-based interventions.

There is evidence that the outcomes of drug treatment (all drug treatment, not only PSIs) can be enhanced with the use of mapping tools.²⁶ Mapping tools are not in themselves a psychosocial intervention but a vehicle that can enhance the effective delivery of treatment. Mapping tools employ a structure known as 'node link mapping' to visually convey key elements for a structured conversation derived from evidence-based PSIs. For more detailed information and examples of mapping tools for drug treatment see *Routes to Recovery via the Community*.²⁷

The most relevant research findings relate to PSIs for various forms of stimulant use. Knapp et al., in a Cochrane review, report that interventions based on cognitive

behavioural, contingency management and community reinforcement approaches appear to be the most effective.¹⁰ Knapp et al. argue that a comprehensive treatment package drawing on these three models may be required for better outcomes, given the multidimensional nature of stimulant dependence. They further argue that for sustained outcomes, treatment needs to support service users to make effective changes to their lives, including abstinence from stimulant use, the ability to work and the ability to maintain successful relationships. A focus on narrow, short-term goals such as reductions in amount or frequency of use is of little benefit in achieving sustained change.¹⁰

Recommendation It is recommended that structured drug treatment is offered to service users with 'higher severity' problems relating to NPS use. Structured drug treatment will be based on an assessment of needs and strengths and on a care plan which is reviewed regularly. The intervention will draw on evidence-based psychosocial approaches and is likely to include motivational interviewing.⁹ As a minimum, structured drug treatment should include: goal setting and planning, feedback and monitoring, and developing social support.⁶ The largest amount of reported evidence for structured drug treatment is for cognitive-behavioural therapy (CBT), contingency management (CM) and the community reinforcement approach (CRA).¹⁰ Specific competences to deliver such interventions, supervision and an appropriate governance framework are required.

2.5.2. Formal psychological treatment

Formal psychological treatment is likely to be effective for people with higher-severity and dependent NPS use. Formal psychological treatment is particularly relevant where a service user has a co-occurring common mental health problem⁴ or other psychological problems. Formal psychological treatment usually consists of a planned, time-limited series of sessions. The intervention will be grounded in a psychological formulation, derived from a process of assessment and evaluated using formal or informal outcome measures. The competences required to deliver this intensity of intervention will be more advanced – of professional registration standard – and a governance and supervision structure will be needed.²⁸ Formal psychological treatment may be delivered as individual therapy or as a group-based intervention. It is likely to draw on one or more of the evidence-based psychological therapy models listed below and may be combined with other evidence-based interventions for psychological problems.

The aims of formal psychological treatment are likely to be a combination of changes: to the substance use, to the psychological problems, but also in related domains (e.g. health, social functioning, criminal justice).

There are high levels of co-occurring mental health problems in drug treatment populations²⁰ and it can be assumed this would be similar for dependent users of NPS.

Some NPS users may have other co-occurring psychological difficulties; for example, there are reports of problematic NPS use associated with psycho-sexual problems.

Treatment services need to be able to screen, assess and provide treatment for these co-occurring difficulties.

Whilst NICE⁴ recommends CBT to treat co-occurring mental health problems, the complexity of the presenting psychological difficulties may limit the impact of these approaches. Other approaches may be required for psycho-sexual problems.

For patients with complex needs, formal psychological treatment may be complemented by a formulation-based approach.²⁸

A psychological formulation is a hypothesis about a person's difficulties and integrates a broad range of biopsychosocial causal factors which link theory with practice to guide the intervention. It is individually determined and may draw upon a range of psychological models to achieve an effective treatment plan.

A psychological formulation can integrate both the substance use behaviour and the co-occurring mental distress in a way that seeks to reveal the function of the substance use for the service user. It can also include consideration of other psychological and behavioural factors, such as sexual behaviour.

A formulation-based approach can incorporate personal meaning and be constructed collaboratively with service users and their care teams.

Some key features of a formulation are that it:

- summarises the service user's core problems;
- suggests how the service user's difficulties may relate to one another, by drawing on psychological theories and principles;
- aims to explain, on the basis of psychological theory, the development and maintenance of the service user's difficulties, at this time and in these situations;
- indicates a plan of intervention which is based in the psychological processes and principles identified;
- is open to revision and reformulation.

A distinguishing characteristic of psychological formulation is its multiple-model perspective – it integrates theory and evidence from a range of psychological models as well as biological, social/societal and cultural domains.

The incorporation of this multiple-model perspective may have particular value in working with service users from marginalised and stigmatised populations, as it explicitly incorporates culture-specific issues.

For example, a recent report²⁹ describes the association of NPS use and sexual behaviours, often referred to as 'chemsex'. As detailed in Part III of this publication, contemporary research has highlighted the frequent use of NPS by men who have sex with men (MSM) in the context of sex. A proportion of this behaviour has also been linked to drug-related and sex-related harms. Sex under the influence or intoxication of substances with the potential for associated harm is by no means a new phenomenon, however.

Bourne et al.²⁹ suggest some NPS offer a specific range of psychological and physical sex-enhancing effects. Where sex and NPS use have, over time, become powerfully associated for an individual who has developed problems, a combined approach to treatment is likely to be required. With a theoretically grounded psychological formulation identifying motivations, meanings and values associated with sexualised drug use, individualised for that service user, a psychological formulation is a basis for a proposed psychological intervention, drawing on evidence-based models of psychological therapy. A small number of studies in the US have looked at the impact of psychological interventions on condom-less sex among methamphetamine-using MSM. Combined cognitive behavioural and CM interventions have shown a positive impact on changing drug use and sexual behaviours among this population.^{30,31} Working with the same population, however, Rajasingham et al.³² suggest that CM fails to address service users' mental health needs or to develop post-intervention relapse prevention plans. A review of three randomised controlled trials (RCTs) examining the outcomes of CBT interventions and HIV risk behaviours among substance-misusing MSM found that while CBT did reduce unprotected anal intercourse in this group, it was unclear whether CBT was more effective than less intensive interventions or mere assessment.³³

Recommendation It is recommended that formal psychological therapy is offered to people with higher-severity and dependent NPS use, and in particular those with co-occurring psychological problems. Formal psychological therapy is derived from a comprehensive assessment, based on a psychological formulation and informed by one or more evidence-based psychological therapy models.

Recommendation It is recommended that higher-intensity PSIs (structured drug treatment and/or formal psychological therapy) are offered to service users where medically assisted detoxification is part of the recommended treatment. Unless detoxification is undertaken as an emergency, higher-intensity PSIs, including motivational interviewing, should be offered before detoxification. Following detoxification, it is essential that higher-intensity PSIs, typically including a relapse prevention model, is offered. Service users completing detoxification may also benefit from formal psychological therapy for any co-occurring psychological problems such as common mental health problems or psycho-sexual problems.

2.6. Residential psychosocial treatment

Residential treatment is defined by the controlled environment where treatment takes place. It generally involves one or more evidence-based high-intensity psychological interventions and requires the same level of competence and governance as the higher-intensity PSIs described in section 2.5. Residential treatment may be preceded by medically assisted detoxification for safe withdrawal from specific substances (see section 1.8).

Service users live within the treatment service (or very nearby) for the duration of the treatment. Residential treatment is considered a more intense form of treatment, often requiring several hours per day of treatment engagement over a minimum

period of typically 12 weeks. The location of the treatment service is generally a distance away from the service user's usual home. Residential treatment is recognised as an important option; however, there is debate around the precise indications for its use and the evidence base is currently far from clear. Almost without exception, the explicit aim of residential treatment is long-term or lifetime abstinence from all substances. Residential treatment is therefore not appropriate for people who are not prepared for this treatment aim.

Broadly, the indications for residential treatment are:

- multiple co-existing psychological, physical and/or social problems;
- poly-drug dependence;
- optimised community treatment has not been effective
- the service user has a treatment goal of long-term abstinence.⁴

Recommendation It is recommended that service users with significant physical, psychological and/or social problems associated with NPS dependence (or use of high severity), who are aiming for long-term abstinence and who have been unable to achieve this in effective community treatment (or who would be highly unlikely to be able to do so), have access to residential treatment, including, where necessary, prior medically assisted detoxification. On successful completion of residential treatment, relapse prevention support should be offered to help service users maintain changes. Service users who leave residential treatment before its completion should be promptly offered support to minimise any return to substance use and minimise the risk of overdose.

2.7. Mutual aid

There is a long tradition of mutual aid in the substance misuse field. Perhaps the best-known are Alcoholic Anonymous (AA) and Narcotic Anonymous (NA), sometimes known as 12-step groups. More recently other forms of mutual aid have been developed, including SMART groups where the approach is derived from CBT. There is a strong evidence base for the outcomes from mutual aid (the research has primarily been with 12-step groups).³⁴

Mutual aid is not a professionally delivered treatment. There is, though, evidence of the benefit of health professionals proactively supporting service users' engagement with mutual aid, often referred to as facilitating access to mutual aid (FAMA); therefore NICE recommends that services routinely provide information on the benefits of mutual aid to service users with higher severity and dependent substance use problems.^{4,7} Public Health England has produced a guide to FAMA.³⁵ In some of the major UK cities there are specific 12-step groups primarily attended by people with current or former problems with some NPS or club drugs such as methamphetamine.

Recommendation It is recommended that service users with higher-severity and dependent NPS use are routinely offered information about mutual aid. This includes

service users completing residential treatment. Where service users show an interest in engaging with mutual aid, it is recommended that additional support along the lines of facilitated access is offered. Mutual aid as a treatment option should be revisited periodically where desired outcomes have not been achieved.

2.8. Models for specific psychosocial approaches

Higher-intensity PSIs for the treatment of substance misuse problems, in the form of structured drug treatment, formal psychological therapy and many of the approaches used in residential treatment, are derived from specific psychological therapy models. The main evidence-based models are described only briefly here, but references are given to sources of more detailed information and to treatment manuals.

2.8.1. Motivational Interviewing

Ambivalence about changing substance use behaviour is common, perhaps the norm, even for people actively seeking treatment. Motivational interviewing as an approach offers a framework for helping people resolve ambivalence to changes to their substance use. Motivational interviewing and its more manualised variant motivational enhancement therapy (MET) have a robust evidence base across a wide range of substances.^{4,7} The use of motivational interviewing is likely to be a part of brief interventions and the early part of structured treatment. A framework for the delivery of competence-based motivational interviewing is described in *Routes to Recovery: Psychosocial Interventions for Drug Misuse*.¹³

2.8.2. Network and environmental therapies

Network and environmental therapies are a range of psychological approaches which seek to utilise social contextual reinforcers to promote and sustain change in substance use. This often involves enlisting the support of (non-using) partners, families or peers. Behavioural couples therapy (BCT) is recommended by NICE for the treatment of drug misuse.^{4,7} Notably, there is specific evidence for BCT with lesbian and gay service users in the treatment of alcohol problems.³⁶ Network and environmental therapies are recommended for the treatment of alcohol problems.^{4,7} The widely recognised importance of social support in achieving positive outcomes for drug problems is reflected in the recommendations made by NICE in *Behaviour Change: Individual Approaches*.⁶

Variants of network and environmental therapies with specific recognition in the treatment of substance misuse are social behaviour network therapy (SBNT), the community reinforcement approach (CRA) and behaviour couples therapy (BCT). On SBNT, see Copello et al.³⁷; on CRA see Miller et al.³⁸; on BCT see O'Farrell and Fals-Stewart.³⁹

2.8.3. CBT-based relapse prevention

Relapse prevention (RP) is a commonly used psychological approach in substance misuse treatment¹¹ and is recommended for the treatment of alcohol problems.^{4,7} However, CBT focused only on drug misuse was not recommended in the NICE guidance on drug misuse.⁴ RP aims to help people make and sustain changes to substance misuse through the identification of thinking and behavioural patterns that typically precede an individual's substance use. RP is considered particularly relevant in helping people sustain changes to substance misuse once they have achieved them, including following medically assisted detoxification, a phase of treatment often referred to as aftercare. For a description of CBT-based RP models, see Marlatt and Donovan⁴⁰ and Mitcheson et al.¹²

Inevitably, innovative developments may take time to be included in high-level meta-analyses. It is worth noting the current attention to what are often referred to as 'third-wave CBT models'. These contemporary developments include mindfulness-based interventions (MBIs), acceptance and commitment therapy (ACT) and dialectical behaviour therapy (DBT). In a systematic review of evidence, Chiesa and Serretti report that MBIs can reduce the use of a range of substances, including stimulant drugs.⁴¹ Zgierska and Marcus⁴² note that the combined findings of early studies of MBIs suggest these may be efficacious for substance misuse problems. Of note, Smout et al.⁴³ conducted a preliminary RCT of ACT for methamphetamine use disorders. While it had no advantage over CBT, Smout et al. describe it as a viable intervention for this population. Zgierska and Marcus note the strength of positive evidence for MBIs with common mental health problems and conclude that they are therefore of value for service users with co-occurring substance misuse and mental health problems.⁴²

2.8.4. Contingency management

Contingency management has a strong evidence base from numerous research trials, carried out primarily in the US, focusing on stimulant use. UK programmes are currently uncommon outside RCTs. CM is one of the psychological interventions recommended for the treatment of drug misuse by NICE.⁴ CM is used to reduce substance use by the provision of tangible (often monetary or material) rewards for the achievement of verifiable behavioural goals, such as negative biological drug screen tests. A framework for the delivery of CM is described in *Routes to Recovery: Psychosocial Interventions for Drug Misuse*.¹³

2.8.5. Psychodynamic therapy

There is no specific literature on the evidence for psychodynamic therapies for the treatment of NPS problems. NICE⁴ did not recommend psychodynamic therapy focused on the treatment of drug misuse for people who misuse cannabis or stimulants or those receiving opioid maintenance treatment. National Treatment Agency for Substance Misuse¹¹ reported one study (of limited strength) where court-enforced counselling resulted in reduced cocaine use.⁴⁴

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Part II: Central nervous system depressants

Depressants (also known as sedatives) are drugs that lower neurotransmission levels. They activate GABA or opioid receptors, and inhibit glutamatergic or catecholaminergic activity. As central nervous system (CNS) depressants, their use can decrease the rate of breathing, decrease heart rate and lead to loss of consciousness, and even coma or death. Taking large or frequent doses can lead to dependence.

A few CNS depressants are used within a club drug context. Generally, depressant drugs appear to increase sociability and enhance mood. Some depressant drugs, such as GHB/GBL and alcohol, also release noradrenaline, so some of their effects may appear to be like those of a stimulant.

Not all drugs with essentially sedative effects are easy to classify. For example, although ketamine is predominantly a sedative drug, inasmuch as it blocks glutamate, its subjective effects have been described as hallucinogenic, as it distorts perceptions of time and space. Ketamine and its analogues are the subject of Chapter 4.

Sedative and depressant drugs used in a club drug-context: inclusions and exclusions

Part II focuses on depressant/sedative drugs most commonly used within a club-drug context in the UK, namely GHB and its precursor GBL, ketamine and its derivatives, and nitrous oxide.

A number of other new CNS depressants are available, which can be broadly categorised as opiates and benzodiazepines. While these substances can be bought online through sites that sell club drugs and NPS, they are outside the remit of this document and guidance as they are not used as 'club drugs' and there is extensive experience in the UK in the management of opiate- and benzodiazepine-related acute and chronic harms. The newly developed opioid receptor agonists include AH-7921, which has analgesic potency similar to that of morphine, and 1-phenylethylpiperidylidene-2-(4-chlorophenyl)sulphonamide (W-15), a potent opiate agonist with a distinctive chemical structure that is not closely related to other established families of opioid drugs. So-called 'designer benzodiazepines' newly available online include diclazepam, phenazepam and nimetazepam (referred to as Happy 5s). Like other new drugs, their potency is unknown and it is not clear why they have been developed, given the profusion of benzodiazepines available. There is some anecdotal evidence from clinical practice that new benzodiazepines like diclazepam are used to help the 'come-down' from stimulants in particular.

Chapter 3

Gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL)

Drug group: depressants

This chapter discusses GHB (gamma-hydroxybutyrate) and its precursor GBL (gamma-butyrolactone). Another precursor of GHB, 1,4-BD (1,4-butanediol), has not been widely available in recent times, but is mentioned in the literature. In the UK, GBL is used more than the other two.

3.1. Street names

Street names at the time of publication include G, GHB, GBL, Gina, liquid E, liquid ecstasy, liquid X, Gamma-O, Blue Verve, Gobbe, Charisma. Other street names are used in particular localities.

3.2. Legal status

GHB, GBL and 1,4-BD are controlled in the UK as Class C Schedule 2 drugs under the Misuse of Drugs Act 1971. However, GBL and 1,4-BD are controlled under that Act only when supplied or possessed with the intention for human consumption, but not when available for legitimate use in industry (see section 3.5).

3.3. Quality of the research evidence

The international evidence on the management of the acute and chronic harms related to the use of GHB and GBL is limited; randomised control trials in particular are not available. Evidence mainly consists of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records. Despite these limitations, data/evidence from these sources is relatively consistent.

3.4. Brief summary of pharmacology

GHB acts primarily as a CNS depressant but at low doses can also produce euphoric effects and effects that appear to be like those of stimulants. GHB is both a metabolite and a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA)

and acts as a neuromodulator in the GABA system, acting on both GABA-B and its own so-called GHB receptors. GBL and 1,4-BD are converted into GHB after they are absorbed.¹

A number of studies have looked at GHB pharmacokinetics in healthy volunteers.²⁻⁶ GHB is absorbed rapidly, is extensively metabolised to carbon dioxide and rapidly eliminated,⁷ mainly through the lungs (less than 5% is excreted in the urine as GHB, although this may be greater in overdose). It has a half-life of only 20–30 minutes.⁸ The effects of GHB usually occur 15–20 minutes after ingestion and can last for up to three to four hours,⁹ with peak effects at 30–60 minutes after ingestion.⁸ It is undetectable in urine after approximately 12 hours.¹⁰

GBL is a precursor of GHB and is non-enzymatically converted in the body into GHB. GBL is absorbed more rapidly than GHB and potentially has a faster onset of action. Its duration of action may also be longer.¹⁰ Some users report that GBL is more potent than GHB. 1,4-BD is another precursor to GHB; it is converted in the liver through a two-step conversion, via hepatic alcohol dehydrogenase to gamma-hydroxybutyraldehyde followed by metabolism into GHB via hepatic acetaldehyde dehydrogenase.^{11,12} Animal studies have shown that both ethanol and fomepizole competitively block the metabolism of 1,4-BD to GHB.^{13,14}

GHB (and therefore GBL and 1,4-BD) has a steep dose–response curve and narrow therapeutic threshold. It can readily cross both the placenta and the blood–brain barrier, leading to profound CNS and respiratory depression.^{8,9} Daily use of GHB/GBL can lead to dependence and the possibility of withdrawal syndrome on cessation of use, which can be severe, with agitation and delirium. Acute GHB/GBL toxicity and acute withdrawal can be life threatening.

3.5. Clinical and other uses

Clinical uses of GHB have included alcohol and opiate detoxification regimens, anti-craving medication after alcohol detoxification,⁹ and as an anaesthetic agent in some European countries (although this latter use is now declining). The sodium salt of GHB, sodium oxybate (Xyrem SPC), is approved for the treatment of narcolepsy with problematic cataplexy in specialist sleep centres the US and Europe.*

GHB was sold in US health food stores for weight control and sedation, until the over-the-counter sales were banned in 1990, following reports of acute intoxication.¹⁵ It has also been sold for its antidepressant and anxiolytic effects and for its cholesterol-lowering effects. It has also been used in bodybuilding, as it has been thought to release growth hormone; however, its anabolic effects are unproven.¹⁶ GHB has been implicated as a facilitator in ‘date rape’, although a systematic review of the international evidence suggests that it is rarely identified in cases of drug-facilitated sexual assaults.¹⁷

* See <http://www.medicinescomplete.com/mc/bnf/current/PHP2146-sodium-oxybate.htm>;
<http://www.medicines.org.uk/emc/medicine/17364/SPC/Xyrem+500+mg+ml+oral+solution>;
<http://www.ukmi.nhs.uk/NewMaterial/html/docs/SodiumOxybateNMP0603.pdf>;
as well as the manufacturer’s website, http://www.xyrem.com/images/Xyrem_Med_Guide.pdf.

GBL and 1,4-BD are used extensively by the chemical industry as precursors for the synthesis of plastics and industrial solvents. They are found in floor-cleaning products, nail polish (previously nail polish removers) and superglue removers.

3.6. Prevalence and patterns of use

At a population level, the use of GHB/GBL in the UK is low and appears to be concentrated among some sub-groups, often in specific contexts. Despite low levels of use, its health costs are relatively high compared with other drugs,¹⁸ and other club drugs in particular, because of its intrinsic toxicity and potentially life-threatening withdrawal syndrome as discussed in section 3.12.2.

Questions regarding GHB/GBL use were added to the Crime Survey for England and Wales (CSEW; formerly the British Crime Survey) in October 2009 in response to concerns about its use. Overall, data from the CSEW show that the use of GHB/GBL in England and Wales remains low, although there was a statistically significant increase in its use by adults aged between 16 and 59 years, from 0.0% in 2010/11 to 0.1% in 2011/12. The 2010/11 survey showed that GHB/GBL was more likely to have been used in the past year by the 16–24-year age group (0.1%) than in the age group 25–59 years (0.0%).¹⁹ Questions about the use of GHB/GBL were not included in the 2012/13 or 2013/14 surveys. No data on GHB/GBL use in Scotland are available, but it is believed that the prevalence is low, as suggested by police seizure data for Scotland 2010–11.²⁰

There is evidence that GHB/GBL is often used as part of a wider poly-drug repertoire (see section 3.10.2). An internet survey of 189 GHB/GBL users reported that a third had taken GHB/GBL during the last month and two-thirds reported mixing GHB/GBL with other drugs.²¹ Available data suggest that GHB/GBL users tend to be a well educated and well functioning group.^{22,23}

GHB/GBL use is concentrated among some sub-groups and in particular settings and geographical areas. A number of European surveys conducted in dance music venues and other targeted settings suggest that the lifetime prevalence of use of GHB/GBL ranges from 3% to 19%.¹⁸

The Global Drug Survey 2012 reported that among UK respondents (69.7% male and 82.7% heterosexual) 'regular clubbers' used GBL and GHB more than other respondents (Table 3.1).²⁴

Table 3.1. Use of GBL and GHB among UK respondents in the 2012 Global Drug Survey

	Lifetime use	Use in past 12 months	Use in the past 12 months by regular clubbers
GBL	7.7%	1.6%	2.5%
GHB	3.8%	1.5%	2.0%

In the UK, mainland Europe, the US and Australia, GHB/GBL use is particularly concentrated among gay men and other MSM, particularly those who frequent night clubs.^{18,21,22,25–28} The 2007 UK Gay Men's Survey of 6155 men suggested that almost 13% had ever used GHB or GBL and 7% have used it in the last year.²⁹ GHB/GBL use is highest among attenders of gay clubs.²⁹ A survey carried out in 2010 in London gay nightclubs suggested there were higher levels of use of GHB/GBL than the study mentioned above, with 34% reporting lifetime GHB use (22% past-year use and 14% past-month use) and 27% reporting GBL lifetime use (24% past-year use and 19% past-month use). On the night of the survey, 7% reported having taken or planning to use GHB, and 14% reported already having taken or planning to take GBL on the night.²⁷

Although its use has been mainly reported in cities, there is one report of a GHB-related hospital acute presentation in rural Wales.³⁰

Due to its pro-sexual effects and muscle relaxant properties, GHB/GBL is often used by MSM in a sexual context. It is one of the drugs commonly implicated in 'chemsex' (see section 1.6.4.2.) and may be associated with high-risk sexual behaviour and thus with an increased risk of sexually transmitted infections. Studies in both the US and the UK have shown that GHB/GBL use is associated with increased sexual risk, with HIV-positive men more likely to use GHB/GBL and more likely to use it in a sexual context,^{28,31,32} than those not known to be infected.²⁹

GHB/GBL is often taken with other drugs, including alcohol, cannabis, ecstasy, stimulants and sildenafil (Viagra).^{22,23} The setting for GHB/GBL use is typically nightclubs, circuit parties, sex parties, saunas and sex clubs,²⁸ although some evidence suggests that GHB/GBL is used in private settings as well.²¹ The setting in which the drug is consumed may be linked to risk, as one study has shown that people who commonly use GHB/GBL in club settings are more likely to report problems than those who usually use it at home.²¹

3.7. Routes of ingestion and frequency of dosing

The routes of administration of GHB/GBL include:

- oral use (this route is the most common, when it is typically diluted in a beverage);
- insufflation;
- injection (though this is rare);
- mucosal (e.g. previously from absorption of nail polish removal pads).

GHB/GBL used for recreational purposes is most usually sold in the form of a liquid formulation, often in bottles or vials. Its taste is described as unpleasant and salty and is therefore typically diluted in a beverage. It is more rarely used as powder, usually GHB sodium salt (capsules or loose) or a waxy substance to which water can be added.¹⁸ The 'irritant' nature of GHB/GBL has been described, with a case report of a user syringing the liquid into capsules to make it easier to swallow.³³

GBL for recreational use in the UK is usually bought from street dealers or via the internet in amounts ranging from 125 ml to 10 litres. The price of the substance differs by locality and over time, but a 2006 report by the Advisory Council on the Misuse of Drugs (ACMD) published in suggested that a 250 ml bottle of 99% pure GBL could be bought for £20, which amounts to 8p per recreational dose.¹ According to anecdotal reports from users at the time of writing (2014), a litre costs £80–£100.

Usually, 1 ml of liquid contains 1 g of GHB, although purity and concentration may vary;^{18,34–36} data for 1,4-BD are limited. Miotto et al. suggest that single doses of GHB can range from 0.5 g to 5 g and those who develop tolerance and dependence will use in the range of more than 25 g per day.³⁴ GBL is far more lipophilic than GHB; hence, typical ingested dosages of GBL (1.5 in a single dose) are lower than those of GHB (with an average single dose ranging from 1 g to 5 g).^{37,38}

GHB/GBL dose is often measured by users in imprecise ‘capfuls’, teaspoons, eye droppers or vials. This imprecise dose measurement is one of the main suggested causes of the acute GHB/GBL-related harms, as users risk overdose because of its steep dose–response curve.

Recreational users will typically use small doses frequently, in the context of binges, or sometimes at night to assist with sleep. Dependent users will ingest GHB/GBL frequently and at regular intervals over prolonged periods. They will generally use multiple daily doses, including at night.³⁴ The mean frequency of dosing in cases of dependence was reported by McDonough et al. to be every 4.4 hours,³⁹ although with case reports and series showing a wide range, from hourly to daily.^{35,40,41}

3.8. Desired effects of GHB/GBL for recreational use

GHB/GBL affects people in different ways and a euphoric dose for one person may be a sedative dose for another.⁴² GHB/GBL tends to produce euphoric and pleasurable effects⁴³ without hangover or other subacute adverse effects, which helps popularise it as a ‘club drug’.¹

The desired effects of GHB/GBL include euphoria, relaxation, increased sociability, disinhibition, confidence boost, social and sexual disinhibition, enhanced libido, increased sexual arousal and enhancement of sexual encounters, with effects being dose-dependent.^{8,18,44–46} The use of GHB/GBL for its stimulant, dissociative and sedating effects have also been reported.^{34,47,48} In addition, some individuals use GHB/GBL after using other drugs (generally stimulants), to help ‘come down’²² or to enhance and modify the effects of drugs³⁴ such as stimulants.

GHB/GBL is also used as self-medication for sleep problems and anxiety. There are reports of people using GHB/GBL in the hope that it will improve cognitive ability, reduce the effects of ageing, reduce depression and anxiety, or make them feel more energised and dance more joyously.⁴⁹

3.9. Mortality

Acute GHB/GBL toxicity and a severe withdrawal syndrome have been associated with fatalities. According to the Office for National Statistics, there were 20 deaths in England and Wales in 2011 where GHB/GBL was mentioned on the death certificate, 13 such deaths in 2012, and 18 in 2013.⁵⁰

The National Programme on Substance Abuse Deaths (NPSAD) database from 1995 to 2006 identified 47 cases in the UK where GHB or GBL was found post-mortem and/or implicated in death.¹ In 2012, NPSAD reported a total of 17 such deaths for the whole of the UK. There was a slight increase from the previous years in the number of GHB/GBL-related deaths in England, with 6 deaths where no substance other than GHB/GBL was implicated, and 11 deaths where GHB/GBL was detected with or without another substance.⁵¹

In Scotland, 3 GHB/GBL-related deaths were reported with no other substances implicated and a total of 5 where GHB or GBL was found either on its own or with other drugs. The co-use of alcohol was implicated in many of these deaths.⁵²

3.10. Acute harms

3.10.1. Acute GHB/GBL toxicity

There are potential acute harms relating to any use of GHB/GBL, as well as dependent use. All GHB/GBL users risk acute toxicity and overdose; tolerance is not fully protective of overdose and people dependent on GHB/GBL are also at risk of acute toxicity. In terms of acute single-dose systemic toxicity, GHB/GBL appears to be the most physiologically toxic club drug, with a safety ratio of 10^{53} and overdoses typically occurring as a consequence of using large concentrations over a short period, or when GHB/GBL is used in combination of other CNS depressants, such as alcohol or benzodiazepines.⁹

The hazard profile of GHB has been described as less favourable than that of many other psychoactive substances. One study concluded that GHB is the most physiologically hazardous drug, partly because the dosage range is narrow⁵³ and varies between individuals and with whether other substances have also been used. The authors commented on particular harm resulting from imprecise dosing of illicit GHB or GBL, which cannot be easily measured.⁵³

As mentioned above, GHB/GBL affects people in different ways and a euphoric dose for one person could be a sedative dose for another.⁴² It has been reported that adverse effects of GHB/GBL happen at a variety of doses, indicating the variable individual responses to the drug.⁵⁴ GHB/GBL intoxication exists within a spectrum of severity and that is influenced by: dose ingested, individual variation and other substances ingested (discussed in more detail below).

The effects of GHB are dose-dependent, as summarised in a recent review (Table 3.2).⁸

Table 3.2. Dose-dependent effects of GHB

Dose	Effects
Below 10 mg/kg	Mild clinical effects: short term anterograde amnesia, hypotonia (relaxed muscles) and euphoria ⁵⁵
20–30 mg/kg	Drowsiness, sleep and myoclonus (jerking of muscles) can happen ^{55,56}
50 mg/kg	May cause coma ^{57–59}
Over 50 mg/kg	May lead to the onset of coma, bradycardia (slowed heart rate) and/or respiratory depression and death. ^{55,57,59}

GHB/GBL has a steep dose–response curve, whereby even a small increase in dose can cause serious toxic effects, such as impaired consciousness and coma. This steep dose–response relationship differentiates GHB/GBL from other drugs.

The usual clinical course after overdose – if other sedative hypnotics (most commonly alcohol) have not been used – is rapid, spontaneous awakening from drug-induced loss of consciousness or coma and uneventful recovery. CNS depression usually persists for 1 to 3 hours, with patients typically making a full recovery within 4–8 hours.^{54,60–62}

Thus, patients with acute intoxication typically: develop signs of intoxication rapidly but then improve quickly.

Overdoses are common among all users – dependent users as well inexperienced, intermittent and regular users (tolerance and dependence do not protect against overdose).²² In an Australian study of 76 GHB users, half reported a history of overdose during which they had lost consciousness.²² In another study, 66% reported some degree of loss of consciousness.³⁴ Similarly, a study of 505 consecutive GHB cases in emergency departments in Barcelona showed that the motive for seeking medical treatment in all cases was reduced consciousness.⁴⁴

The use of other drugs and alcohol can increase the toxic effects of GHB and is discussed in section 3.10.2. In addition to the GHB-related adverse effects, the adulterant compounds may also have serious toxic effects.¹⁸ As with alcohol, and unlike with benzodiazepines, there is no antagonist or antidote.

Because of GHB's short elimination half-life, people can progress from deep coma to wakefulness over about 30 minutes. A 30-month review of an Australian emergency department reported that if ventilation was not required, the great majority improved rapidly and were discharged straight from the emergency department, without a need for further medical treatment.^{63,64}

In European cities, accidental GHB/GBL overdoses in night clubs account for a substantial proportion of drug-related emergencies that require ambulance, emergency or hospital services.¹⁸ A similar picture may exist in the UK, as suggested by a retrospective review of a clinical toxicology database of a large London inner-city emergency department which showed that 38% of all poisonings with drugs of misuse in 2006 were GHB/GBL-related. The total number of presentations was 420 and 158 (37.6%) included the use of GHB or GBL.⁶⁵

3.10.1.1. The features of acute GHB/GBL toxicity

The reported effects of acute GHB/GBL toxicity are summarised as follows:

- **Mild/moderate effects** include nausea, hypersalivation, vomiting, diarrhoea, drowsiness, headache, ataxia, dizziness, confusion, amnesia, urinary incontinence, tremor, myoclonus, hypotonia, agitation, euphoria and hypothermia.
- **Severe effects** include coma, convulsions, bradycardia, ECG abnormalities (e.g. U waves), hypotension (or rarely hypertension after intravenous use), Cheyne-Stokes respiration and respiratory depression leading to respiratory arrest. Metabolic acidosis has been reported.

Laboratory investigations may also indicate hypernatraemia, hypokalaemia, hyperglycaemia and metabolic acidosis.

GHB/GBL produces CNS and respiratory depression of relatively short duration. Psychotic episodes may occur. It has also been suggested that GHB/GBL intoxication should be considered a differential diagnosis for patients presenting to an ED with acute agitation.⁴⁷

Box 3.1. Reported neurological and psychiatric features of GHB/GBL intoxication

CNS symptoms: dose-related. Patients may therefore present with CNS symptoms ranging from sudden drowsiness through to unresponsive coma, depending on dose^{44,54–56,60,61,63–76} **Common**

Amnesia^{77,78} **Common**

Ataxia^{45,47,57,61,71,77–113} **Common**

Hypotonia^{57,66,74,79,114} **Common**

Disorientation^{44,61, 78,84,110} **Common**

Hyporeflexia^{91,100,105,109} **Common**

Dizziness^{45,68,77,92,93,94,110} **Common**

Tremor^{57,80} **Common**

Confusion^{68,78,79,93,94} **Common**

Myoclonus^{54,57,58,60,77,90,115–117} **Common**

Hallucination^{83,84,93,94} **Common**

Convulsions (seizures or seizure-like activity) have been reported^{34,57,60,61,63–65,68,69,72,74,78,87,89,93,94,97,108,113,114} but most studies have shown them to be uncommon. They may occur secondary to hypoxia or due to other substances used⁸

Somnolence^{78,82,90,112} **Common**

Agitation,⁴⁷ bizarre behaviour and combativeness, either at presentation or when waking^{44,47,55,56,60,61,63,66,68,71,75–78,80,81,84,85,88,92–94,96,98,101,106,108,110,114,115}

Slurred speech^{80,83,84} **Common**

Miosis^{44,68} **Common**

Dysarthria^{44,77} **Common**

Less common neurological effects include bruxism,⁹⁸ vertigo,⁵⁷ delusion,¹¹⁰ extrapyramidal side-effects,⁸³ dystonia,⁸³ athetoid posturing⁹⁸

Confusion^{68,84,66} **Common**

Mydriasis (wide pupils)^{44,68,72,80,85,86,90,92,93}

Headache^{44,85} **Common**

Horizontal and vertical gaze nystagmus^{79,80,83–85}

Reduced coordination^{80,93} **Common**

Pupils may be sluggish and non-reactive^{66,72,94,107}

Euphoria **Common**

One report of paroxysmal sympathetic surge¹¹⁸

Box 3.2. Reported medical features of GHB/GBL intoxication**Cardiovascular effects**

Bradycardia^{44,57,60,61,65,68,72,76–78,80,84,89,92,93,95,96,98, 100,102,106–109,112,114,115} **Common**

Mild bradycardia without haemodynamic compromise is the most common cardiovascular effect and has been noted in recreational drug users⁵⁴

Tachycardia and hypertension^{61,63,72,77–79,81,93,106}

Hypotension^{44,57,63,68,74,77,84,89,98,101,102,107,112,119} Rare when GHB/GBL used on its own; generally when GHB/GBL co-ingested with other substances^{54,68}

ECG abnormalities occur occasionally⁶³

Chest tightness^{44,94}

Palpitations⁴⁴

Respiratory effects

Dose-related respiratory depression^{56,57,60,61,65,68,71,72,75,77,78,81,88,92,93,107} Respiratory failure is normally the cause of death from GHB/GBL

Tachypnoea⁶³

Bradypnoea^{44,63,64,66,77,84,91,92,98,100,101,104,107} **Common**

Pneumothorax¹⁰⁹

Periodic (Cheyne-Stokes) respirations^{114,120,121}

Cyanosis^{66,72}

Pulmonary aspiration^{61,66–68,70,73,107}

Pulmonary oedema^{77,88,105,122,123}

Apnoea and respiratory failure^{54,56,93}

Hypothermia

Hypothermia^{44,54,60,63,68,71,74,78,98,100,107,109,110} **Common**

Metabolic features

Hyperglycaemia^{61, 88, 106}

Elevated creatine activity/rhabdomyolysis^{60, 68, 85, 112, 114,124}

Gastrointestinal symptoms

Nausea and vomiting^{57,61,59,60,63,65,66,68,71,74,77,78,82,84,89,9–94,97,109,110,115,123} **Common**

Incontinence (urine and stools)^{68,77,78,93,94,98,109,112,113}

Salivation^{114,125}

Diarrhoea^{126,127}

Abdominal pain¹¹⁰

Diaphoresis^{56,71,77,78,81,84,112,128}

Reported features of GHB/GBL intoxication are listed in Boxes 3.1 and 3.2. It is important to note that other additional symptoms or features may occur due to co-used ethanol or other recreational drugs.

The CNS symptoms of acute toxicity can vary, depending on ingested dose, from sudden drowsiness to unresponsiveness and profound coma. CNS depression typically persists for 1–3 hours, with patients making a complete recovery typically within 4–8 hours.

Coma accounts for a significant proportion of GHB/GBL-related presentations to EDs, with a reported range of 16–33%.⁶⁸ For example, a third of cases in a Swiss study⁶⁸ presented to hospital with coma, 28% of cases of a US study⁵⁴ and 16% of cases in a study conducted in Spain.⁶⁰ In a case series of presentations to a London ED, approximately 16% of cases had severe coma at presentation, with a score on the Glasgow Coma Scale (GCS) of 3. In this study, 47% of patients had a GCS score ≤ 8 , which is

the usual cut-off for intubation.⁶⁵ A case series of 88 patients presenting to medical services after taking GHB reported a GCS score of 3 and 33% had a score of 4–8.⁵⁴

Vomiting in acute intoxication is common. The London-based study mentioned above reported that vomiting occurred in 17% of presentations,⁶⁵ while Garrison et al. reported vomiting in 22% of presentations.¹²⁸ Other studies have reported higher rates: 30% of the presentations in a US ED study⁵⁴ and more than half of cases of overdose in an Australian study.²² Vomiting in individuals with reduced consciousness (especially when the GCS score is less than 8 out of 15) is believed to increase the risk of aspiration due to the lack of protective airway reflexes in people with neurological depression.¹²⁹ Indeed, aspiration in patients intoxicated with GHB/GBL needs to be considered a significant risk, particularly in those with reduced consciousness. Local clinical protocols should include steps to assess and reduce the likelihood of vomiting and subsequent aspiration.

Convulsions – or seizures or seizure-like activity – associated with GHB/GBL have been reported,^{34,60,63,65,68,72,87,93,113,130} especially in severe cases of acute intoxication, although studies suggest that they are uncommon.⁸ It has been argued that it is difficult to determine the true frequency of ‘seizures’, as GHB and its analogues have been shown to cause myoclonic jerks, which – in pre-hospital settings in particular – may be misinterpreted as a seizure.¹²⁹

Hypothermia is usually not severe, but can be common. For example, in a series of 88 cases of GHB/GBL overdose, 55% were assessed to have an initial temperature of 36°C or less and 25% an initial temperature of 35°C or less.⁵⁴ Bradycardia is also common. In the same case series of 88 GHB overdose patients, over a third (36%) developed bradycardia, although only one case was severe enough to require atropine.⁵⁴

Acute GHB/GBL toxicity can cause amnesia, which increases the risk of relapse because users do not remember the experience of acute intoxication and overdose.¹³¹ As mentioned above, GHB can cause profound unconsciousness and the steep dose–response curve puts the user at risk of death. The co-ingestion of alcohol is a significant added risk factor, but GHB/GBL intoxication alone can cause death.¹

Other reported effects of GHB/GBL use include one observational case report of acute central serous chorioretinopathy.¹³²

3.10.1.2. Acute withdrawal

People who use at least daily may commonly develop tolerance and dependence. Withdrawal syndrome following abstinence or dose reduction after prolonged use can be severe and must be treated as a medical emergency.

For more details on withdrawal see section 3.12.2.

3.10.2. Poly-drug use and drug interactions

The co-ingestion of alcohol (ethanol) and/or other recreational drugs may contribute to some of the other clinical features seen in patients presenting with GHB/GBL and or GHB/GBL toxicity.¹³³ A number of authors have suggested that GHB users who

co-ingest alcohol are more likely to develop severe complications related to GHB use. A double-blind, placebo-controlled, cross-over volunteer study that investigated the potential for toxicity associated with GHB alone compared with GHB and alcohol co-ingestion showed that GHB plus ethanol was associated with more adverse effects, in particular hypotension and hypoxia; there were no differences in GHB/GBL concentrations between the groups.¹³⁴

Co-ingestion of GHB/GBL and alcohol has been associated with increased agitation⁶⁸ and aggressive behaviour. Patients who used alcohol were also more likely to vomit.⁶⁸ There is evidence that when GHB/GBL is taken in combination with other drugs (including alcohol or stimulants), the duration and depth of coma are greater than when it is taken alone, and recovery times are longer.^{44,135,68}

GHB is rapidly eliminated by metabolism to succinic semialdehyde (SSA) via the GHB-dehydrogenase enzyme, and then to succinic acid via the SSA-dehydrogenase enzyme. Several drugs (i.e. valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram, cyanide) have been shown to inhibit GHB-dehydrogenase. However, the clinical significance of the co-administration of such agents and GHB remains unknown.^{136,137}

3.10.3. GHB and HIV antiretroviral therapy

While clearance of GHB from the systemic circulation occurs rapidly by oxidation to succinic acid,¹³⁸ animal data suggest that GHB is also a substrate of first-pass metabolism (while not proven, this may involve the enzymes CYP2D6 and CYP3A4). Therefore, co-administration of GHB with CYP2D6 inhibitors (i.e. cobicistat) or CYP3A4 inhibitors (i.e. ritonavir, cobicistat) may lead to raised systemic exposures of GHB and increased toxicity.

It has been recommended that GHB/GBL should be used with caution by HIV-seropositive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (i.e. toxoplasmosis, cryptococcal meningitis), as GHB/GBL may precipitate seizure-like activity. GHB/GBL use may also cause severe nausea, vomiting and gastrointestinal tract irritation, and adversely effect absorption of antiretroviral therapy.¹³⁹ There are also concerns about compliance with HIV medication while intoxicated, especially during prolonged binges, which may complicate antiretroviral therapy and affect adherence.¹³⁹

3.11. Clinical management of acute toxicity

3.11.1. Identification and assessment

Diagnosis of acute GHB/GBL toxicity should be made on clinical assessment. There are no rapid urine or serum field tests, so analytical assessment should not be considered a component of routine diagnosis. It has been suggested by Wood et al. that the diagnosis of acute GHB/GBL toxicity be based on the recognition of the clinical toxidrome associated with the overdose of GHB/GBL.¹²⁹

Standard medical assessment is always indicated, so that other causes of the presentation can be excluded. The ease of making a clinical diagnosis often depends on understanding the circumstances in which an individual was found and the frequency of managing patients with acute GHB/GBL intoxication.

Problems relating to the identification of GHB/GBL intoxication are linked to the similarities in clinical features to alcohol, opiate and/or benzodiazepine intoxication,^{140,8} or similarities to other clinical presentations, such as hypoglycaemia. Given the similarity to acute opioid toxicity, it is recommended by TOXBASE® that, where there is clinical uncertainty, it may be worth considering a trial of the opioid antagonist naloxone, although it is not effective in managing acute GHB/GBL intoxication.

Diagnosis is also complicated by frequency of other co-intoxicants¹⁴¹ and by the diversity of clinical presentation.⁴⁷ That is, some or all of clinical features of acute GHB/GBL toxicity may be 'masked' by other co-ingested substances (e.g. an individual may present with drowsiness and normal heart rate due to co-ingestion of GHB/GBL and a stimulant such as cocaine or amphetamine).

3.11.2. Clinical management of overdose and acute toxicity

No randomised controlled trials have looked at the management of acute GHB/GBL toxicity but there is consistency in the evidence reviewed that the treatment of GHB/GBL acute toxicity should consist of symptom-directed supportive care with an emphasis on respiratory support. Wood et al. suggest that the duration of reduced consciousness (particularly non-responsive coma) is generally short-lived, with the majority of patients recovering fully within 2–3 hours of the onset of coma.¹²⁹

Overall, the evidence suggests the following:

The protection of airways and proper airway management is recommended because vomiting is common.^{61,75,109,121,142} However, it has also been suggested that 'prophylactic' intubation in cases of vomiting is not indicated⁵⁴ and it has been argued that routine intubation of patients with acute GHB/GBL toxicity is not recommended unless patients exhibit vomiting, seizures or other clinical indications for intubation.¹²⁹ Clinical consensus suggests that there does not appear to be a need to intubate purely on the basis of GCS score, as in other medical and trauma patients.

For up-to-date guidance on the management of GHB/GBL acute toxicity, 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/Chemicals/Management-Pages/GHB-overdose---features-and-management>

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

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

Reports in the literature indicate that intubation is needed in 3–13% of cases.^{54,60,63,68,124} One study found a greater requirement for mechanical ventilation for patients who had ingested GHB/GBL with other drugs or alcohol, as the duration and depth of coma were greater than when it was taken alone.⁴⁴

Gastric decontamination (e.g. activated charcoal) is not recommended, as its effects are uncertain. There are no antidotes for GHB/GBL poisoning.⁸ It may be worth giving naloxone to treat possible opiate poisoning where there is an uncertain presentation or opiate use is suspected. Pharmacological intervention is rarely required for bradycardia.

Case series have shown that where mechanical ventilation has not been required, consciousness was recovered within 5 hours.¹ Expert consensus has highlighted the need to fully investigate unconscious patients, particularly when the diagnosis is unclear. CT scanning may be indicated, particularly when convulsions occur, although there is no robust evidence on the routine use of CT scanning specifically for GHB/GBL overdoses.

Some patients may have a fluctuating course on recovery, where they have periods of agitation alongside periods of drowsiness or coma. These patients can sometimes be difficult to manage, since they require appropriate sedation for their periods of agitation, which may worsen the degree of sedation when it occurs. Should this occur, there may be a need for appropriate respiratory support until the patient has fully recovered. Dependent users may begin to go into withdrawal on recovery from the overdose – see section 3.12.2.

Outside clinical settings, in night clubs for example, harm reduction information should stress the need to put people in the recovery position and call for an ambulance. GHB/GBL users should similarly be told to put people with signs of acute intoxication in the recovery position.

3.11.3. Treatment outcome

Patients with GHB/GBL acute toxicity will typically develop symptoms quickly, but will also improve rapidly. Even in more severe cases, patients will usually make a full recovery, provided they are hospitalised and receive appropriate supportive care.⁸ Studies have shown that patients will regain a GCS score of 15 in a short time after presentation (a median of 76 minutes in one study), albeit this is longer for those with severely reduced consciousness, typically resulting from poly-substance use.^{44,63} They also show a rapid rate of discharge from hospital,^{44,63} although people presenting to hospital with a low GCS may have a longer recovery period.⁶⁵

A retrospective study of patients presenting to a large London inner-city ED with acute poisoning with self-reported GHB/GBL toxicity reported on the disposition of patients with acute GHB/GBL intoxication. The majority (92.2%) were discharged directly or self-discharged from ED or required only a short period of observation in the ED observation ward. Fewer than 1 in 10 (7.8%) required admission to hospital. Among those, the majority were admitted to critical care facilities, usually because

of significant neurological or respiratory compromise and the need for airway protection and intubation. The study also looked at length of stay and reported an overall median stay of 2.8 hours: discharged or self-discharged directly from ED 2.4 hours (range 1.7–3); admitted to ED observation ward 5.6 hours (range 3.6–8.6); admitted to general medical ward 15.6 hours; admitted to a critical care facility 18.7 hours (range 10.1–39.2).⁶⁵

As amnesia is a direct effect of GHB/GBL, patients may recover with no recall of GHB/GBL intoxication or overdose.³⁴ In a study of 42 users, 13% had amnesia during GHB use and 45% after GBL use.³⁴ As noted above, patients may be at risk of relapse or may delay treatment because they do not remember their experience of overdose or severe withdrawal.¹³¹

3.11.4. Acute withdrawal following detoxification

In GBL/GHB-dependent people, rapid improvement from acute toxicity may be followed by deterioration as withdrawal symptoms develop if they are dependent on GHB/GBL (for details on withdrawal see section 3.12.2). Withdrawal symptoms may manifest quickly, or up to 24–48 hours later, and the delayed onset of withdrawal symptoms must be considered in the management of acute toxicity.¹⁴³ A vital part of discharge instructions to patients, friends and carers is to inform them about the potential for these symptoms to recur after discharge.¹⁴³

In the majority of published cases of GHB/GBL withdrawal, detoxification was unplanned and treatment started after the patient presented in crisis, usually to an ED.³⁹ Acute withdrawal is potentially life threatening and it is recommended that cases are considered a medical emergency. It is also recommended that all dependent users of GHB/GBL are advised not to stop use abruptly or to attempt self-detoxification. Medical assistance should always be sought.

3.12. Harms associated with chronic use

3.12.1. Dependence

The regular, prolonged use of GHB/GBL and its analogues can lead to physiological dependence.⁸ Its typical features include difficulty controlling the amount used, neglect of other activities and withdrawal. Part of the dependence syndrome is tolerance, in which larger doses are needed over time to produce the same psychoactive effects. Long-term users therefore typically use higher doses than naïve users.¹⁸ Users have reported taking larger doses in order to achieve previous effects or use just 'to normalise' themselves rather than to get high.⁴⁰ Cross-tolerance between GHB/GBL and alcohol may exist.

At a social level, dependence has been described by patients to be the opposite to why they chose to use GHB/GBL in the first place: rather than enhancing sociability, GHB/GBL dependence leads to introversion, lack of motivation and failing to maintain contact with family and non-using friends; other concerns included loss of employment and absenteeism.²³

3.12.2. The GHB/GBL withdrawal syndrome

The potential of GHB/GBL to produce dependence is well recognised. Dependent users will consume GHB/GBL at regular intervals during the day and at night, sometimes as often as every 1–3 hours,⁹ in order to avoid withdrawal.

GHB/GBL withdrawal can appear clinically similar to withdrawal from opioids, benzodiazepines and alcohol,⁸ and problems relating to the identification of GHB/GBL intoxication and withdrawal are linked to the similarities in clinical features.¹⁴⁰ However, although the autonomic features of GHB/GBL withdrawal are less prominent than for alcohol withdrawal, symptoms are often more prolonged (up to 2 weeks, occasionally longer) and are typically more resistant to treatment with benzodiazepines.

GHB/GBL withdrawal can also have similarities to clinical presentations such as hypoglycaemia or sympathomimetic toxicity, typically associated with stimulant use.

3.12.2.1. Predictors of withdrawal

Dependent users will develop withdrawal symptoms on reduction or cessation of use, which can be severe and life threatening.^{39,126,144,145} GHB/GBL withdrawal is on a spectrum that varies in clinical severity.

There is increasing evidence that daily use of GHB/GBL is a predictor of withdrawal. In their review, McDonough et al. report a minimum daily dose associated with withdrawal is approximately 18 g for GHB and 10 g for GBL,³⁹ but it is possible that it occurs at lower daily doses. Withdrawal can be seen after as little as 2–3 months of use,³⁹ or even a shorter time after high-frequency use.

3.12.2.2. Rapid onset and duration of withdrawal syndrome

One distinctive feature of GHB/GBL is the quick onset of withdrawal. It can happen 30 minutes after the last dose, but more typically it is a few hours. GHB/GBL withdrawal symptoms have been reported to last from 3 to 21 days,^{8,39} with one review reporting a mean of 9 days.³⁹

Wood et al. report that in their clinical experience, 50% of those who present to hospital with acute GHB/GBL withdrawal will require barbiturates and admission to intensive care, as they typically present with delirium.¹⁴⁶

3.12.2.3. Individual variations and unpredictability of the withdrawal syndrome

Although there are similarities between cases of withdrawal reported in the literature, there are also wide variations in both the withdrawal symptoms and the clinical responses between and within patients.¹⁴⁷ Withdrawal symptoms can be self-limiting in some patients, but others can present with more severe withdrawal that can progress to delirium.⁹

3.12.2.4. GHB/GBL withdrawal symptoms

The early symptoms of GHB/GBL withdrawal typically include insomnia, tremor, confusion, nausea and vomiting. Over the next 12–48 hours, tachycardia, hypertension, agitation, seizures and/or myoclonic jerks and hallucinations may develop.

Withdrawal symptoms reported in the literature are summarised in Box 3.3.

It is not possible to determine accurately how common these symptoms are.

A review of 36 ED presentations reported that the early symptoms of withdrawal were tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), seizures (7%) and rhabdomyolysis (7%).¹⁴⁵

McDonough et al. in their review reported that an 8-hourly dosing was the minimum frequency associated with withdrawal delirium.³⁹ There are indications that heavy, frequent users are most likely to progress to severe delirium. It has been proposed that withdrawal in cases of co-dependence on GHB/GBL and another CNS depressant

Box 3.3. GHB withdrawal symptoms

Commonly reported symptoms

Hallucinations – visual and auditory^{9,15,41,126,145,148–162}

Anxiety^{15,23,34,40,41,59,126,149,150,156,163–165}

Tremors^{23,36,40,41,59,140,148–151,154,156,157,159–164}

Paranoia^{9,15,40,41,126,153–156,159,162}

Tachycardia^{15,34,41,126,145,148–151,153,156–159,163,164}

Insomnia^{15,23,36,41,59,148,149,151,153,156,158,162}

Hypertension^{41,126,148,149,158,159,164}

Disorientation^{15,126,145,149,150,153,156,158,162}

Sweating^{36,40,41,126,148,149,151,154–157,159,163}

Confusion^{15,126,140,149,153,156,160}

Agitation^{34,126,140,145,153,155,157,158,160,166}

Aggression/combativeness^{40,126,150,152,159}

Other reported symptoms

Depression^{36,41,156}

Tachypnoea¹⁵⁴

Miosis¹⁵³

Nausea and vomiting^{126,163}

Nystagmus^{15,157,162,164,}

Diarrhoea^{126,165}

Cardiac palpitations^{35,160,164}

Abdominal pain (less common)¹⁶⁴

Dyspnoea¹⁶⁰

Severe withdrawal

Delirium^{23,34,41,140,145,148,157,158,160}

Seizures^{40,126,140,145,153} – may become life-threatening

Psychosis^{67,151,153,156,159,160,161}

Withdrawal mimicking schizophrenia¹⁶⁷

Rhabdomyolysis^{145, 149, 161}

Medical complications reported during withdrawal include sepsis, myoglobinuria, Wernicke's encephalopathy without alcohol dependence

(opiates or other sedatives) or a stimulant are likely to be more severe, but such cases have not been described in the literature.³⁹

Seizures associated with GHB/GBL withdrawal appear to be less common than with alcohol and are reported in fewer than 10% of cases.¹²⁹

3.13. Management of harms from chronic use

GBL has been described as a mild skin irritant and a strong mucous membrane irritant. It can penetrate the epidermis and cause rashes or eczema.¹

Little is known about the long-term harms of GHB/GBL that are secondary to acute harms or dependence. It is recommended that more research be carried out on the long-term effects of GHB/GBL, including psychiatric (and cognitive), physical and teratogenicity-related harms. This includes the recommendation by Mitto et al. to study the possibility of persistent problems with memory acquisition as a result of GHB/GBL use.¹⁶⁸

Among MSM in particular, GHB/GBL is often used in a sexual context and in a context of potential high-risk sexual behaviour. Studies have shown that GHB/GBL use is associated with increased sexual risk and potential transmission of HIV, as well as other sexually transmitted and blood-borne infections¹⁶⁹⁻¹⁷¹ (see section 3.10.3).

3.13.1. Clinical management of dependence

3.13.1.1. Identification and assessment of GHB/GBL dependence and withdrawal

The NEPTUNE group consensus was that the warning signs of dependence might be the use of GHB/GBL during the week when not out clubbing or engaging in similar social activities. Alert signs for dependence are the following:

- daily use on multiple times throughout the day;
- waking at night to use;
- using other drugs to prevent symptoms overnight;
- symptoms on days not using;
- not able to go a day without use.

There are no validated GHB/GBL withdrawal scales, but it may be reasonable to use alcohol or benzodiazepine withdrawal scales.⁹ However, in cases of emergency acute withdrawal, many would recommend not using scales and instead treating on the basis of symptomatic control, since non-GHB-specific scales do not always pick up the degree of neuropsychiatric symptoms, which could lead to underdosing and then escalation of delirium.

In specialist drug treatment clinical practice, the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar) has been used, as well as the Alcohol Withdrawal Scale (AWS). Other scales used include: the Subjective Withdrawal

Scale (SWS), which is based on the Subjective Opiate Withdrawal Scale, where all subjective criteria of the DSM-IV-TR withdrawal syndromes were added to SWS; and the Objective Withdrawal Scale, which is based on the Objective Opiate Withdrawal Scale, where nursing staff record their observations.¹⁷²

There are no validated tools for the identification of or screening for harmful GHB/GBL use in non-drug specific settings. Winstock and Mitcheson have provided helpful guidance for addressing substance misuse issues in general practice.¹⁷³

It is worth noting that some individuals self-medicate with baclofen or ethanol or benzodiazepines to prevent GHB/GBL withdrawal. This can also be harmful and must be discouraged. Self-detoxification from GHB/GBL can be dangerous and should be avoided, as withdrawal symptoms can be severe and potentially life threatening. GHB/GBL users who wish to stop should be encouraged to seek medical assistance. If they want to reduce GHB/GBL use on their own, they should do so in very small increments and with the support of health professionals. Consumption diaries may be useful.

Attempts at self-detoxification from GHB/GBL can be ineffective. In one study of 56 users recruited via the internet, respondents had unsuccessfully attempted to quit on average 4.07 times and 30% had been previously treated for GHB/GBL misuse.⁴⁹

3.13.1.2. Psychosocial and pharmacological support

Chapter 2 discusses in general terms the psychosocial interventions for the use of club drugs. These are applicable to the management of the chronic harms of GHB use, as well as aftercare and support, and so are not discussed further here. The pharmacological interventions are discussed below.

3.13.2. Clinical management of withdrawal

No randomised controlled trials or robust prospective clinical trials have investigated GHB/GBL withdrawal. The research evidence on the management of GHB/GBL withdrawal is instead based mainly on case reports and series and it is therefore not possible to draw robust recommendations.

For up-to-date guidance on the management of GHB/GBL withdrawal, 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/Chemicals/Management-Pages/GHB-withdrawal---features-and-management1>

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

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

It is, though, consistently suggested that symptomatic treatment is indicated for GHB/GBL withdrawal syndrome. The review of the evidence shows that benzodiazepines are most typically used for this purpose.^{15,126,149,153,154,158,163,165} Combined evidence suggests that benzodiazepines are the first line of treatment, but adjuncts may be helpful to control symptoms.¹⁴⁹ Baclofen and barbiturates have been described as second-line adjuncts.^{39,41,55,126,129,145} TOXBASE® recommends that withdrawal symptoms can be effectively treated with a combination of diazepam and baclofen and this has been used successfully in clinical practice, as part of medically assisted detoxification.²³ However, clinicians must be aware of the risks of patients taking the baclofen on top of their use of GHB/GBL and this leading to coma and respiratory distress.¹⁷⁴ There is anecdotal evidence that some GHB/GBL users are also buying baclofen online.

A wide range of medications have been used and described as potentially helpful in GHB/GBL withdrawal management. However, supporting evidence for any of these medications is mainly based on a small number of case reports and case series. The decision on which additional agent to use depends on the clinical presentation. Anti-psychotics should be used with caution due to the risk of neuroleptic malignant syndrome and seizure.

Medications which have been used to manage acute withdrawal are listed in Box 3.4.

Box 3.4. Medications used to manage acute GHB/GBL withdrawal

Diazepam^{126,143,165,175}

Baclofen^{23,140,156}

Barbiturates^{41, 59, 157, 159, 161}

Benzodiazepines are safe and effective in managing most cases

Barbiturates can be used in benzodiazepine refractory cases³⁹

Carbamazepine¹⁵⁶

Gabapentin¹⁵⁶

Chloral hydrate^{151,156}

Clonidine^{35,156}

Paroxetine³⁵

Beta blockers^{35,127}

Bromocriptine¹⁴⁵

Trazadone^{41,150,156}

Fentanyl¹⁴⁸

Propofol^{77, 48, 161}

Antipsychotics^{15,126,150,151,153,155,159,160,161,162,166}

Antipsychotics, including haloperidol, should be administered with caution^{151,157,160,176}

Typical antipsychotics should be avoided due to the risk of developing NMS type syndromes¹⁵⁶

Intramuscular typical antipsychotics in GHB withdrawal should be used with caution¹⁶¹

Antipsychotic not indicated unless delirium is present¹⁶⁷

Lorazepam and/or droperidol for the management of agitation⁴⁷

Olanzapine¹⁶⁰

Pentobarbital in an inpatient setting. ⁴¹

Propranol³⁵

Pharmaceutical GHB.³⁵ Gradual dose tapering can be an effective way to achieve withdrawal from dependent GHB use. However, this requires high motivation and careful monitoring in an in-patient setting

3.13.2.1 Medical complications reported during withdrawal

A 2004 review by Mc Donough et al.³⁹ of 38 cases reported the following complications during withdrawal: sepsis, rhabdomyolysis and Wernicke's encephalopathy – without alcohol dependence. No frank withdrawal seizures were seen. Rosenberg et al. suggest that all cases of GHB withdrawal delirium be considered medical emergencies and be managed in critical care settings, rather than psychiatric settings. The involvement of both disciplines, however, may be required.¹⁶¹

3.13.3. Medically assisted elective or planned withdrawal and detoxification

There is limited evidence on the provision of medically assisted withdrawal, as most case reports and series are concerned with acute withdrawal. There are, though, a few reports of elective medically-assisted withdrawal²³ and it has been argued that it is best if detoxification is carried out on an elective basis,²³ planned in advance so that withdrawal symptoms can be identified and treated early, as most patients presenting symptomatically following enforced abstinence have presented with more severe symptoms and increased risk of delirium.⁴¹ This approach also enables planning of post-withdrawal support and recovery.

There seems to be no consensus on the best clinical settings for the detoxification of patients with GHB/GBL dependence. Intensive care, hospital inpatient basis or in outpatient specialist drug treatment centres have all been suggested. Some have recommended that withdrawal be monitored in an intensive care unit (ICU) along with continuous monitoring of vital parameters because of the severity of associated symptoms.^{8,177,178} Others have described successful outpatient detoxification.²³

There have been some attempts to identify the parameters and to develop algorithms for the management of GHB/GBL detoxification in specialist drug treatment or acute centres on an inpatient or outpatient basis,³⁹ as well as to define the medication and monitoring required.^{23,39}

3.13.4. Aftercare and supporting recovery

There are few studies of the longer-term outcomes of detoxification. It is recommended that research be funded and carried out. Relapse to further use following GHB/GBL detoxification may be high, as suggested by some case series and case reports.^{30,156}

In elective, medically assisted detoxification, aftercare is an integral part of treatment and should be planned at the onset of the intervention. The risk of relapse is addressed through psychological interventions, as well as through peer support groups such as Narcotics Anonymous or Alcoholics Anonymous (for more information see Chapter 2).

3.14. Public health and safety

GHB/GBL use can have a negative impact on public health and safety. Studies have shown that it is associated with increased sexual risk and potential transmission of HIV, as well as other sexually transmitted infections and blood-borne infections.^{169,170,171} The links between GHB/GBL use and increased aggression (especially in combination with alcohol) should also be kept in mind, as should the possibility that GHB/GBL is used in drug-facilitated sexual assaults.

GHB/GBL is associated with the abrupt onset of sleep, which can have dangerous consequences if driving or operating heavy machinery.⁹ However, the lack of hangover or sub-acute effects may encourage some to drive under the influence.

One study also noted that re-arrests for driving under the influence of GHB/GBL were not uncommon.¹⁷⁹

3.15. Harm reduction

3.15.1. Supporting patients undergoing outpatient medically assisted GHB/GBL withdrawal

Patients undergoing outpatient medically assisted GHB/GBL withdrawal should be provided with a pro-forma letter describing their detoxification and medication regime, to be presented to ED in case of severe withdrawal.

3.15.2. Advice for users S-T-A-Y-I-N-G S-A-F-E on GHB/GBL

- S** Seek medical attention immediately if you have taken too much GHB/GBL. Do not use other drugs in the hope of reversing the effects.
- T** Two or more substances used at the same time increase the risk of overdose significantly (especially sedatives e.g. alcohol, ketamine).
- A** Always measure GHB/GBL doses accurately (use for example syringes or pipettes). Wait until the effects are felt and do not re-dose for at least 2 hours.
- Y** You should avoid using GBL on your own and always use in a safe place and with someone who has not taken it, as it is common to become unconscious.
- I** If you have used and are going to sleep, sleep on your side in case you are sick. Place sleeping or unconscious friends in the recovery position.
- N** Never drink GHB/GBL straight out of a bottle or pour a dose straight out of a bottle. Always dilute in water and add food colouring to avoid accidental drinking. *Never* keep GBL in drinks bottles, especially in public venues, where it might be drunk by others not aware of the content.
- G** GHB/GBL is physically addictive and dependence can happen quickly. Avoid frequent use, especially daily use.

- S** Severe and potentially serious GHB/GBL withdrawal symptoms occur if you are dependent and you miss a dose or reduce amounts taken abruptly.
- A** Acute withdrawal symptoms and have no GHB/GBL? Seek medical help immediately in an emergency department. It can be a very serious medical emergency.
- F** Find a medical support for planned GHB/GBL detoxification. Do not attempt to stop abruptly on your own. If you want to reduce your dose, do so in very small doses until you find medical support.
- E** Employ methods to stabilise your use; consumption diaries can be very helpful. Keep a GHB/GBL diary and record of your doses and times you use.

Users should also be reminded of safe sexual practices, given the association between GHB/GBL and chemsex and other forms of high-risk sexual behaviour.

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Chapter 4

Ketamine and methoxetamine

Drug type: depressant/dissociative

4.1. 'Dissociative' drugs

'Dissociative' drugs can distort perceptions of sight and sound and create feelings of detachment or dissociation from the self and the environment; however, these mind-altering effects are not hallucinations. Dissociative drugs, such as ketamine and phencyclidine, were initially developed as anaesthetics for surgery, but then became used for recreational purposes.

Ketamine hydrochloride is one of the dissociative drugs most commonly used for recreational purposes in the UK. The recreational use of ketamine analogues has also been reported; these include methoxetamine ((RS)-2-(ethylamino)-2-(3-methoxyphenyl) cyclohexanone) and 3-MeO-PCE (N-ethyl-1-(3-methoxyphenyl) cyclohexanamine). Methoxetamine is the ketamine analogue that is most extensively discussed here, because the evidence suggests it is more widely used for recreational purposes than other analogues and because the evidence base is larger than it is for other analogues. Other dissociatives include, but are not limited to, phencyclidine (PCP or 'Angel Dust'), the 3- and 4-methoxy analogues of phencyclidine – namely 1-[1-(3-methoxyphenyl) cyclohexyl]piperidine and 1-[1-(4-methoxyphenyl)cyclohexyl]piperidine – N-ethyl norketamine, N-ethylketamine, tiletamine, dextromethorphan – and nitrous oxide (discussed in Chapter 5). N-ethyl norketamine, currently a so-called legal high, has effects similar to ketamine and is sold mainly on the internet. More recently, new substances have appeared on the market: diphenidine, which is 1-(1,2-Diphenylethyl) piperidine, and methoxphenidine, which is 1-[1-(2-methoxyphenyl)-2-phenylethyl]-piperidine; these, like ketamine and its analogues, are all NMDA receptor antagonists.

Methoxetamine was at a point one of the more popular ketamine analogues. As it is not included in the Crime Survey for England and Wales (CSEW), it is not possible to determine how prevalent its use is in the UK. There is anecdotal evidence, however, that it is limited and that it has decreased in recent years. There was also a reduction in National Poisons Information Service (NPIS) activity relating to methoxetamine, following it becoming subject to a temporary class drug order in April 2012, with calls and TOXBASE® enquiries becoming infrequent.¹ It is likely that these reductions resulted from 'market forces', reflecting the fact that users may not like the effect of these drugs.

4.2. Street names

Street names for ketamine at the time of publication include: K, Ket, Special K, Kit-Kat, Cat Valium, Super K, Vitamin K. Cornflakes, Cereal and Level.

Street names for methoxetamine at time of publication include: M-ket, K-max, Mexxy, MXE powder, Special M and METH-O.

Other names for both may be used locally.

4.3. Legal status

Ketamine is currently a Class B drug under the Misuse of Drugs Act 1971 and is placed in Schedule 2 of the Misuse of Drugs Regulations 2001.

Methoxetamine was the first drug to be subject to a temporary class drug order (TCDO), in April 2012. It is now a Class B drug under the Misuse of Drugs Act 1971 (Schedule 1).

4.4. Quality of the research evidence

In comparison with other club drugs, the international evidence on the management of the acute and chronic harms related to the use of ketamine is relatively wide and includes studies of healthy volunteers and animal studies.

The evidence on ketamine analogues is very limited, in contrast. Evidence on the management of methoxetamine's acute and chronic harms, especially where there was analytic confirmation of its use, is very limited and confined to a few case reports.

4.5. Brief summary of pharmacology

Ketamine is a predominantly sedative drug, but its complex neurochemical profile reflects its actions as a dissociative, anaesthetic, psychostimulant and analgesic substance.²

Ketamine is part of the arylcyclohexylamine group of compounds, which act primarily as non-competitive antagonists at glutamate receptors of the N-methyl-D-aspartate (NMDA) sub-type. It also acts at dopamine D2 and 5-HT_{2A} receptors and the activation of 5-HT_{2A} receptors is thought to be related to perceptual disorders and hallucinations. Ketamine also shows affinity for mu, delta, and sigma opioid receptors and affects monoamine transporters.²

Ketamine is a non-competitive NMDA receptor antagonist that acts as a dissociative anaesthetic with analgesic and amnesic properties. It is a derivative of phencyclidine (PCP), and both are arylcyclohexylamines. Like PCP, ketamine stimulates the vital functions of heartbeat and respiration, though it is less toxic and shorter acting than PCP, which is a Class A drug.³

The term 'dissociative' suggests that sensory loss and analgesia, as well as amnesia, are not accompanied by actual loss of consciousness.⁴ As a dissociative anaesthetic, ketamine has the capacity to induce narcosis and narcosis-like states in which consciousness appears to be separated from the body.⁵ Its use can lead to a trance-like cataleptic state, unconsciousness, amnesia and deep analgesia, but with intact ocular, laryngeal and pharyngeal reflexes.⁶ Ketamine impairs psychomotor performance in a dose-dependent fashion.

Ketamine has a plasma half-life of 2–4 hours.⁷ Peak plasma concentrations are reached within a minute when ketamine is injected intravenously, 5–15 minutes when injected intramuscularly or snorted, and 4–6 hours when taken orally.^{8,9}

Enzyme kinetic studies have shown that for ketamine the initial metabolic steps in humans (N-de-ethylation) are catalysed by CYP2B6 and CYP3A4. Therefore, caution should be addressed when co-administered orally with CYP3A4 and CYP2B6 inhibitors (such as ritonavir and cobicistat).^{10,11}

Methoxetamine, which is 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, or 3-MeO-2-Oxo-PCE, is an analogue of ketamine. Its analogues are 1-[1-(3-methoxyphenyl)cyclohexyl]-piperidine (methoxyphencyclidine; 3-MeO-PCP) and N-ethyl-1-phenylcyclohexylamine (eticyclidine).

Methoxetamine first appeared in 2010 and was synthesised as a close structural analogue of ketamine in order to elude the classification of ketamine while retaining its psychoactive properties.¹² Because of its structural similarities to PCP and ketamine, it has been assumed that the effects of methoxetamine are similar.¹³

Methoxetamine is both a dopamine reuptake inhibitor and an NMDA receptor blocker; its affinity for the NMDA receptor is comparable to or higher than that of ketamine. In addition, methoxetamine (in addition to PCP and its analogues) has affinity for the serotonin transporters.¹⁴

Methoxetamine has been marketed to drug users as much more powerful and as having longer-lasting effects than ketamine (these characteristics derive from its N-ethyl group). It has also been claimed that it is a 'bladder-friendly' alternative to ketamine, although there is no evidence to support this (or indeed to refute it). There are also indications that methoxetamine has a shorter half-life than PCP, but longer than ketamine, and that the psychoactive effects should be anticipated to last longer than would be expected for ketamine.¹³ Although the group modification, from 2-chloro to 3-methoxy, seems to give methoxetamine lower levels of analgesic and anaesthetic properties than ketamine, it may be responsible for a half-life that is longer than that of ketamine.⁴

4.6. Medical uses of ketamine

Ketamine is used as an anaesthetic and a powerful analgesic, particularly in paediatric, emergency medicine and veterinary medicine, and is considered as a safe battlefield anaesthetic due to its pharmacological profile. It also has a medical role in the management of pain in both humans and animals.

A number of studies have investigated the role of ketamine in treatment-resistant depression and major depressive disorders.¹⁵⁻¹⁷ Experimental studies are being conducted on the use of ketamine as a pharmacological agent for modelling psychosis. The Advisory Council on the Misuse of Drugs (ACMD) has recommended the need for further research into the role of ketamine as an analgesic in chronic cancer pain (palliative care) and non-cancer pain.¹

There are currently no clinical or non-clinical uses of methoxetamine. However, as an analogue of ketamine, it could be of pharmaceutical interest for treatment-resistant depression if it were to show rapid antidepressant properties similar to those of ketamine.^{14,18}

4.7. Prevalence and patterns of use

4.7.1. Prevalence of use in the UK

The recreational use of ketamine has been characterised by the EMCDDA as having ‘potential for more widespread diffusion’,¹⁹ although currently its use in Europe is still relatively low, lower than that of ecstasy,¹⁹ and is concentrated among particular sub-groups. In the UK, ketamine use escalated in the 1990s on the ‘rave scene’, first as an adulterant of ecstasy, before becoming increasingly mainstream.²⁰

Measurement of the use of ketamine by the British Crime Survey (BCS; which is now the Crime Survey for England and Wales, CSEW) started in 2006/07, when it was suggested that it had been used in the past year by 0.3% of 16–59-year-olds. In 2013/14, ketamine use in the past year was reported by 0.6% of the adult population (aged 16–59 years), a statistically significant increase from 0.4% in 2012/13.²¹

The CSEW in 2013/14 estimated that 1.8% of people between the ages of 16 and 24 years (a total of around 100,000) had used ketamine in the previous year. In the 16–59 age group, it was estimated that 200,000 people had used done so (0.6%), with ketamine being the sixth most commonly used substance (Table 4.1).

Table 4.1. *Prevalence of ketamine use as found in the Crime Survey for England and Wales, 2013/14*

Age group and use	Prevalence
16–24-year-olds reporting ketamine use in past year, 2013/14	1.8%
16–59-year-olds reporting ketamine use in past year, 2012/13	0.6%

There was a statistically significant increase in past-year use of ketamine among all adults from 2012/13, when it was used by 0.4% of adults, to 2013/14. This was also the case among the 16–24-year age group, with an increase from 0.8%.

Ketamine use is higher among some sub-cultures, lifestyles and occupations.²² These include clubbers,^{20,23–30} ‘travellers’, ‘free party scene’,^{31,32} gay men and MSM^{27,28,33–35} young injectors, self-exploratory people²⁸ and workers in the medical field.^{36,37} In a 2011 survey in a gay-friendly club, 10% reported it as their favourite drug and intended to use it on the night of the survey.³⁸

Ketamine is associated with ‘clubbing’, as well as post-club ‘chill-out’, when it is used for extending clubbing experience and as part of the drugs repertoire or stages in clubbing.³⁹ Of the respondents to the Global Drug Survey 2013 survey (2012/13 data) 50.6% reported lifetime use of ketamine and 31.5% use in the past month.⁴⁰

However, despite the association of ketamine with clubbing and post-clubbing use, a study has reported that the most commonly endorsed settings were home or a friend’s house or somewhere else familiar.⁴¹ In addition, there is some evidence that its use in clubs varies significantly within the different dance ‘scenes’ and regions. In surveys of the users of the night-time economy and clubs, it was shown that ketamine use was highest use in gay-friendly clubs, dance clubs playing ‘hard dance’ music, ‘funky house’ and ‘trance’ music and lowest in ‘straight’ (heterosexual) bars and those playing ‘drum and bass’ music.⁴²

The 2011/12 CSEW reported that ketamine users generally have high rates of simultaneous poly-use, with 48% using another drug the last time they used ketamine (third highest after methadone users, at 58% and ecstasy users, at 49%). Ketamine users were also more likely, compared with the users of any other illicit substance, to have used (concurrently) other drugs in the past year and past month.⁴³

There is some evidence from the UK that initiation in ketamine use may take place at a slightly older age than for other substances, and that it is possible more experienced users add ketamine to their poly-use repertoire.³⁹

Research carried out in the US, England and Australia suggests that ketamine users tend to be white, male, under 30 years old, urban and moderately well educated.^{20,28,33,44} In the UK, the CSEW also indicates that ketamine users are more likely to be male, single, in the 20–24-year age group, unemployed or a student. Differences between the various sub-groups have been shown. For instance, Morgan et al.⁴⁵ found that frequent and daily users had spent significantly fewer years in education than infrequent or non-users.

Ketamine is typically used intranasally, by insufflation. It is rarely injected. A study conducted in Scotland, for example, found that ketamine was injected by only 0.9% of users.⁴⁶

No population data are available on the use of methoxetamine in the UK, but a 2012 ACMD report stated that there was some evidence of its use in England, Scotland and Wales. It is not clear how much it is used or whether geographic differences exist.⁴⁷ However, and as mentioned above, there is anecdotal evidence that the use of methoxetamine has become negligible.

4.7.2. Ketamine use and high-risk sexual and injecting behaviours

Like other club drugs, ketamine is used as part of a socially active lifestyle and is associated with elevated, even pronounced, sexual health risks.⁴⁸ The Global Drug Survey showed that, compared with the general population, clubbers are more socially active, have more concurrent partners, use condoms less consistently and have higher rates of sexually transmitted infections.⁴⁸

Ketamine is associated with an increased incidence of unsafe sex among gay men.^{49,50-52} A US study of gay and bisexual men attending 'circuit parties' in three cities found that over 60% had used ketamine at parties in the past year and unsafe sexual behaviour was associated with frequent ketamine use.⁵¹ One study suggested that ketamine use (as well as GHB use) was associated with unprotected anal intercourse with regular partners, whereas methamphetamine was associated with unprotected anal intercourse with casual partners.³⁵

Ketamine is rarely injected (typically being taken intranasally) but some use by injection has been reported. Laukenau et al. studied young ketamine injectors in US cities and described two types of ketamine injectors, with different demographic profiles: experienced injecting drug users (IDUs), who injected a number of drugs and who tended to be homeless youth and homeless travellers;^{53,54} and new IDUs, who initiated injecting with ketamine and tended to have stable housing and who associated with others who used ketamine.⁵⁴

The injecting of ketamine in the UK has not been systematically documented. There is some anecdotal evidence from the few UK treatment centres that provide treatment pathways to ketamine users that a minority of users inject this drug (intravenously and/or intramuscularly). There is also some anecdotal evidence which suggests that it is possible that a minority of older injecting opiate drug users also inject ketamine.⁵⁵

US studies have found 'hidden' populations of ketamine injectors in US cities but it is not possible to determine whether those findings are relevant to the UK. A 2002 study among ketamine injectors found that a slight majority had injected other substances prior to injecting ketamine for the first time (56%) but a large minority (44%) began their injecting career with ketamine. The median age at first injecting ketamine (18 years) was slightly older than injecting other drugs (17 years). Most ketamine injectors were poly-users: 56% had used one or more additional drug before, during or after their last ketamine injection, while 44% had not.⁵⁴

In interviews with ketamine injectors, subjects reported the advantages of injecting over snorting: sniffing aggravated the nasal passage and injecting produced a 'cleaner' high. Those who developed tolerance from sniffing found that injecting was a more potent and reliable mode of ingestion.⁵⁴ Most reported that the main reason for injecting was to achieve the 'k-hole' (where the user experiences feelings of detachment and perceptions appear divorced from reality), which was more reliably achieved and intensely experienced by injecting.⁵⁴ Among those who injected ketamine only, intramuscular injecting was more common than intravenous injecting.

Injecting ketamine was shown to be associated with high-risk behaviours. Multiple injections were typical, for example 8 to 10 injections over several hours.⁵⁴ Multiple injecting of any substance has health implications.⁵⁴

4.8. Routes of ingestion, dosing and frequency of dosing

4.8.1. Ketamine

Illicit ketamine in the UK is mainly in powder form, typically sold in gram doses. It is less frequently available as a liquid, in which form it is possibly diverted from pharmaceutical supplies. Illicit ketamine for recreational use is often sold as a powder of fine crystal and is crushed for insufflation. It is usually white or transparent but can also be off-white or brown. Doses for recreational use are known as 'bumps' and are often measured as the quantity of powder that fits on the tip of a domestic key, a method therefore known as 'keying'. Ketamine is sometimes sold in tablet form (in which form it is on occasion falsely sold to users as ecstasy). Ketamine is sometimes dissolved for injecting and then has a faster and more potent effect.

Ketamine is rarely taken orally, as it will then be metabolised into norketamine, which produces a sedative effect rather than the desired psychedelic effect. It can also be smoked, used rectally^{56,57} or swallowed in a wrap of paper.

The onset of the effects of ketamine is likely to occur approximately 5 minutes (but up to 30 minutes) after insufflation, the most common form of use. Effects occur in a matter of seconds or minutes after injection, smoking and smoke inhalation. This rapid onset of effect is thought to increase its potential for misuse. The effects themselves are generally short-lived, typically lasting 1–4 hours,⁵⁸ depending on dose, tolerance, individual factors and other drugs ingested. This short duration of effect may promote bingeing; ketamine users in a session will typically self-administer several doses in order to maintain psychotropic effects over time,⁵⁹ until supplies are exhausted.^{60,61} On the other hand, the short duration of effects may also increase its appeal over longer-lasting hallucinogens.³⁹

A typical recreational dose is approximately 10–25% of the effective general anaesthetic dose.⁶ Single doses for intranasal use vary widely.^{6,61,62} A follow-up of the Mixmag survey looked at both typical amounts used in a 'session' and the number of days of consecutive use. It reported that just under a third of respondents (31%) used less than 0.125 g; just over a third (35%) used between 0.25 g and 0.50 g, and 34% used more than 1 g per session. Five per cent reported using more than 5 g in a typical session. The mean number of maximum days of consecutive use was 3.5 days, with 11% reporting using ketamine on seven or more consecutive days. Seventy per cent used ketamine 1–4 days per month, 16% 5–8 days and 13% 9 or more days per month.⁶³

The small number of specialist treatment services offering specific treatment to ketamine users report that most of their patients use ketamine most days or every day and use up to several grams per day.¹ The highest dose noted in a series of 60 patients attending three clinical urology centres for a ketamine-related urological syndrome was 20 g per day.⁶⁴

4.8.2. Methoxetamine

Methoxetamine is generally sold as a white crystal powder, but can be found in tablet form. It is generally used by insufflation, but can be used rectally, by sublingual application and by injection (intramuscular mainly, but also intravenous).^{13,65} It is also used orally, usually swallowed in a cigarette paper, or as tablets.

The range of doses reported is 20–100 mg for oral administration and 10–50 mg for intramuscular injection.^{4,13,65} The effects of methoxetamine were described as lasting 1–3 hours⁶⁵ by one report, but drug user websites investigated by Corazza et al. stated that the duration of action of methoxetamine ranges from 5 to 7 hours when insufflated, less (approximately 1 hour) when administered by intramuscular injection.⁵⁸ The onset of the effects of methoxetamine have been described to start 10–20 minutes after ingestion,⁶⁵ but can be delayed by 30–90 minutes after insufflation.⁴ This could have serious implications, as users may ingest a second dose thinking that the first dose was inadequate. The effects after intramuscular injection are faster, with onset after approximately 5 minutes.⁵⁸ Compulsive re-dosing has also been described.⁵⁸

Powders and tablets sold as methoxetamine have been found typically to include a range of other compounds and adulterants, including mephedrone, caffeine and cocaine.⁴⁷

4.9. Desired effects for recreational use

4.9.1. Ketamine

The mind-altering effects of ketamine make it attractive to some drug users, along with its lack of hangover, short duration and relatively low cost. One of the earliest studies on the recreational use of ketamine found that users perceived it as a safe and potent hallucinogen with short duration of action and an equal balance of positive and negative effects.⁶⁶

According to Teltzrow et al., ketamine has characteristic subjective effects which differ according to individual and setting of use.⁶⁷ Overall, however, it can produce a range of experiences, depending on dose.⁶⁸

- At low doses, ketamine produces distortion of time and space, visual and auditory hallucinations and mild dissociative effects.⁶⁹ It also has stimulant-type properties.⁷⁰
- At high doses, it produces more severe dissociation, known by some users as the 'k-hole', where the user experiences feelings of intense detachment and perceptions appear completely divorced from reality.⁶⁹

Ketamine has been described as able to induce a 'raft' of intense experiences, including some that can be characterised as positive and negative psychotic-like features.⁷¹ Ketamine can act like a stimulant at low doses and can cause potent psychedelic experiences in moderate or high doses. It is dissociative inasmuch as it causes users to feel both sedated and separate from their bodies.⁵⁴ Ketamine exhibits features of

a hallucinogenic drug and its use leads to alterations in mood and thought content. The combination of effects of ketamine has been described by some as 'alcohol-like intoxication, cocaine-like stimulation, opiate-like calming, and cannabis-like imagery'.⁷²

Moore et al. referred to the 'playful' effect of ketamine, in that it leads to improved moods and a child-like state. The intensity of ketamine was also emphasised.³⁹ Its effects include euphoria, depersonalisation and derealisation, feelings of universal empathy and experiencing synaesthesia (combinations of sense experiences such as sound and colour).⁷³ Ketamine users also report that it enhances creativity and that it is used to manage the 'come-down' from other drugs, such as stimulants.

Ketamine users often experience floating sensations, sensory distortions and transcendental phenomena, such as mystical insight, spiritual trips, revelations or alternative realities.⁶⁹ Ketamine is sought by some because it induces a 'separate reality', 'near death', 'lack of fear of death' and out-of-body experiences.⁷⁴ States similar to those reported as near-death experiences have been described and include altered perceptions of time, a strong sense of detachment from the physical body and a sense of peace and joy.⁷⁵

There are individual variations in motivations to use ketamine, as well as in what constitutes desired or unwanted effects. These have been described by a study as revolving around axes of sociability and intensity, with control over effect being an important concept. The voluntary versus involuntary entry into the k-hole³⁹ is a salient example: for some it is too intense; for others it is a desired journey or place. Interviews with users suggest that the dose is a key point of control, which users associate with the possibility of negative or positive consequences of ketamine use. It has been reported that some users 'test' doses of ketamine to assess the strength of batches³⁹ and then adjust doses for desired effects. Self-administration of titrated ketamine is attempted by users to achieve the desired amount of dissociative sensation, hallucination and transcendental experience.⁶⁶

In addition to dose, frequency of use and past exposure have been self-reported as influencing the experience. In a study of recreational users, 58% interviewed said they had experienced the k-hole and that this was related to increased exposure to the drug (more than 20 times).²⁸

Ketamine is also used for self-medication for depression and studies are currently being conducted to examine its possible antidepressant action. There is also anecdotal evidence that it is also used as self-medication for sleep and anxiety. Anecdotal evidence also suggests that it is commonly used by MSM for some forms of anal sex ('fisting') because of its anaesthetic and muscle-relaxing effects.

4.9.2. Methoxetamine

Reports from users suggest that methoxetamine produces ketamine-like effects. It has been marketed as much more powerful and longer-lasting than ketamine (but less so than PCP).^{4,13} Although the effects have been described as broadly similar to, albeit more intense than, those of ketamine, there may be individual variations. One

patient implied that the clinical effects of methoxetamine were subjectively very different from his previous ketamine use.⁷⁶

The effects and dosage of methoxetamine are linked to mode of ingestion. Typically, it works as a short-acting mood enhancer, with powerful visual hallucinogenic and dissociative properties. The desired effects include euphoria, empathy, 'cosiness', intensification of sensory experiences, especially while listening to music, a mild to strong sense of dissociation, distortion of the sense of reality, vivid hallucinations, introspection and brief antidepressant effects.⁴ There is one report of the use of methoxetamine as an analgesic for self-medication for chronic foot pain.⁷⁷

An 'm-hole' has been described by users, typically referring to a subjective state of dissociation, which mimics the out-of-body experiences of near-death experiences,^{75,78} and is often accompanied by feelings of derealisation, depersonalisation and disorientation, as well as vivid hallucinations.⁴

4.10. Mortality

No deaths have been reported associated with the medical use of ketamine. In terms of recreational use, fatalities solely linked to ketamine toxicity are relatively rare. Ketamine-related deaths have been reported in adults after intravenous doses of 500–1000 mg.^{79,80}

A study by the National Programme for Substance Abuse Deaths (NPSAD) identified 23 deaths in the UK from 1993 to 2006 where ketamine was mentioned in the death certificate or coroner's report. However, ketamine was used on its own in only four of these cases, suggesting the particular risk is posed by poly-drug use and drug interaction. Nonetheless, the four fatalities associated with ketamine on its own have led some to question the high safety profile often attributed to ketamine.⁷⁸

One of the limitations of the data on drug-related mortality was highlighted by the authors of the NPSAD study: the fact that even if ketamine was recorded in the post-mortem examination, this did not necessarily mean that it had contributed directly to the death. The four deaths from ketamine alone could, for instance, have been associated with the increased likelihood of accidents caused by the drug's dissociative effects.⁷⁸ The effects of ketamine, notably a reduced awareness of risk, a reduced perception of pain, a lack of coordination, a temporary paralysis and an inability to speak, would indeed put users at significant risk of injury or accidents. Although it has been argued that the highest risk of mortality from ketamine is through accidental death when intoxicated,^{57,81} there is little scientific evidence to support this at present.⁸²

4.11. Acute ketamine toxicity*

In comparison with other drugs, ketamine in itself has a wide margin of safety,⁸² but it is often co-ingested with other substances, which increases both its associated harms and those of other substances. It also gives rise to a greater risk of accidents (see section 4.11.3) and chronic use can lead to urological problems, which can be severe (see section 4.14.4).

Ketamine is characterised by its ability to cause unconsciousness, amnesia and analgesia, while sparing airway reflexes and maintaining haemodynamic stability.⁶ Coughing and swallowing reflexes are maintained with minor suppression of the gag reflex, even when a user is very intoxicated, thus reducing the potential risk for users, if ketamine is used on its own.⁸²

The Morgan and Curran review suggests the lack of severe acute physical health consequences, with no adverse outcome reported from large overdose, where no other substances are co-ingested.⁸² The main features of acute intoxication associated with ketamine are related to its psychedelic, dissociative and hallucinogenic properties.

In humans, a single dose of ketamine induces dose-dependent impairments in working and episodic memory, which can have a profound effect on the user's ability to function.⁸³ Ketamine is associated with direct neurotoxicity and can cause acute neuropsychiatric effects, such as agitation or ketamine-related psychotic states. Generally, clinical features are related to physical harm (e.g. agitation or accidents, and behaviours resulting from dissociative effects), but systemic toxicity with cardiovascular effects can occur and can be severe.

Ketamine stimulates the cardiovascular system, leading to increased heart rate, cardiac output and blood pressure,⁸² and this will present a risk for people with hypertension or severe cardiac disease, and people at risk of stroke and raised intracranial pressure. Risks are increased with co-ingestion of stimulants⁸² and should be emphasised in harm reduction messages (section 4.16).

4.11.1. Features of acute ketamine toxicity

The reported acute effects of ketamine use are summarised in Box 4.1.

Case reports provide some insight into how common these ketamine-related effects are. In a study by Ng et al.⁹² which reviewed 233 cases of presentations to an emergency department, the most common presenting symptoms were: impaired consciousness (45%), abdominal pain (21%), lower urinary tract symptoms (12%) and dizziness (12%). The most common physical symptoms included high blood pressure (40%), tachycardia (39%), abdominal tenderness (18%) and chest discomfort and palpitations (11%). However, no patient had serious cardiovascular complications (e.g. myocardial infarction or significant arrhythmias). In that study, 46% of patients

* SPC data ketamine hydrochloride for injection can be found (for Ketalar) at <http://www.medicines.org.uk/emc/medicine/12939/SPC/Ketalar+Injection/#PRODUCTINFO>. SPC states that respiratory depression may occur with overdosage.

Box 4.1. The reported acute effects of ketamine use**Dermatological**

Transient rash, predominantly in face and neck

Gastrointestinal

Nausea

Vomiting

Neurobehavioural effects/psychiatric effects^{66,83,84}

Hallucinations (visual and auditory)

Slurred speech

Dizziness

Numbness

Confusion

Blurred vision

Insomnia

Decreased sexual motivation

Cognitive impairment

Aggression

Paranoia and display of dissociative-type symptoms

Ataxia

Acute dystonia (one report)

Agitation (agitated patients are at risk of other effects including hyperthermia, rhabdomyolysis, self-injury, enhanced perception, depersonalisation, movement disorders and confusion)

Paralysis and muscle rigidity

Ketamine-related psychotic states (typically short-lived with complete resolution).^{71,85} Among patients with schizophrenia stabilised on an antipsychotic, however, ketamine can cause a relapse of psychotic symptoms,⁸⁶ which are idiosyncratic to those each individual exhibited during the acute phase of their illness^{87,88}

Delirium

Polyneuropathy

Seizures

Convulsions

Cardiovascular and respirator⁸⁹⁻⁹¹

Self-resolving sinus tachycardia (most commonly reported)

Hypertension (common)

Chest pain

Palpitation

Transient major Brugada ECG patterns (one case report)

Raised intracranial pressure

Pulmonary oedema

Respiratory depression

Cardiac and respiratory arrest Increased muscle tone and activity may produce hyperpyrexia

had a period of altered consciousness at some point after ketamine ingestion. This effect of ketamine was short-lived, however; only 14% of the patients had a score on the Glasgow Coma Scale of less than 15 when examined in hospital. Among patients who had blood tests performed, leukocytosis (in 36%) and a raised creatinine kinase level (in 32%) were the most common abnormalities, whereas 16% had abnormal liver function test results and 3% had abnormal renal function test results. Most of the patients were managed solely in the emergency department (72%) and 85% had no or only minor complaints.⁹²

There are few reports (albeit they are increasing in number) of methoxetamine use with analytical confirmation of the use of the substance.^{13,93} The effects of methoxetamine are dose dependent and include mild euphoria, hallucinations, disorientation, confusion, vertigo, analgesia, numbness, anxiety, tachycardia, hypertension, nausea, vomiting, diarrhoea, insomnia, agitation, sweating, catatonia and hypertonia; as well as elevated creatine kinase.¹³ Opiate-like effects have been described by a user (quoted by Rosenbaum et al.⁶⁵), as well as respiratory depression, antidepressant effects and amelioration of phantom limb pain. Cognitive impairment has also been reported.⁴⁷ Partial amnesia to preceding events was noted in one report.⁷⁷

Methoxetamine can cause rapid-onset neurological impairment; reversible cerebellar impairment has also been reported.⁹⁴ A case series on the effects associated with methoxetamine use reported cerebellar ataxia, incoordination, dysarthria and nystagmus.⁷⁶ Cerebellar signs were reversible in all cases observed, but recovery could extend over several days.⁷⁶ Nystagmus and tremor have been reported.^{13,93,95}

A report of three presentations with confirmed methoxetamine consumption at an emergency department shows that acute effects include ketamine-like dissociative/catatonic symptoms, as well as features of sympathomimetic activation, with marked tachycardia and hypertension and agitation or aggression.^{93,96}

Methoxetamine seems to have more severe side-effects than ketamine.⁵⁸ It has greater effects than ketamine in terms of hypertension and other stimulant-like effects, including agitation, tachycardia and cerebellar features, such as ataxia.⁴⁷ People have presented at hospital with methoxetamine intoxication with impaired consciousness. One report of three cases mentioned a patient presenting to hospital with a score on the GCS of 13, another 10 and the third 7.⁷⁶

Corazza et al. cite a report of a fatality following an unconfirmed intravenous injection of both methoxetamine (8–100 mg) in addition to 400 mg of 5,6-methylenedioxy-2-aminoindane (MDAI).⁵⁸

4.11.2. Acute withdrawal

For withdrawal see section 4.13.2.

4.11.3. Poly-drug use: complicating factors for acute toxicity

Acute ketamine toxicity is often complicated by poly-drug use, which is common. In one study of attenders at an emergency department, 89% of self-reported ketamine users stated that they had used another drug and/or alcohol.⁸⁹ It is therefore recommended that when people present with acute toxicity after ketamine use, clinicians consider the possible impact of other drugs ingested.⁶ Poly-drug use has also been implicated in death (section 4.10).

4.12. Management of ketamine-related acute harms

4.12.1. Identification and assessment of acute toxicity

Diagnosis of acute ketamine intoxication in an ED setting should be made on clinical assessment and the recognition of the clinical effects of ketamine, also taking into account the common co-ingestion of a number of substances, including alcohol.

A case series of US ED presentations suggested that the diagnosis of ketamine should be considered when people (especially young people) present with agitation, tachycardia and either visual hallucinations or nystagmus, although the absence of the latter two findings does not rule out the possibility of ketamine misuse. The authors also recommend that if symptoms are not improving, they should investigate other drugs co-ingested or another differential diagnosis.⁹⁰

Because the onset of the effects of ketamine intoxication are rapid and are generally short-lived, people will typically develop the adverse effects in the setting where the drug was ingested, in night clubs for example, and symptoms may resolve before they reach hospital. Indeed, some clubs provide a room or area where unwell users of club drugs are initially assessed and managed prior to transfer to hospital, if required.⁹⁷ Wood et al. analysed the patient presentations, one such facility over a five-month period in 2008/09. Of the 173 presentations for recreational drug toxicity, 37.9% were for ketamine, which was the second most frequently mentioned drug, after GHB/GBL. However, the authors stated that ketamine was not as commonly seen in the emergency department where they worked.⁹⁸

Information on presentation to the hospital EDs resulting from ketamine toxicity is limited. In the UK, ketamine was the seventh most frequently searched for drug in TOXBASE® enquiries in 2012/13, at 2933 enquiries, but this was a 14.2% reduction from the previous year. A reduction was also noted in telephone enquiries over the same period.⁹⁹

4.12.2. Clinical management of acute toxicity

No antidote exists for ketamine overdose. The effects of ketamine are not reversed by naloxone and no other agents are available to reverse the effect on humans.⁷ Activated charcoal is not necessary after ketamine acute intoxication, unless there is evidence that a co-ingestant may be contributing to the patient's symptoms or, in the case of a large ingestion, if the patient presents very early.

Most patients will improve rapidly following acute ketamine toxicity.⁶ Although randomised controlled trials and other robust studies are not available, there is consistency in case reports and series that patients are best managed with:

- standard supportive care, with special attention to cardiac and respiratory functions, as the effects of the drug are usually short-lived;^{6,90,100}

For up-to-date guidance on the management of ketamine acute toxicity, 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://TOXBASE.org/Poisons-Index-A-Z/K-Products/Ketamine/>

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

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

- benzodiazepines, where the patient is agitated;
- consideration of other causes for clinical presentation, for example co-ingestion of other psychoactive drugs, head injury, hypoglycaemia etc.
- removal of the person from auditory and visual stimulation until symptoms resolve has been recommended. A quiet environment, with minimum of external stimuli, may prevent excessive agitation.⁶

Observation of the patient until vital signs and mental state have normalised is also recommended. If symptoms fail to improve within an hour of presentation, the diagnosis and the management should be reviewed.^{6,90}

Profoundly obtunded (altered level of consciousness) patients may require airway support, intravenous fluids and titrated benzodiazepine therapy if they are agitated, hyperthermic or show overt sympathomimetic signs.⁹²

As for ketamine, in the management of acute methoxetamine intoxication observation and symptom-directed supportive care¹³ are recommended; cardiovascular and respiratory support is sometimes needed. Oral diazepam and midazolam have been prescribed.

For up-to-date guidance on the management of methoxetamine acute toxicity, 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/K-Products/Methoxetamine/>

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

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

4.12.3. Outcome of treatment for acute toxicity

A study of presentations at a Hong Kong ED⁹² reported that most of the patients (197/233; 85%) developed no, or only minor, complications. The majority (168/233; 72%) were safely managed in the emergency department with supportive measures, including intravenous fluid and benzodiazepines for agitation. The five patients requiring management in an intensive care setting had all co-ingested other drugs that could have contributed to their clinical status.⁹²

4.13. Harms associated with chronic ketamine use

4.13.1. Ketamine dependence

There is evidence that the administration of NMDA receptor agonists, such as ketamine, increases the release of dopamine in the nucleus accumbens, which is typically associated with addiction liability.¹⁰¹ There are case reports of ketamine dependence,^{37,68,102,103} but a lack of large studies, so the incidence is not known. It can be argued that the ICD-10 criteria for 'dependence syndrome' can be applied in some cases of chronic ketamine use.

Frequent ketamine use is associated with tolerance. Animal studies^{104,105} and human studies (children undergoing anaesthesia¹⁰⁶) have shown a rapid development of tolerance with repeated ketamine dosing. A study of Australian recreational ketamine users found that 22% reported physical tolerance to ketamine.²⁸ Frequent users of recreational ketamine report escalating dose, with one case report of a 600% increase from dose at first use⁶¹ and another a reported 760% increase from the initiation dose.⁴¹ Also of concern among frequent users are the compulsive patterns of behaviour: bingeing or using without stopping until supplies run out.⁴¹

There are no reports of methoxetamine dependence, but withdrawal has been described by users. Corazza et al. investigated through their analysis of drug user websites the effects of the chronic methoxetamine use. Withdrawal symptoms were described and included low mood and depressive thoughts, cognitive impairment for many hours, as well as insomnia and suicide attempts.⁴

4.13.2. Ketamine withdrawal

There is conflicting evidence on the existence of a specific ketamine withdrawal syndrome following cessation of ketamine use but a specific ketamine withdrawal syndrome has not yet been described.⁸² In a study of 30 daily users, 28 reported having tried to stop taking ketamine but failing; all reported ketamine cravings as the reason for failure. The study also found that 12 of the 30 daily users reported withdrawal symptoms – anxiety, shaking, sweating and palpitations.⁶¹ Other studies also reported craving and somatic and psychological symptoms (e.g. anxiety) of ketamine withdrawal.^{73,107,108}

Clinical experience suggests that ketamine withdrawal does exist. Although ketamine rarely produces serious withdrawal symptoms, the marked drug tolerance and psychological dependence might contribute to the difficulty in abstaining.¹⁰⁹

It has been argued that in cases of sustained and heavy use, the existence of a ketamine withdrawal syndrome must be considered.⁷³ Although ketamine has a short half-life, metabolites are present for some hours and may be responsible for continuing symptoms.⁷³ In addition, the symptoms of acute withdrawal may be short-lived and therefore not identified.¹¹⁰ However, case reports have described somatic and psychological aspects of anxiety as withdrawal symptoms.^{73,107,108} One case report mentioned withdrawal symptoms such as 'chills', autonomic arousal, lacrimation, restlessness, nightmares and psychological craving, with further ketamine use to relieve these symptoms.¹⁰⁸ Another described in detail the effects of discontinuation of use on one patient, which included craving and drug hunting, anxiety, shaking, sweating, palpitations, tiredness, low appetite and low mood.⁷³

4.13.3. Other harms of chronic use of ketamine

4.13.3.1. Ketamine-induced damage to the urinary tract

Ketamine use is associated with damage to the urinary system, which can be in the form of severe and in some cases irreversible bladder damage. This has been referred to as ketamine-induced ulcerative cystitis,⁸² although some have argued that it would be more appropriate and concise to describe it as ketamine-induced uropathy.¹¹¹ The mechanism of damage from ketamine is not yet clear but the effects, which are not specific to the bladder, are most likely to result from direct toxicity of ketamine or its metabolites. Damage can affect the entire urinary tract.⁶⁴

The urological syndrome associated with ketamine use can lead to severe clinical symptoms:⁶⁴ a small, very painful bladder, dysuria, painful haematuria, urge incontinence, frequent and urgent urination, nocturia, obstruction of the upper urinary tract, papillary necrosis, and hepatic dysfunction.^{64,111-113} Auxiliary examination showed cases of patients with symptoms including the following: sterile pyuria, contracted bladder (involving chronic inflammation with ulceration), erythematous swelling, necrotic mucosa, thin epithelium with neutrophilic and lymphoplasmic cell infiltration in bladder mucosa, collagen and adipose tissue and bladder wall fibrosis with or without vesico-ureteric reflux and involvement of the upper urinary tract.¹¹¹

Cystoscopic inspection of the bladder also often shows a denuded urothelium, which, in the most severe cases, may slough off as intact sheets of cells. There are reports of young patients at an end-stage of the disease process who required cystectomy (bladder removal) and reconstruction,⁶⁴ with a serious impact on life expectancy.

It has been reported that 20–30% of ketamine users suffer from lower urinary tract symptoms.^{41,112} A study assessing the prevalence of urinary symptoms in a large cohort of non-treatment-seeking ketamine users found that harms to the urinary tract are dose related and are particularly common among regular and dependent users. Urinary symptoms are associated with an increased frequency of use and increased

amount used per session.¹ However, the duration and/or amount of ketamine used to induce lower urinary tract symptoms is not known.

The time of onset of lower urinary tract symptoms following ketamine misuse varies from a few days to a few years following the onset of use, with the severity being in part determined by the chronicity of use. Up to 100% of those using more than 5 g per day report urinary symptoms.¹¹⁴ Because of the severe bladder pain, users frequently self-medicate for severe pain with ketamine, as the only effective means of pain relief they know, thus perpetuating the damage to their urinary tract.⁶⁴

Studies of patients in chronic pain and palliative care receiving ketamine suggest individual variations, with some individuals are more susceptible than others to ketamine-related urological damage.⁶⁴ Some series have reported a slight male predominance, but this is insignificant and not universally reported.¹¹⁵ At the present time, it would seem that ketamine-induced vesicopathy does not exhibit any gender bias.¹¹²

There is also a link between chronic ketamine use and kidney dysfunction. Hydronephrosis secondary to stenosis (narrowing) of the ureter seems to be an emerging health problem associated with frequent and high-dose ketamine use.⁸² Chu et al.¹¹² reported in their study of ketamine-induced ulcerative cystitis that 51% of patients presented with unilateral or bilateral hydronephrosis. Four patients also showed papillary necrosis and this led to renal failure in one. Patients presenting with a history of ketamine use and urological symptoms need to have their kidneys imaged to rule out ureteric strictures.

Methoxetamine was marketed as more 'bladder friendly' than ketamine. However, there is emerging evidence from an animal study that exposure to methoxetamine can induce changes in the kidney and bladder after daily use, suggesting that chronic use of methoxetamine in humans may be associated with similar lower urinary tract symptoms, as those described for chronic ketamine use.¹¹⁶

4.13.3.2. Gastrointestinal toxicity

People with prolonged and heavy use of ketamine have reported intense abdominal pain, referred to by users as 'k-cramps'.⁴¹ The Ng study of presentations to EDs reported that 21% of ketamine patients presented with abdominal pain and 15% had abnormal liver function.⁹²

Little is currently known about ketamine-induced abdominal pain. A small number of case reports^{113,117,118} have reported colic-like, upper gastric pain in young ketamine users who also presented with abnormal liver function. CT scans showed dilation of the common bile duct, mimicking cholecystitis. These symptoms appear to resolve once the patient stops using ketamine. In one UK case, a person had a dilated common bile duct that regressed with abstinence but recurred following a return to ketamine use.¹¹⁷ It has been postulated that biliary tree dilation might be related to dysfunction of the sphincter of Oddi, but the exact pathophysiology remains unknown.^{92,113,117,118}

4.13.3.3. Diabetic ketoacidosis (DKA)

Ketamine can precipitate DKA in type 1 diabetes. The metabolic acidosis can be severe and has, in some cases, been associated with rhabdomyolysis.^{119–138}

4.13.3.4. Drug interaction in HIV treatment

The use of ketamine raises general issues of adherence to antiretroviral regimens. As a substrate of the CYP450 system (specifically 3A4), ketamine may interact with certain antiretroviral medications, particularly the protease inhibitors with CYP450 inhibitive properties.¹³⁹ Also, its cardiovascular effects may be deleterious among any patients with underlying heart disease or lipid abnormalities.

4.13.3.5. Neurobehavioural, psychiatric and psychological effects

4.13.3.5.1. Cognitive impairment and memory impairment

Overall, studies have shown that infrequent ketamine users do not appear to experience long-term cognitive impairment. However, there is evidence that frequent ketamine users do have profound impairments of their short-term and long-term memory, although many studies have been cross-sectional and hence unable to address causation.⁸²

Neuropsychological harms appear to be related to frequency and quantity of dosing. Cognitive impairment and long-term psychological effects can result from prolonged use.⁴⁵ Ketamine is associated with direct neurotoxicity and can cause acute neuropsychiatric effects. One longitudinal study showed that frequent ketamine use impaired visual recognition and spatial working memory; the degree of impairment was correlated with changes in the level of ketamine use over 12 months.⁸¹ Acute and acute-on-chronic use has been associated with impaired information handling within working memory and episodic memory, as well as deficits in semantic processing,^{83,140} with men more affected than women.¹⁴¹

A case control study found that frequent ketamine use is associated with impairment of working memory, episodic memory, executive function and psychological well-being.¹⁴² One-year follow-up with the same group showed the frequent users on increasing doses were more likely to have cognitive deficits, especially with spatial working memory and pattern recognition memory tasks, with both short-term and long-term memory affected.⁴⁵

One study has shown that delusional thinking was positively correlated with the amount used by frequent users and persisted despite abstinence.¹⁴² A dose-dependent relationship was found at one-year follow-up, with frequent users more delusional than infrequent, abstinent and non-users.⁴⁵

Taking ketamine regularly has detrimental effects on memory function which last beyond the acute effects of the drug. Research suggests frequent use of ketamine produces long-lasting impairments in episodic memory and aspects of retrieval from semantic memory, which goes beyond ingestion.⁵⁹

A three-year longitudinal study of people who had ceased or reduced ketamine use reported that some may continue to experience drug-related symptoms three years later. This is particularly in relation to impairment of episodic memory which was still present three years later and possibly also attentional functioning. Schizotypal symptoms and perceptual distortion may also continue after ketamine cessation.¹⁴³

Research on infrequent users (defined as taking ketamine more than once a month but less than three times per week) and daily ketamine users found that scores on measures for delusion, dissociation and schizotypy were higher in the daily users.^{20,45} Morgan et al. found that daily ketamine users had patterns of symptoms similar to individuals in the prodromal phase of schizophrenia.⁴⁵ Long-term ketamine users have more pronounced and persistent neuropsychiatric symptoms, generally characterised as schizophrenia-like symptoms. However, there is no evidence of clinically significant positive or negative psychotic symptoms among infrequent users.¹⁴⁴ There is also little evidence of a link between chronic heavy use of ketamine and diagnosis of a psychotic disorder.⁸²

4.13.3.5.2. Depression

Frequent use of ketamine is typified by increased dissociative and depressive symptoms⁴⁵ (as well as subtle visual anomalies¹⁰³). Morgan et al.'s longitudinal study⁴⁵ found increased levels of depression in both daily users and ex-ketamine users over the course of one year, but not among infrequent users. However, the depression was not at clinical levels and the increase was not correlated with changes in ketamine use.⁸²

In contrast, there is some evidence that ketamine may be of therapeutic use for the management of treatment-resistant depression,^{15,16,145} as well as post-traumatic stress disorder.¹⁴⁶ A recent large clinical trial testing the efficacy of intravenous ketamine in mood disorders reported that it was associated with a rapid and large antidepressant effect at 24 hours, significantly superior to midazolam. Ketamine appears to possess rapid antidepressant effects independent of its transient psychoactive effects.¹⁴⁷

4.13.3.5.3. Neurological effects

Animal studies have shown that ketamine is directly neurotoxic. Abnormalities were also found in ketamine-dependent patients in bilateral frontal (including corpus callosum and anterior cingulate cortex) and left temporoparietal white matter. A recent human study of 41 ketamine-dependent users and 44 drug-free volunteers showed bilateral degeneration of frontal and left temporoparietal white matter in ketamine users.¹⁴⁸ The study also reported that fractional anisotropy* values negatively correlated with the total lifetime ketamine consumption.¹⁴⁸

A case report has also demonstrated a reduction of frontal grey matter volume in ketamine-dependent patients. This reduction was correlated with duration of

* White matter integrity can be studied by examining the degree of fractional anisotropy; this is a measure that quantifies the restriction (anisotropy) of water diffusion by tissue microstructure in each image voxel.

ketamine use; reduction in the left superior frontal gyrus correlated with estimated total lifetime consumption.¹⁴⁹

4.13.3.6. Social harms

A study of 100 recreational users of ketamine found that while one in five stated that they had ever experienced severe side-effects, more than a third (38%) reported having to deal with someone else who had suffered badly following ketamine use. The most common reported problems were in the areas of employment (20%), relationships (5%), financial (5%) and legal (1%).²⁸ The authors suggest that the problems were likely linked to the neurochemical consequences of ketamine use and the toxicity that might result.²⁸

4.14. Management of harms related to chronic ketamine use

4.14.1. Numbers in specialist drug treatment for ketamine-related harms and dependence

Presentations among adults (18 years and over) in England for treatment for ketamine have risen year on year between 2005–06 and 2010–11 from 114 to 845 patients, falling to 751 in 2011–12. This rise followed by a reduction in presentation was also reported for young people under the age of 18, whereby numbers rose from 25 in 2005–05 to 405 in 2010–11 then falling to 387 in 2011–12.¹⁵⁰

4.14.2. Identification and assessment

The first step for the identification of ketamine use and harms by specialist treatment services is to include questions relating to ketamine in routine care. The modification of existing national data collection tools is indicated, such as the Treatment Outcome Profile (TOP) forms. Assessment of ketamine use is similar to assessment for other drug use, with the addition of screening questions on urological and gastrointestinal symptoms and questions on the direct consequences of dissociation (e.g. cognitive impairment, sexual behaviours).

4.14.3. Psychosocial and pharmacological support

4.14.3.1. Psychological support

Information on psychosocial support is presented in Chapter 2 and is relevant for ketamine users.

A small number of ketamine-specific studies have also been conducted. Copeland et al. suggest that the harms that require further investigation are the association of ketamine use with unsafe sex and injecting behaviours and its neurotoxic effects. They also argue that effective brief and early interventions are needed for those who

are at risk of harm because of ketamine intoxication and/or excessive and regular consumption. Interventions should address ketamine use in situations where there is a heightened risk of accidental death because cognition is impaired.⁷

Critchlow described the treatment of a person with dependence on ketamine that involved three motivational interviewing sessions in the first instance.⁷³ Jansen and Maxwell suggest an abstinence-oriented approach be used for ketamine, similar to that used for psychostimulants.¹⁵¹ They suggest following the model used for cocaine and amphetamine dependence, with abstinence from all drugs from day 1. This may require the therapist to avoid being confrontational to prevent treatment drop-out; relapse prevention is also indicated.⁶⁰

4.14.3.2. Pharmacological interventions for dependence and withdrawal

Ketamine withdrawal is described in section 4.13.2. Only one case report is available and that describes medically assisted detoxification carried out in conjunction with three sessions of motivational interviewing. Detoxification was carried out using a reducing regimen of diazepam over three days. The regimen was successful and eliminated the majority of withdrawal symptoms.⁷³

Others have also suggested that, in cases of sustained heavy use and where acute withdrawal syndrome is a possibility, a benzodiazepine detoxification regimen modified from alcohol detoxification regimens may lessen the symptoms arising from discontinuation.¹⁵² It has been suggested that symptomatic management of withdrawal is indicated in some cases, with low-dose benzodiazepine as a starting point. There are no studies to support the use of other pharmaceutical agents, so any prescribing must be carried out based on clinical assessment.

4.14.3.3. Aftercare and support

Chapter 2 presents information on aftercare. A few ketamine-specific studies have been conducted, with some suggesting that ketamine users' ability and willingness to abstain from using the drug may be low, even when (and perhaps because) experiencing significant urological problems. Chu et al. showed that 9 out of 24 ketamine users with bladder problems were able to abstain from the drug and complete the Pelvic Pain and Urgency/Frequency questionnaire.¹¹² Another study found that only 3 out of 10 patients stayed ketamine free for more than one year.¹⁰⁹

4.14.4. Management of urinary tract problems

It is recommended that patients with recurrent urological problems, or patients with unexplained urinary symptoms, are assessed by a urologist to exclude other causes and evaluate any damage. Any patients with unexplained symptoms should be screened for ketamine use.⁶⁴ Appropriate support to stop ketamine use must be available, as well as advice regarding appropriate medical pain relief.

The most effective treatment for ketamine-related urological problems is cessation of use and it is essential that use of ketamine is stopped upon recognition of symptoms. Strategies are limited when use continues.¹⁵³ If drug cessation is achieved, the syndrome may be partially or completely reversed, but if ketamine use persists, so do symptoms. In a few patients, however, symptoms persist despite stopping drug use.⁶³ Patients should also be referred to specialist drug services.⁶⁴ A survey of UK urologists suggested that approximately a third of urological problems resolved after drug cessation, a third remain static and a third progressed.¹⁵³

Treatment for urinary tract symptoms is either symptomatic (analgesia, urinary diversion) or the treatment of complications (e.g. percutaneous nephrostomy insertion).¹⁵³ Early stages of the urological syndrome may present in casual or weekend users as episodes of cystitis, which can be treated empirically⁶⁴ (based on practical experience and observation). More frequent users may have irreversible damage and scarring. The most affected patients may require major surgery, in the form of cystectomy and bladder reconstruction.⁶⁴

Where ketamine is identified as a factor, it has been recommended that renal function be assessed; a CT urogram can also be an important investigation to reveal the extent of the disease. A urine culture is mandatory. A routine evaluation of the upper tracts with a CT urogram can rule out ureteric stricture and cystoscopy can be used to assess bladder capacity.⁶⁴ In patients with normal renal function and with an ultrasound that shows no hydronephrosis, a CT scan may not be necessary.¹⁵⁴

A strategy for the treatment of ketamine-related urological problems has been suggested by Wood et al.⁶⁴ Central to this is the requirement for patients to stop their ketamine use. However, this may be complicated by a need for pain control in those with ulcerative cystitis. This will require the treating team to develop an alternative pain management plan with the patient. There may also be a lack of motivation to abstain and non-compliance with urological investigation and treatment appointments.⁶⁴

Winstock et al. recommended a multidisciplinary approach promoting harm reduction, cessation and early referral, to avoid progression to severe and irreversible urological pathologies.⁶³ Similarly, Wood et al. suggest a need for liaison between specialist drug services and local urology services.⁶³ Some drug agencies have developed proactive models.⁶⁴ However, this is not always possible, as patients can see urology departments outside their residential area. In this case, support is best organised by the general practitioner.⁶⁴

4.15. Public health and public safety

4.15.1. Viral and bacterial infections

Studies have reported that ketamine injecting is associated with high-risk behaviours like the sharing of injecting equipment and paraphernalia,^{155,156} poly-drug use^{156,157} and multiple injections. Ketamine injecting puts the user at risk of viral and bacterial infections and hence the potential risk of their transmission to others.

4.15.2. Accidents and assaults

Ketamine impairs psychomotor functioning dose dependently and higher doses increase the risk of accidents.¹⁵⁸ Ketamine use has been associated with driving accidents in Hong Kong: 9% of fatal drug and alcohol-related single-car collisions during 1996–2000 involved ketamine.¹⁵⁹ New regulation (coming into force in March 2015) has identified ketamine as one of the specified controlled drugs for the purposes of section 5A of the Road Traffic Act 1988.¹⁶⁰

Ketamine use can place the user at risk of sexual assault, although studies have suggested that ketamine is not implicated in drug-facilitated assault.^{161,162}

4.16. Harm reduction

It has been recommended that all ketamine users are given the standard harm reduction advice, which includes not using the drug when alone, avoiding poly-use and co-ingestion of other substances, including alcohol, and information on a safe environment and safer injecting techniques.^{7,59}

The following more specific harm reduction advice should be given to ketamine users:

- Users should be advised to measure dose carefully and start with a small test dose. They should also be advised to measure intervals between doses accurately.
- The use of ketamine with other drugs including alcohol should be avoided.⁷
- Users should minimise the risk of accidental injury by ensuring that intoxicated friends are always accompanied by others who are not.⁸² The dissociative effects of ketamine puts users at risk: drowning in shallow waters, including a bath, and hypothermia from long walks have been highlighted as risks.
- Users should be made aware of the link to urological problems, and other ketamine-related harms.
- Users who develop tolerance and who find themselves needing to use increasingly higher doses, and who are using more frequently than intended, should be advised to monitor their intake. Diaries and electronic tools can be very useful.
- Advice should be given to users that those acutely intoxicated should not be left alone in case of accidents and should have with them someone who has not used the substance.⁸²
- Users should be made aware of the potential neurological and cognitive changes following frequent use of ketamine, which can result in poor performance at school, college or work.⁸²
- Ketamine users who feel depressed and anxious when stopping or reducing ketamine should be encouraged to seek professional help to manage their symptoms during a gradual reduction or detoxification.

- Users should be made aware that the anaesthetic topical effects of ketamine mean that they may not feel pain from tissue trauma and extra caution must be exercised with any sexual activity which risks tissue damage (e.g. 'fisting').
- Daily use of ketamine should be avoided, due to the urological risks.
- Ketamine users with urological problems should be strongly encouraged to cease using the drug.
- Advice should be given to users with urological problems not to deliberately dehydrate and to seek medical help and referral to a specialist to reduce the risk of permanent harm.

Corazza et al. in their analysis of internet sites found that users themselves suggested that dosages should increase only gradually. Users recommended that doses of 50 mg should not be exceeded on the first occasion of use, or when the drug was taken orally. The websites also advised users not to use methoxetamine with alcohol, tetrahydrocannabinol, selective serotonin reuptake inhibitors or monoamine oxidase inhibitors. Users were advised to try a test dose of a few milligrams and to wait 2 hours before re-dosing.

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Chapter 5

Nitrous oxide

Drug group: depressant/dissociative/inhalant

5.1. Street names

Street names at the time of publication include: Laughing Gas, Hippie Crack, Whippets (cartridges of nitrous oxide), Chargers, Bulbs.

Other names may be used locally.

5.2. Legal status

In the UK it is legal to sell nitrous oxide to people aged over 18 but not under if may be assumed that they are likely to be inhaling it. The sale of nitrous oxide for catering and other legitimate reasons is legal, although its sale in gas-filled balloons or canisters intended for human recreational use violates the Medicines Act.¹

5.3. Quality of the research evidence

The evidence on the management of the acute and chronic harms associated with the recreational use of nitrous oxide is limited, consists mainly of case reports, with occasional experimental studies into acute effects. There are few findings on acute harms and interventions relating to the use of the drug, but consistent findings on the chronic effects of prolonged nitrous oxide use.

5.4. Brief summary of pharmacology

Nitrous oxide is a gas whose pharmacology is not well studied and existing evidence is not conclusive. It has been suggested, however, that opioid receptors may be responsible for its analgesic properties² and a study has shown that naloxone inhibits its analgesic effects.³ Furthermore, nitrous oxide may act as an N-methyl-D-aspartate (NMDA) antagonist, similar in nature to ketamine, another anaesthetic (Chapter 4).² It works primarily via the opiate system, mediating the release of beta-endorphins and directly binding to mu, delta and kappa opiate receptors.⁴ Nitrous oxide is used clinically as an anaesthetic gas with pain-relieving properties.

It is also a 'dissociative' drug. Although the effects of the drug on the brain are not fully understood, its dissociative effects are probably caused by preventing the normal action of the NMDA receptor.

Nitrous oxide is rapidly absorbed via pulmonary circulation.⁴ Due to high lipid solubility it passes easily through the blood–brain barrier and has a rapid onset of action; it is cleared from the body within a few hours.⁵

The use of nitrous oxide leads to vitamin B12 depletion, which is believed to be due to its effect on cobalt in vitamin B12, whereby the vitamin is converted from an active, monovalent form to an inactive, bivalent form.⁶

5.5. Clinical and other legitimate uses of nitrous oxide

Nitrous oxide has been used as a medical anaesthetic for over 150 years and continues to be widely used for medical, dental and veterinary purposes. It is also used for analgesia and can help relieve anxiety. It is used in various settings, including ambulances, emergency departments, relief for women in labour and in dentistry, where its short duration of action is an advantage.¹ The use of nitrous oxide in anaesthesia, however, has long been challenged because of the hazards posed to both clinicians through unintended occupational exposure and patients by its haematological, neurological, myocardial and immunological effects, and because it can lead to postoperative nausea and vomiting and expansion of air-filled spaces.⁷

Nitrous oxide has been shown to ameliorate craving and withdrawal symptoms from alcohol, opioid, nicotine, cocaine and cannabis.^{8–13}

Outside of human and animal applications, nitrous oxide is used as a fuel additive, as an oxidising agent to increase the power of cars, as a component of rocket fuel, as an aerosol dispersant and in the catering industry in the dispensing of whipped cream. This forms the basis of its legal sale on websites in the form of small canisters or larger tanks, which are labelled with ‘approved for food use’ and not intended for recreational use.¹

5.6. Prevalence and patterns of use

The use of nitrous oxide for recreational purposes is not new, as ‘laughing gas parties’ were popular in Victorian times, mostly in the context of variety performances in music halls, theatres and carnivals. There is anecdotal evidence that nitrous oxide is currently popular for use in some clubs and music festivals, where it is bought as gas-filled balloons. This has led to moves by the Medicines and Healthcare Products Regulatory Agency (MHRA) to control the drug’s supply under section 52 of the 1968 Medicines Act.¹⁴

The use of nitrous oxide for recreational use was recorded in the Crime Survey for England and Wales (CSEW; formerly the British Crime Survey) for the first time in 2012/13. The 2013/14 CSEW found that:

- 2.3% of adults aged 16–59 had taken nitrous oxide in the last year;

- 7.6% aged 16–24 had taken nitrous oxide in the last year.

This prevalence was not significantly different from that in the previous year.

The 2011/12 *MixMag* Global Drug Survey reported lifetime recreational use by 49.6% of UK respondents and past-year use by 27.2%, and past-year use by 43% of UK regular clubbers.¹⁵ The 2011 report from the UK Advisory Council on the Misuse of Drugs (ACMD) on novel psychoactive substances presented anecdotal evidence of widespread use at the Glastonbury Festival in 2010.¹

Wood et al. investigated the use of nitrous oxide among 330 men who have sex with men (MSM) in gay-friendly London clubs. Levels of use reported were lower than those reported in the Global Drug Survey, with 28.1% reporting lifetime use and 11.9% use in the previous year.¹⁶

5.7. Routes of ingestion and frequency of dosing

Nitrous oxide is used for its euphoric effects. The onset of the effects is immediate and they last for approximately two minutes; users may take many 'hits' over a few hours.

Nitrous oxide is a colourless gas that is slightly sweet smelling and tasting. It is typically inhaled, sometimes referred to as 'nagging', commonly from balloons or steel bulbs. The latter (sometimes called chargers) are small cartridges containing highly pressurised nitrous oxide that are available from catering suppliers and used for whipped cream. These containers or cylinders are sometimes referred to as whippet/whippit. Cylinders vary by brand, but are approximately 6 cm long, 1.8 cm wide and have a wall approximately 2 mm thick to withstand the pressure of the gas. Most contain approximately 8 g of nitrous oxide under pressure and are non-refillable.

These 'bulbs' are supplied with a dispenser into which, when fitted, they release their compressed gas. If the dispenser is not filled with cream, the nozzle simply releases the gas only. A balloon can be placed over the nozzle to capture the nitrous oxide.¹⁴ Alternatively, 'whippets' can be opened with the 'cracker' on the cream dispenser and the nitrous oxide again released into a balloon, from which it then can be inhaled.

Both whippets and crackers can be obtained from online suppliers and in 'head shops'. The quality (purity) of the nitrous oxide depends on its source. Products intended for food use are of higher quality, especially if they originate from the UK. Products for industrial use may be adulterated or impure. Regular and long-term users of nitrous oxide in particular should be aware of impurity. The typical cost at the time of writing is £3 for a balloon-full, but it seems to be common to buy in bulk, for parties, at around 24 chargers for £10, which is less than 50p a balloon.*

* This was ascertained by searching a listing of small advertisements for the London area (<http://www.gumtree.com/other-kitchen-appliances/london/nitrous+oxide>).

Nitrous oxide is also available in much larger gas cylinders intended for medical or industrial use. The use of these, for purposes other than those intended, can be dangerous. Unsafe methods include breathing directly from a cylinder using a face mask, opening a cylinder tank in a car or small room or filling a bag with the gas and putting it over the head. Cylinder tanks of nitrous oxide intended for cars can contain harmful contaminants like sulphur dioxide.

Case studies have shown that the average number of containers/whippets inhaled in a session is usually fewer than 5;¹⁷ for example, a survey of students in Auckland found that recreational use typically amounted to 2–5 containers in a session.¹⁸ However, other studies report a range of 10–100 bulbs used in one session.^{17–28} Recreational users will typically inhale a number of small, imprecise doses from small containers and consequently it may be difficult to assess the quantity of nitrous oxide.

An experimental study testing the effects of nitrous oxide in 12 volunteers found that the primary effects were found only at the inhalation of 20% to 40% concentrations.²⁹ At the inhalation of 40% nitrous oxide (the highest concentration tested), subjects were confused, sedated, high, dysphoric and stimulated, but fatigue and depression were observed once the effects had worn off.

As nitrous oxide is used as an anaesthetic, official advice has been issued on the short-term occupational exposure limit, to avoid harms. The advice on this ranges from 25 parts per million (ppm) to 100 ppm,⁷ and may provide an indication of the level at which harms can occur in recreational users. The harms resulting from nitrous oxide are largely determined by its mode of use rather than its direct physiological effects. Inhalation through balloons or canisters is relatively safe, whereas the use of airtight bags, masks or respirators carries a high risk of asphyxiation.¹⁴

5.8. Desired effects of nitrous oxide for recreational use

Nitrous oxide is used recreationally to induce euphoria. Its effects are very short-lasting and typically include a rush of dizziness, relaxation, laughing fits, auditory distortions and sometimes hallucinations. As an anaesthetic gas, it affects coordination and awareness. It is reported that some people use it to self-manage pain and anxiety. Nitrous oxide consumption also reduces psychomotor performance.³⁰

There is variability in the subjective effects of the drug. In one study, 12 individuals (under controlled, blinded conditions) were given a choice between oxygen and nitrous oxide after a sampling period for both. There was significant individual variability in the reported effects of the drug. Those who reported feelings of 'tingling', 'drunk', 'dreamy', 'coasting', 'floating' and 'having pleasant bodily sensations' during the nitrous oxide sampling period chose nitrous oxide more often during the choice period.³⁰

There is disagreement in the literature as to whether there are gender differences in the effects of nitrous oxide.^{29,31}

5.9. Mortality

A number of cases of death by asphyxiation are reported among individuals who were using nitrous oxide at the time. Although nitrous oxide does not depress the respiratory drive significantly, the normal physiological response to hypoxia is blunted when 50% nitrous oxide is given and deaths are often in relation to bags put over the head in order to facilitate inhalation³² or inhalation in cars.

5.10. Acute harms

5.10.1. Acute toxicity

The 2011 ACMD report on novel psychoactive substances suggested that nitrous oxide typically has few short-term adverse effects, other than headache for some.¹ Harms are likely to result from disorientation and unsteadiness caused by inhalation (e.g. falling down²⁹). There are also isolated instances in the literature of hypothermic skin trauma resulting from contact with chilled canisters.³³

Nonetheless, acute exposure to nitrous oxide may irritate the respiratory tract and acute use of inhalants in general can result in sneezing, coughing, excess salivation and conjunctival erythema.⁴ It can also cause asphyxia, headache, nausea, vomiting,

Box 5.1. Features of acute intoxication with nitrous oxide

Respiratory effects

Asphyxia
Hypoxia

Neurological and psychiatric effects

CNS depression
Convulsions
Psychiatric symptoms
Headache
Myeloneuropathy
Polyneuropathy
Dizziness
Excitement
Paraesthesias
Paralysis
Psychosis

Cardiovascular effects

Hypertension
Cardiac dysrhythmias
Megaloblastic anaemia
Leukopenia
Anoxia

Metabolic features

Thrombocytopenia

Gastrointestinal symptoms

Nausea and vomiting

dizziness and excitement, and to central nervous system (CNS) depression, convulsions and death. Hypertension and cardiac dysrhythmias are possible. Patients can present with altered mental state, paraesthesias, ataxia and weakness or spasticity of the legs.⁷ Nausea, cyanosis and fainting have been reported as a result of nitrous oxide.³⁴ The features are summarised in Box 5.1.

When nitrous oxide is inhaled from a balloon it displaces the air in the lungs, thus temporarily preventing oxygen from entering the bloodstream and potentially causing tachycardia and transient peripheral neurological symptoms. There have been reports of fatalities after acute exposure, due to asphyxiation.^{35,36}

Nitrous oxide is insoluble in blood, and therefore rapidly clears into the alveoli from the blood once inhalation has ceased.³⁷ At the high concentrations (e.g. >70%) used in anaesthesia there is the potential for hypoxia if a high concentration of oxygen is not then provided. Nitrous oxide may have effects on immune function, but the evidence is unclear on this issue.⁷

There is a risk that users may confuse the much more toxic or potent gases or volatile substances, such as butane, with nitrous oxide. If a patient requires admission to an emergency department, there is a chance that he or she has used butane, which does not only have different effects but also different harms. The use of nitrous oxide is not as life-threatening as the use of butane, which can cause arrhythmia and increases the risk of sudden cardiac arrest. Life-threatening risks of nitrous oxide are linked to mode of use, which may lead to hypoxia or anoxia.

5.10.2. Acute withdrawal

For withdrawal see section 5.12.1.1.

5.10.3. Poly-drug use and drug interactions

There may be some increase in the effects of nitrous oxide when it is combined with alcohol.³⁸ It is possible that nitrous oxide ingested at the same time as stimulants has a greater effect on blood pressure and heart rate. There is anecdotal evidence that nitrous oxide can briefly enhance the effects of psychedelics like LSD, or bring the effects back strongly when the drug is wearing off, which could be very frightening if unexpected.

As it is not metabolised by the liver, the potential for drug interactions with other agents, including antiretrovirals, is very low.

5.11. Clinical management of acute toxicity

5.11.1. Identification and assessment of acute toxicity

The diagnosis of acute nitrous oxide toxicity should be made by clinical assessment. There are no rapid urine or serum field tests, so analytical assessment should not be

For up-to-date guidance on the management of nitrous oxide acute toxicity, 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/N-Products/Nitrous-oxide/>

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

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

considered a component of routine diagnosis. Assessment should be based on the recognition of the clinical toxidrome associated with nitrous oxide and the potentially harmful modes of use.

5.11.2. Clinical management of acute toxicity

The management of acute harms resulting from nitrous oxide include removal from exposure and providing symptomatic treatment for any resultant problems. TOXBASE® recommends observation for at least one hour after exposure and a need to perform a 12-lead ECG and a full blood count in symptomatic patients. Where there is chronic use of nitrous oxide, it is recommended that B12 concentration is checked in symptomatic patients (see section 5.12.2).

5.12. Harms associated with chronic use and dependence

5.12.1. Dependence

There are currently no reported instances of nitrous oxide dependence in the literature, and it has been suggested that its addictive potential is low as it is only a partial opiate agonist and its euphoric effects fade rapidly.²⁰ However, as the effects are short-lasting and pleasurable, people may use it re-dose frequently. There is anecdotal evidence of psychological dependence, and daily use of nitrous oxide should be avoided in particular by people with mental health problems or other psychological vulnerability.³⁹

5.12.1.1. Withdrawal

Nitrous oxide is sometimes used in a compulsive way by some individuals, possibly explaining one of its street names, 'hippie crack'. There are no significant withdrawal symptoms aside from the desire to use more nitrous oxide.

5.12.2. Other harms – vitamin B12 deficiency

The harms caused by nitrous oxide tend to stem from heavy usage and specifically the depletion of vitamin B12 by oxidising the cobalt moiety of the vitamin.^{23,40,41} By inactivating vitamin B12, a critical cofactor in haematopoiesis and lipid membrane formation, nitrous oxide can cause anaemia and neuropathy; severe myeloneuropathy is one complication of nitrous oxide use.²³

Regular or long-term use of nitrous oxide has been associated with leukopenia, thrombocytopenia, myeloneuropathy²³ and vitamin B12 deficiency leading to severe megaloblastic anaemia.⁴² It can also lead to neurological complications and psychiatric symptoms, including psychosis, paralysis, paraesthesiae and sensory loss, though these can respond to vitamin B12 replacement. One case report has described peripheral neuropathy⁴³ and a number of others have given details of myelopathy^{5,17,23,24,26,44–49} and polyneuropathy⁴³ as a result of sustained nitrous oxide misuse and associated vitamin B12 deficiency. This has been seen to present with paralysis²¹ and ataxia,²³ and may be confused with Guillain–Barré syndrome.²⁶ A case report of cardiac arrest has been published.²¹

Although the evidence is limited, it is possible that nitrous oxide can worsen some mental health problems, and its use has been linked to manic relapse.⁵⁰ One case report describes a psychotic episode occurring in a patient with no history of psychosis who had been regularly using nitrous oxide.⁴²

There is a growing body of evidence, mainly from animal studies, that nitrous oxide may have some neurotoxic effects. Rat studies suggest long-term developmental issues such as memory impairment, but the long-term cognitive outcomes in humans remain unknown.²

5.13. Management of harms related to chronic use

Suggested treatment for the chronic harms related to the use of nitrous oxide resulting from vitamin B deficiency include parenteral folic acid,^{23,44} intramuscular vitamin B12 injection^{17,23,43,45,47} and intravenous methylprednisolone.⁵ A number of studies have shown that stopping exposure and introducing vitamin B supplementation may result in either partial or complete recovery, although this can take months.⁴⁵ A case report suggests that where symptoms persist, methionine treatment has been successful where B12 treatment alone has failed.⁵¹

One case report has highlighted the need to consider vitamin B12 deficiency in patients who arrive at a hospital with psychiatric manifestations who report a history of nitrous oxide exposure or misuse in the recent or remote past.⁴²

5.13.1. Psychosocial and pharmacological support

There is no relevant pharmacological support. For psychosocial support, see Chapter 2.

5.14. Harm reduction and public health

The inhalation of nitrous oxide through the balloon method may carry less risk than other methods and minimises the risk of anoxia. Users will drop the balloon if they are getting too hypoxic or lose consciousness. Other methods may carry more risk, in that the user may become unconscious through anoxia and continue to have insufficient access to oxygen.

The following harm reduction measures have been identified:¹⁴

- Users should always inhale nitrous oxide from a balloon – never from a tube or mask, or directly from a dispenser or compressed air tank.
- Users must be careful not to confuse nitrous oxide with other gases and volatile substances, which have far greater risks.
- Users should avoid inhaling while standing up and should be aware of their immediate surroundings (e.g. steep drops, fires, rivers).
- The use of nitrous oxide should be avoided in particular by people with problems with low blood pressure or any mental health issues.
- Users should stop inhaling if they feel any physical discomfort, such as ‘pins and needles’ or numbness.
- Regular and long-term users of nitrous oxide in particular should be aware of the purity of the products they use and of the impact of any impurities.

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Part III: Stimulants

A wide range of substances are used recreationally for their stimulant effect, notably of course caffeine and nicotine. Illicit substances so used include cocaine, the range of amphetamine-type substances (ATS) and piperidols. Substances with a stimulant effect have been used by successive generations, and psychostimulants form a large proportion of club drugs and novel psycho-active substances. The toxic effects of the latter have not been well studied, but are expected to be similar to those of better-understood stimulants.

The patterns of effects of the various stimulant agents vary, but stimulant drugs overall stimulate the brain and central nervous system by increasing the activity of key neurotransmitters, such as noradrenaline, dopamine and serotonin. This takes place through a number of mechanisms, including increasing release of and/or inhibiting reuptake of these chemicals.

The extent to which a specific drug elevates these levels will determine the effect. Drugs that elevate dopamine significantly will induce greater reward and pleasure or even euphoria, but are also more likely to increase a desire to re-dose. Those that elevate noradrenaline will be less euphoric, but may increase alertness and cause anxiety. They also increase strain on the heart and circulatory system.

There are other new stimulant-type drugs (NPS) that are not used for their psycho-active effects, but as appetite suppressants and 'fat burners'. These include appetite suppressants and 'fat-burners' which can have adverse effects, but which fall outside the remit of this document.

Part III begins with a chapter on non-amphetamine-type stimulants, cocaine and synthetic cocaine derivatives, as well as piperazines (the last only briefly because their use has faded away in the UK since 1-benzylpiperazine became a controlled substance in 2009). Chapter 7 then gives an overview of the wide range of amphetamines that are currently used recreationally in the UK, before Chapters 8–11 give further details on more specific groups.

Chapter 6

Cocaine, synthetic cocaine derivatives and piperazines

This chapter reviews the literature on recreationally used stimulants which are not phenethylamines. These include cocaine as well as synthetic cocaine derivatives, and piperazine. Crack cocaine is not recreationally used as a 'club drug' and is therefore excluded from this review, which focuses on powder cocaine only.

6.1. Cocaine: an overview

Powder cocaine has been used in the UK for a number of decades and remains the second most commonly used drug in the country, after cannabis. It is the drug that is most commonly used in a 'club drug' context (unlike crack cocaine).

Generally speaking, clinicians in the UK have experience in managing the harms of powder cocaine and there is a body of evidence relating to its acute toxicity and to dependence in particular. This document will therefore not cover cocaine to the same extent and level of detail as for the other novel substances. In particular, this chapter will not address the management of chronic harms of (powder) cocaine and cocaine dependence. Cocaine-related disorders are clearly identified in ICD-10* and there is a large body of evidence on cocaine-related harm and its management, including the management of dependence and withdrawal.¹⁻⁶ This includes a number of Cochrane reviews.[†]

This chapter will, though, address the most common *acute* health problems associated with cocaine. In addition, it ends with a brief section on piperazines, which, like cocaine, are sympathomimetic stimulants but not phenethylamines, as are the other stimulant drugs discussed in Part III (Chapters 7–11).

There are no Cochrane reviews relating to cocaine acute intoxication and the evidence-base is not as substantial as it is for dependence. Acute cocaine intoxication is a common reason for presentation to emergency departments in the UK and elsewhere in Europe,⁷ but the data show that there is an under-recognition of acute cocaine toxicity in patients presenting with chest pain.⁸⁹

There are aspects of acute cocaine toxicity that are different from the acute toxicity associated with the stimulants to be covered in the other chapters in Part III of this document, in particular myocardial ischaemia and chest pain (related to vasospasm) and arrhythmias (related to ion channel effects). Cocaine-induced psychosis (CIP) is

* See <http://www.icd10data.com/ICD10CM/Codes/F01-F99/F10-F19/F14>.

† Further examples can be accessed at <http://www.thecochranelibrary.com/details/browseReviews/579489/Cocaine.html>.

also a recognised cause of presentation to emergency departments. This chapter therefore focuses on cardiovascular disorders and psychosis.

6.2. Legal status and pharmacology

Cocaine is a Class A Schedule 1 drug under the Misuse of Drugs Act 1971.

Cocaine increases the activity of monoamine neurotransmitters in the central and peripheral nervous system by blocking reuptake transporters of dopamine, nor-adrenaline and serotonin. In addition, cocaine modulates preprodynorphin and the mu and kappa receptors of the endogenous opiate system.¹⁰ Cocaine stimulates the sympathetic nervous system.

6.3. Prevalence, patterns of use, desired and unwanted effects and routes of ingestion

The 2013 report from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) indicated that approximately 2.5 million young adults (aged 15–34) in the European Union had used the drug in the previous year, with high levels of use concentrated in the UK, Denmark, Spain, Ireland and Italy.¹¹ However, these countries with high levels of use have reported in recent years a declining trend in cocaine use, as well as in treatment demand.¹¹

The use of cocaine powder continues to be relatively high in the UK, in comparison with most other European countries. The 2013/14 report from the Crime Survey for England and Wales (CSEW) indicated that cocaine was the second most commonly used drug after cannabis by all adults in the UK between the ages of 16 and 59 years: 2.4% had used it in the previous year. This was significantly higher than in 2012/13, when it was used by 1.9% of adults. It was also significantly higher than in 1996 (0.6%), although it was lower than during the peak of its use, in 2008/09 (3%).

After a period of decline in the purity of cocaine powder sold on the illicit market in the UK, the mean purity of the drug increased in 2011,¹² as it did in other countries with sizeable consumer markets, such as France and Germany.¹³ The impact of this on recreational use remains to be seen.

The desired effects of cocaine use are feelings of increased energy, alertness and intense euphoria, as well as a decrease in tiredness, appetite and sleep. Unwanted effects include fear, irritation, panic attacks, paranoia, impaired judgement, delusions and disturbance of sleep. Weight loss and hallucinations occur with increased doses or a more efficient route of administration.¹⁴ Following binges in particular, a user is often anhedonic, irritable and anxious, and has low mood.^{15–17}

Cocaine intoxication has been associated with anorexia, insomnia, anxiety and motor hyperactivity. It is linked with increased adrenergic tonus, manifested by diaphoresis, dilated but reactive pupils, hyper-reflexia and tachycardia. Stereotypical movements of face, mouth and extremities and even grand mal seizures may be present.¹⁸

Cocaine can be smoked, snorted or used intravenously. It is absorbed readily through all mucosae. The peak effect occurs 1–90 minutes after administration, depending on the route. The half-life varies between a few seconds and 20 minutes, depending again on the mode of administration (inhalation, intravenous administration or snorting, respectively). After oral use, the half-life is longest, at approximately 3 hours.¹⁹

6.4. Mortality

Figure 6.1 shows the mortality associated with cocaine use in the UK (data from the Office for National Statistics).²⁰

Cocaine users have an increased mortality compared with the general population.^{21–23} Cardiac disease is a common cause of cocaine-related sudden death and a number of post-mortem studies have demonstrated an extremely wide range of serum cocaine concentrations in individuals who died following its use, suggesting that no blood concentration is always safe.²⁴ Cocaine users often smoke and have a high use of alcohol, which will also have an impact on risk. The combination of cocaine and cigarette use results in greater increases in heart rate and vasoconstriction than either cocaine use or cigarette smoking alone.²⁵ Similarly, cocaine and alcohol combine to be metabolised to a reinforcing compound, cocaethylene, and the combination is substantially more toxic than either substance on its own. Cocaethylene is a cocaine metabolite, formed in the liver only in the presence of ethanol; it depresses the myocardium, causing cardiotoxicity.²⁶

A study by Lucena et al., of a consecutive series of 686 sudden deaths, found that myocardial infarction was the most common cardiac condition responsible for sudden death following cocaine use, with some patients having occlusive coronary thrombosis with acute infarction and others having organised, recanalised thrombus and remote infarction.²⁷

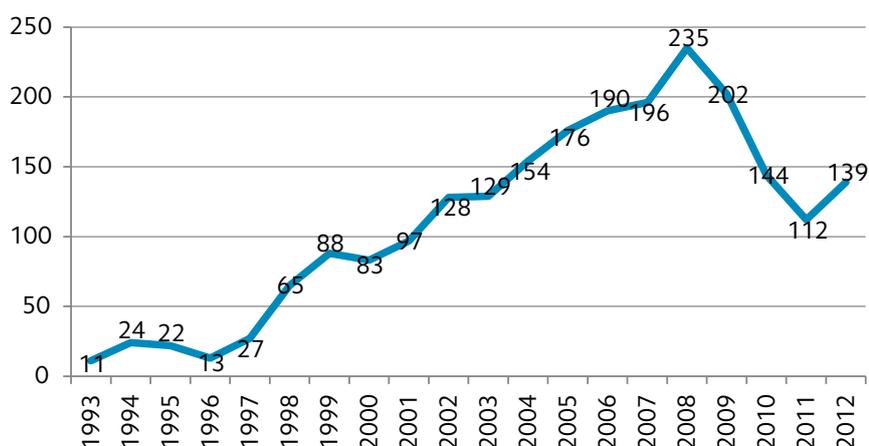


Figure 6.1. Number of drug-related deaths where cocaine was mentioned in the death certificate, England and Wales, death registered between 1993 and 2012

6.5. Acute harms

Problems relating to acute cocaine intoxication are relatively common, although many users will not experience any. Cocaine can cause a range of acute health-related problems and even sudden death (section 6.4).

Cocaine use has been associated with a number of medical complications, which result from acute and chronic use and may differ according to the route of administration. Medical complications may involve all of the body's major organs and systems.²⁸

The harms related to acute cocaine intoxication and to chronic use have been summarised as follows:⁷

- cardiovascular disorders (including ischaemia, acute coronary syndrome, arrhythmia);
- cerebrovascular disorders and neurological impairment (cerebrovascular accident or stroke, and status epilepticus);
- psychiatric disorders (euphoria, dysphoria, agitation, anxiety, suicidal thoughts, paranoid psychosis and depression);
- respiratory disorders, either acute (pulmonary oedema, pulmonary infarction, haemoptysis) or chronic (e.g. pulmonary hypertension);
- genitourinary and obstetric disorders, either acute (acute renal failure, mediated by rhabdomyolysis or direct toxicity, testicular infarction, placental abruption, spontaneous abortion) or chronic (premature birth, growth retardation);
- gastrointestinal complications (mesenteric ischaemia or infarction);
- musculoskeletal and dermatological disorders.

Chronic cocaine use has also been associated with hepatocellular damage.²⁸

6.5.1. Acute toxicity

TOXBASE® (accessed 6 January 2015) has identified the features of cocaine-related toxicity, which include euphoria, agitation, tachycardia, tachypnoea, sweating, ataxia, dilated pupils, nausea, vomiting, headache, delirium and hallucinations. Complications related to cocaine toxicity include hypertension, chest pain (often non-ischaemic), myocardial ischaemia and infarction, as well as cardiac dysrhythmias, coronary artery dissection,²⁹ aortic dissection, convulsions, subarachnoid and intracerebral haemorrhage, cerebral infarction and gastrointestinal (gut) ischaemia. There may also be hyperpyrexia, rhabdomyolysis, renal failure, hypokalaemic paralysis,³⁰ metabolic acidosis and cardiorespiratory arrest. Choreoathetoid movements have also been reported.³¹ Serotonin syndrome may occur (for more information see Chapter 7).

The most common acute health problems associated with cocaine include neurological impairments and cardiovascular and cerebrovascular effects. These are associated with both acute intoxication and chronic use.³² Common non-cardiac

features of acute cocaine toxicity include seizures, hyperthermia and intracerebral haemorrhage or infarction. Hyperthermia is possible and can be life-threatening.²⁸ Agitation, anxiety, aggression and cocaine-induced psychosis are also common³³ and psychiatric symptoms can include suicidal thoughts.²⁸

A Spanish study of 720 regular cocaine users aged 18–20 who were not regular heroin users found that 27% had experienced acute cocaine intoxication during the previous year. Of these, 35% presented symptoms of psychosis (hallucinations or delirium) and more than 50% reported chest pain.³⁴

6.5.1.1. Cardiovascular disorders

There are many cardiovascular consequences of cocaine use and these can be severe. Cocaine has unique mechanisms of cardiotoxicity, which include sympathomimetic effects, blockade of sodium and potassium channels, oxidative stress and mitochondrial damage, and disruption of excitation–contraction coupling. In combination, these effects increase myocardial oxygen demand while simultaneously decreasing oxygen supply.³⁵

Cocaine has multiple cardiovascular and haematological effects that likely contribute to the development of myocardial ischaemia and/or myocardial infarction (MI). It blocks the reuptake of noradrenaline and dopamine at the presynaptic adrenergic terminals, causing an accumulation of catecholamines at the postsynaptic receptor and thus acting as a powerful sympathomimetic agent.³⁶ Indeed, cocaine use has been associated with myocardial ischaemia and/or acute coronary syndrome (ACS).^{37,38} US survey data have suggested that cocaine use is the cause of approximately a quarter of all fatal myocardial infarctions in patients who are 45 years or younger.³⁹

A common symptom of people presenting to emergency departments is non-traumatic chest pain.⁴⁰ Chest pain and other complaints suggestive of coronary ischaemia are among the most common complaints of patients presenting to emergency departments following cocaine use.^{41–45} Cocaine-associated chest pain has been described as having a pressure-like quality.⁴⁶

However, the presence of chest pain is not universal in cases of cocaine-associated MI. The American Heart Association's guidelines on the management of cocaine-related chest pain and MI suggested that chest pain may have little value in distinguishing an ischaemic from a non-ischaemic cause in these patients.³⁶ In one study, only 44% of 91 patients with cocaine-associated MI reported antecedent chest pain.⁴⁴ Another study showed that in 130 patients with cocaine-associated MI, there was equal distribution between anterior (45%) and inferior (44%) MI, and most were non-Q wave (61%).⁴⁷ Cocaine-associated chest pain may be caused not only by MI but also by aortic dissection, and the American Heart Association's guidance suggests that this must be considered in the differential diagnosis.³⁶

It has been shown that, in persons who are otherwise at relatively low risk, the risk of acute MI is increased by a factor of 24 during the 60 minutes after the use of cocaine,³⁷ when the blood cocaine concentration is highest.^{37,46,48} However, this is not

always the case, as the onset of symptoms was also reported several hours after the administration of the drug, when the blood concentration of cocaine is low or even undetectable.^{37,49}

The risk is unrelated to the amount ingested, the route of administration and the frequency of use; it has been reported with doses ranging from very small amounts to 2000 mg, after ingestion by all routes, and in habitual as well as first-time users.^{24,40} There is also evidence that cocaine-related MI occurs in individuals who use the drug infrequently (e.g. less than once a month).^{27,37} It has been suggested that cocaine users with atherosclerotic coronary artery disease are probably at greater risk of an ischaemic event after cocaine use than are cocaine users without coronary artery disease.^{50,51}

The accurate identification of patients with cocaine-related MI may be difficult, for a number of reasons.⁴⁰ The electrocardiogram may be abnormal in many patients with chest pain after cocaine use, even in the absence of MI. In addition, serum creatine kinase concentrations are not a reliable indicator of myocardial injury, since they are elevated in about half of cocaine users who do not have MI.⁴⁰ It has been suggested that this elevation of serum creatine kinase may be due to rhabdomyolysis.^{50,51}

There is very little information on the prevalence of recent cocaine use in individuals presenting to the emergency department (ED) with chest pain and/or suspected acute coronary syndrome (ACS) in the UK or elsewhere. A 12-month retrospective review of all suspected myocardial ischaemia/ACS presentations to a London ED (1 January to 31 December 2008) found 54 cases (1.9% of the 2810 presentations) with self-reported cocaine use before the onset of symptoms. Among the self-reporting cocaine users, 20 individuals (37.0%) had one or more features of potential cocaine sympathomimetic toxicity at presentation to the ED. Agitation/anxiety was most commonly observed (in 14 cases), followed by tachycardia (10), systolic hypertension (6), diastolic hypertension (2) and hyperpyrexia (1).³⁸

US studies have shown that approximately 6% of patients who come to the ED with cocaine-associated chest pain have enzymatic evidence of MI.^{46,52}

There are potential cardiovascular complications resulting from cocaine-related MI.^{36,40,48} A study of 130 such patients found that 38% had additional cardiac complications; heart failure occurred in 7% and arrhythmias in up to 43%. Notably, 90% of these complications occurred within the first 12 hours of presentation to the hospital.⁴⁸ It has been reported that patients who continue to use cocaine after their initial hospitalisation and have a higher cumulative risk of MI and associated complications.³⁶

Cocaine use also causes increased endothelial production of endothelin, a potent vasoconstrictor,⁵³ and decreased production of nitric oxide, a potent vasodilator,⁵⁴ effects that may promote vasoconstriction.⁴⁰ Cocaine use has been associated with accelerated coronary atherosclerosis in individuals who do not have other atherosclerotic risk factors. In Lucena et al.'s study, this was present in 76% of the sudden cocaine-related deaths.²⁷

In addition to being a nidus for plaque rupture and subsequent platelet aggregation and thrombus formation, sites of atherosclerotic narrowing manifest enhanced coronary arterial vasoconstriction in response to cocaine.⁵⁵ Post-mortem studies of long-term cocaine users have shown premature atherosclerotic coronary artery disease, which may be associated with a nidus for such thrombus formation⁵⁶ and cocaine may induce thrombus formation in the coronary arteries.⁵⁷ It has been suggested that thrombus formation may be promoted by the fact that cocaine use is associated with enhanced platelet activation and aggregability⁵⁸⁻⁶⁰ as well as increases in the concentration of plasminogen-activator inhibitor,⁶¹ which may promote thrombus formation.

Long-term use of cocaine is also associated with cocaine-induced myocardial dysfunction and can cause left ventricular hypertrophy⁶² and systolic⁴⁰ and diastolic dysfunction.⁶³ This may be caused in some cases by the metabolic disturbances and acid-base disturbances (or both) that accompany cocaine intoxication. In other cases it may be caused by a direct toxic effect of the drug.⁴⁰ There is also some evidence that repeated exposure to cocaine may induce left ventricular systolic dysfunction.⁴⁰

Dysrhythmias are also associated with the drug. The sodium-channel-blocking properties of cocaine and its ability to induce an enhanced sympathetic state are likely to produce or exacerbate cardiac arrhythmias.⁴⁰ Cocaine can produce arrhythmias either through the production of myocardial ischaemia or as a direct result of ion channel alterations. It can cause arrhythmias in the absence of any myocardial ischaemia.⁶⁴⁻⁶⁶ It has been suggested that this is due to the actions of cocaine and its major metabolites on cardiac ion channel function and alteration of the 'normal' cardiac action potential.⁶⁷

Cocaine-related life-threatening arrhythmias and sudden death caused by arrhythmia occur most often in patients with myocardial ischaemia or infarction or in those with non-ischaemic myocellular damage.⁴⁰ Long-term cocaine use is associated with increased left ventricular mass and wall thickness, which is known to be a risk factor for ventricular dysrhythmias. It has been suggested that this may provide the substrate that facilitates the development of arrhythmias in some cocaine users.⁴⁰

Cocaine use can cause both acute and chronic dissection of the aorta,⁶⁸ a potentially life-threatening condition in which there is bleeding into and along the wall of the aorta. This probably results from the severe transient increase in systemic arterial blood pressure caused by the drug.⁷

In addition to MI and aortic dissection, cocaine use may lead to pulmonary hypertension and associated chest pain and dyspnoea.⁶⁹

The intravenous injection of all drugs is associated with endocarditis, but a study has suggested that the use of cocaine appears to be a greater independent risk factor than the use of other drugs.⁷⁰ In addition to endocarditis, it is thought that the increases in heart rate and blood pressure that result from cocaine use may lead to valvular and vascular injury that predisposes to bacterial invasion; the immunosuppressive effects of cocaine may further increase the risk of infection.^{32,71}

6.5.1.2. Cerebrovascular disorders

The acute and chronic use of cocaine may cause haemorrhagic or ischaemic stroke and the association between cocaine use and stroke has been observed for many years.⁷²⁻⁷⁵ although some studies have contested these findings.³⁹ Recently, a systematic review has reported that epidemiological evidence suggests that cocaine use increases the risk of stroke, but that more research is needed to quantify this risk; such research should consider stroke type, hypertension variation, frequency and length of cocaine use, as well as amphetamine co-use.⁷⁶

A number of factors may be involved, including vasospasm, cerebral vasculitis, enhanced platelet aggregation, cardio-embolism and hypertensive surges associated with altered cerebral auto-regulation.⁷⁷

Seizures associated with cocaine typically occur after chronic use, but may also result after the initial use of cocaine, through any route of administration.⁷ Most cocaine-related seizures occur within minutes and almost always within 90 minutes, when there is peak concentration of cocaine in the blood.⁷⁸

Cocaine-induced seizures are usually single, generalised seizures. However, status epilepticus can also occur after cocaine use. Seizures can occur in patients with or without a history of seizure disorder, but the prevalence of cocaine-induced seizures is twice as high in people with a history of non-cocaine-related seizures as in those without a history of seizure disorder. Seizures caused by cocaine may be lethal, primarily because of associated cocaine-induced hyperthermia, systemic acidosis, cardiac dysrhythmias and cardiac arrest.⁷

6.5.1.3. Cocaine-induced psychosis

Cocaine-induced psychosis has been recognised for decades, especially in emergency departments.⁷⁹ Cocaine has a wide range of neuropsychiatric effects, including transient psychotic symptoms. These symptoms include paranoia and hallucinations,⁸⁰⁻⁸² violence and aggression,^{4,83,84,85,86,87,88,89} repetitive or stereotyped simple behaviours and repetitive complex behaviours such as drawing and writing. The term 'cocaine-induced psychosis' (CIP) has been used to describe this syndrome. These symptoms typically disappear with abstinence.⁹⁰⁻⁹²

As with other psychostimulants, cocaine can produce psychotic syndromes in healthy individuals. Among the majority of those with schizophrenia, cocaine use – at doses which would not be psychogenic in healthy individuals – will exacerbate psychotic symptoms.¹⁸ Compliance with antipsychotic medication in those diagnosed by schizophrenia will not prevent a relapse or worsening of psychotic symptoms if stimulants, including cocaine, are used.⁹³

It is difficult to estimate the prevalence of CIP among cocaine users; different studies have reported prevalence ranging from 48% to 88%.⁹⁴⁻⁹⁶ CIP is common in cocaine-dependent patients who seek treatment.⁷⁹ The factors found to increase the risk CIP include the amount of cocaine ingested^{79,97-99} and early onset of cocaine use.^{82,95,98} There are reports that the early onset of cocaine dependence, or onset in vulnerable

periods of brain development, may increase the severity of CIP.^{98,100} However, one study found that the number of years of cocaine use was not linked to CIP.¹⁰¹ In comparison with nasal insufflation (snorting), the smoking⁹⁹ or injecting¹⁰² of cocaine may increase the risk of CIP. A history of cannabis dependence was associated in a study with CIP⁷⁹ and another study found that adolescent onset of cannabis use increased the risk of CIP in cocaine-dependent individuals.⁹⁵

It has also been reported that the severity of the substance use disorder is associated with the prevalence of psychotic symptoms, and that the prevalence of CIP is higher in dependent individuals than in other users of cocaine,⁹⁴ and in the most severely dependent patients.^{94,95} Some studies have observed that drug-dependent individuals with cocaine-induced paranoia are at higher risk of developing a psychotic disorder.^{15,103} CIP has been linked to hostile behaviours and antisocial personality disorder (ASPD).⁷⁹ Studies have suggested a pattern in which stimulants generate hostility through psychotic symptoms. For example, the use of cocaine may lead to a perception of the environment as a hostile and threatening place, and increase impulsivity. Thus CIP can trigger hostile behaviours.^{104,105}

6.6. Management of cocaine-related acute harms

6.6.1. Hospital presentation with acute cocaine intoxication

Cocaine is the illicit drug that leads to the most ED visits in the US, with 138 per 100,000 population in 2009.¹⁰⁶ In the European Union, a study was carried looking at cocaine-related emergency admissions; data were obtained from 17 of the member states at that time. In the most recent year for which data were available, the UK reported the most cocaine-related emergency episodes, followed by Spain, Italy and the Netherlands.¹⁰⁷

In the UK in 2010/11, 2247 hospital inpatient discharges recorded cocaine poisoning and 4209 inpatient discharges recorded mental and behavioural cocaine-related disorders.⁷ It is widely acknowledged that these figures grossly underestimate the overall prevalence of patients presenting with acute cocaine-related toxicity, as coding is often based on presenting symptoms (e.g. chest pain) rather than cause (e.g. cocaine use).³³ In addition, there is under-recognition of acute cocaine toxicity in patients presenting with chest pain and a study has shown, for example, that although junior medical staff in a London hospital were aware that cocaine is a risk factor for ACS and acute MI, they were not likely to ask about it in routine clinical practice or to record its use/non-use in the case notes.⁸

6.6.2. Management of cocaine-induced cardiovascular disorders

It has been argued that it is essential that patients presenting with chest pain or suspected ACS are asked about cocaine use,^{8,38} as the management of these patients is different from the management of those with ACS secondary to 'classical' cardiovascular risk factors.^{36,40,45,108}

Some guidance is available on the management of cardiovascular disorders induced by cocaine use, from the American Heart Association³⁶ and others.^{40,45,108} The evidence on the management of other cocaine-related disorders has also been reviewed, including the treatment of patients with cocaine-induced arrhythmias¹⁰⁹ and the management of cocaine-induced cardiac arrhythmias due to cardiac ion channel dysfunction.⁶⁷

The management of cocaine-induced cardiovascular harms can be complex and readers should seek up-to-date guidance from TOXBASE®.

For up-to-date guidance on the management of cocaine acute toxicity, 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/C-Products/Cocaine/>

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

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

It has been argued that as cocaine toxicity is a dynamic process, patients are best served by close observation until stability has been assured.¹⁰⁹ Overall, however, in most instances treatment of cocaine intoxication is supportive.

The evidence base on the management of cocaine-related cardiovascular harms reflects some of the controversies regarding therapeutic strategies. This includes the disagreement on the use of beta-blockers in the management of cocaine-induced chest pains and MI. Cardiology guidelines, for instance from the American Heart Association, mentioned above, recommend against their use^{36,110,111} because of the potential lethality of an interaction between cocaine and a beta-adrenergic receptor antagonist, as shown by a recent case report, for example.¹¹²

However, some have argued recently that there may be a role for certain beta-blockers in ameliorating the cardiovascular, as well as central nervous system, effects of cocaine.¹¹³ A retrospective study of consecutive patients admitted to San Francisco General Hospital between 2001 and 2006 with chest pain and urine toxicological test results positive for cocaine found that beta-blockers did not appear to be associated with adverse events in patients with chest pain and recent cocaine use.¹¹⁴

Similarly, there is controversy over the management of cocaine-associated cardiac arrhythmias, including the use of sodium bicarbonate and lidocaine.⁶⁷

6.6.3. Management of cocaine-induced psychosis

A systematic review has concluded that, in the absence of better evidence, treatment of stimulant-induced psychosis, including CIP, should involve efforts to encourage abstinence from stimulants and treatment with antipsychotic drugs until the acute

symptoms settle. It is also argued that this should be followed by regular low doses of antipsychotics for those who have experienced more than one episode of psychosis.⁹³

Treatment for CIP includes providing a safe environment, managing agitation, and addressing the underlying substance use disorder. It has been argued by Nunes et al. that because schizophrenia and cocaine use are multifaceted conditions, no simple solution exists for their clinical management. While reliance on established treatment guidelines and best practices is the optimal *modus operandi*, clinicians must assess patient presentation to institute the proper individually tailored management strategy.¹⁸

6.6.4. Discharge and onward referral

It has been argued that when the patient is ready for discharge, referral to a drug treatment programme is likely to be the most important intervention to help prevent a recurrence of an emergency presentation.¹⁰⁹ However, there is some evidence that ED visits for cocaine-related chest pain represent missed opportunities to link patients to drug treatment, and interventions are needed to motivate patients to seek care.¹¹⁵

6.7. Chronic use and dependence and their clinical management

6.7.1. Cocaine dependence and its management

Cocaine use is associated with dependence. This is a major public health problem that is characterised by recidivism and a host of medical and psychosocial complications.¹¹⁶

There is a large body of evidence on the management of cocaine dependence and associated harms,¹⁻⁶ including a number of Cochrane reviews.* There is still no pharmacological treatment of proven efficacy. In the last two decades, a number of trials have been conducted using antidepressants, antipsychotics, anticonvulsants and dopaminergic medications. The potential usefulness of disulfiram has been reported and there is an interest in assessing the efficacy of psychostimulants for use as replacement therapy.¹¹⁷ Work is currently being undertaken on a cocaine vaccine that could lead the immune system to generate specific antibodies that would bind the drug while it is still in the bloodstream and prevent it from entering the brain.¹¹⁸

Psychosocial interventions remain the cornerstone of treatment. Although there are important differences in the neuropsychiatric and medical consequences of cocaine when compared with amphetamine use disorders, there is currently no evidence for a differential treatment effect of any psychosocial treatment in the management of these disorders.¹¹⁹ For detailed information on the psychosocial interventions relevant to cocaine users, see Chapter 2.

* See for further examples <http://www.thecochranelibrary.com/details/browseReviews/579489/Cocaine.html> (accessed 31 October 2013).

6.7.2. Access to cocaine-dependence treatment in the UK

The UK National Drug Treatment Monitoring System (NDTMS) reports that 5% of all adults in drug treatment in England in 2013/14 had a primary problem with powder cocaine (10,610 individuals). This group had a median age of 30, lower than the median age of those using opiates only (38 years) but older than those in treatment for cannabis misuse (median age 26 years). Data provided through the Treatment Outcome Profile (TOP) suggest that people treated for powder cocaine misuse typically have better outcomes at six-month review than people who use opiates, with 76% of people in treatment for cocaine misuse classified as abstinent or improved at review. An analysis of new treatment presentation over 9 years (from 2005/06 to 2013/14) found that cocaine users were most likely to have completed treatment than those with another primary problem drug, with 55% having done so without subsequently returning.¹²⁰

These data reflect those reported in an in-depth analysis of NDTMS data pertaining to users of powder cocaine over a period of 6 months in 2008-09 and which reported: 'Effective treatment is available for people who have a powder-cocaine problem – seven in ten of those who come into treatment either stop using or reduce their use substantially within six months'. The report showed that within 6 months of entering treatment, 61% had abstained from using cocaine for at least 28 days and a further 11% had cut their use significantly.¹²¹

6.8. Synthetic cocaine derivatives

'Synthetic cocaine' is the slang term sometimes used for substances that are sold online as a legal alternative to cocaine.¹²² A small number of synthetic cocaine substitutes are available and include the relatively recently reported RTI 111 (dichloropane ((-)-2 β -carbomethoxy-3 β -(3,4-dichlorophenyl)tropane, RTI-111, O-401), RTI 121 ((-)-2 β -carboisopropoxy-3 β -(4-iodophenyl)tropane, RTI-121, IPCIT) and RTI-126 ((-)-2 β -(1,2,4-oxadiazol-5-methyl)-3 β -phenyltropane).

Fluorotropacocaine (pFBT), with a structure closely related to that of cocaine, was first reported in the European Union by Finland in 2008. Its adverse effects were first reported in Ireland in 2010, where it was identified in two products sold by 'head shop' (shops where drug paraphernalia and/or so-called legal highs are sold). Both 3-(*p*-fluorobenzoyloxy)tropane (pFBT) and dimethocaine have been sold from retail websites as 'research chemicals' or have been identified in 'legal highs'.^{123,124}

There are reports of the use of some synthetic cocaine in the UK and in a survey conducted in London gay nightclubs in July 2011 9.9% of respondents reported lifetime use of 'synthetic cocaine' and 3.5% reported using it in the past month.¹²⁵ No information was available on which synthetic cocaine this was.

Little is known about the detailed pharmacokinetics and pharmacodynamics of pFBT in humans.¹²³ However, the drug has close structural similarities to cocaine and is likely to have similar pharmacology.¹²⁴ Animal studies have shown that it is associated with a longer half-life than cocaine, suggesting that its effects are likely to last longer.¹²⁴ In

animals, dimethocaine has stimulant effects and inhibits dopamine uptake almost as effectively as cocaine. Animal studies demonstrate a lower potency of dimethocaine compared with cocaine.¹²⁶ User accounts on the internet note that dimethocaine produces a mild stimulant effect.¹²³

As with cocaine, *p*FBT is anecdotally reported to cause hypertension, tachycardia, anxiety and temporary psychosis in humans.¹²⁷ The symptoms of acute intoxication include increased heart rate, increased breathing rates and raised blood pressure. Patients experience differing levels of anxiety and a small number of cases of psychotic episodes have been reported.¹²⁷ One case report described a patient presenting with excitement, xerostomia (dry mouth), chest pain, dyspnoea, tachycardia and hypertension. Blood glucose and creatine kinase were elevated.¹²²

At the time of writing, neither of these substances are under international control, and apart from Denmark (*p*FBT) and Romania (dimethocaine) there are no national controls in the European Union.

6.9. Piperazines

Other stimulants which are not phenethylamines include the piperazines. Piperazines, notably 1-benzylpiperazine (BZP), is a stimulant with similar action to amphetamine sulphate and with effects similar to dextroamphetamine (but with approximately one-tenth of the potency) and other sympathomimetics.

To a large extent, the use of BZP in the UK has faded away since its control in 2009. It was often sold as hydrochloride salt, usually white powder in capsules or pressed into tablets. A typical dose is 100–250 mg. Tablets have often been passed off as ecstasy, although they are also sold as BZP. In a survey carried out in gay nightclubs in London, 9.3% of respondents reported using BZP and 1.6% had done so in the last month.¹²⁵

High doses of BZP are associated with a sympathomimetic toxidrome.¹²⁸ The most common reported adverse effects associated with BZP are palpitations, agitation, vomiting, anxiety, confusion and seizures.^{129,130} The most serious effects are metabolic acidosis, seizures, prolongation of ventricular repolarisation and possibly also toxic paranoid psychosis and hyponatraemia. Two severe cases of BZP poisoning associated with multi-organ failure have been reported.¹²⁸

It has been reported that many of the formulations sold in tablets as BZP also contain other drugs, including 1-(3-trifluoromethylphenyl) piperazine (TFMPP). This combination has been reported to produce subjective effects similar to those observed with MDMA (ecstasy – see Chapter 10), although human studies are limited.¹²⁴ Inducible clonus, dissociative symptoms, bruxism (excessive grinding of teeth) and nausea have been reported as resulting from this combination.¹³¹

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Chapter 7

Amphetamine-type substances (ATS): an overview

Drug group: stimulant

The use of amphetamine-type substances (ATS) for their psychoactive effects is a global and growing phenomenon and, in recent years, there has been a significant increase in the production and use of ATS worldwide, both legal and illicit. The 2013 report of the United Nations Office on Drugs and Crime (UNODC) on the challenges of new psychoactive substances reported that the ATS market has always been characterised by a large variety of substances, but, in recent years, new psychoactive substances (NPS) have rapidly emerged in this market, purportedly as 'legal' alternatives to controlled drugs, causing similar effects to the latter, with the potential to pose serious risks to public health and safety.¹

The term 'amphetamine-type stimulants (ATS)' is used to refer to the following groups of substances or amphetamine analogues with stimulant effects: including phenethylamines; methcathinone and other synthetic cathinones; and benzofurans.

Phenethylamines are a broad range of compounds that share a common phenylethan-2-amine structure and include stimulants (e.g. amphetamine itself), entactogens (e.g. MDMA, considered in Chapter 10), and hallucinogens (e.g. 2C-E). Amphetamine, methamphetamine and MDMA are the most commonly used. The phenethylamines also include ring-substituted substances such as the '2C series', ring-substituted amphetamines such as the 'D series' (e.g. DOI, DOC), benzodifurans (e.g. Bromo-Dragonfly, 2C-B-Fly) and others (e.g. *p*-methoxymethamphetamine, PMMA). Phenethylamines in the 'D series' are described as longer lasting, more potent and more liable to induce vasoconstriction than other members of the phenethylamine family.² PMA, PMMA and 4-methylthioamphetamine have been more often associated with incidental deaths than other phenethylamines. PMA and PMMA are known to have a particularly high toxicity.³ A number of amphetamine derivatives have also appeared on the market in recent years, including various aminoindanes, 2-amino-tetralins and benzofurans, 2-aminoindane, 5-IAI, AMMI, DFMDA, MMAI, MDMAI and MDAT. Methiopropamine – a thiophene ring-based structural analogue of methamphetamine – is also sold as a 'legal high' alternative to cocaine; brands include Charlie Sheen and China White.

Studies have shown that phenethylamines have three different principal effects: central stimulant action; hallucinogenic action; and 'other' psychoactive action.⁴ Some produce more than one of these effects.⁵

Some substances, such as MDMA, also have entactogenic/empathogenic effects and cause unusual changes in consciousness, leading to euphoria and an intense love of self and others.⁶

Methcathinone and other synthetic cathinones, which include mephedrone, are closely related to the phenethylamine family. They are characterised by the presence of a beta-keto group on the side chain of the phenethylamines. Typically, synthetic cathinones have an amphetamine-type analogue; mephedrone and methyldone (discussed in Chapter 9) are structurally related to amphetamine, methamphetamine and MDMA.⁷

Benzofurans, specifically 5- and 6-APB, are ring-substituted amphetamine derivatives. These have appeared on the market in recent years. They are related to methylenedioxyphenethylamines, such as MDMA and MDA. For pragmatic reasons, these will be discussed at the end of the Chapter 10, on ecstasy (MDMA).

7.1. Pharmacology

While amphetamines are classed as stimulants, their pharmacological effects appear to be different from other stimulants; for example, cocaine prevents dopamine reuptake while amphetamines increase its release. The effects of amphetamines (and especially of methamphetamine, discussed in Chapter 8), also last longer than those of cocaine.⁸ It is generally believed that dopamine reuptake blockade – in particular in the nucleus accumbens – is the most important action of cocaine. On the other hand, enhancing the release of dopamine in the nucleus accumbens appears to be the mediating effect of amphetamines^{8,9} and amphetamines increase the release of newly synthesised noradrenaline and dopamine.^{8,10} ATS can reverse the action of the transporters facilitating neurotransmitter efflux* into the synaptic cleft and displace newly synthesised neurotransmitters from the vesicle stores. They also inhibit monoamine oxidase (the enzyme responsible of the metabolism of the neurotransmitters).¹¹

Amphetamine itself, as well as the ATS, are derivatives of a beta-phenylethylamine core structure and are kinetically and dynamically characterised by: easily crossing the blood–brain barrier; resistance to brain biotransformation; and the release of monoamine neurotransmitters from nerve endings. All the structural features that enable these physiological characteristics are present in the simplest derivative, amphetamine, as well as other ATS.¹²

Pharmacokinetically, amphetamines are a homogeneous group of drugs, with a high oral bioavailability and low plasma protein binding (typically less than 20%). Their elimination half-lives range from 6 to 12 hours and renal and hepatic elimination occurs. Many amphetamines are extensively metabolised by the liver, but a significant proportion of several of these drugs is usually excreted without prior biotransformation.^{12,13} Chemically, amphetamines are weak basic drugs (with pKa value of

* Active *efflux* is a mechanism also responsible for the moving of toxic substances and antibiotics out of the cell.

approximately 9.9); they also have low molecular weight. This means that they can cross cellular membranes and lipidic layers easily, reaching high levels in tissues and biological fluids with a pH lower than blood, including saliva and sweat.^{12,14}

ATS share common properties, but their effects must not be seen as homogeneous. Some stimulants, such as MDMA, have distinct social and emotional effects, leading some to propose that they should be classed as 'entactogens'. ATS sit on a continuum of stimulant, hallucinogenic and euphoriant effects and, indeed, many have a combination of such effects. Methamphetamine is the only ATS compound that is smoked.

7.2. Medical and other legitimate uses of amphetamines

The clinical uses of amphetamines are currently limited. Dexedrine (dexamphetamine sulphate) is used in the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD). Methylphenidate (Ritalin) has a similar chemical structure and has effects to amphetamine and is also used for the treatment of ADHD. Ethylphenidate is currently a commonly used so-called 'legal high'.

Chapters 8–10 describe in greater detail the clinical and other legitimate uses of the specific substances.

7.3. Prevalence and patterns of use

Globally, ATS are the second most commonly recreationally used psychoactive drugs after cannabis. Recent global estimates suggest that the use of ATS now exceeds that of heroin and cocaine combined.¹⁵ The 2013 *World Drug Report* stated that there are signs that the market for ATS is expanding. The use of ATS, excluding ecstasy, remains widespread and appears to be expanding in most regions. Seizures of methamphetamine constituted 71% of the global ATS seizures.¹⁶ In 2011, an estimated 0.7% of the world population aged 15–64 (or 33.8 million people) had used ATS in the preceding year (excluding ecstasy).¹⁶

The recreational use of illicit stimulants and amphetamines has been well established in the UK for a number of decades now. Amphetamine sulphate use assumed what was described as 'epidemic proportions' among young people in the 1960s¹⁷ and, although there was a decline in the scale of its use in the 1970s, its continued use was described by Klee in the late 1990s to represent 'the love of speed' or the 'enduring attraction of amphetamine sulphate for British youth'.¹⁷

In the UK, amphetamine sulphate continues to be the most commonly used stimulant, with a reported lifetime use by 10.4% of adults between the ages of 16 and 59 years in 2012/13. It is the second most common drug ever used, after cannabis (30% of adults) in 2012/13. The use of amphetamines nonetheless decreased among all adults as well as young adults (16–24 years) between 1996 and 2003, although there was no

change to 2012/13 and to 2013/14 from the previous year (2011/12).¹⁸

NEPTUNE will not cover guidance specific to the harms associated with amphetamine sulphate because there is extensive experience in the management of this drug, spanning many decades. Instead, the guidance will focus on substances that have become available on the UK recreational drug scene more recently, in particular methamphetamine (Chapter 8) and mephedrone (Chapter 9), around which clinical experience is limited.

The WHO suggested that there is no typical profile for ATS users and there is a wide range of desired effects from ATS. ATS are used by students and drivers to stay awake and concentrate, used by athletes to enhance performance, and used at parties and clubs to increase sociability.¹⁹ ATS are also used to increase confidence and lift mood, lose weight and increase sex drive. A WHO 1997 report on ATS classified the patterns of use in the following way:²⁰

- 1 Instrumental use.** Amphetamines are exploited by the users to achieve desired goals, such as improve concentration and ward off fatigue.
- 2 Sub-cultural/recreational use.** Their stimulant properties are exploited to allow the user to remain active for longer periods in social and recreational settings, such as at music and dance events and all-night drinking venues.
- 3 Chronic use.** For several reasons, including craving, tolerance and withdrawal, some amphetamine users develop chronic patterns of consumption to relieve unwanted effects of abstinence or in the context of dependence.

7.4. Routes of ingestion and dosing

The purity of street drugs varies widely. Depending on the substance, ATS can be taken orally, by insufflation or injected; methamphetamine is the only stimulant which can be smoked. The association between route of administration and risks associated with use has been well documented. Smoked and injected ATS are more likely to lead to dependence than oral use,¹² while injecting increases the risks of transmission of blood-borne viruses.²¹

The effects of ATS generally appear 30–40 minutes after ingestion and can last for 4–8 hours, but there are variations, depending on the ATS used, the dose, the potency and the length of the effects, as well as tolerance. Some ATS, such as the 2 desoxy form (2-DPMP, found in Ivory Wave) have particularly long-lasting effects and have longer half-lives.^{22–24} There are also wide differences in physiological effects, with paramethoxyamphetamine (PMA) for example, having a much steeper dose–response curve than MDMA.

Although more robust evidence is required, there is some anecdotal evidence of an increase in the UK of injecting of ATS, such as mephedrone and methamphetamine. Among populations in treatment, figures from the National Drug Treatment Monitoring System (NDTMS) suggest that injecting may be a growing issue, up in four years from 6% to 8% in 2011/12. This is particularly so among methamphetamine users, with 24% reported injecting in 2011/12.²⁵

There is anecdotal evidence of the injecting of ethylphenidate (sometimes known as 'Ching' or 'Mr White') in Scotland in particular. Anecdotally, this has been linked to repeated injecting and is associated with severe vein damage and other injection injury. Research is needed into this potentially high-risk pattern.

This increase of injecting among people who use ATS as their main drug was also reported by the 2012 Unlinked Anonymous Monitoring (UAM) survey of people who inject drugs (PWID): from 4.5% (81/1796) in 2002 to 12% (173/1438) in 2012.^{26,27} This was reiterated in November 2014 by Public Health England, which reported a rise in the injecting of amphetamine and ATS in England, Wales and Northern Ireland, from 3.5% in 2003 to 11% in 2013, although this remains less common than the injecting of opiates.²⁸ In Scotland, the proportion of people who had injected in the past six months and who reported amphetamine as their main drug of injection was low (1.3% in 2011/12) and less than 1% of respondents reported the injecting of ATS.²⁹

There is evidence that injection of ATS is associated with high levels of infection risk.²⁶ ATS are injected more frequently than other substances (such as heroin).²⁶ The UAM survey also reported that those who injected amphetamine and ATS as their main drug were more likely to report the sharing of injecting equipment than those who reported using other main drugs.²⁶ Those who reported injecting ATS alone as their main drug were also significantly less likely to have ever had an HIV test or a hepatitis C test than those who reported other main drugs.²⁶

7.5. Desired and unwanted subjective effects of ATS

Overall, ATS are used for their stimulant, euphoric, anorectic and, in the case of some substances, empathogenic, entactogenic and hallucinogenic properties. ATS produce feelings of euphoria and relief from fatigue; they may improve performance on simple tasks and increase activity levels.⁸ It is thought that the misuse liability of amphetamines is related to their euphorogenic effects.^{8,30}

Unwanted subjective effects of amphetamines include increased anxiety, insomnia, irritability, aggression, restlessness and paranoia, and in some cases violent behaviour. Psychotic symptoms can occur when using amphetamines and can last for days or weeks. The 'come-down' from ATS, which is distinct from the physiological withdrawal observed in many dependent users, can last up to a few days; users may feel tired, anxious, depressed and some may experience restlessness, insomnia, muscle ache and fasciculation. Its intensity will depend on the substance, the dose consumed and the individual. Serotonin syndrome or toxicity is a potential risk (see section 7.7.2 for details on the serotonin syndrome).

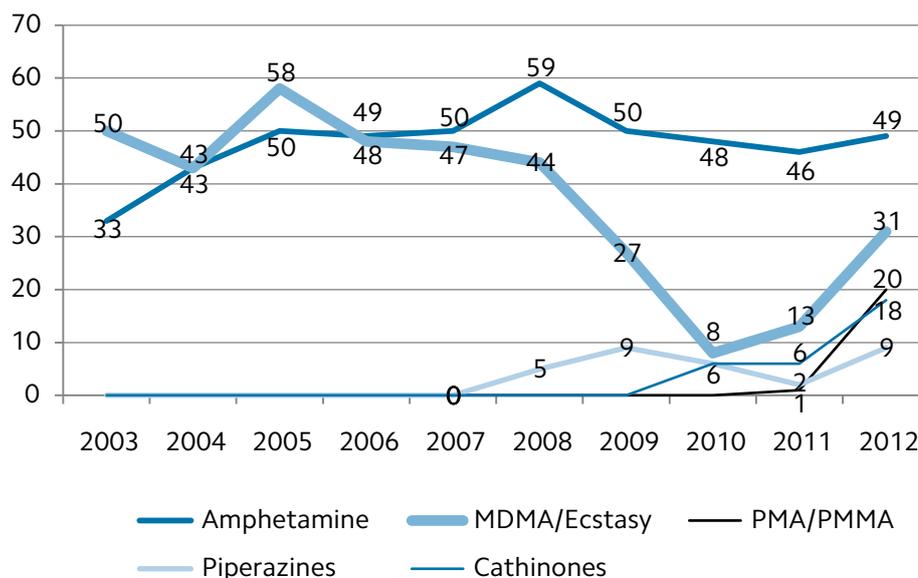


Figure 7.1. Numbers of drug-related deaths where stimulants were mentioned in the death certificate, England and Wales death registered between 2003 and 2012

7.6. Mortality

Mortality data relating to stimulant use from the Office for National Statistics from 2003 to 2012 are plotted in Figure 7.1.

Mortality among amphetamine users is relatively low in comparison with other 'problem drugs'. It is associated with longer drug careers and with injecting.³¹ Deaths are often caused by blood-borne viruses and infectious diseases or damage to the cardiovascular system. Non-fatal overdoses related to amphetamine use, on the other hand, are common.^{21,32,33} Amphetamine overdoses constitute only a small proportion of fatal overdoses, and are mainly associated with co-ingestion of opioids.³⁴ Direct amphetamine-related mortality typically occurs as a result of heart attacks, seizures, cardiac arrhythmias or respiratory failures.³³

7.7. Acute harms

Stimulants have actions on multiple receptor sites within the central nervous system (CNS), with patterns of effects varying between the drugs. Predominantly stimulant drugs inhibit monoamine (especially dopamine) reuptake and are associated with a sympathomimetic toxidrome. Entactogenic drugs provoke central serotonin release, while newer hallucinogens are serotonin receptor agonists and therefore serotonergic effects predominate in toxicity.²

The variations between substances are not only in relation to the severity of effects but also their duration. For example, there are reports of symptoms of 2-DPMP toxicity still being manifested 5–7 days after ingestion.³⁵

The factors that have an effect on the severity of acute ATS-related harm include the following:¹²

- dose and frequency of use;
- route of administration;
- environmental conditions (including temperature, stressful environment and overcrowding, intense physical activity, too much or too little fluid intake);
- individual variations and characteristics (including age, ethnicity, gender, physiological and physiopathological states, co-ingestion/poly-use, by-products of chemical synthesis).

7.7.1. Features of acute toxicity

Chapters 8–10 give detailed information on the features of acute toxicity of the selected drugs. Overall, ATS increase heart rate, blood pressure and breathing rates, constrict blood vessels, dilate pupils and release glucose and lipids into the bloodstream.¹¹ The toxicity, neurotoxicity and cardiotoxicity of amphetamines has been well documented, as has its impact on mental health.²¹

The acute toxic effects of amphetamine-type substances as summarised by TOXBASE® are presented in Box 7.1.*

Box 7.1. *The acute toxic effects of amphetamine-type substances*

Tremor	Chest pain
Sweating	Palpitations
Dilated pupils	Dyspnoea
Agitation	Systemic hypotension
Confusion	Hypertension
Headache	Narrow-complex tachycardias
Anxiety	Ventricular tachycardia
Vomiting	Ventricular fibrillation
Abdominal pain	Hyperpyrexia
Seizures	Metabolic acidosis
Hallucinations or delusions	Serotonin syndrome

There is a risk that the use of amphetamine induces strokes and heart attacks because it raises blood pressure and constricts blood vessels. People at risk of heart disease or strokes are more likely to experience such complications.^{12,36} Hyperthermia is one

* References here and below to TOXBASE® relate to the website <http://www.toxbase.org>. Note that registration is required for full access to this site, and registration is available only to UK clinicians. The information was taken from the site in March 2014, during the preparation of this chapter, and further evidence may have incorporated since that time.

of the most life-threatening acute physiological consequences of ATS intoxication, with case reports suggesting that its incidence and severity varies between drugs, with those most implicated being methamphetamine, MDMA, MDEA and PMA.^{12,37,38} Hyperthermia associated with these drugs appears to be responsible for fatal complications, including rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, multiple organ failure and acidosis.^{12,36,39,40} Hepatocellular injury caused by ATS is well established, although not yet completely understood;¹² it may arise from both acute and chronic use of amphetamine.^{12,36}

7.7.2. Serotonin syndrome

Serotonin syndrome is a clinical condition that occurs as a result of a drug-induced increases in intrasynaptic serotonin levels, primarily resulting in activation of serotonin 2A receptors in the central nervous system.⁴¹ It is argued by some that the term 'serotonin toxicity' is preferable to 'serotonin syndrome', especially in relation to more severe cases, because it describes the serotonin excess more accurately.^{41,42} In this document, the term 'serotonin syndrome' and 'serotonin toxicity' are used interchangeably.

Serotonin syndrome is a potentially life-threatening adverse reaction to the use of particular drugs (illicit or prescribed) or the interaction between drugs. A number of ATS used for recreational purposes are associated with serotonin syndrome, including (but not limited to) MDMA, MDPV, PMA and mephedrone, as well as methamphetamine and cocaine. There is also a dose–effect relationship; high doses or repeated doses of MDMA, for example, intensify serotonin release.⁴³ In addition, the simultaneous use of multiple serotonergic substances (e.g. ecstasy and methamphetamine) increases the risk of serotonin syndrome.⁴⁴

Drugs used therapeutically are also associated with serotonin syndrome (Box 7.2).^{45–55}

It has been reported that the syndrome occurs in approximately 14–16% of individuals who have overdosed on SSRIs,⁵⁶ but a single therapeutic dose of SSRI has also been associated with it.⁴⁶ The use of illicit substances with therapeutic drugs increases the risks of serotonin toxicity. There is evidence that some users deliberately use MAOIs to enhance the effect of psychoactive substances and/or help during the

Box 7.2. Therapeutic drugs used that are associated with serotonin syndrome

Monoamine oxidase inhibitors (MAOIs)	Antibiotics
Tricyclic antidepressants	Weight-reduction agents
Selective serotonin reuptake inhibitors (SSRIs; also called serotonin-specific reuptake inhibitors)	Antiemetics
Opiate analgesics	Antimigraine agents
Tramadol	Herbal products
Over-the-counter cough medicines	Psychoactive drugs used for recreational purposes

recovery period. For example, in an Australian study of ecstasy users, 1 in 25 reported deliberately combining ecstasy and moclobemide.^{57,58}

Three critical features have been described as critical in understanding the disorder:

- serotonin syndrome is a predictable consequence of excess serotonergic agonism of CNS receptors and peripheral serotonergic receptors;
- excess serotonin produces a spectrum of clinical findings;
- the clinical manifestations range from the barely perceptible to lethal. Signs of excess serotonin range in mild cases from tremor and diarrhoea to neuromuscular rigidity and hyperthermia in life-threatening cases.⁵⁹

Serotonin syndrome has three classic features of:

- mental state changes,
- autonomic hyperactivity
- neuromuscular abnormalities

Not all patients with the syndrome manifest signs and symptoms of all three features.⁵⁹ In a study of 2222 consecutive cases of self-poisoning with serotonergic drugs, the clinical findings that had a statistically significant association with serotonin syndrome were primarily neuromuscular (including hyperreflexia, inducible clonus, myoclonus, ocular clonus, spontaneous clonus, peripheral hypertonicity and shivering), as well as autonomic derangement (including tachycardia on admission, hyperpyrexia, mydriasis, diaphoresis and diarrhoea) and mental health/psychiatric symptoms (agitation and delirium).⁶⁰ There is also evidence that, in severe cases, stroke, myocardial infarction, severe hyponatraemia, rhabdomyolysis, disseminated intravascular coagulation (DIC) and renal failure may occur. Hepatocellular damage has also been reported, on TOXBASE® and elsewhere.⁴¹

The clinical symptoms are on a spectrum of severity, from mild to life-threatening (Table 7.1).⁵⁹

Table 7.1. Clinical symptoms of the serotonin syndrome: severity spectrum

Mild	Patients can be afebrile. Tachycardia possible, shivering, diaphoresis, mydriasis
Moderate	Tachycardia, hypertension, hyperthermia (40°C is common), mydriasis, hyperactive bowel sounds, diaphoresis, hyperreflexia and clonus (considerably greater in lower extremities than upper); patient may exhibit horizontal ocular clonus; mild agitation or hypervigilance, slightly pressured speech; repetitive rotation of the head with the neck held in moderate extension
Severe	Severe hypertension and tachycardia that might deteriorate abruptly into frank shock. Patient may have agitated delirium, muscle rigidity and hypertonicity and increase in muscle tone (considerably greater in lower extremities than upper). Muscle hyperactivity may produce a core temperature of more 41.1°C in some cases. Metabolic acidosis, rhabdomyolysis, elevated levels of serum aminotransferase and creatinine, seizures, renal failure, disseminated intravascular coagulopathy.

There is a dose–effect relationship, with more severe cases involving a combination of serotonergic drugs, rather than a single one. The simultaneous use of multiple stimulants increases the risk of serotonin toxicity and problems relating to sympathomimetic over-stimulation, such as dehydration and hyperthermia,⁶¹ and cardiovascular problems,⁶² as well as increasing the chances of neurotoxicity.⁶³ The risk is not only increased when two serotonergic psychoactive substances are co-ingested, but also when one psychoactive substance is ingested with a range of serotonin-releasing illicit drugs as well as medications (Box 7.2).^{45–55}

Monoamine oxidase inhibitors (MAOIs) are strongly associated with serotonin syndrome or toxicity, especially when these are used in combination with a number of other drugs, including methylenedioxypropylamphetamine (MDPV),^{47,64–66} mephedrone, methylenedioxypropylamphetamine (MDPV),^{67,68} butylone, methylone⁶⁸ and phenethylamines (2C-I).⁶⁹ The potentially life-threatening interaction may have serious implications for people on antidepressants who also use these recreational substances.⁷⁰

Serotonin toxicity generally presents abruptly and can progress quickly, sometimes within minutes,⁷¹ especially when a combination of serotonergic drugs has been used.⁴¹ It has been suggested that patients with serotonin toxicity will develop clinical manifestations within 6 hours.⁴¹ Where a combination of drugs has been used, signs and symptoms will start when the second drug reaches effective blood levels, usually after one or two doses.⁴¹

7.8. Management of the acute harms associated with use of ATS

7.8.1. Identification and assessment of acute toxicity

Chapters 8–10 provide detailed information on the identification and diagnosis of acute toxicity specific to each drug discussed.

Overall for ATS, clear airway management and adequate ventilation in case of unconsciousness is recommended. In case of cardiac arrest, TOXBASE® recommends cardiopulmonary resuscitation (CPR), which should be continued for at least 1 hour and stopped only after discussion with a senior clinician. Prolonged resuscitation for

For up-to-date guidance on the management of ATS acute toxicity, 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/A-Products/Amphetamine-related-Drugs-of-Abuse/>

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

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

cardiac arrest is recommended following poisoning, as recovery with good neurological outcome may occur. This should be the case for all overdoses of recreational drugs, particularly as most patients are young and fit.

The benefits of gastric decontamination are uncertain, but TOXBASE® recommends oral activated charcoal if any amount of an ATS has been ingested within 1 hour, provided the airway can be protected. It also recommends that asymptomatic patients are observed for at least 4 hours, or 8 hours for patients who have ingested sustained-release preparations.

7.8.2. Management of serotonin syndrome

It has been suggested that people with serotonin syndrome related to the use of psychoactive substances such as ecstasy usually present to hospitals with advanced symptoms because some of the early, mild signs of the syndrome are often perceived as normal drug effects.^{47,70}

There are no laboratory tests to confirm the diagnosis. Serotonin syndrome is difficult to diagnose for a number of reasons, which include the variability in clinical manifestations, lack of awareness of the syndrome and limitations of the diagnostic criteria, which in turn may contribute to the lack of recognition.⁴¹ It has been argued that when assessing a patient with serotonin syndrome, the key elements of the history include the quantity and type of drugs ingested and the evolution and rate of progression of symptoms.⁷² Boyer et al. suggest that clinicians should consider serotonin syndrome for patients who present with tremor, clonus or akathisia with no additional extrapyramidal signs, after consideration of the patient history and physical examination.⁵⁹

A formalised diagnostic approach to serotonin syndrome is the 'Hunter Serotonin Toxicity Criteria: decision rules',⁷³ based on the presence or absence of seven clinical features (Figure 7.2). Of all the clinical features, clonus was considered the most important sign (spontaneous, inducible and ocular).

```

IF (spontaneous clonus = yes)
THEN serotonin toxicity = YES

ELSE IF (inducible clonus =yes)
AND [(agitation =yes) OR (diaphoresis = yes)]
THEN serotonin toxicity = YES

ELSE IF (ocular clonus = yes)
AND [(agitation = yes) OR (diaphoresis = yes)]
THEN serotonin toxicity = YES

ELSE IF (tremor = yes) AND (hyperreflexia = yes)
THEN serotonin toxicity = YES

ELSE IF (hypertonic = yes) AND (temperature >38°C)
AND [(ocular clonus = yes) OR (inducible clonus =yes)]
THEN serotonin toxicity = YES

```

Figure 7.2. Hunter Serotonin Toxicity Criteria: decision rules (in the presence of a serotonergic agent)

For up-to-date guidance on the management of serotonin syndrome, 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/S-Products/Serotonin-syndrome/>

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

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

Most cases of serotonin syndrome are mild and may be treated by withdrawal of the offending agent and supportive care. Most mild cases will resolve spontaneously within 24 hours. Patients with moderate or severe cases of serotonin syndrome require hospitalisation. Although many cases will resolve within 24 hours after cessation of the drugs involved and initiation of treatment, clinical symptoms may persist for longer in cases involving serotonergic drugs with long duration of action, active metabolites or long half-lives.⁵⁹ If serotonin syndrome is recognised and complications are managed appropriately, the prognosis is favourable.⁷⁴

Benzodiazepines are the standard treatment for the agitation and tremor. It has been suggested that, 5-HT_{2A} antagonists (cyproheptadine and chlorpromazine) could be used in more severe cases,⁴¹ as they have been successfully used to treat serotonin syndrome following overdose. However, there are no controlled trials to support this, and there is a risk of convulsions as serotonin toxicity lowers the seizure threshold.

The agitation, autonomic instability and hyperthermia need to be controlled.^{59,75} In moderate cases of serotonin syndrome, patients may have cardiorespiratory abnormalities and pyrexia, which should be treated aggressively.⁴¹ Death of patients with serotonin syndrome is normally due to hyperpyrexia-induced multi-organ failure and it is therefore essential to rapidly lower the patient's temperature if it exceeds 39°C. (TOXBASE® recommends ice-baths and internal cooling devices, wherever available). Critically ill patients may require neuromuscular paralysis, sedation and intubation.⁷⁴

Life-threatening serotonin syndrome may occur in 50% of cases of combined ingestion of an MAOI and an SSRI recreational drug, such as ecstasy. Rapid deterioration generally occurs and it has been recommended that patients be transferred to intensive care; toxicology investigations are also strongly recommended.⁴¹ The long half-life of some MAOIs (e.g. phenelzine, tranylcypromine) means that users could still be susceptible to interactions with ATS such as ecstasy up to 2 weeks after they have stopped using the drug.^{76,77}

7.9. Harms associated with chronic use of ATS

7.9.1. Dependence and withdrawal

The WHO has estimated that 11% of ATS users become dependent and may require specialist interventions. However, even occasional users may experience physical, social or psychological harms and may progress to more harmful or dependent drug use.⁷⁸

Dopamine dysfunction has been reported as the main neurobiological mechanism in amphetamine dependence.¹¹ Amphetamines in general have low protein binding, which gives high bioavailability and supports their easy diffusion from the plasma to the extravascular compartment.¹⁴ It has been reported that people dependent on amphetamines may have a larger volume of distribution and longer plasma elimination half-life relative to drug-naïve individuals (6 versus 4 l/kg). This is probably due to tissue sequestration as a result of the development of pharmacokinetic tolerance to the drug.^{12,14} Dependence on ATS is characterised by increased tolerance and withdrawal symptoms on cessation, which include sleep and appetite disturbances, fatigue, depression, irritability, craving, depression, anxiety and agitation. It is also characterised by the inability to reduce drug use despite significant negative social, health and psychological problems associated with use.

Amphetamine withdrawal is extremely common, with 87.6% of the 647 participants with amphetamine dependence of one study reporting six or more signs of amphetamine withdrawal listed in DSM.⁷⁹ There are variations in the level of intensity

Table 7.2. *Three phases of ATS withdrawal*

Phase ⁷⁸	Time since last stimulant use	Common signs and symptoms
'Crash'	Typically commences 12–24 hours after last amphetamine use and subsides by 2–4 days	Exhaustion, fatigue, agitation and irritability, depression, muscle ache akathisia Sleep disturbances (typically increased sleep, although insomnia or restless sleep may occur)
'Withdrawal'	Typically commences 2–4 days after last use, peaks in severity over 7–10 days and then subsides over 2–4 weeks	Strong cravings Fluctuating mood and energy levels, alternating between irritability, restlessness, anxiety and agitation Fatigue, lack of energy May mimic narcolepsy
'Extinction'	Weeks to months (requires integration between withdrawal and post-withdrawal services)	Gradual resumption of normal mood with episodic fluctuations in mood and energy levels, alternating between irritability, restlessness, anxiety, agitation, fatigue, lack of energy Episodic cravings Disturbed sleep

of withdrawal from the various ATS, as discussed in Chapters 8–10. For amphetamine withdrawal⁸⁰ (amphetamine, dextroamphetamine and methamphetamine), when heavy chronic users discontinue their use abruptly, many will report time-limited withdrawal symptoms that commence up to 24 hours after their last dose and can last for three weeks or more. These can be sufficiently severe to result in relapse to drug use.

Phases of withdrawal include the initial 'crash', which resolves within approximately a week.^{81,82} Severe symptoms include increased sleep (but of poor quality), increased appetite and a cluster of depression-related symptoms. Phase 2 is a sub-acute protracted set of withdrawal symptoms which are not well defined but include continued sleep disturbances and increased appetite.^{81,82} Some symptoms may continue for weeks or months.

The WHO Technical Brief 2 on ATS⁷⁸ outlines three phases of ATS withdrawal. These are set out in Table 7.2.

7.9.2. Physical and psychiatric/psychological harms from chronic use

It is clear that amphetamine has a cardiotoxic effect and has been associated with chronic cardiac pathology. The risks of coronary artery disease are probably compounded by the chronic effect of amphetamines (including methamphetamine) in the heart tissue, as well as the effects of amphetamine intoxication, and this may be a cause of premature mortality, although other factors – such as tobacco and alcohol use – are often additional factors.⁸³ Hepatocellular damage may also occur from the chronic use of amphetamine.^{12,36}

Amphetamine dependence has been associated with depression, anxiety, psychotic disorders,⁸⁴ attention deficit hyperactivity disorder (ADHD)⁸⁵ and antisocial personality disorder.⁸⁶ It has also been associated with sexual risk behaviour and increased risk of HIV³² and a tendency to suicide.⁸⁷

A minority of people who use amphetamines will develop a psychotic episode that requires care from emergency departments or psychiatric units.⁸⁸ A Cochrane review of treatment for amphetamine psychosis noted that it is difficult to determine in any robust way the prevalence of amphetamine-induced psychosis at local or global levels. The epidemiology of the disorder indicates that patients with the symptoms of psychosis due to amphetamine present to emergency departments and psychiatric units at low rates compared with the census of all patients; it also reports that significant psychotic symptoms are common to users with more extensive and severe patterns of amphetamine use.⁸⁸

Common symptoms of amphetamine-induced psychosis include paranoid and/or persecutory delusions, as well as auditory and visual hallucinations, with extreme agitation. However, even among those who use amphetamine frequently, psychotic symptoms are more likely to be sub-clinical and not to require highly intensive interventions. The development of psychosis and sub-clinical symptoms is related to the

cumulative quantity of amphetamine ingestion, or the individual's lifetime history of amphetamine use.⁸⁸

There are similarities in clinical presentation between amphetamine-induced psychosis and schizophrenia, but the psychotic symptoms may be due solely to the heavy use of amphetamine, or heavy use of amphetamines may underlie a vulnerability to schizophrenia.⁸⁸ There are some indications that the two disorders may be linked genetically, with a study suggesting that relatives of the users of methamphetamine with a lifetime history of amphetamine psychosis are five times more likely to have schizophrenia than methamphetamine users without such a history.⁸⁹

7.10. Management of harms associated with chronic use

7.10.1. Identification and assessment of ATS use and dependence⁹⁰

The diagnosis of amphetamine use and dependence is based on criteria listed in the *International Classification of Diseases* (ICD-10). Amphetamine dependence is diagnosed if three or more of the following have been experienced or exhibited at some time during the previous 12 months:

- a strong desire or sense of compulsion to take stimulants;
- difficulties in controlling stimulant-taking behaviour in terms of its onset, termination or levels of use;
- a physiological withdrawal state when stimulant use has ceased or been reduced;
- evidence of tolerance, such that increased doses of stimulants are required in order to achieve the effects originally produced by lower doses;
- progressive neglect of alternative pleasures or interests because of stimulant use;
- persisting with stimulant use despite clear evidence of overtly harmful consequences.⁹⁰

Daily use of amphetamine is considered to be the most harmful pattern; it often has adverse outcomes for the health and psychosocial functioning of the user. However, the use of amphetamines on a weekly basis or more has been associated with adverse effects, and injecting and smoking are associated with higher risk. Typically, the threshold signalling a high risk of developing dependence starts after 6–12 months of weekly use, although there are reports of users experiencing problems even after relatively low levels of exposure.²¹

7.10.2. Stepped care for ATS users

The WHO Technical Brief on ATS⁹⁰ recommends that services for ATS users are provided at a series of levels, as set out in Table 7.3.

Table 7.3. Stepped care for ATS users

	Type of user suited to intervention	Activities/interventions
Step 1	Occasional ATS users believed to be at relatively low risk	<i>Personal care activities:</i> Self/family care in reducing/stopping drug use. Self-help groups, informal community-based care Information about the risks of drug use, brief counselling, peer outreach and education, drop-in centres, skills and vocational training, rehabilitation and reintegration services
Step 2	'Problem' ATS users	Drug services in <i>primary health-care</i> settings: assessment, brief counselling, harm reduction information, needle and syringe programmes, referral to specialist services if required, assistance with basic symptomatic detoxification and withdrawal. Referral back to the community for support, rehabilitation and reintegration services or referral to expert care
Step 3	Heavy/dependent ATS users	Specialised <i>drug dependence clinical care:</i> Assessment of dependence, pharmacologically assisted withdrawal, harm reduction, needle and syringe programmes, outpatient and/or inpatient or residential treatment and specialised counselling, referral to rehabilitation and reintegration services, and back to the community for support
Activities to be undertaken at every step	All users	Case management and counselling are important at every stage – though the exact technique and intensity will depend on the profile of the ATS user Also important is the provision of opportunities for ATS users to undergo vocational training and assistance to gain employment, as well as improve family relations, deal with legal problems and assist in the development of new recreational activities and social networks in the community

7.10.3. Psychosocial and pharmacological support for the management of dependence

At the time of writing, psychosocial interventions remain the best treatment option for the management of amphetamine dependence.¹¹

7.10.3.1. Psychosocial interventions

For details on psychosocial interventions see Chapter 2.

Data are available on psychosocial interventions specific to stimulants and/or ATS. A Cochrane review of the psychosocial interventions for cocaine and psychostimulant amphetamine-related disorders, reported little significant behavioural changes, with reductions in rates of consumption after an intervention. In addition, current evidence does not support a single treatment approach that is able to tackle the

multidimensional facets of addiction and to yield better outcomes to resolve the chronic relapsing nature of addiction and its consequences.^{91,92}

Nonetheless, a comparison between different types of behavioural interventions by the Cochrane review⁹¹ showed results in favour of treatment with some form of contingency management in respect to reducing treatment drop-outs and decreasing use and abstinence.⁹¹ The more comprehensive behavioural treatment, in which a contingency management program is provided in addition to a community reinforcement approach had significantly better results when compared to groups of patients receiving drug counselling or behavioural treatment only, without the added incentive programme involving vouchers to be exchanged for goods contingent on cocaine-negative urine samples.⁹¹

The Cochrane Review's conclusions in terms of implication for practice were that, until further studies are available, clinicians may consider contingency management techniques as a good treatment approach, provided this can be replicated in a particular therapeutic setting. However, desired outcomes will not be achieved if the patient's readiness for treatment and change is not managed and addressed. Treatment interventions need to be adequate to the particular stage of recovery a patient is in at the time she or he seeks treatment.⁹¹

The Cochrane review suggests that currently, the best results for treating psychostimulant dependence are those of behaviour treatment with contingency management, in association with community reinforcement and workplace behaviour interventions, but these have limitations. Reductions in the amount or frequency of use is a benefit, but short-term reduction is of little lasting value. A patient must make effective changes in his/her life including sustained abstinence and the ability to work and maintain successful relationships with others. The nature and amount of treatment must be based on the range of problems a given patient faces. The review therefore conclude from the best available evidence, clinicians should take into account the fact that the best treatment has to match the patient's needs.⁹¹

The WHO Technical Brief 2⁷⁸ suggests that crisis interventions may be needed in some instances for psychiatric symptoms, such as persecutory delusions or perceptual disturbances. It also recommends brief interventions, targeting ATS users to engage them in a discussion about their substance use and steer the discussion to encourage a person to decide if they want to change their behaviour. Brief interventions on their own have been shown to be successful at promoting behaviour change and can often be used as the first stage of more intensive treatment if needed. Information and counselling may also be needed, and a variety of approaches have been used from client-centred to open-ended counselling.⁷⁸

Gender differences have been described by a few studies. Some have argued that there is some evidence of sexual dimorphism in response to stimulants, with some preliminary evidence that suggests a potential biological mechanism involving brain-derived neurotrophic factor that might contribute to these differences and that additional research is needed.⁹³ Clinical and pre-clinical studies have for example found that women amphetamine users reported higher frequency of amphetamine

use than men.^{93–95} A human laboratory study suggested that women self-administer more frequently but a lower dose of amphetamine than men.⁹⁶ It can be argued that although more research is needed before any conclusions are made clinicians may want to consider gender-specific issues as an important element in the management of amphetamines.

7.10.3.2. Pharmacological interventions

Pharmacological interventions specific to each drug will be discussed in detail in all relevant chapters. Most of the research was carried out on treatment for methamphetamine use and a recent Cochrane review of the efficacy of psychostimulant drugs for amphetamine abuse or dependence has concluded that it does not support the use of psychostimulant medications at the tested doses, as a replacement for amphetamines. The review also added that these conclusions may change in the future, as the number of included studies and participants were limited and information on outcomes were missing.¹¹

There are some recommendation for symptomatic treatment of withdrawal. The WHO Technical Brief 2 on ATS recommends that treatment for severe insomnia be provided with light sedatives and hydration is maintained. Clinicians should be aware that depressive symptoms of varying severity may occur during or after withdrawal and there may be risk of suicide.⁷⁸

7.10.4. Management of amphetamine psychosis

The resolution of symptoms among those who experience amphetamine-induced psychosis usually occurs with abstinence, although it may be incomplete, thus increasing risks of relapse.⁹⁷ Symptoms usually resolve with medication, which is as for schizophrenia,⁹⁸ including antipsychotics and benzodiazepines.⁸⁸

A Cochrane review⁸⁸ of the pharmacological treatment for amphetamine psychosis identified only one study that met criteria for inclusion. This randomised controlled trial with 58 participants showed that antipsychotic medication reduced symptoms of amphetamine psychosis effectively, with the newer-generation medication olanzapine showing significantly greater safety and tolerability than the more commonly used haloperidol controls, measured by the frequency and severity of extrapyramidal symptoms.⁹⁹ However, the review also added that although antipsychotic medications have shown their efficacy in providing short-term relief when a heavy user of amphetamines experiences psychosis, there is no evidence regarding the long-term use of these medications for preventing relapse into psychosis.⁸⁸

Because of the similarities in the clinical presentations of amphetamine psychosis and schizophrenia, it has been suggested that distinguishing between them is often determined by the quick resolution of symptoms in amphetamine psychosis, which is not a likely outcome of schizophrenia.^{88,100} It has also been argued that the management, treatment and response to acute amphetamine psychosis are much like those for schizophrenia and antipsychotics produce similar results.^{88,101}

7.10.5. Aftercare and support

See Chapter 2 on psychosocial interventions.

7.11. Public health and safety and harm reduction

The WHO Technical Brief on ATS suggests that clinicians should advise users of ATS (including methamphetamine) to reduce harms by taking into account the following:⁷⁸

- ATS can stimulate excessive physical activity, leading to overheating. Users should therefore ensure they drink enough fluids, while taking care not to drink too much (not more than one pint in one hour when dancing) as this can cause hyponatraemia (an electrolyte disturbance in which the sodium ion concentration in the plasma is lower than normal).
- Users should not combine ATS with other drugs, including alcohol. The simultaneous use of more than one drug can cause serotonin syndrome, which can be severe.
- Users should think about safer sex. Methamphetamine in particular can increase sexual desire and the ability to have sex for longer periods. Users should always protect themselves by using condoms.
- Straws used for snorting should not be shared, as they carry the risk of transmission of blood-borne viruses.
- Where ATS are injected, users should never share equipment. They should also rotate sites to avoid vein damage.
- Users should avoid taking ATS too many days in a row, to avoid dependence and to give their bodies a rest.

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Chapter 8

Methamphetamine

Drug group: stimulant

The use of methamphetamine in the UK continues to be relatively uncommon, with its use limited to specific populations and contexts, most particularly men who have sex with men (MSM). However, a discussion of methamphetamine harms and their management is included in this guidance document because of both the level of harms relating to the use of this substance and the lack of experience in the management of its harms in the UK.

Methamphetamine hydrochloride is stable and volatises easily so can be smoked, unlike amphetamine sulphate.

8.1. Street names

Street names at the time of publication include Crystal Meth, Tina, Christine, Ice, Glass, Crank, Yaba and Crazy Medicine. Other street names may be used locally.

8.2. Legal status

Methamphetamine and 4-methylamphetamine are Class A drugs under the Misuse of Drugs Act 1971.

8.3. Quality of the research evidence

There is a much larger and more robust body of evidence on methamphetamine harms and treatment than for other club drugs. This includes a number of well conducted randomised controlled trials (RCTs) and Cochrane reviews, especially in relation to dependence.

However, most of the research evidence on methamphetamine comes from the US, Australia and South East Asia. UK and European research is much more limited, reflecting the currently low rates of use across most of Europe. Some of the findings of international studies may be less relevant in a UK context, especially those relating to epidemiology and trends.

8.4. Brief overview of pharmacology

Methamphetamine is an *N*, α -dimethylphenethylamine and a member of the phenethylamine family. It is a synthetic stimulant and a derivative of amphetamine.¹ Methamphetamine is a potent psychomotor stimulant with strong physiological effects on the peripheral and central nervous systems, resulting in physical and psychological effects.² It is typically described as a more potent stimulant than non-methylated amphetamines. It is highly lipophilic, and in comparison with amphetamine at similar doses crosses the blood–brain barrier more easily, is more potent and has a more pronounced and a longer-lasting stimulant effect.³ Methamphetamine has short-term and long-term effects that are similar to those produced by cocaine, but they last longer and can be more severe.⁴

The action of methamphetamine and other amphetamines have been well described.^{2,5,6,7} Methamphetamine increases the activity of the noradrenergic and dopamine neurotransmitter systems. It increases the release and blocks the reuptake of dopamine. It has an active metabolite, amphetamine, and two inactive metabolites, *p*-OH-amphetamine and noradrenaline. It is oxidised and metabolised in the liver through enzymatic degradation primarily involving cytochrome P450-2D6. Approximately 10% of Caucasians are deficient in this enzyme, and a study has suggested that this makes them particularly sensitive to the effects of methamphetamine, as they lack the ability to metabolise and excrete the drug efficiently.⁸

Chronic methamphetamine alters brain function. Brain imaging studies have shown changes in the activity of the dopamine system that are associated with reduced motor skills and impaired verbal learning.⁹ Imaging studies of methamphetamine-dependent individuals have found structural abnormalities: severe grey-matter deficits in the cingulate, limbic and paralimbic cortices, smaller hippocampal volumes, significant white-matter hypertrophy, medial temporal lobe damage and striatal enlargement.^{10,11}

Studies have also shown severe structural and functional changes in areas of the brain associated with emotion and memory,^{11,12} as well as neurochemical and metabolite changes in the ventral striatum.^{13,14} Prolonged use has been reported to lead to down-regulation of dopamine D₂ receptors and uptake sites.¹⁵ A state of hypodopaminergic activity has been reported.^{16,17}

The psychiatric consequences of methamphetamine use are theorised to be secondary to its mechanisms of action: methamphetamine enters the synaptic neurons via monoamine transporters and, once in the neurons, displaces the monoamines from vesicular and intracellular locations, pushing the monoamines into the extraneuronal spaces. Long-term use is associated with alterations in the levels of monoamines implicated with stimulant use, which include noradrenaline, serotonin and dopamine.^{18,19}

8.5. Clinical and other legitimate uses of methamphetamine

Methamphetamine has been used in the treatment of narcolepsy and attention deficit hyperactivity disorder (ADHD). There is also some research on other therapeutic uses of methamphetamine. A rat study looked at whether low-dose methamphetamine could prevent neuronal loss and improve functional behaviour after severe traumatic brain injury (TBI). It found that low doses elicited a robust neuro-protective response, resulting in significant improvements in behavioural and cognitive function.²⁰

8.6. Prevalence and patterns of use

Methamphetamine is one of the most widely misused drugs in the world, with over 35 million users estimated. However, at a European level, the use of methamphetamine has historically been low, with some exceptions, notably in the Czech Republic and, more recently, Norway and Slovakia. However, there are some indications that methamphetamine is increasing in availability and data from some European countries suggest that it may be replacing amphetamine.^{21,22}

In the UK, methamphetamine use is still limited, and amphetamine sulphate continues to be much more available and widely used. Data from the Crime Survey for England and Wales (CSEW) on the use of methamphetamine have been collected since 2008/09 and show the following, with no statistically significant changes over the years. Use of methamphetamine in the last year was reported by 0.1% of adults (16–59 years) in all six annual surveys, with no significant differences between young adults and all 16–59-year-olds in the proportion of people reporting its use.²³

Other UK data also suggest its limited use. A retrospective study on the number of enquiries to the poison centres of two large inner-city hospitals from 2000 to the end of 2006, as well as the National Poisons Information Centre 2005/06, reported that there was no evidence of increasing use of methamphetamine or that acute methamphetamine poisoning was a significant clinical problem in comparison with other established, drugs such as MDMA.²⁴

The prevalence of methamphetamine use is higher among some sub-groups (e.g. 'clubbers'), although their rates still remain lower than for other club drugs. Among the UK sample from the Global Drug Survey in 2012 3.8% of respondents reported ever trying methamphetamine, with 0.8% reporting use in the last 12 months and 0.2% in the last month. The percentage of methamphetamine users among those described as 'regular clubbers' was higher, with 1% reporting use in the last 12 months.²⁵

There is some evidence that methamphetamine use is more common among MSM than it is among the general population and that its use is mainly concentrated in this population. This was shown by the 2013/14 CSEW, which analysed responses by sexual orientation where this was self-reported (these data have to be treated with caution because of the small number of respondents involved). The results are presented in Table 8.1.

Table 8.1. *Proportion of 16–59-year-olds reporting methamphetamine use in the past year (3-year combined data-sets 2011/12, 2012/13 and 2013/14)²³*

Heterosexual: all	Male heterosexual	Female heterosexual	Gay or bisexual: all	Male gay or bisexual	Female lesbian or bisexual
0.0%	0.1%	0.0%	0.6%	1.1%	0.0%

Other data from targeted surveys also suggest that in the UK the use of methamphetamine may be higher among MSM than the general population. These surveys, although not comparable, suggest rates of use that are higher than those reported by the CSEW,^{26–28} with for example a 2007 survey of London MSM estimating use of methamphetamine in the past year at 7.8%²⁹ and a survey carried out in 2010 reporting 8.7%.³⁰

Studies have also shown differences in the use of methamphetamine within populations of MSM. Like other international research, UK studies have reported that HIV-positive men are more likely to use methamphetamine than other MSM.^{30–34} US studies have shown that the incidence of HIV among MSM who use methamphetamine is more than double that among MSM who do not use methamphetamine.³⁵

There are also differences based on geography, with methamphetamine found in metropolitan areas mainly (e.g. London and Manchester). In the UK methamphetamine is more widely used by gay men in London than elsewhere in the country.^{29,30} A recent study also showed differences within London, with higher prevalence in areas such as Lambeth, Southwark and Lewisham (LSL), which are home to large populations of gay and bisexual men, and have a large gay commercial scene and sex-on-premises venues. In these locations methamphetamine use in the past four weeks (4.9% of LSL respondents) was higher than among gay men elsewhere in London (2.9%) and substantially higher than elsewhere in England (0.7%).³⁰ Methamphetamine is associated with ‘chemsex’, as discussed in greater detail in section 8.10.2.

There is no evidence that the use of methamphetamine is becoming more widespread among MSM in the UK, although one report suggested that its use appears to be increasing, albeit slowly and certainly not exponentially.³⁰ There is also no evidence that its use is becoming more mainstream in the UK, or whether it will ever expand to the wider population. Drug-using cultures differ and methamphetamine use may not follow the same pathways as in other parts of the world, including the US and Australia, where its use has expanded beyond MSM populations.

US and other studies have shown a change over time in the sociodemographic characteristics of methamphetamine users. A study of treatment admissions from the California Alcohol and Drug Data System from 1992 to 2002 showed not only a five-fold increase of methamphetamine admission, but also a shift towards usage by minority ethnic groups and a more vulnerable population in terms of homelessness, chronic mental health problems and disability. There was also a substantial increase in people reporting a legal supervision status (criminal justice intervention).³⁶ In the UK, this vulnerable population is currently typically more associated with crack cocaine and opiate use.

8.7. Routes of ingestion and dosing

The most common form of methamphetamine is a hydrochloride salt, which comes as a white or off-white bitter-tasting powder, or as purer crystals that are soluble in water. It can also come in tablets, which carry logos similar to those on ecstasy tablets.

Most of the methamphetamine used in the UK is in the crystalline form. It is currently mainly smoked but it is also snorted, injected intravenously (known as 'slamming' among MSM in the UK), used anally (known as 'booty bumping') or inserted into the urethra. It has been noted that if too much methamphetamine is inserted anally, it may not all be completely dissolved and there is a risk of abrasion of condoms resulting from friction with this undissolved methamphetamine, which can contribute to the condom breaking.³⁷

There is some evidence that smoking methamphetamine has more harmful psychological effects and a higher addictive potential than snorting or swallowing the drug, and that smokers have levels of dependence approaching those seen among methamphetamine injectors.^{38,39}

Methamphetamine is rapidly absorbed after ingestion and its half-life is 8–13 hours.⁴⁰ The stimulant effects depend on a number of factors, including route of ingestion and dose; they may last between 6 and 12 hours, but longer durations have been reported.⁴¹ Intravenous injection and smoking have a rapid onset of action. Following oral administration, peak concentrations are seen in 2.6–3.6 hours and the mean elimination half-life is 10.1 hours (range 6.4–15 hours). Following intravenous use the mean half-life is slightly longer (12.2 hours).

Methamphetamine is expensive in the UK, with a cost of up to £260 per gram, which is much above the cost in countries where it is more highly prevalent.⁴² It is also considerably more expensive than other stimulant drugs, including cocaine, at approximately £50–£100 per gram.

8.8. Desired effects for recreational use and unwanted effects

The effects of methamphetamine result from a surge in newly synthesised catecholamines and serotonin; these include excitation, well-being, increased alertness, energy and confidence, highly focused attention and decreased appetite. Methamphetamine use creates feelings of increased confidence, sociability and euphoria.⁴³ In methamphetamine-naïve individuals, acute doses can improve cognitive processing. Studies show that single low to moderate doses increase arousal and alertness, and improve attention and concentration, particularly among those who are sleep-deprived. Methamphetamine has an apparent aphrodisiac effect, with increased sexual drive, decreased fatigue and loss of sexual inhibition. It can delay ejaculation, assist longer intercourse and decrease humoral secretions.^{44,45} Paradoxically, there is evidence that long-term use is associated with decreased sexual functioning in some men.⁴⁶

Higher dose of methamphetamine can cause dysphoria, restlessness and anxiety, and are associated with tremors and dyskinesia. In binge use of methamphetamine, the euphoric effects decrease over time, while dysphoria and compulsive behaviour increase. Bingeing has also been reported to induce sleeplessness, hallucinations and paranoia.⁴⁷

The negative psychological effects of methamphetamine use may include anxiety, restlessness, insomnia, grandiosity, paranoia, psychosis, hallucinations (including delusional parasitosis), depression, unprovoked aggressive or violent behaviour and irritability. Individuals can talk excessively, be agitated, aggressive and restless, and may be observed performing repetitive meaningless tasks.⁸

Unwanted effects of methamphetamines have been reported to be common. A US study of 350 individuals found that the majority reported problems associated with methamphetamine use, which included weight loss (84%), sleeplessness (78%), financial problems (73%), paranoia (67%), legal problems (63%), hallucinations (61%), work problems (60%), violent behaviour (57%), dental problems (55%), skin problems (36%) and high blood pressure (24%).⁴⁸ In the UK Gay Men's Sex Survey 2007, 40.4% of men who had used methamphetamine in the past year reported concerns about this drug.²⁶

The 'come-down' from methamphetamine is one of the most common unwanted effects reported by users.⁴⁹ Users may feel irritable, restless, anxious, depressed and lethargic, and there are reports of the use of benzodiazepines or heroin to soften the come-down. It has been reported in New Zealand that it is often sold in a package with GHB/GBL to help with its come-down effects.⁵⁰ Anecdotal evidence from the UK suggests that the two substances are sometimes used together.

8.9. Mortality

A study of cohorts of individuals in California hospitalised from 1990 to 2005 with a diagnosis of disorders relating to methamphetamine, cocaine, alcohol, opiates and cannabis and followed up for 16 years (74,139 individuals and 4122 deaths) found that hospitalised methamphetamine users had a higher mortality risk than the users of all substances, except for opiates. The standardised mortality rate for methamphetamine found by the study was 4.67, which is similar to rates found by studies in inpatient or treatment settings in the Czech Republic,⁵¹ Denmark⁵² and Taiwan,⁵³ but slightly larger than those reported by a community-based sample of amphetamine users in Sweden.⁵⁴

Deaths associated with methamphetamine have been attributed to homicide, suicide, motor vehicle accidents, manufacturing, distribution and sales of the drug as well as its direct toxic effects.⁵⁵ Biologically based causes include stroke and cerebral haemorrhage, cardiovascular collapse, pulmonary oedema, myocardial infarction, hyperpyrexia and renal failure.^{56,57}

For up-to-date guidance on the management of methamphetamine acute toxicity, 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/M-Products/Methamphetamine/>

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

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

8.10. Acute harms

8.10.1. Acute toxicity

The features of acute toxicity are summarised in Box 8.1. The relevant literature is discussed in section 8.11.

8.10.1.1. Cardiovascular and respiratory harms

The acute (and chronic) use of methamphetamine can severely affect the cardiovascular system.⁸ It causes an acceleration of heart and lung action through vasoconstriction and bronchodilation, while muscle activity is primed via transient

Box 8.1. Feature of acute methamphetamine toxicity

Cardiovascular and respiratory

Narrow-complex tachycardias (common)
Chest pain
Palpitations
Systemic hypotension or hypertension
Ventricular tachycardia or ventricular fibrillation.
Dyspnoea

Gastrointestinal and urological

Abdominal pain
Vomiting
Metabolic acidosis

Neurological, psychiatric and central nervous system

Tremor
Sweating
Dilated pupils
Agitation
Confusion
Headache
Anxiety
Seizures
Hallucinations or delusions
Hyperpyrexia (may be severe)
Serotonin syndrome (especially if more than one stimulant drug has been used) (serotonin syndrome is discussed in depth in section 7.7.2).

hyperglycaemia and dilation of blood vessels in skeletal muscles.⁵⁸ Some non-essential physiological activity is inhibited (e.g. stomach and intestinal function); levels of stress hormones – including cortisol and adrenocorticotrophic hormone – are increased by 200% in humans following ingestion⁵⁹ and remain elevated for hours.² Tachycardia and hypertension are common features of methamphetamine toxicity.⁴

Chest pain is a common complaint associated with methamphetamine use,⁶⁰ with one study reporting that they account for 38% of emergency department visits and 28% of admissions among patients using methamphetamine.⁶¹ It has also been suggested that although in some patients chest pain is due to methamphetamine-induced hypertension, tachycardia or anxiety, acute coronary syndrome (ACS) is common among methamphetamine users. One study recommended that patients with chest pain in the context of methamphetamine use should be evaluated for ACS.⁶² The prevalence of ACS was found to be 25% in a small series of patients presenting to an emergency department with chest pain after methamphetamine use.⁶³

Methamphetamine users have significantly higher rates of coronary artery disease than the general population.⁶⁴ Even those with normal coronary arteries are at risk of methamphetamine-induced myocardial infarction, because of coronary spasm, which may be refractory to intracoronary vasodilator therapy.⁶⁵ The putative mechanisms of myocardial infarction in the context of methamphetamine use include accelerated atherosclerosis, rupture of pre-existing atherosclerotic plaques, hypercoagulability and epicardial coronary artery spasm.^{65,66} Acute myocardial infarction following methamphetamine use can be severe and can result in cardiogenic shock and death.⁶⁷

There is an association between methamphetamine use and cardiomyopathy, with different levels of problems reported by studies in areas where the prevalence of methamphetamine use is high. A study in Hawaii (where methamphetamine use is high) reported that methamphetamine use accounts for 40% of all admissions of patients under the age of 45 years with cardiomyopathy. More than 20% of with heart failure were former or current methamphetamine users.⁶⁸ A US registry containing information on more than 11,000 patients with decompensated heart failure reported that more than 5% were stimulant users.⁶⁹

One case series reported that more than a quarter (27.2%) of methamphetamine-intoxicated patients had a prolonged corrected QT interval ($QTc > 440$ ms), suggesting that methamphetamine-induced alterations in cardiac conduction may be partly responsible for the drug's dysrhythmogenic effects.⁷⁰

Other conditions related to methamphetamine intoxication include premature ventricular contractions, premature supraventricular contractions, accelerated atrioventricular conduction, atrioventricular block, intraventricular conduction delay, bundle branch block, ventricular tachycardia, ventricular fibrillation, and supraventricular tachycardia.^{63,70,71} Methamphetamine-induced dysrhythmias may also occur because of myocardial ischaemia or infarction.⁶⁰

Methamphetamine use may also be associated with aortic dissection and carries a greater risk for that than cocaine; it may be second only to hypertension in its importance as a risk factor for aortic dissection.⁷² Methamphetamine can cause

cerebral stroke, haemorrhage and hypertension.^{40,73} Like other drugs injected, the injection of methamphetamine has been associated with endocarditis.⁶⁰ Cardiovascular events are often involved in medical complications and death associated with methamphetamine.⁷⁴ The ingestion of large quantities of methamphetamine has been associated with cerebrovascular haemorrhage.^{75,76,77}

The risks associated with the long-term use of methamphetamine are discussed in section 8.12.

8.10.1.2. Hyperthermia

The ingestion of large quantities of methamphetamine has been associated with hyperthermia, above 41°C.⁷⁵⁻⁷⁷

8.10.1.3. Rhabdomyolysis

A five-year US study found that 43% of patients who presented to an emergency department with rhabdomyolysis were positive for methamphetamine.⁷⁸

8.10.1.4. Urological

The ingestion of large quantities of methamphetamine has been associated with renal and liver failure.⁷⁵⁻⁷⁷

8.10.2. Methamphetamine use and high-risk sexual behaviours

There are current anecdotal reports in the UK of high-risk behaviours associated with methamphetamine among a minority of gay men,⁷⁹ with this drug most commonly associated with what is referred to as 'chemsex', or sometimes as 'party and play', which is used to describe sex between men that occurs under the influence of drugs taken immediately before and/or during the sexual session.³⁰ Three patterns of behaviour are associated with methamphetamine use: high-risk sex, sexualised injecting and the sharing of injecting equipment.

The use of club drugs in a sexual context has been described.^{80,81} Methamphetamine is one of the drugs most commonly used in a sexual context (chemsex) in the UK⁷⁹ and elsewhere. In a US study of 60 MSM, 68% reported using methamphetamine during sex more than 50% of the time.⁸²

A relatively large body of evidence shows the heightened sexual risk-taking associated with methamphetamine use⁸³⁻⁸⁹ and a relationship has been observed between increased severity of methamphetamine use and HIV risk.⁸⁸ Methamphetamine use has also been associated with sexually transmitted infections (STI), with studies showing that MSM who use methamphetamines, regardless of their HIV status, have a greater risk of STIs than those who do not.^{32,90}

There is some evidence that compared with use of other drugs, methamphetamine use is a particularly strong predictor of unprotected anal sex among MSM.^{91,92} It has

also been associated with increased rates of STIs,^{35,93,94} including HIV infection.^{80,95–103} Men who use methamphetamine are 1.5–2.9 times more likely to acquire HIV than those who do not.^{87,104–107} There is also an association between methamphetamine use and rates of HIV and hepatitis C.^{108–115}

Studies also suggest that HIV-positive MSM who use methamphetamine are significantly more likely than MSM who do not use methamphetamine (regardless of their HIV status) to engage in unprotected anal sex,^{32,116–118} and group sex,¹¹⁹ to have multiple sexual partners,^{29,32,116,120,121} to find sexual partners on the internet,³² to have sex with an injecting drug user¹¹⁶ and to be intoxicated during sex.^{32,116} Among HIV-infected MSM men who have a sero-discordant partner (i.e. HIV negative, or status unknown), the use of methamphetamine is significantly associated with unprotected anal sex.^{33,122,123}

A number of factors and sub-groups of methamphetamine users have been associated with particularly high-risk behaviours for transmission of HIV and STIs. These include methamphetamine users who use sildenafil (Viagra)^{91–93,123,124} or other illicit drugs during sex,^{125,126} those who exchange sex for methamphetamine,¹²⁷ those who report high levels of sexual compulsivity,^{123,128} those who engage in sexual encounters in public spaces^{34,129} and those who report methamphetamine binges.¹³⁰

A recent review of outcomes among MSM who use methamphetamines has reported a low adherence to medication by HIV-positive MSM who use methamphetamine. This, the authors believe, may contribute to the transmission of HIV virus resistant to medication which has been seen in newly infected MSM who use methamphetamine.⁸⁹

However, it is important to note that a *causal* link between methamphetamine use and STIs, HIV and other blood-borne viruses (BBV) has not been established. There is some evidence that individuals who engage in high-risk sexual activity are more likely to use recreational drugs¹³¹ and evidence that among MSM recreational drug use in general (rather than methamphetamine use specifically) is associated with high-risk activity.^{132,133}

The link between methamphetamine use and high-risk sexual activities is not unique to MSM, although most of the research has been carried out among MSM and less evidence is available for heterosexuals.¹³⁴ Studies of male and female heterosexual populations also suggest that methamphetamine users have a higher frequency of sexual activity, have more sexual partners and engage in higher-risk sexual behaviours (unprotected vaginal sex and anal sex) than the users of any other drugs.^{135–139}

8.10.3. Injecting risks

There is some anecdotal evidence of injecting methamphetamine among a minority of MSM in London (sometimes in combination with mephedrone), taking place at sex parties or other social gatherings, where people may share injecting equipment. For some people, injecting appears to have become sexualised. This combination of factors has been described as ‘a perfect storm for transmission of both HIV and HCV [hepatitis C], as well as a catalogue of ensuing mental health problems’.⁷⁹

It has been noted that HIV-positive men are more likely to inject psychoactive substances (including methamphetamine) than other MSM, with injecting increasingly common with older age, peaking among men in their 40s.³⁰ There are some reports from methamphetamine users of increased sexual desires with injecting methamphetamine, in comparison with other forms of methamphetamine use.^{140,141}

Injecting is a serious public health concern, as well as heightening risks and harms to the individual user.¹⁴² The evidence on the elevated injecting-related risk behaviours among methamphetamine users in comparison with other injectors has been ambiguous.^{84,143–145} Regardless, methamphetamine injecting has been identified as a significant risk factor and injectors often present with more complex needs. Studies have shown that methamphetamine injectors are more dependent than non-injectors,¹⁴⁶ are at increased risk of non-fatal overdose,¹⁴⁷ are more likely to engage in HIV-risk behaviours;^{143,148–150} and a study has reported a higher prevalence of STIs than among non-injecting methamphetamine users.¹⁵¹

Methamphetamine injectors are more likely to have co-morbid psychiatric disorders than are non-injecting methamphetamine users.^{152,153} There is also evidence that methamphetamine injectors may be more likely to attempt suicide than those who smoke or snort the drug,^{153,154} with a seven-year study reporting that people who injected methamphetamine had an 80% greater risk of attempting suicide than those who did not inject, even after taking into account a wide range of potential confounders. The study also showed a dose–response relationship between frequency of injecting methamphetamine and suicidal behaviour. The conclusion was that individuals who inject methamphetamine should be considered at high risk of suicide among populations of methamphetamine users, as well as the broader injecting population.¹⁵⁵

8.10.4. Acute harms of poly-drug use and drug interactions

The high level of poly-drug use among methamphetamine users has been well established.¹⁵⁶ Cross-sectional population surveys suggest that the concurrent use of alcohol and cocaine is particularly common.¹⁵⁷ This can cause harm as it increases blood pressure. Methamphetamine can also mask the effects of alcohol, which may increase the risk of alcohol poisoning and accidents due to false feelings of being sober. Concurrent use of amphetamine and cannabis can increase psychotic symptoms in some users. Methamphetamine used with heroin can lead to respiratory depression and can increase the risk of heroin overdose.¹ The combination of methamphetamine and cocaine has been shown to increase substantially the cardiotoxic effects of both drugs.¹⁵⁸

The co-ingestion of GHB and methamphetamine might increase the risk of GHB overdose, as methamphetamine can mask the signs of acute toxicity. There are also risks associated with the use of methamphetamine with other serotonergic substances. Informal reports from specialist UK ‘club drug’ clinics and some UK research³⁰ suggest that methamphetamine is often used in combination with mephedrone, another stimulant, leading to a potential risk of serotonin toxicity (on which, see section 7.7.2).

The potential for drug interactions with CYP2D6 inhibitors is high and co-administration of these agents may increase the toxicity of methamphetamine. Well known CYP2D6 inhibitors include: amiodarone, citalopram, codeine, fluoxetine, haloperidol, methadone, paroxetine and valproic acid. Among the antiretrovirals, while low-dose ritonavir does not seem to affect CYP2D6 activity,¹⁵⁹ the newer booster cobicistat is included in the list of CYP2D6 inhibitors.

8.10.5. Acute withdrawal

For withdrawal see section 8.12.2.

8.10.6. Emergency hospital admissions

In countries where rates of methamphetamine use are high, admissions to emergency departments (EDs) are reportedly very common. US data demonstrate that regular users of methamphetamine have a high rate of presentation to ED^{61,160,161} and there is some evidence that adult methamphetamine users use ED and other hospital resources more than the users of other substances.^{61,162} A Canadian study of homeless and street-based youth reported that frequent injecting of methamphetamine was associated with increased risk of ED utilisation.¹⁵⁵ Studies have shown that 1–2% of all ED visits are related to methamphetamine in endemic areas, with psychiatric conditions being the most common complaints.^{154,163–173}

No such data are available for the UK, where the prevalence of methamphetamine use is low. However, 0.46% of drug-related presentations to an inner city hospital ED between 1 October 2005 and 31 December 2006 were related to self-reported methamphetamine use.²⁴

In comparison with other patients presenting to EDs for toxicology-related issues, some studies have shown that those presenting with methamphetamine-related problems are more agitated, violent and aggressive and more likely to present on arrival with tachycardia and hypertension.^{174,175}

In terms of mental health presentations, a study of psychiatric admissions to EDs reported that there were no differences in heart rate, admission route or cost of care of methamphetamine-related visits and other visits. This, according to the study, suggests that methamphetamine users presenting for psychiatric problems are clinically similar to non-amphetamine users with psychiatric problems.¹⁷⁶

Studies have also shown relatively high levels of methamphetamine-related hospital presentations for psychiatric problems. Psychiatric symptoms, including acute psychosis, depression and anxiety disorders, have been associated with both acute and chronic methamphetamine use.^{154,163–176}

Some studies have also suggested that more amphetamine-related presentations to EDs were for psychiatric problems than for other problems; 18% of methamphetamine-related ED visits were associated with psychiatric complaints or diagnosis, representing the largest patient sub-group visiting EDs with psychiatric issues.^{163,176}

In the US, where rates of methamphetamine use are significantly higher than in the UK, a study reported that methamphetamine-related psychiatric visits to EDs represented 7.6% of all psychiatric attendances at EDs, a percentage which the authors described as 'disproportionate'. In comparison, 1.8% of all trauma visits were methamphetamine-related and 2.1% of presentations with chest pain were methamphetamine-related.¹⁷⁶

8.11. Management of acute harms

TOXBASE® recommends that where a patient has impaired consciousness, emergency clinicians should ensure clear airways and adequate ventilation. As with other amphetamines, in the event of cardiac arrest, resuscitation should be continued for at least 1 hour and only stopped after discussion with a senior clinician. Prolonged resuscitation for cardiac arrest is recommended following poisoning, as recovery with good neurological outcome may occur.

TOXBASE® also suggests that the benefit of gastric decontamination is uncertain. Clinicians should consider oral activated charcoal if methamphetamine has been ingested within 1 hour, provided the airway can be protected. Asymptomatic patients should be observed for at least 4 hours, or 8 hours for patients who have ingested sustained-release preparations. Agitated adults can be sedated with an initial dose of oral or intravenous diazepam.

8.12. Harms of chronic use and dependence

8.12.1. Dependence

The risk of dependence with methamphetamine use is high. Tolerance to methamphetamine takes place when the drug is taken frequently, leading to users taking higher doses or using more frequently or changing the route of administration in order to get the desired effect.* There is some emerging evidence that craving to methamphetamine cues can be measured in dependent individuals¹⁷⁷⁻¹⁷⁹ and that cue-elicited methamphetamine craving is a strong predictor of subsequent use.¹⁸⁰

There is some evidence that methamphetamine-dependent users show a decrease in everyday functioning, disruption in everyday activities and increased errors in planning a daily schedule. Methamphetamine dependence has also been linked to impairments in the domains of communication, work and recreation.^{181,182} There is also evidence that the chronic use of methamphetamine causes cognitive deficits after withdrawal.¹⁸³⁻¹⁸⁵ Studies have also shown that this may be associated with disruptions of the dopaminergic and serotonergic systems.^{183,186-189} Chronic use of methamphetamine causes neurochemical and neuroanatomical changes, which includes memory impairment.

* Section 7.9.1 has discussed ICD-10 criteria for harmful use and dependent use and should be referred to when reading the present chapter. It also offers additional information on dependence on amphetamine-type substances.

Dependence results in deficits in memory and in decision-making and verbal reasoning.²² There is limited evidence that this functional deficit continues several months after abstinence.^{182,190} One study has reported deteriorating cognitive performance during the first three months of abstinence from methamphetamine, with abstinent patients or abstinent patients with a recent lapse scoring worse on neuropsychological testing than patients with on-going methamphetamine use. This reflects the difficulties in attention, understanding and memory often encountered in methamphetamine patients in treatment settings.¹⁸⁴ Although it needs to be substantiated by larger studies, Henry et al. suggest that this may have important implications for treatment interventions, as individuals with poor functional ability may have difficulty responding to cognitive-behavioural therapy (CBT) and the cognitive enhancement techniques commonly used in the treatment of methamphetamine misuse.¹⁹⁰

8.12.2. Withdrawal

Methamphetamine is associated with a clear withdrawal syndrome. A time-limited withdrawal syndrome may occur within 24 hours of the last dose when heavy chronic users of methamphetamine cease to use the drug abruptly. The withdrawal syndrome is common and severe enough to cause relapse outside a contained environment.¹⁹¹

Chapter 7 (the overview of amphetamine-type substances) has discussed in greater detail the phases of amphetamine withdrawal and should be read in conjunction with this present one. Phases of withdrawal symptoms have also been identified with methamphetamine users. For example, a study of 21 inpatients suggested that methamphetamine withdrawal has two phases: an acute phase lasting 7–10 days, in which overall symptom severity declines in a linear pattern from a high initial peak; and a sub-acute phase lasting at least a further 2 weeks, with some studies reporting much longer periods.¹⁹² Withdrawal from methamphetamine has been described as more characterised by psychological and psychiatric symptoms than physical symptoms.⁵⁶

Table 8.2. *The two phases of methamphetamine withdrawal.*

Acute withdrawal symptoms	Longer-term withdrawal symptoms (can last up to 12 months)
Severe dysphoria	Anhedonia
Irritability	Impaired social functioning
Melancholia	Intense craving
Anxiety	Hyper-arousal
Hypersomnia and marked fatigue,	Vegetative symptoms
Intense craving	Anxiety-related symptoms
Paranoia	Severe dysphoria
Intensity of post-binge dysphoria can lead to suicide ideation and attempts have also been linked to withdrawal ^{56,197} (for more information on the withdrawal syndrome see Chapter 7)	Mood volatility
Akathisia/restless legs	Irritability
	Sleep pattern disruption

Table 8.2 outlines the two phases of methamphetamine withdrawal, according to the reported symptoms.^{48,56,76,153,193–197}

Greater severity of withdrawal symptoms in methamphetamine-dependent individuals has been reported among those who are older, who have been using methamphetamine longer and who have more severe methamphetamine use disorder.^{192,197}

8.12.3. Physiological, psychological and psychiatric effects of long-term use and dependence

Chronic use has been associated with malnourishment.¹⁹⁸

8.12.3.1. Cardiovascular effects

Long-term use of methamphetamine can result in severe cardiovascular complications related to chronic hypertension and cardiovascular disease, such as angina, arrhythmias, valvular disease, haemorrhagic/ischaemic strokes and a high incidence of myocardial infarction.^{67,68,76,199–203}

8.12.3.2. Neurological effects

The chronic CNS hyperstimulation can lead to frequent headaches, tremors, athetoid movements and seizures.⁸ There is evidence that users of amphetamine-type substances, including methamphetamine, may have an above-normal risk of developing Parkinson's disease (PD) because of enduring damage to the brain's dopamine neurons. This was shown by a retrospective population-based cohort study of inpatient hospital episodes and death records from 1990 through to 2005 in California. Patients at least 30 years of age were followed for up to 16 years. The study found that methamphetamine users had a 76% increased risk of developing Parkinson's disease in comparison with the matched population proxy control group. The authors noted that this finding may be limited to high-dose, chronic methamphetamine users and only when they reach middle and older age, when they have suffered age-related loss of dopamine neurons.²⁰⁴

8.12.3.3. Pulmonary and respiratory harms

The smoking of methamphetamine can cause respiratory symptoms and disorders such as pulmonary oedema, bronchitis, pulmonary hypertension, haemoptysis and granuloma.⁸ Methamphetamine is associated with pulmonary arterial hypertension (PAH),²⁰⁵ although its precise role remains unclear.⁶⁰

8.12.3.4. Blood-borne infections, and haematological, gastrointestinal and urological effects

Methamphetamine has been reported to cause acute liver injury, with hepatic necrosis and centrilobular degeneration, even in the absence of hepatitis.²⁰⁶ Mesenteric infarction,²⁰⁷ segmental ischaemic colitis, vasculitis or vasospasm with spontaneous

resolution have been reported.²⁰⁸ Severe acute necrotic haemorrhagic pancreatitis has been reported in cases of sudden death of chronic methamphetamine users.⁶⁰

Because of the increased likelihood of high-risk sexual behaviours discussed in section 8.10.2, methamphetamine users are more likely to be diagnosed with a sexually transmitted infection than non-users.^{135,138} Methamphetamine users are also at greater risk of viral hepatitis, especially where the drug is injected, but even among methamphetamine smokers and insufflators, hepatitis C is more common than it is in the general population.²⁰⁹⁻²¹¹

8.12.3.5. Oral/dental health

Methamphetamine use is associated with 'meth mouth', which is a constellation of symptoms, but it has been suggested that lifestyle factors, rather than the drug, may also be at play,²¹² including poor personal hygiene and malnutrition.²¹³ Symptoms includes severe tooth decay and loss of teeth, advanced tooth wear, tooth fracture, and oral soft-tissue inflammation and breakdown.^{214,215} A study of 301 adults dependent on methamphetamine found that 41.3% had oral or dental disease. They also had significantly more missing teeth than controls. The injecting of methamphetamine was significantly more likely to be associated with missing teeth than smoking the drug.²¹²

8.12.3.6. Dermatological

Methamphetamine users may suffer from skin lesions resulting from compulsive scratching (due to formication – a sense of having ants under the skin). These lesions can result in bacterial cellulitis and, in some cases, bacteraemia and sepsis. In a case series of methamphetamine users presenting to an emergency department, skin infection accounted for 6% of the initial presentations and 54% of subsequent admissions to hospital.⁶¹

8.12.3.7. Pott puffy tumour

There is a case report of Pott puffy tumour (PPT) associated with the intranasal use of methamphetamine. This is an anterior extension of a frontal sinus infection that results in frontal bone osteomyelitis and subperiosteal abscess.²¹⁶

8.12.3.8. Ophthalmological harms

Acute unilateral vision loss has been reported following a single dose of intranasal methamphetamine use and is believed to be due to ischaemic optic neuropathy secondary to methamphetamine-induced vasospasm and methamphetamine-associated vasculitis.^{217,218}

8.12.3.9. Psychological and psychiatric effects

The frequent and prolonged use of methamphetamine has a number of adverse effects. There are direct physiological effects, but the cognitive and behavioural changes associated with its use may be secondary to neurotoxicity.²¹⁹

There is a well established association between methamphetamine use and mental health problems.^{76,220} Studies have found elevated rates of mood disorders, anxiety disorders and antisocial personality even after treatment.²²¹ Depressive disorders and symptoms are frequently associated with methamphetamine use.^{170,172,173,222–225} The high prevalence of substance misuse among people with bipolar disorders or major depressive disorders has been established for a number of years.²²⁶ It is also well established that substance misuse can exacerbate mental health problems.²²⁷ There is some evidence that serious psychiatric disorders may emerge or worsen as a result of methamphetamine use,^{48,56,153,228,229} including increased risk of suicide.²³⁰

The state of catecholamine and serotonin depletion after several days of methamphetamine use can manifest itself as exhaustion, depression, lethargy and anhedonia. Psychological symptoms include persistent anxiety, paranoia, insomnia, auditory hallucinations, delusion, psychotic or violent behaviour and suicidal or homicidal thinking,⁸ although violent behaviour is not an inevitable outcome of even heavy long-term use.²³¹ Some of the symptoms can resemble those of paranoid schizophrenia.²²

Methamphetamine-induced psychotic disorder has been associated with the chronic, high-dose and continuous use of methamphetamine.²³² Symptoms may include paranoid delusions, persecutory delusions and other delusions, and auditory, visual and tactile hallucinations. The disorder is often associated with mood disturbances.²³³ While sustained and high doses of methamphetamine can cause symptoms that resemble those of psychosis, relatively few studies have observed this in people using only methamphetamine who have no history of mental illness.² Nonetheless, a US study of 43 methamphetamine-dependent users and 42 cocaine-dependent users reported psychotic symptoms in at least 60% of both groups.¹⁶⁷ An Australian study of 27 treatment-seeking methamphetamine users with no prior diagnosis of schizophrenia, or other psychotic disorder, found that 18% had what was referred to by the authors as 'clinically significant' psychotic symptoms.³⁹

Symptoms usually remit after acute intoxication but some individuals may develop psychosis weeks or months after stopping methamphetamine,^{233,234} and may prove to be refractory to antipsychotic medication.²³⁵

Stress can precipitate spontaneous psychosis in former methamphetamine users who are abstinent.²³⁶

Much of the literature on persistent methamphetamine psychosis comes from Japan, where methamphetamine has been illicitly used for over 50 years, which suggests that persistent methamphetamine psychosis is not uncommon.²³⁵ Japanese studies also reported that psychotic symptoms may recur where there is new exposure to the drug.^{235,237–241} Japanese research has also reported discouraging results with standard antipsychotic drugs, as many patients remain clinically psychotic after many months of treatment.^{234,242}

8.12.3.10. Cognitive effects

Neuroimaging in chronic users has shown significant neural damage in patients and evidence of cognitive impairment, but it is not established whether the link is causal.^{40,243}

8.12.4. Co-morbidities of methamphetamine use disorders and HIV

Methamphetamine has been shown to interfere with the efficacy of HIV medication and treatment.²⁴⁴ Its use has been linked to non-adherence to medication regimens²⁴⁵ and there is a suggestion that it may be associated with increased viral loads, even among those taking antiretroviral medication.²⁴⁶

Both methamphetamine use and HIV may be associated with impaired cognitive function, and in combination may result in greater impairment than each condition alone.²⁴⁴ There is evidence that hepatitis C increases these cognitive deficits.²⁴⁷

8.13. Management of harms of chronic and dependent use of methamphetamine

8.13.1. Identification and assessment of dependence

The identification and assessment of chronic use of methamphetamine and ensuing harms are similar to those for ATS in general (see Chapter 7), but with particular vigilance to the issues pertaining to MSM, who are currently the group in the UK who mostly use methamphetamine.

8.13.2. Psychosocial interventions for dependence

Studies have shown that some people dependent on drugs may achieve abstinence without the need for treatment.²⁴⁸

At present, the most effective treatments for methamphetamine addiction are psychosocial interventions and behavioural therapies. Historically, treatment for stimulant dependence has relied on cognitive-behavioural therapy (CBT), with efforts to integrate contingency management (CM) (for more information see Chapter 7).

Overall, the evidence suggests that psychosocial interventions, such as CBT and CM, are moderately effective in achieving methamphetamine abstinence.²⁴⁹ A Cochrane review of psychosocial interventions for cocaine and psychostimulant amphetamine disorders reported that comparisons between different types of behavioural interventions showed results in favour of treatments with some form of contingency management with respect to both reducing drop-outs and lowering use. However, the review also reports there are few significant behavioural changes even after reductions in drug consumption following an intervention. The authors conclude that there are no data supporting a single-treatment approach that is able to tackle the

multidimensional facets of addiction and to resolve the chronic, relapsing nature of addiction, with all its correlates and consequences.²⁵⁰

A number of US studies have reported the effectiveness of CM within specific research and drug treatment settings,²⁵¹ as well as outside those settings.²⁵² CM in combination with other interventions, such as CBT, has proved to be modestly effective at reducing methamphetamine dependence.^{252–255} CM was also shown to have superior efficacy to CBT during drug treatment.^{251,256}

Similarly, there is some evidence that behavioural-based treatment for methamphetamine misuse can be effective in reducing HIV infections, in terms not only of injecting behaviours but also of unsafe sexual practices.¹⁰² Studies have shown the effectiveness of CM with methamphetamine users in changing other risk behaviours. For example, a pilot study of 35 MSM (not in drug treatment) who were given post-exposure prophylaxis (PEP) and CM showed that this may be useful as a combination HIV prevention strategy.²⁵⁷

Although psychosocial and behavioural interventions have been the most effective treatment for methamphetamine use, some argue that their role is still in question. CM, in particular, has shown benefit but a key limitation includes its failure to address adequately mental health needs or develop relapse prevention plans for after the intervention.⁸⁹ There is also some evidence that CM is not likely to have a sustained and large effect on methamphetamine use.²⁵⁸ One randomised controlled trial of CM to reduce methamphetamine use and sexual risk studied 217 non-treatment-seekers over 12 weeks and found that CM was potentially associated with an increase in methamphetamine use and decreases in sexual risk, but these were not statistically significant.²⁵⁸

As relapse rates are high,²⁵⁹ there have been calls for more work in improving methamphetamine treatment. Further research into cognitive-behavioural and behavioural treatments for methamphetamine users is required, with a focus on increasing the duration of the effect of intervention and improving its effectiveness among patients with more complex presentations.²⁶⁰

8.13.2.1. Implementation of CM

Some studies have looked in greater detail at the impact of CM and at variations in CM models used and which specific factors were most effective in producing positive treatment outcomes. Roll et al. found that there were significant differences in terms of a CM schedule's ability to initiate and maintain abstinence. The schedule based on an escalating programme of reinforcement with a reset contingency (developed by Higgins²⁶¹) showed the best results for a successful treatment episode.²⁶²

Ling Murtaugh et al. found, in their study of 162 MSM methamphetamine-dependent users, that it was the act of voucher redemption, rather than the receipt or size of payment, that affected subsequent abstinence from methamphetamine. Participants who delayed spending the vouchers, and those who saved the vouchers, had worse outcomes once they did finally redeem them. The authors recommend that frequent

purchases in incentive-based programmes should be promoted to improve abstinence outcomes.²⁶³

8.13.3. Pharmacological interventions for methamphetamine dependence and withdrawal

The need to develop safe and effective medication for methamphetamine dependence continues to be a global strategic aim. According to the US National Institute on Drug Abuse (NIDA), one approach currently tried is to target the activity of glial cells with a drug called AV411 (ibudilast). This has been shown to inhibit methamphetamine self-administration in rats; it is now being studied in clinical trials to establish its safety and effectiveness in humans. Other approaches currently under study use the body's immune system to neutralise the drug in the bloodstream before it reaches the brain. These approaches involve injecting a user with (anti)methamphetamine antibodies or with vaccines that stimulate the body to produce its own antibodies.²⁶⁴ A clinical study is currently being conducted to establish the safety of an anti-methamphetamine monoclonal antibody, known as mAb7F9, in human methamphetamine users.²⁶⁴

As well as new compounds, a number of medications approved for other conditions have been tested for their efficacy and safety in treating methamphetamine dependence. These have included serotonergic agonists, dopaminergic agonists, monoamine agonists and mixed monoamine agonists/antagonists.^{57,82,265–280}

For the moment, however, psychosocial therapies continue to be the cornerstone of treatment, with drug therapy regarded as an adjunct rather than a replacement for psychosocial approaches.⁸ There is currently no approved pharmacotherapy for methamphetamine dependence²⁵⁹ and no specific medication to counteract the effects of methamphetamine, or prolong abstinence.

A recent Cochrane review²⁸¹ of the efficacy and safety of psychostimulant medications for amphetamine dependence (dexamphetamine, bupropion, methylphenidate and modafinil), in addition to psychosocial interventions, reported that no significant differences were found between psychostimulants and placebo for any of the studied outcomes. Overall retention in studies was low (50.4%). Psychostimulants did not reduce amphetamine use, or amphetamine craving, and did not increase sustained abstinence. The proportion of dropouts due to adverse events was similar for psychostimulants and placebo. The review concluded that the evidence does not support the prescribing of psychostimulants (at the tested doses) as replacement therapy, although further research may change this conclusion.²⁸¹

A small double-blind placebo-controlled study on the use of N-acetyl cysteine plus naltrexone found no significant difference with placebo on treatment outcomes.²⁷⁶

Other trials conducted with methamphetamine users have tested selegiline, ondansetron, paroxetine,²⁶⁷ fluoxetine^{282,283} and sertraline,^{253,269} usually accompanied by a psychosocial structured therapy. A placebo-controlled trial studying the selective serotonin reuptake inhibitor sertraline, for the treatment of methamphetamine use showed that subjects receiving sertraline did not show improvements in depressive

symptoms or craving compared with those who did not receive it.²⁶⁹ It has been argued that, overall, results suggest that sertraline, and possibly *all* selective serotonin reuptake inhibitors, are ineffective and may even be contraindicated for methamphetamine dependence.²⁶⁹

A number of small studies have suggested that there may be a potential for the use of mirtazapine (a noradrenergic and specific serotonergic antidepressant).^{8,82,284} Mirtazapine (in addition to counselling) was shown to reduce use among active methamphetamine users.⁸² It was also shown to lessen the symptoms of methamphetamine withdrawal (including the subjective symptoms) over 10 days of abstinence, with reductions in agitation, anxiety, fatigue, irritability, paranoid ideation, anhedonia, vivid dreams and suicide ideation. It also increased the amount of sleep.²⁷⁷

The impact of mirtazapine, in addition to counselling, on sexual behaviours that were shown by one study is noteworthy. A 12-week double-blind trial of mirtazapine among 60 MSM found that most sexual risk behaviours decreased significantly in the mirtazapine arm of the study in comparison with the placebo arm, even though both arms received HIV risk-reduction counselling at baseline. The study also found that the reduction in sexual risks was associated with a reduction in negative test results for amphetamine use, perhaps suggesting a possible causal pathway between the two outcomes.⁸²

Not all studies of mirtazapine have shown its effectiveness in the management of methamphetamine dependence.²⁷⁸ One study which focused on patients with acute withdrawal symptoms showed that it does not facilitate retention or recruitment in outpatient methamphetamine withdrawal treatment.²⁷⁸

The use of anticonvulsants has also been investigated. A randomised controlled trial of 140 methamphetamine-dependent adults prescribed topiramate (at doses of up to 200 mg/day) suggested that this medication does not promote abstinence. However, there is some indication that it may reduce amounts ingested and can reduce relapse rates among those already abstinent.²⁶⁵

Similarly, a trial randomly assigning people to an active medication regimen – comprising flumazenil (2 mg infusions on days 1, 2, 3, 22, 23), gabapentin (1200 mg to day 40) and hydroxyzine (50 mg to day 10) – or placebo showed that the regimen was no more effective than placebo in reducing methamphetamine use, retaining patients in treatment or reducing craving.²⁸⁵ These results were different from those of another study using the same protocol that found fewer positive urine tests for methamphetamine throughout the trial and decreased cravings.²⁷⁵ Differences may be due to study conditions and different demographic characteristics of participants in a private medical setting.²⁸⁵

A double-blind study of 60 subjects with bipolar or major depressive disorder and methamphetamine dependence randomised them to placebo or citicolin, an over-the-counter nutritional supplement (2000 mg/day), for 12 weeks. A significant between-group difference in depressive symptoms was observed. The study also showed significantly higher completion rates among those on citicolin than those on placebo.²²⁷

8.13.4. Treatment effectiveness, impact, retention and completion

Some studies have shown that, when methamphetamine users seek treatment, there is a substantial likelihood of treatment drop-out and relapse,³⁶ although the treatment outcomes for methamphetamine users are not necessarily different from those of the users other drugs.^{286,287} There is, though, a lack of treatment provision.²⁸⁸

Treatment for methamphetamine use/dependence can have a positive impact on other high-risk behaviours. A study on CM and CBT for MSM found that those who reported the greatest decrease in methamphetamine use also reported the greatest and quickest reduction in depressive symptoms and high-risk sexual behaviour.²⁸⁹ The authors suggest that lowering methamphetamine use can have an effect on depression and sexual behaviour and that some users who respond well to treatment may show improvements in these co-occurring problems, without the need for more intensive targeted interventions.²⁸⁹

Similar findings were reported by other studies.⁸² There is some evidence that interventions to reduce or eliminate methamphetamine use for MSM in drug treatment settings also produce reductions in high-risk sexual behaviours and resultant HIV transmission. Drug treatment may be an important part of an HIV/STI prevention strategy for MSM.²⁵¹ One study of methamphetamine users found that longer treatment retention and greater rates of treatment completion were significantly related to greater reductions in risky sexual and injecting behaviours and were associated with reductions in HIV risk three years after treatment.²⁹⁰

There is a growing body of evidence on the factors that help predict methamphetamine treatment success, and most particularly failure, including retention in treatment and treatment completion.³⁶ There is consistent evidence that poorer outcomes are associated with:

- greater frequency of use prior to treatment,^{36,270,291–294}
- more extensive history of previous treatment;^{292,293,295}
- lower educational attainment,^{36,292} although conflicting evidence on this has been reported.^{291,294}

Other factors have also been associated with success or failure, but the evidence is either limited or inconsistent. These include greater craving for methamphetamine,¹⁸⁰ legal coercion of treatment,³⁶ residential versus outpatient treatment,²⁹² shorter treatment duration,²⁹⁵ disability,³⁶ selling methamphetamine²⁹⁵ and intravenous use.^{36,293} Race, gender and ethnicity have also been associated with treatment success or failure, but the findings have differed between the studies.

Similar factors were identified as affecting health-related quality of life (HRQOL) for those completing treatment. A study of the HRQOL trajectories of 723 people dependent on methamphetamine, resulting from treatment completion and continued care over one year, found greater improvements in mental health. It described 'fairly static' trajectories in physical health status, in comparison with those who did not complete treatment or who continued to use services. The study showed differential

patterns of health improvement. Factors identified as negatively affecting HRQOL included unemployment, lifetime trauma, suicide history, interpersonal conflict, continued use of methamphetamine, poly-drug use and medical and psychiatric impairment.²⁹⁶ The study also found that higher education was associated with a poorer health outcome, a finding that is not supported by the literature. The authors speculated that this might be because drug use among highly educated subjects can lead to a lower perceived health status, with the subjects not being able to maintain previous health standards and not able to fulfil goals they had set before drug use. The study also showed poorer health outcomes for women on methamphetamine.²⁹⁶

The frequency of use at entry to treatment and early treatment responsiveness have been identified as predictors of treatment success. One study of 60 individuals looked at whether cognitive performance can predict success in treating methamphetamine dependence, and considered whether cognitive performance is more or less predictive of treatment success than the established factors, such as frequency of use.²⁹⁷

The study found that, although a few neurocognitive and psychiatric variables were associated with treatment outcome, the frequency of methamphetamine use at the study outset was a much stronger predictor of outcomes. Participants who had two or fewer urine tests positive for methamphetamine during the first two weeks were much more likely to complete treatment and achieve abstinence in the majority of the treatment weeks,²⁹⁷ a finding that was consistent with several other studies.^{36,270,291-293,298}

The authors suggest that it is possible that this finding was partially due to study design. Nonetheless, the study did show that patterns of methamphetamine use during the initial stages of treatment were able to predict the outcomes in terms of continued use and treatment attendance. A few cognitive measures were related to treatment outcome, but these did not allow for prediction after adjustment for methamphetamine use at the beginning of the study. The authors concluded that clinicians who want to identify patients at risk of treatment failure should use multiple urine tests. They also suggest that it is more plausible to predict treatment failure than treatment success.²⁹⁷

Similarly, a study of bupropion found that early treatment responsiveness may be important for positive outcomes, a finding consistent with smoking cessation²⁷³ and with some research in cocaine treatment.^{273,274} Data analysis showed that the inability of users to provide at least three methamphetamine-free samples in the first two weeks of treatment was associated with a likelihood of treatment failure exceeding 90%. The authors suggest that clinicians prescribing bupropion can predict treatment failures confidently within two weeks when they carry out drug testing three times a week, with weekly testing yielding acceptable predictive power within three weeks. The ability to predict treatment failure was substantially more precise than the prediction of treatment success, which the authors attributed partially to the overall treatment failure rates. The absence of an early response predicts treatment failure better than the presence of an early good response predicts treatment success. The authors therefore suggest that this prediction of treatment failure is relevant to clinicians, as it signals the need to change treatment modality and intensity.²⁷²

8.13.5. Access to treatment

People dependent on methamphetamine may not access treatment services for many years and there is often a delay between first use, first recognising a problem with methamphetamine, and first treatment assessment. Different studies have shown a range for average length of time for the first treatment. An Australian study found that methamphetamine users can wait an average of five years from first experiencing problems to seeking treatment.²⁹⁹ US studies have reported an average of eight³⁰⁰ and nine years.⁴⁸

There are many reasons why this may be the case. A US study reported a common belief among methamphetamine users that it is a 'functional drug', which may encourage frequent and prolonged daily use.^{48,301} Similarly, Kenny et al. reported common reasons for not seeking methamphetamine treatment: users did not believe that they were dependent (despite meeting DSM-IV criteria for dependence); they did not feel that regular use of methamphetamine warranted formal treatment; they discounted their dependence; and they recognised their dependence but were not ready to do anything about it.³⁰²

There is also some non-UK evidence that treatment services may not be, or be perceived to be, accessible to methamphetamine users. An Australian study^{303,304} suggested that the reasons for the under-representation of methamphetamine users in the treatment system include poor orientation of services for this group, lack of information about treatment options and little confidence in the effectiveness of programmes.

Barriers to treatment are not only constructed by service users but also by clinical staff. A study has also looked into barriers to methamphetamine treatment from the perspective of treatment providers, who saw barriers as extensive and wide-ranging. They included the particular personality characteristics of methamphetamine users, complexities associated with mental health co-morbidity, waiting periods resulting in loss to treatment, the binge nature of methamphetamine use, lack of pharmacological options and negative attitudes of staff towards this patient group.³⁰⁵

Improved understanding of the ways methamphetamine users access other treatment services could be used to facilitate effective referral pathways. Studies have looked at the factors, and user characteristics, that make individuals more likely to seek support.^{306,307} GPs have been identified as a likely common starting point for patients seeking referral, for all drug-related problems.³⁰⁸

Quinn et al.'s study suggests that service utilisation for other problems, such as mental health or other drug problems, increases the likelihood of accessing treatment for methamphetamine use.³⁰⁷ They suggest that contact with other services may increase the opportunity for treatment of methamphetamine misuse and break down barriers to professional support, such as ignorance of the services available and stigma associated with service utilisation.³⁰⁹ People who use services for other issues are more receptive to seeking treatment for methamphetamine misuse.³⁰⁷ The authors also note that these findings suggest a need to facilitate professional support pathways for treating methamphetamine users who engage in harmful use patterns.³⁰⁷

The availability of appropriate and relevant services has been identified as enhancing service uptake. Australian studies have suggested that methamphetamine injectors are more likely than those who smoke or snort the drug to seek and receive treatment from specialist services.^{307,310,311} It has been suggested that there is greater availability of services for people who inject and fewer barriers to treatment (such as needle exchanges).

In comparison with other substances such as opiates, it may be important to make the treatment settings specific to methamphetamine users, to accommodate the different nature of methamphetamine dependence and withdrawals. Although this may be beyond the means of many drug treatment systems and services, services can undertake some small changes that could have a large impact on user perception, such as allocating some time each day for methamphetamine clients or allocating specific staff or rooms with specific methamphetamine resources.³⁰²

The cultural competence of services has also been identified as enhancing treatment uptake. A study of behavioural psychological interventions on depression, sexual risk behaviour and methamphetamine use among 162 MSM found that a gay-specific CBT intervention reported the greatest reduction in all three outcomes.²⁸⁹

Treatment readiness may also be key to accessing support for methamphetamine problems. Quinn et al. found that two key factors were associated with seeking help for methamphetamine problems: seeking help from family or peers in the year before entry into the study; and adoption of personal methods for the reduction or cessation of methamphetamine use.³⁰⁷ It has been suggested that targeted interventions to identify and access individuals when they first experience readiness to change could be important. Motivational interviewing and stepped care could be beneficial.

One study found that only a small number of methamphetamine-using participants had reported access to more intensive drug treatment services (i.e. residential detoxification and/or rehabilitation), maybe suggesting a preference for low- rather than high-threshold treatment services,^{307,312} or that many individuals feel that they are able to address harmful and/or dependent use without the need for intensive professional intervention.²⁴⁸

8.13.6. Aftercare and support

See section 7.10.5.

8.14. Harm reduction

The implications of driving under the influence of methamphetamine has been discussed.³¹³

Harm reduction is covered in Chapter 7.

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Chapter 9

Mephedrone and other synthetic cathinones

Drug group: stimulants

Mephedrone (4-methylmethcathinone) is the most commonly used synthetic cathinone in the UK and is therefore the focus of this chapter. There are approximately 30 synthetic cathinones and those used for recreational purposes include methylenedioxypropylamphetamine (MDPV), butylone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, methedrone, methylone, pyrovalerone, 3-MeOMC; 3-MMC; 4-BMC; 4-MEC; 4-MeO-a-PVP; 4-MeO-PBP; 4-MeO-PV9; 4-MPD; 4F-PV8; 4FPV9; 4F-PVP; a-PBT; a-PHP; a-PVT; dibutylone; DL-4662; ethylone; MDPPP; MOPPP; NEB; pentedrone; PV-8. By 2012 more than 30 synthetic cathinones had been notified in the European Union as potential drugs of misuse.¹ During 2013, seven more synthetic cathinones were notified by the member states for the first time through the EU Early Warning System.²

Synthetic cathinones are beta-keto phenethylamines. Typically, they have an amphetamine-type analogue, which means that they are structurally related to amphetamine, methamphetamine and MDMA. Other synthetic cathinones recently identified on the drug market are analogues of pyrovalerone (3,4-methylenedioxypropylamphetamine and naphyrone).³

9.1. Street names

Street names for mephedrone at the time of publication include: Bubble(s), Miaow, Meow Meow, 4-MMC, Mcat, Sub-coca, Toot, Top Cat, Meph, M1, Drone, Spice E, Charge, Rush, Ronzio, Fiskrens, MMC Hammer, Bounce; Moonshine, Neo drones, Plant feeder, Roxy, SC spirit, White magic, Mad-dog, Bubbleluv, and Challenge (which ketamine is also known as). Other local names may also exist.

The term 'bath salts' is mainly used in the US to refer to a number of synthetic cathinones and will appear in the American literature.

9.2. Legal status

Mephedrone and other cathinone derivatives are Class B Schedule 2 drugs under the Misuse of Drugs Act 1971 (except the antidepressant bupropion and those already controlled under the Act, including cathinone itself, which is Class C).

9.3. Quality of the research evidence

Currently, the bulk of the UK and European literature on the harm associated with the use of synthetic cathinones and the management of those harms focuses on mephedrone, and to some extent MDPV, reflecting their higher prevalence of use relative to other synthetic cathinones. The international evidence on the management of the acute and chronic harms related to the use of mephedrone and other synthetic cathinones is limited. There are a few case reports and series and a small number of prospective observational studies, retrospective series and analyses of patient records, user surveys and qualitative studies. Not all studies have analytical confirmation of cathinone use, reducing the ability to draw robust conclusions and make recommendations.

US studies generally refer to the whole group of so-called 'bath salts' and tend to include findings relating to methylenedioxypyrovalerone (MDPV) in particular, as well as mephedrone and other synthetic cathinones. Some do not specify what compounds are involved in the 'bath salts' discussed and were therefore not included in this review.

9.4. Brief summary of pharmacology

The natural analogue to synthetic cathinones is the active compound in the leaves of the khat plant (*Catha edulis*), which have been chewed for centuries in parts of Africa and the Arabian Peninsula for their stimulant properties.⁴ Mephedrone was first synthesised in 1929 and has been widely available on mainland Europe since 2007, and in the UK since 2009.

Like amphetamines, cathinones act as central nervous system stimulants, although they are generally less potent than amphetamine. Synthetic cathinones are amphetamine-like behavioural stimulants which have similar effects to amphetamine on monoamine reuptake, including serotonin, dopamine and noradrenaline.⁵ They also have a similarly strong sympathomimetic effect.

Synthetic cathinones exert their stimulant effects through increasing synaptic concentration of dopamine, serotonin and noradrenaline. They are able to inhibit monoamine uptake transporters producing a decreased clearance of the neurotransmitters from the synapse. They may cause release of biogenic amines from intracellular stores.⁶ Synthetic cathinones are generally less able than amphetamines to cross the blood-brain barrier because the beta-keto group causes an increase in polarity.⁷

Mephedrone is produced by replacement of the 4-position aromatic hydrogen of cathinone with a methyl group, and carries a similar molecular structure to many common street drugs, including amphetamine and MDMA.⁸

Mephedrone and methylone were consistently found to act as potent inhibitors of the uptake of all three monoamines. Mephedrone and methylone are approximately equipotent inhibitors of all three monoamine transporters, with potencies comparable to that of MDMA.⁹

The ability of mephedrone to cause subjective effects resembling those of MDMA is likely to have contributed to its relatively widespread use. However, its ability to cause dopamine release may be problematic, inasmuch as in comparison with MDMA, mephedrone may have a greater liability to misuse, resembling that of dopamine-releasing agents, such as methamphetamine.¹⁰

Following oral administration, maximum mephedrone concentrations are achieved after 0.5–1 hour. Its absolute bioavailability is low (10%) and it is moderately protein bound ($21.59 \pm 3.67\%$). Animal and human studies showed that mephedrone is metabolised by different phase I reactions (i.e. demethylation, oxidation, etc.). These may be undertaken by different CYP450 isoenzymes (e.g. CYP2D6 and CYP3A4). Phase II reactions (i.e. glucuronidation) are also involved in mephedrone's metabolism.^{11–13}

9.5. Clinical uses of mephedrone and synthetic cathinones

Currently, bupropion is the only cathinone derivative that carries a medical indication in the US and Europe. It is used for the treatment of depression and as a smoking-cessation aid.¹⁴ It has been specifically exempted from the legislation that has made many cathinones Class B Schedule 2 in the Misuse of Drugs Act 1971, because of its clinical utility and it having no propensity to misuse.

9.6. Prevalence and patterns of use

The rapid increase in the use of mephedrone in 2009 in the UK was noted by a number of studies.^{15,16} There are suggestions that in the UK and Holland, this was associated with the poor quality of cocaine and ecstasy at the time. Its popularity was also enhanced by its relative low cost, easy availability due to its 'legal' status before 2010 and its desired effects.^{14,15,17}

There is a mixed picture of its availability and prevalence of use in the UK after the ban.¹⁸ Some studies have suggested the control of the drug in 2010 did not stop the spread of its use,^{19,20} while others have suggested it did.²¹ There are indications that its use is in now decline, although it remains one of the most prevalent club drugs, (or novel psychoactive substances (NPS), used and reductions in use cannot necessarily be attributed to legal control.

Nonetheless, data from the Crime Survey for England and Wales (CSEW; formerly the British Crime Survey)²² suggest that mephedrone use (at all in the previous year) among 16–59-year-olds fell from 1.4% in 2010/11 to 0.6% in 2013/4, although it remained the joint fifth most commonly used drug among adults. A reduction was also noted in the 16–24-year age group, from 3.3% in 2010/11 to 1.9% in 2013/4.

As with other club drugs, the use of mephedrone is associated with lifestyle. The CSEW 2013/14 reported that the use of mephedrone (in the previous year) was around 20 times higher among those who had visited a nightclub four or more times

in the past month (5.8%) than among those who had not visited a nightclub in the past month (0.3%).

UK data from the self-selected respondents of the 2012 Global Drug Survey reported 42.7% lifetime use and 19.5% in the last year. Prevalence of use among regular clubbers (in the last year) was reported as 30%. Yet, even among this group there is some evidence of a reduction in its use since its peak. Indeed, the 2012 Global Drug Survey²³ also suggested a decline in its popularity. Similarly, in an analysis of pooled urine from 12 portable urinals in central London, mephedrone was only present in 6 urinals; in contrast, cocaine, cannabis and MDMA were present in 11 and amphetamine was present in 10.²⁴ The UK National Poisons Information Service (NIPS) also reported a reduction of activity relating to mephedrone in its annual reports since 2010/11.^{25,26}

However, the decline of mephedrone use may not be universal and differences may exist based on sexuality and geography. Two surveys in a gay-friendly nightclub suggested that its use had in fact increased substantially. A study conducted in 2010 among people attending gay-friendly nightclubs in south London reported that mephedrone was the drug most commonly used, with 27% reporting using it or planning to use it on the night.¹⁶ A follow-up study one year after the control of the drug suggested that mephedrone remained the most popular drug in this setting and that its use had increased substantially in 2011, with 41% of respondents reporting they had used it or were planning to use it on the night. The most commonly reported favourite drug by respondents was mephedrone (20.4%).²⁷ Similarly, in 2013 the Welsh government reported an increase in the use of NPS and most particularly mephedrone in the past two years, as well as a rise in mephedrone-related referrals.²⁸

Among most mephedrone users, the drug is often taken as part of a wider repertoire of substances. The CSEW 2012 survey suggested that 25% of mephedrone users were simultaneous poly-users. Studies of people who frequented the night-time economy in London and Lancashire found that mephedrone had been added to the existing drug repertoire. It did not act as a gateway to other drug use for those with no pre-existing drug use and mephedrone did not lead to a wholesale displacement of other drugs.^{15,29} Other evidence suggests that poly-substance use is common among mephedrone users, with other substances ingested including alcohol, cannabis, cocaine, ecstasy and ketamine.³⁰ Alcohol and cannabis are reported in one survey as the most commonly co-ingested substances.^{31,32} There is also anecdotal evidence from clinical practice that mephedrone is used in combination with methamphetamine by men who have sex with men (MSM) in particular.

There is evidence that some users co-ingest more than one substance not only to enhance the desired effects but also to attempt to reduce the harmful effects. Popular combinations reported are mephedrone or MDPV in combination with the following drugs:^{30,31,33-39}

- alcohol, propranolol or another beta-blocker to offset tachycardia;
- cannabis, diazepam or alprazolam for anxiety and overstimulation;
- famotidine, omeprazole or domperidone for stomach pain;

- other psychostimulants such as cocaine, amphetamine, modafinil, trifluoromethylphenylpiperazine, benzylpiperazine, butylone, methylone or pentylone to enhance stimulant and entactogenic effects;
- opiates, such as morphine or tramadol, to create 'speedball'-like effects;
- GHB/GBL to enhance sexual stimulation;
- ketamine or zopiclone to enhance visual hallucinations.

There is limited evidence that synthetic stimulants, especially cathinones, are replacing opioids in countries reporting heroin shortages. The motive for the transition from injecting heroin to cathinones is unclear, but may be linked to easy availability and perceived high quality of the new drugs.² There have been reports of mephedrone injecting from Romania, Slovenia and Ireland,⁴⁰ as well as the Channel Islands.

There have been reports of some mephedrone injecting in opiate-using people in the UK, but the evidence is mainly anecdotal.⁴¹ A 2012 *Druglink* survey carried out among police forces, drug agencies and drug user groups mentioned the growing cohort of people injecting mephedrone, although this evidence is again mainly anecdotal. The report suggests that some of these injectors were heroin and crack users known to drug services, as well as new injectors who had made the transition from oral or intranasal use of mephedrone.⁴² However, harder evidence is not yet available to substantiate these claims. A more systematic study was carried out in Ireland through the analysis of urine collected from attendees of a methadone maintenance clinic, which found that 14% were positive for mephedrone and 3% for methylone.⁴³

Little has been published on patterns of mephedrone injecting in the UK. There are anecdotal reports of an increase in the injecting of mephedrone (sometimes together with methamphetamine) among some MSM in London at sex parties or chill-outs, where many people share equipment without sterilising it.⁴⁴ One qualitative Irish study of 11 attendees of low-threshold harm-reduction services reported that compulsive re-injecting with excessive binge use over long periods was common, despite the fact that respondents were aware of the risks of injecting and of safer injecting practices. In this small cohort, 7 of the 11 were homeless, and injecting in public spaces and groin injecting were common. Mephedrone was not the first drug injected and its use appears to be an extension to other drugs also injected.³⁸

9.7. Routes of ingestion, dosing and frequency of dosing

Before its control in the UK in 2010, mephedrone was sold mainly through internet websites, 'head shops' and local street-level drug dealers. Although it is still available for sale on the internet through sites not based in the UK, there is some evidence that since its classification there has been a shift towards the purchase of the drug from street dealers. Users are paying a higher price than before control, for what is perceived to be a lower-quality product.^{16,19}

Mephedrone is typically sold as a white or off-white crystalline powder, with a light yellow hue.⁴⁵ Some users have reported its distinctive unpleasant smell³⁷ and some that their body sweat had developed a 'chemical smell' as a result of its use. Mephedrone powder is often sold in small plastic bags (typically 1 g doses), but there are reports of its sale as tablets pressed from the powder or as capsules containing the powder. At the time of writing, the cost of 1 g of mephedrone was approximately £20,⁴⁶ but with local and regional variations in price.

Mephedrone is water soluble. It is typically either snorted or swallowed (usually wrapped in a cigarette paper – a process known as 'bombing') or added to a drink (sometimes referred to as 'whizzy water'). It is also used by 'dabbing' (rubbing on the gum), rectally, by smoking, or by injection (intramuscular and intravenous).^{15,32,41} Users have also reported multiple concomitant routes of use.^{31,4–49}

A cross-sectional anonymous online survey of mephedrone users (recruited as part of a larger study exploring patterns of drug use among those associated with the dance music scene) was carried out in 2010. It suggested that the most common route of use was intranasally (65.9%), with women significantly more likely than men to use the drug through snorting (76.2% and 67.2% respectively).⁴⁸ Snorting is often carried out through the 'keying' method, whereby a user will dip a key in the powder and snort the powder off the key (it is estimated that five to eight keys would represent a 1 g dose).¹⁴ There are suggestions that the insufflation of mephedrone is associated with significant nasal irritation, which has led some users to switch to oral ingestion.⁵⁰

Intranasal use may be associated with greater liability to misuse than oral use.^{48,51} A survey carried out among 947 UK mephedrone users, contacted before the control of the substance in 2010, reported that the amount of drug used in a typical session was significantly larger for those snorting (mean 0.97 g, SD 0.91) than for those using it orally (mean 0.74 g, SD 0.64). Those who snorted the drug reported significantly more days of use per month (mean 4.85, SD 5.11) than those who used it orally (mean 3.21 days, SD 3.01). Those who snorted the drug were significantly more likely to use it more frequently, with 59.2% having used it at least monthly over the last 12 months.⁴⁸

The onset of the desired effects of mephedrone is linked to the route of administration, being within a few minutes through nasal insufflation or intravenous injection and 15–45 minutes following oral ingestion. The onset of the effects following oral use can be delayed in the presence of food.⁵² Rectal administration has been described by users as having a faster onset and the effects require lower doses.³⁷

The duration of the effects are also linked to mode of use. The effect last up to 2–3 hours following nasal or oral use, albeit with a shorter duration where ingested through nasal insufflation, but only 15–30 minutes following intravenous use. Some users combine routes of use in a single session, for instance first snorting it and then using it orally in order to achieve both a fast effect and a longer-lasting effect.⁵²

The relatively short duration of effects of mephedrone is associated with repeated dosing during a single session.⁵² Regardless of the route of ingestion the majority of mephedrone users will repeatedly re-dose within a single session to maintain the

desired effect (sometimes referred to as 'fiending'), leading to 'bingeing'.⁵³ An animal study has reported vigorous mephedrone self-administration behaviour in rats, eliciting response levels that appear to match, or even exceed, those seen with other drugs of misuse.⁵⁴

Typically, users ingest mephedrone in staggered doses, between 0.5 g and 1 g per session. Although a UK survey of clubbers found that approximately a quarter of mephedrone users took more than 1 g in a typical session,⁴⁸ other studies reported oral doses of 1–2 g⁵⁵ or even higher.¹⁴ The same survey respondents reported that the average duration of a single session was 10.4 hours and that there was a correlation between total amount used and the duration of a session.⁴⁸

9.8. Desired and undesired effects for recreational use

The reported desired effects of mephedrone include its stimulant and sympathomimetic effects, similar to those of MDMA (ecstasy) and cocaine.^{15,37,48,52,56,57} Reasons for its appeal include the fact that it is non-potent and short-acting. Mephedrone is used for both its mood-enhancing properties and its role as a psychomotor stimulant in social situations.⁴⁸ Users report stimulant-related subjective effects such as euphoria, increased concentration, the urge to move, talkativeness, reduced appetite and wakefulness. Desired effects also include stimulation, enhanced appreciation of music, mood elevation, reduced hostility, improved mental function and increased energy.^{15,19,30,48} At higher doses, perceptual distortions or hallucinations and the empathogenic properties of mephedrone have been reported.^{15,19,48}

There is some evidence that some users ingest stimulant and hallucinogenic drugs in general to increase sexual thoughts, intensify sexual desire, enhance sensuality, improve sexual functioning and prolong sexual performance. A dose–response relationship between mephedrone and heightened sex drive has been reported.^{48,58} Users have reported heightened sensuality, disinhibition, prolonged performance for males, the ability to reach climax for females and sexual behaviours which they would not engage in while sober.^{58–63} However, the effects of mephedrone also depend on combinations and types of drugs used, dosage, length of time used, sexual roles, normative risk, settings and the individual's experiences and expectation.^{60,64}

Surveys suggest that approximately 20–56% of users of mephedrone have experienced adverse effects^{31,65} and these are similar to those reported for amphetamine, methamphetamine and MDMA.⁶⁶ There is evidence that the most of severe unwanted effects may be associated with high doses and/or prolonged use.⁵²

However, there are important individual variations and similar doses may have significantly different effects and consequences in different individuals.⁶⁷ It has been suggested that it is impossible to determine what a 'safe' dose is, as negative effects may present with any dosage taken.⁶⁸

The most common unwanted effects of mephedrone reported by users are summarised in Box 9.1.^{17,37,43,48,52,57,65}

Box 9.1. Some common unwanted effects of mephedrone, as reported by users^{17,37,43,48,52,57,65}

Jaw clenching
 Reduced appetite
 Nasal irritation and nose bleeds
 Nausea and vomiting
 Discolouration of extremities and joints
 Insomnia and/or nightmares
 'Head rush'
 Inability to concentrate and/or to focus visually
 Memory problems
 Altered conscious levels
 Anxiety
 Agitation
 Hallucinations and delusions
 Headaches
 Tremors and convulsions
 Raised body temperature
 Chest pains
 Elevated heart rate

A survey of 900 clubbers using mephedrone suggested that the frequency of specific unwanted effects (predetermined by the study) as follows: excessive sweating (67.2%), headaches (50.7%), palpitations (43.4%), nausea (37%) and cold blue finger and toes (15.3%).⁴⁸ Similarly, in a Scottish student survey more than half (56%) of those who had used mephedrone reported having at least one unwanted effect, at the following frequency: bruxism (teeth grinding) (28.3%), paranoia (24.9%), sore nasal passages (24.4%), hot flushes (23.4%), sore mouth/throat (22.9%), nose bleeds (22.4%), suppressed appetite (21.5%), blurred vision (21.0%), palpitations (20.5%), insomnia (19.5%), hallucinations (18.0%), nausea/vomiting (17.1%) and blue/cold extremities (14.6%).⁶⁵ Other unwanted effects include difficulties with urination, poor concentration and aggression.

9.9. Mortality

A study of data from the National Programme on Substance Misuse Deaths (NPSAD)* showed that most deaths occurred when more than one substance was ingested, and especially when alcohol was one of these.⁶⁹ Nonetheless, in a small number of cases in the UK, death was directly related to mephedrone on its own, which confirms the concerns regarding the acute toxicity potential of the drug itself.⁶⁹

In the same study, Schifanno et al. found that factors associated with mephedrone-associated death were young age (mean age 29 years), male and with previous history of substance misuse. They also noted the excess number of mephedrone-associated

* To be recorded in the NPSAD database as a drug-related death, at least one of the following criteria must be met: presence of one or more psychoactive substances directly implicated in death; history of dependence or misuse of drugs; and presence of controlled drugs at post-mortem examination.

deaths between Saturdays and Tuesdays, linked to the more frequent ingestion of the drug at weekends.⁶⁹ A cause of concern resulting from UK observation was self-harm, especially hanging, which was identified as the mechanism of death in almost 30% of inquests, and bizarre risk behaviour in a further 6 cases (9.7%). This led the authors to question whether mephedrone, either in its own or used with other substances, may have an acute potential to cause or exacerbate psychosis and/or depression, thus facilitating bizarre behaviour or self-harm.⁶⁹

9.10. Acute harms

9.10.1. Acute toxicity

Case reports and case series relating to hospital presentations with acute mephedrone toxicity^{41,49,32,70,71,72} describe sympathomimetic clinical features⁴⁹ and clinical effects consistent with stimulant intoxication.⁷² Triangulation of data from a number of sources present a picture of mephedrone acute toxicity (Box 9.2) that is consistent with that seen with the use of other sympathomimetic recreational drugs, such as amphetamine, cocaine and MDMA.⁷³

Box 9.2. Features of acute mephedrone toxicity

Cardiovascular

Hypertension, tachycardia, chest pain, palpitation, diaphoresis, hot flushes, shortness of breath, palpitations, cardiac arrest, peripheral vasoconstriction

Cognitive

Confusion, improved concentration, alertness, amnesia, cravings, empathy/feelings of closeness, dysphoria

Dermatological

Unusual sweat odour, rash

ENT

Sore nasal passages, mouth/throat pain, epistaxis

Gastrointestinal

Nausea/vomiting, anorexia, dry mouth, abdominal pain, sore mouth/throat

Metabolic

Elevated creatinine, metabolic acidosis

Neurological psychiatric/ psychological

Anxiety, panic, depression, irritability, lack of motivation, anhedonia, sexual arousal, sociability, euphoria, insomnia, bruxism, headache, dizziness/light-headedness, tinnitus, seizures, nystagmus, mydriasis, blurred vision, numbness, blue/cold extremities, fever, paraesthesias, visual and auditory hallucinations, paranoid delusions, intensification of sensory experiences, reduced consciousness, agitation, aggression, short-term psychosis, short-term mania

Musculoskeletal

Increase in muscle tone, trismus

Respiratory

Dyspnoea

Serotonin syndrome

Cardiac, psychiatric and neurological symptoms are the most common reported effects that require medical care.⁷⁴ Serotonin syndrome may occur, especially when the user has been exposed to two or more drugs that increase the effects of serotonin, either as an acute overdose or taken regularly. There are reports of serious cardiovascular and neurological effects and some reports of hallucination, chest pains and convulsions.

Reports of other effects of mephedrone toxicity include the following:

- emerging evidence that when intoxicated, mephedrone use can impair working memory acutely;⁵³
- hyponatraemia;^{41,71,75}
- a case of mephedrone-induced euvoelaemic hypoosmotic hyponatraemia with encephalopathy and raised intracranial pressure;⁷¹
- a case report of posterior reversible encephalopathy syndrome (PRES);⁷⁶
- a case report of myocarditis;⁷⁰
- a case report of catatonia;⁷⁷
- a case report of spontaneous subcutaneous emphysema associated with mephedrone use, which did not require airway support;⁷⁸
- a case report of methaemoglobinemia, a serious complication caused by a number of oxidising drugs;⁷⁹
- a case report of serotonin syndrome, with the patient becoming hyperthermic;⁸⁰
- a case report of MDPV-induced serotonin syndrome;⁸¹
- a case report of severe refractory left ventricular failure.⁸³

In addition, one case report highlighted the potential danger of mephedrone to people with diabetes. A patient with type 1 diabetes developed ketoacidosis following self-reported mephedrone use. Cathinone compounds may directly increase the risk of diabetic ketoacidosis by stimulating the central nervous system. They may also indirectly impair an individual's ability to manage diabetes through changes in cognitive function and behaviour.⁸²

It is not possible to quantify accurately how common these presentations are. A US case series of 35 patients presenting at an emergency department with toxicity relating to synthetic cathinones reported that:

- 91% had neurological symptoms;
- 77% had cardiovascular symptoms;
- 49% had psychological symptoms.⁷²

In the UK, a report of a case series of 72 patients with self-reported acute mephedrone toxicity⁴⁵ indicated that the most common symptoms on presentation to hospital, or before, were: agitation (38.9%); tachycardia (36.1); palpitations (25.0%); vomiting

(13.9%); clinically significant hypertension (13.9%); chest pain (12.5%); severe tachycardia (8.3%); headaches (7.2%); self-limiting pre-hospital seizures (6.9%).

Because users cannot be certain of the actual content of the preparation they are taking, or its purity, exposure can be variable.^{84,85} A number of adulterants have been reported and include, but are not limited to, caffeine, paracetamol, cocaine, amphetamine and ketamine.⁸⁶

9.10.2. Harms from high-risk injecting and sexual behaviour

There is some evidence that mephedrone hydrochloride (the common form in the UK) is sometimes injected. The limited research describing this practice strongly suggests its potential for unpleasant side-effects. Intravenous users of mephedrone report paracitosis (leading to scratching and gouging of the skin of the face, necks and arms in particular), paranoia, suicidal ideation and severe insomnia, especially after prolonged use.⁵²

In a small qualitative Irish study, participants reported unwanted effects which included intense paranoia, violent behaviour and aggression, and the emergence of Parkinson-type symptoms, in the form of spasm, 'wobbling' and permanent numbness in the extremities. Injectors also report intense burning sensations at injection sites, limb abscesses, and vein clotting, damage and recession. These result from drug toxicity, crystallisation of the drug when diluted and syringe flushing practices. They also report multi-drug and serial drug injecting. Heroin is used in an attempt to manage the intense 'rush' and avoid an unpleasant come-down from mephedrone.³⁸

As with other club drugs, mephedrone use has been linked to high-risk sexual behaviours among heterosexual men and MSM.^{30,63} There is some anecdotal evidence of mephedrone injecting among MSM in London (referred to as 'slamming'), sometimes in combination with methamphetamine and injecting behaviours that put users at high risk of HIV and hepatitis.⁴⁴

9.10.3. Acute withdrawal

For withdrawal see section 9.12.2.

9.10.4. Poly-drug use and drug interaction

The co-ingestion of other substances alongside mephedrone appears to increase harm. The reports of most mephedrone-associated deaths in the UK indicate poly-drug use.⁶⁹ Alcohol in particular may potentiate the effects of mephedrone.^{87,88} A two-patient case study found that large quantities of alcohol ingested with mephedrone may lead to serious cardiac arrhythmias.⁸⁹ The co-ingestion of two stimulants is likely to increase mephedrone toxicity, as well as its potential harm,³⁴ including the risk of serotonin syndrome or toxicity (see section 7.7.2).

An animal study found that mephedrone enhances the neurotoxicity of methamphetamine, amphetamine and MDMA, substances that are commonly used alongside

mephedrone.⁹⁰ There is also one reported death resulting from a combination of GHB and mephedrone, albeit with no analytical confirmation of the substances used.⁹¹

As CYP2D6 and CYP3A4 may be involved in mephedrone metabolism, inhibitors of these metabolic enzymes could increase the systemic exposure to mephedrone and lead to increased toxicity. Among the antiretrovirals, these would be ritonavir (a CYP3A4 inhibitor at low boosting doses) and cobicistat (a CYP3A4 and CYP2D6 inhibitor). The role of ritonavir's inducing effect on glucuronidation and its impact on mephedrone exposure remains unclear.

9.11. Management of acute harms

9.11.1. Identification and assessment of mephedrone toxicity

There are currently no rapid urine or serum tests for the confirmation of the ingestion of mephedrone (or of other drugs often co-ingested). It is recommended that diagnosis is made on clinical assessment, with other causes of presentation excluded and recognition of the associated clinical toxidrome.

Data from the National Poisons Information Service show that in the UK in 2012–13, the section on mephedrone was more frequently accessed on TOXBASE[®] than the sections on other drugs of misuse, and mephedrone similarly ranked seventh in telephone enquiries, although reductions in numbers of the latter were noted over the course of three years.²⁶ In 2012–13, 76 phone enquiries about mephedrone were made (-2.6% from the previous year) and the TOXBASE[®] mephedrone webpages were accessed 8432 times (an increase of 36.1% from previous year).⁹²

It is not possible to determine accurately the numbers of presentations to hospital associated with mephedrone toxicity or indeed admissions resulting from the use of any recreational drug, not least because presentations with acute toxicity are assigned a wide variety of primary codes, which are likely to relate to symptoms rather than cause.⁹³ In addition, toxicological screening is not usually carried out for patients presenting to emergency departments because the results are typically not available in time to inform the patient's management. Mephedrone is also often used as part of a wider repertoire of drugs ingested and thus effects may be due to other substances.⁵²

Two UK case series of presentations to an emergency department (ED) for acute mephedrone toxicity provide some insight into numbers. A study carried out in the ED of Aberdeen Royal Infirmary from 1 December 2009 to April 2010 (before the mephedrone ban in the UK) reported 89 cases in total; self-reports suggested that 33% had ingested mephedrone only, 30% mephedrone and alcohol, and 35% co-ingestion of other substances.⁹⁴ A study looking at the impact of the control of mephedrone on presentations to an inner-London ED reported 58 cases in the year before control and 55 in the year after control, showing that presentations for mephedrone-related harms continued after the classification of the drug.^{21,32,52}

It is suggested that clinicians should consider methedrone upon presentation with psychosis.

For up-to-date guidance on the management of mephedrone acute toxicity, 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/M-Products/Mephedrone/>

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

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

9.11.2. Management of acute toxicity

No randomised controlled trials or other large robust studies have looked at the management of acute mephedrone intoxication, but there is consistency from case series and reports that treatment should consist of symptom-directed supportive care. It has been argued that, given the similarities with cocaine and amphetamine, management strategies similar to those recommended for intoxication with those drugs might be useful.⁷⁴

Symptom-directed supportive care for acute stimulant intoxication may include the management of agitation, convulsions, metabolic acidosis, hypertension, hypotension and rhabdomyolysis. The management of serotonin syndrome may also be indicated. TOXBASE® suggests the observation of asymptomatic patients for at least 4 hours, or 8 hours for patients who have ingested sustained-release preparations. It also suggests that agitated adults be sedated with an initial dose of oral or intravenous diazepam (0.1–0.3 mg/kg body weight). Larger doses may be required.

Other than benzodiazepines, some case studies have reported the use of propofol, haloperidol and other antipsychotics,^{34,95} although it is also argued that antipsychotics should be used cautiously with synthetic cathinone intoxication, as they increase seizure activity.⁹⁶ One report described lorazepam as effective for agitation and various sympathomimetic features of mephedrone use.⁴⁹ In another case report, a treatment regimen of as-needed doses of quetiapine and lorazepam for paranoid ideation, agitation and anxiety was found to be clinically useful.

9.11.3. Treatment outcome

People who present to hospitals generally make a good recovery. The majority (84.7%) of the 72 patients presenting to hospital with acute toxicity described in one case series⁴⁵ were discharged either directly from the emergency department or from a short-stay observation ward; the other 15.3% were admitted to hospital, with 11.1% admitted for observation/management on a general internal medicine ward, and 4.2% required admission to intensive care. Overall, 13.9% required benzodiazepines (oral or intravenous) for ongoing agitation at, or after, presentation to the hospital. All but one patient were discharged, with no long-term sequelae at the time of discharge,

and the length of stay following presentation ranged from 0.3 to 30 hours (a mean of 6.7 hours, SD 7.3 hours).⁴⁵

9.11.4. Management of acute withdrawal

See section 9.12.2.

9.12. Harms associated with chronic use

9.12.1. Dependence

There is emerging evidence that mephedrone has a dependence potential. It has been argued that the ability of mephedrone to cause striatal dopamine release may be problematic inasmuch as, in comparison with MDMA, mephedrone may have an enhanced liability to misuse, more resembling that of dopamine-releasing agents such as methamphetamine.¹⁰ One animal study suggests that the dopaminergic effects of mephedrone may contribute to its addictive potential.⁹⁷

A report from the Advisory Council on the Misuse of Drugs (ACMD) on cathinones suggests that, because of its similarity to amphetamine, they carry a similar risk of dependency, with chronic use leading to dependence and a cycle of bingeing and periods of recovery associated with depression.¹⁴ There is one published case report of dependence on mephedrone based on ICD-10 criteria⁹⁸ where dependence led to psychotic symptoms. Other studies have also shown the potential for dependence. In one study of 100 mephedrone users, 30% met three or more of the DSM-IV criteria for stimulant dependence, with evidence of a strong compulsion to use the drug.³⁰ In a Scottish school survey, 17.6% of those who had used mephedrone reported 'addiction/dependency' symptoms relating to their use of mephedrone.⁶⁵ Similarly, a survey of 797 UK clubbers who had used mephedrone reported that it was 'as or more addictive' than cocaine.⁴⁸ In another survey, 50% of 1500 mephedrone users considered it to be addictive.³¹

There is increasing evidence that mephedrone causes a strong and repeated compulsion to use,^{17,65} that tolerance to mephedrone develops quickly and that users tend to consume higher doses more frequently. Subjective reports of craving suggest that mephedrone may have a greater potential for repetitive and compulsive use than MDMA,^{17,31,65} although these observations are made on the basis of self-reports. Emerging evidence on the subjective effects of mephedrone suggests that its ingestion is associated with 'wanting more'^{17,30,53} and this was shown to be elevated significantly when users were sober but anticipated use in the near future.⁵³

9.12.2. Withdrawal

There are a few reports of craving for mephedrone^{15,37,65} and of withdrawal. There are users' reports that the development of cravings for mephedrone may be linked to increased frequency of use.⁴⁸ A survey of users also suggested that those who

ingested the drug through nasal insufflation were more likely than those who used it orally to rate it as more addictive than cocaine,⁴⁸ possibly reflecting the more rapid onset and shorter duration of desired effects of mephedrone when it is used nasally. Craving for mephedrone has been described as stronger than for ecstasy.¹⁷

A study of 100 users by Winstock et al. suggested that the most frequent effects related to withdrawal after a session of mephedrone use were tiredness, insomnia, nasal congestion and impaired concentration. Other withdrawal symptoms include depression, anxiety, increased appetite, irritability, unusual sweat odours and urge or craving to use.³⁰

Mephedrone was described by a frequent and heavy user in a case report as providing a more intense initial euphoria and a more severe withdrawal syndrome than MDPV.⁹⁹ In this case report, the user, who also reported a history of opiate and methamphetamine use, reported mephedrone withdrawal as the most unpleasant drug withdrawal he had experienced. He reported that discontinuation of mephedrone resulted in agitation and dysphoria within a few hours, which was more severe than that of cocaine or methamphetamine, and which was accompanied by an increase in muscle tone, the alleviation of which required constant movement.⁹⁹ He reported that only methamphetamine gave some degree of relief to the withdrawal.⁹⁹

9.12.3. Other harms: risk of systemic and viral infections

Like other club drugs, the impact of mephedrone on sexual behaviour can affect the transmission of blood-borne viruses and sexually transmitted infections.⁶³ Moreover, mephedrone is associated with compulsive and frequent injecting, making its users at particular risk of the acquisition and transmission of blood-borne viruses. To this are added the risks specifically linked to the injection of mephedrone, which can include limb abscesses and vein clotting, damage and recession. This places injectors at risk of septicaemia, endocarditis, deep-vein thrombosis and other complications.

9.13. Management of harms related to chronic use and dependence

9.13.1. Clinical management of chronic use and dependence

See Chapter 7 on the identification and assessment of dependence on ATS in general (section 7.10.1), which apply to mephedrone, as does the guidance on psychosocial and pharmacological support and intervention (section 7.10.3).

9.13.2. Management of withdrawal

There are no pharmacological regimes for the management of withdrawal, although those with psychological dependency may require medical treatment for their symptoms on discontinuation. Ongoing psychological support may be required, including for the prevention of relapse.⁵²

There have been no randomised controlled trials for treatment of either acute intoxication or withdrawal. Reports suggest supportive treatment with low to moderate doses of benzodiazepines for agitation and paranoia. A treatment regime of olanzapine⁹⁸ was described in a case report of dependence on mephedrone (diagnosis based on ICD-10 criteria) and where dependence had led to psychotic symptoms. Another case report described a patient put on antidepressants for residual symptoms of depressed mood, anhedonia and hopelessness present in all his periods of abstinence.⁹⁹ A further case report described a pharmacological intervention for MPDV withdrawal involving risperidone, which was effective for symptoms of disorganisation, delusions and hallucinations.¹⁰⁰

9.13.3. Presentation to specialist drug treatment services

In England, there was an 82% increase in mephedrone presentations between 2011/12 and 2013/14, from 900 in to 1,641.¹⁰¹

In Northern Ireland, 150 people presented for treatment of mephedrone misuse from 1 April 2011 to 31 March 2012 (118 males and 32 females; 19 were under 18 years, 69 were aged 18–25 years and 62 were over 25 years; 37 had had previous experience of drug treatment and 113 had not).¹⁰²

9.13.4. Aftercare and support

See section 7.10.5.

9.14. Public health and harm reduction

Winstock et al. recommend as harm reduction:⁵¹

- avoiding using regularly to avoid developing tolerance;
- not using with stimulants or large amounts of alcohol and/or other depressants;
- not injecting;
- avoiding dehydration;
- avoiding overheating.

See also the general comments in Chapter 7.

9.14.1. Public safety: driving

An analysis of 376 cases of alleged driving under the influence of drugs found 6 cases of driving under the influence of mephedrone. Mephedrone can affect driving inasmuch as it can produce poor concentration, hallucinations and psychosis.¹⁰³

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Ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) and drugs with similar effects

Drug group: stimulant

This chapter uses the term 'ecstasy' to refer to illicit drug products that contain MDMA (3,4-methylenedioxy-N-methylamphetamine) as their only, or primary, psychoactive component. Despite some changes in the prevalence of its use, MDMA has been a popular drug for many decades in the UK.

MDMA is structurally similar to both amphetamine-type stimulants and to mescaline-type hallucinogens, but is pharmacologically different from other substance classes.¹ In addition to their stimulant and hallucinogenic effects, MDMA and similar substances share properties that are sometimes referred to as 'entactogenic'^{2,3} or empathogenic.^{4,5} This has been defined as combining a psychostimulant effect with highly unusual changes in consciousness, leading to euphoria and an intense love of self and others.⁵ MDMA presents a good example of the difficulties in drawing clear distinctions between empathogens and stimulants, as it combines both properties.⁶

This chapter also addresses issues pertaining to the consumption of MDMA-like novel psychoactive substances (NPS),⁶ which include other substituted amphetamines (see Table 10.1). Some cathinones and benzofurans also mimic the effects of MDMA (see Chapter 9), although there are subtle differences in their psychic effects.⁶

Users of 'ecstasy' may use the term strictly to mean MDMA, or generically to mean any substance with a similar effect. Users may deliberately acquire and consume one of the named entactogens listed in Table 10.1, or may consume them unknowingly^{7,8} in products they obtain as 'ecstasy'.

There are significant variations in the compounds found in products sold on the market as 'ecstasy'. Studies have shown variations in the purity of MDMA over time and location, and variations in the compounds found in tablets sold as ecstasy,⁸⁻¹² Over the years, the latter have included non-MDMA products such as MDA, benzofuran, methylone,¹³ piperazines such as BZP¹⁴ and, more recently, PMA and PMMA.

There are also significant variations in the potency of tablets, even among those sold as the same product or 'brand' and containing MDMA as the main active ingredient. In a study carried out from November 2013 to July 2014, 24 separate groups of tablets sold as 'ecstasy' in the Glasgow area were analysed to quantify their MDMA content, to determine the common dose and to identify any other drugs in the tablets. There

Table 10.1. Entactogens MDMA and MDMA-like novel psychoactive substances:

Chemical name		Street names (these come and go, and other names may be used locally)
Substituted methylenedioxyphenethylamines¹⁸		
3,4-methylenedioxy-N-methylamphetamine	MDMA	Ecstasy, E, Molly, Mandy, MD,
3,4-methylenedioxy-N-ethylamphetamine	MDEA, MDE	Eve
1,3-benzodioxolyl-N-methylbutanamine (<i>N-methyl-1,3-benzodioxolylbutanamine</i>)	MBDB ¹⁹	Eden, Methyl-J
3,4-methylenedioxyamphetamine	MDA	Tenamphetamine, love drug, ⁸ Sass
Other substituted amphetamines²		
4-methylthioamphetamine	4-MTA ¹⁹	Flatliners ²⁰
para-methoxyamphetamine 4-methoxyamphetamine	PMA, 4-MA (note that another drug, 4-methylamphetamine, shares this name)	Dr Death, Death
para-methoxy-N-methylamphetamine <i>4-methoxy-N-methylamphetamine</i>	PMMA, 4-MMA	Dr Death Death

Table 10.2. Other substances used for their entactogenic properties

Chemical name		Street name
3,4-methylenedioxy-N-methylcathinone <i>bk-3,4-methylenedioxymethamphetamine</i>	bk-MDMA (MDMC, methylone)	Methylone MDMC, bk-MDMA, or 'Molly'
β -keto-N-methylbenzodioxolylbutanamine <i>B1</i>	bk-MBDB (beta-ketone-MBDB)	Butylone

was a 5.7-fold difference in the lowest to the highest concentration found. Variations were even found between tablets that carried the same logo and looked identical.¹⁵

A small number of samples analysed by a Welsh drug testing service demonstrate that methylone and MDA have been recently sold in the UK as 'ecstasy' or under their own names.* Only two samples were tested by this service that were presented as MDAI and contained MDAI; a further 6 samples presented as MDAI contained other drugs, in line with evidence of the misrepresentation of MDAI purchased online.¹⁶ Four samples presented as other drugs contained MDAI. Benzofuran derivatives, such as 5- and 6-APB, were certainly available for purchase and in use since around 2011, but their use was not widely reported in surveys.¹⁷ Whether they remain in use following the 2014 ban, or whether they are replaced by vendors with other entactogen NPS, remains to be seen.

* This paragraph refers to the Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS), whose website (<http://www.wedinos.org>) was searched in September 2014 using the keyword search 'methylone', 'MDA' and 'MDAI'.

A number of other substances are also used for their entactogenic properties, including some cathinones (particularly those which are also beta-keto analogues of methylenedioxyphenethylamines²¹). They are listed in Table 10.2

Some benzofurans derivatives, indanylalkylamine derivatives and aminoindane derivatives are also used recreationally for similar effects. They are addressed briefly at the end of this chapter.

10.1. Street names

Street names used at the time of publication include the ones listed in Tables 10.1 and 10.2. Other street names may be used locally.

10.1.1. Tablets, pills and capsules

The term 'ecstasy' (often shortened to 'E', 'XTC' etc.) is most often used for pressed tablets or capsules ('pills', 'beans', 'Es', 'bickies' 'bangers' etc.) containing a dose of MDMA. Users may also refer to such products by the variable 'branding' colour, shape, imprinted logo with which manufacturers make them distinguishable (e.g. 'White Doves', 'Yellow Superman', 'Apples', 'Pink Hexagons').

10.1.2. Crystals and powders

Ecstasy powders and crystals are often referred to by users as 'MDMA' or 'pure MDMA' as opposed to the tablet form, which is referred to as 'ecstasy'.

Specific names include Mandy, MD, Mad Dog and Molly (the term currently used in US pop culture, so more likely to be adopted by a younger generation of users). A dose wrapped in tissue or cigarette paper for swallowing may be called a 'bomb' or 'parachute'.

10.2. Legal status

MDMA is a Class A drug under the Misuse of Drugs Act 1971. Other entactogens are controlled across the classes (Table 10.3). New entactogenic substances that fall outside legal control may emerge.

Table 10.3. *Legal status of entactogens (as of February 2015)*

Classification under Misuse of Drugs Act 1971	Drug
Class A	MDMA, MDEA, MDA, MBDB, 4-MTA, PMA, PMMA
Class B	bk-MDMA (methylo), bk-MBDB (butylone), 5-APB, 6-APB, 5-APDB, 6-APDB, 5-MAPB, 6-MAPB, 5-EAPB, 5-APDI ²²
Class C	MDAI (Isle of Man)
Uncontrolled ('legal highs')	MDAI (excluding Isle of Man), 5-IAI

10.3. Quality of research evidence

Although much more is known about MDMA than other club drugs, the evidence is limited on its acute and chronic harms, and on the management of those harms particular. Much of the clinical evidence is derived from individual case reports and case series and a small number of prospective observational studies, retrospective audits and analysis of patient records.

A number of reviews of the evidence have been carried out,²³⁻²⁵ but there is still no consensus on some of the harms among leading ecstasy researchers.^{26,27} For example, Parrott emphasises the accumulation of literature detailing the harms of the drug, particularly chronic neurotoxic effects.^{24,25} However, his conclusions have been contested.²⁶ A recent review by Cole takes a more critical approach to the evidence base, emphasising the lack of certainty about many of the harms putatively attributed to ecstasy. He suggests that the number of clinical presentations relating to ecstasy is far smaller than would be expected, given the high prevalence of its use.²⁷

As with other NPS and club drugs, the reliability of case reports is inconsistent. Many lack toxicological confirmation. Some authors have suggested that such case studies fail to convince that ecstasy use is, on balance, the most plausible explanation for the clinical observations.^{28,29} However, despite these limitations, these sources have built up a consistent picture of common patterns of acute ecstasy toxicity.

The evidence relating to specific NPS analogues of MDMA, used for entactogenic effects, is much more limited, consisting of a small amount of animal and in vitro research on their pharmacology and some case studies of acute toxicity. However, reports of their effects and toxicity generally fall within the range described in the larger literature on ecstasy,¹⁸ and on amphetamine-type stimulants (ATS), so useful inferences can be made from the existing literature.

10.4. Brief summary of pharmacology

MDMA and other ecstasy-type drugs have phenethylamine-derived molecular structures, and can be thought of, pharmacologically, as atypical ATS. MDMA has multiple actions at different targets: it is a releaser and reuptake inhibitor of the monoamines serotonin, dopamine and noradrenaline.^{30,31} It also has an MAOI effect and acts directly as an agonist at receptors, including the 5HT_{2A} receptor, the serotonin receptor responsible for psychedelic effects.³⁰ Its action on the noradrenaline transporter appears to explain much of the euphoric psychostimulant effect,³² with the powerful serotonergic action being chiefly responsible for its pharmacological divergence from typical psychostimulants.^{33,34}

However, among the stimulant and psychedelic drugs, the risk-effect profiles of ecstasy-like drugs are unique, and comparison with drug classes with divergent properties can misguide as much as inform, so they have been increasingly seen as neither classical hallucinogens nor classical stimulants.²

In addition to its stimulant effects (such as increased energy, euphoria) and cardiovascular effects common to ATS and cocaine, MDMA-produces characteristic alterations

of mood and perception, particularly increased empathy, feelings of emotional well-being, sociability and sensuality.^{2,35} This has led to MDMA being described as intermediate between (or combining some properties of) stimulants and psychedelic hallucinogens.²

This family of drugs with shared MDMA-like emotional and behavioural effects are known as 'entactogens',^{1,36} although this word has not gained universal use. The word 'empathogen' has also been used to describe drugs sharing the psychoactive properties of MDMA.⁴ These drugs have been described as capable of inducing a reversible controlled alteration of consciousness in humans characterised by emotional relaxation, feelings of happiness and empathy with other persons² that has been called the 'entactogenic syndrome'.³⁷ MDMA induces altered states of consciousness characterised by increase empathy with others³⁸ and an 'open mind' state, characterised by heightened self-acceptance and openness for communication, and a decrease of fear responses, without psychedelic-like effects.² Other typical entactogen effects, including subjective 'relaxation',³⁹ 'peacefulness',³⁶ 'closeness to others'⁴⁰ and 'empathy',⁴⁰ may diverge from the effects expected from ATS.

There is uncertainty regarding the pharmacology specific to the 'entactogenic' effects of MDMA and related drugs. In addition to the direct serotonergic effects on mood, the serotonin transporter (SERT), upon which MDMA and its analogues act, appears to mediate the release of the neuropeptide hormones oxytocin and prolactin.⁴¹ The action of MDMA on SERT are hypothesised to contribute to its pro-social, entactogenic effects.

Doses or serum concentrations of MDMA and related drugs are often not closely associated with the level of acute harm observed, and lifetime dosage may not be closely associated with the degree of chronic harm either. One suggested explanation is that genetic polymorphisms affecting the hepatic metabolism of MDMA play a mediating role in toxicity.³⁴ The metabolism of MDMA (via steps which include pharmacologically active and toxic metabolites) is affected by the pattern of dosing,⁴² with the metabolism of subsequent doses being inhibited by the limited availability of the cytochrome P450 (CYP2D6) enzyme.^{30,43}

Paramethoxyamphetamine (PMA) and paramethoxymethamphetamine (PMMA) are potent noradrenaline and serotonin transporter inhibitors and releasers of these monoamines. They are associated with higher morbidity and mortality, particularly attributable to hyperthermia.^{44,45} They have a potential for causing greater serotonin toxicity. PMA, PMMA and 4-MTA are often characterised by severe hyperthermia, probably resulting from severe serotonin toxicity arising from the combined effects of marked serotonin release and strong monoamine oxidase inhibition.⁴⁶⁻⁵¹ Their hyperthermic properties are stronger than those of MDMA.⁵² In combination with MDMA and other serotonergic drugs, this risk is multiplied further.⁵³

MDMA is rapidly absorbed. It typically takes 20–60 minutes to take effect, reaching peak effects between 60 and 90 minutes, and lasting up to 5 hours.⁵⁴ The half-life of a typical dose of 100 mg is around 8–9 hours.³⁰ While actively partying on ecstasy, saliva levels of cortisol can rise to more than eight times baseline levels.⁵⁵

The onset of the effects of similar substances varies. User reports suggest the effects of MDAI are felt within 10–12 minutes of oral consumption. The duration of its effects has also been reported by users as varying considerably between individuals, with effects peaking after 30–45 minutes, to up to 3 hours,⁵⁶ a variability that has been attributed partially to products containing substances other than MDAI.⁵⁷

The onset of the effects of PMA is significantly later. This has caused concern, especially when users take it thinking it is MDMA. Users may take another dose, thinking that the first one has had no effect. There is, therefore, the risk of overdose, including fatal overdose.

10.5. Clinical uses

MDMA is a Schedule 1 drug with no well supported and no licensed clinical uses. However, prior to being classified and scheduled, MDMA was used to facilitate psychotherapy.⁵⁸

In recent years, some research into its psychotherapeutic use has continued, despite the legal barriers to this, and MDMA has now reached phase II clinical trials as an adjunct to psychotherapy for treatment-resistant post-traumatic stress disorder (PTSD). The first small-scale pilots have demonstrated good preliminary results with minimal adverse effects, but larger trials are needed.⁵⁹

MDMA is hypothesised to support and enhance psychotherapy by increasing the subject's access to emotionally upsetting material, modulating the associated level of arousal and strengthening the therapeutic alliance.⁶⁰ MDMA is known to have major effects on serotonergic neurotransmission, but a downstream consequence of its effects on serotonin is the release of oxytocin and vasopressin, which may have relevance to producing trust and may reduce the threat response of being asked to revisit traumatic memories.⁶¹ Brain imaging studies show reduced amygdala activity after MDMA administration, plus changes in the response to angry and happy facial expressions.⁴ Nonetheless, marked differences of view are apparent among experts,^{26,62} with other scientists believing that the evidence of MDMA's toxicity is already sufficient to conclude that 'there are no safe clinical applications for MDMA'.⁶³

10.6. Prevalence and patterns of use

The recreational use of ecstasy has well established in the UK for a number of decades. Prevalence has varied over time but data from the Crime Survey for England and Wales (CSEW)⁶⁴ shows that in 2013/14 it was the third most prevalent illicit drug after cannabis and cocaine, with 1.6% of adults aged 16–59 and 3.9% of young adults (16–24) having used it in the last year. While this represents one of the highest rates of use in Europe, last-year use in England and Wales had fallen overall from a high of 2.1% in 2001/12 (6.8% among 16–24s).⁶⁴

Much less is known about the use of other MDMA-like NPS. Prevalence estimates of the use of PMA/PMMA are unavailable, but an Australian study reported that a majority

of patients presenting with severe symptoms following the use of what had been sold as 'ecstasy' had in fact consumed PMA.⁴⁷ Deliberate use of PMA and PMMA is negligible to non-existent.⁴⁷

The 'reliability' of ecstasy, determined by users in terms of the substance sold containing a significant quantity of MDMA as the primary active compound, has been variable,⁶⁵ and may be linked to changing patterns of use over the years. Between 2012/13 and 2013/14 there was a significant rise in use of ecstasy again,⁶⁴ although not to 2001/12 levels. This is possibly linked to the apparent increase in ecstasy products containing 'reliably' large amounts of MDMA,⁶⁶ which appears once again to be the norm in the UK,⁶⁶ following a dip in quality around 2008/09. It has been argued that this dip may have helped drive the emergence of mephedrone as a club drug.⁶⁷ In the most recent available data, the average seized tablet contained around 100 mg of MDMA;⁶⁶ such tablets correspond to user preferences, having the optimal ratio of desired to unwanted effects.⁶⁸

In the early years of ecstasy's emergence as a recreational drug, it was strongly associated with underground raves, 'acid house' and associated dance subcultures. As use has become more widespread, settings of use and types of users have diversified.⁶⁹ Clubs, parties and festivals remain the key locations for use, accompanying music and dancing.

Ecstasy has been reported as the favourite drug of surveyed club-goers, and the drug has been described as central to the culture of the British club scene.⁷⁰ Data from 2013/14 suggest that ecstasy use in the last year was around 15 times higher among those who had visited a nightclub at least four times in the past month (11.9%) compared with those who had not visited a nightclub in the past month (0.8%).⁶⁴

Those frequenting certain clubbing environments, differentiated for example by dance music genres, may show even higher rates of use. A majority may have a history of recent ecstasy use,^{71,72} and use 'ever' can be almost ubiquitous, as high as 96% of respondents of a 1999 survey of readers of *Mixmag*, a clubbing culture magazine.⁷³

Although the use of ecstasy is linked to the use of the night-time economy, use in other settings, such as homes, is not unusual.^{74,75} The number of deaths among drug-dependent solitary users may suggest that non-clubbing users could be over-represented among the clinical population.²³

The CSEW finds that students were twice as likely to use ecstasy than people in employment (who are more likely to use cocaine than students).⁶⁴ Over the three years of data to 2013/14, people who self-identify as gay or bisexual were far more likely to be last-year users of ecstasy (5%) than heterosexual people (1.3%), although this is likely simply to reflect the higher overall prevalence of all drug use in this group. Asian/Asian British people (0.1%) and Black/Black British people (0.3%) were less represented among users of ecstasy than White people (1.6%) or people of mixed ethnicity (2.3%).⁶⁴ As with other drugs, men were more likely to have used ecstasy than women (2.3% versus 0.9% respectively in 2013/14). Ecstasy is used by people across the socioeconomic spectrum.⁶⁴

Most people who try ecstasy will not escalate to regular or sustained use.²⁴ A Dutch study recruited ecstasy-naïve subjects who said they were probably going to try the drug. Of the 64 who did so in the next one to two years, more than half consumed only one tablet or less.⁷⁶ Ecstasy is typically used occasionally.²⁴ CSEW data show that 86% of last-year ecstasy users took it less frequently than monthly, 10% monthly, and 4% more regularly than monthly.⁶⁴

While CSEW data show only a minority (4%) of last-year users use ecstasy more than once a month,⁶⁴ using ecstasy on many or most weekends is not uncommon among users sampled at clubs and raves.⁷⁷ Use of ecstasy several times a week, or even daily,⁷⁸ has been recorded, although this is exceptional and very likely to be linked to comorbidities.⁷⁸⁻⁸⁰ One case has been reported of a poly-drug user who self-reported the consumption of 40,000 ecstasy tablets between the ages of 21 and 30, before ceasing use following several collapses.⁸¹ Bingeing for up to 48 hours and using up to 25 tablets has been reported,²⁴ but there is a lack of recent evidence, and the number of tablets is an imprecise guide to the total dose taken.

The tendency is for tolerance to the positive effects of ecstasy to build up with use,⁸² leading to diminishing returns from consumption. This may be protective against sustained heavy use or addiction.²⁴ It has been suggested that regular users often follow a trajectory of discovering and strongly liking MDMA, using it most weekends, sometimes with escalating dosages, for a year or two, suffering increasing adverse effects with decreasing enjoyment ('losing the magic') and then reducing or ceasing use spontaneously.⁸³ This pattern of decline has been described as almost unique among recreational drugs.⁸³

A minority of ecstasy users will develop problems and will access drug treatment services, especially when no other problem drugs were also involved. Between 2006/07 and 2011, adults over the age of 18 years in England and Wales receiving treatment for drug use, which included problematic ecstasy use, use fell from 2138 to 1018.^{66,84} In 2013/14, only 201 people (less than 0.1%) cited it as their main problem drug; but 964 people presented to treatment and cited ecstasy as one of their problem drugs.⁸⁵

Ecstasy users are highly likely to be poly-drug users.^{86,87} The CSEW does not record poly-drug use annually; 2012 data⁸⁸ show that ecstasy was commonly taken simultaneously with alcohol almost all of the time (95%) and with other illicit substances about half of the time (49%). When used simultaneously with other illicit drugs, the most common co-intoxicant was cannabis (64%), followed by cocaine (44%) and amphetamines (18%).⁸⁸ Poly-use was shown elsewhere. In a large Australian sample of regular ecstasy users, 62% said they usually consumed more than five 'standard drinks' (equivalent to more than 6 UK alcohol units) when they took ecstasy.⁸⁹

Ecstasy users have higher levels of consumption of alcohol, cigarettes and cannabis than non-ecstasy users, but while they may combine ecstasy with alcohol and other drugs, ecstasy intoxication itself may not increase the likelihood of using other drugs at times where ecstasy is not used.⁹⁰

However, among ecstasy users, heavy and frequent users are significantly more likely to use other stimulants and psychedelics at higher intensities than lighter ecstasy

users.⁸⁶ Studies suggest that the heavier an individual's ecstasy use, the heavier and more varied their poly-drug use will be.⁸⁶ This could reflect the fact that people with higher levels of use may also be more likely to use other drugs with stimulant and hallucinogenic properties. Scholey et al. suggest that this may represent a greater need (on the part of people with high levels of use) to boost drug effects as they become tolerant to the effects of MDMA.⁸⁶

10.7. Forms, routes of ingestions and frequency of dosing

Ecstasy is available in a number of forms, mainly as powder/crystals or as pills, tablets and capsules. Currently in the UK, powder and crystals are most commonly used. In the Global Drug Survey 2014 UK sample, MDMA powder/crystals were twice as commonly used as tablets.⁹¹ It is unclear whether this current dominance of crystals and powders is a universal or reflects the preference for these as a 'premium' product⁷⁰ among the Global Drug Survey sample – the crystals in particular are reputed among users to be a purer and more reliable product than tablets.⁷⁰ That form first became widespread against the backdrop of unreliable or low-dose tablets sold in 2009 and after. However, as of 2012, the average dose in seized tablets was much higher (102 mg) than in the 'poor quality' ecstasy sold in preceding years.⁶⁶ However, powder and crystals are no longer necessarily less adulterated or misrepresented than tablets. Indeed, a small but significant proportion of 'MDMA' crystals currently analysed are in fact methylone.⁹²

Ecstasy is typically taken orally,¹⁸ including in its powder/crystal form, which can be 'bombed' (wrapped in a cigarette paper or tissue and swallowed).²⁴ Some users consume ecstasy by licking a finger and dipping it into powder⁹³ or through 'dabbing' on gums.

When not consumed orally, it may be insufflated,⁹¹ which is particularly common among experienced users.⁶⁹ User forums⁹⁴ report that the insufflation of ecstasy is painful and gives a shorter high, but with a rapid onset. According to the Global Drug Survey, oral ingestion remains the preferred method of administering MDMA, with only 15% of users snorting it.⁹¹ Insufflation may be used as an alternative to oral use,¹⁸ or sometimes as an additional route of administration for a boost, following oral ingestion.⁹⁵ Rectal¹⁸ ('plugging' or 'booty bumping') and injecting are uncommon.^{24,80} The latter has been described as 'too intense to enjoy', leading to reversion to oral use.⁹⁶ Other entactogens, such as 5-APB and 6-APB,⁹⁷ are also most often used orally.

The reported MDMA content of a single ecstasy tablet or capsule of powder has varied from no MDMA content at all to doses as high as 245 mg or 270 mg.^{98,99} The higher doses are likely to cause toxicity, being well above the dose that seems associated with the best ratio of wanted to unwanted effects (about 100 mg).^{68,100} Similarly, in a case of a fatality linked to consumption of two capsules thought to be 'ecstasy', a further single capsule from the batch was found to contain 422 mg bk-MDMA (methylone) and 53 mg bk-MBDB (butylone), far higher than typical reported doses.⁷

As mentioned in section 10.1, even tablets of the same 'brand', can vary between batches, or can be easily mimicked in an uncontrolled market. Tablets of the same appearance may not deliver a consistent dose, or even contain the same psychoactive substance. In 1999, identical-looking 'Dove' tablets were shown to range in dose from 19 mg to 140 mg of MDMA.¹⁰⁰ More recently, when two 'Yellow Rockstar' tablets from Glasgow were analysed, one contained 82 mg of MDMA, lower than doses administered to healthy humans in a recent research study,¹⁰¹ and the other contained PMA and PMMA, along with caffeine.¹⁵

Doses consumed by the 'bombing' method (powder, typically wrapped in cigarette paper and swallowed) may be higher than average tablet doses.²⁴ There was an apparent increase in 2013 of the number of ecstasy users who accessed emergency treatment, according to reports to the Global Drug Survey. Users linked this to the current dominance of high-purity MDMA powder over pills, with Winstock suggesting that users may lack awareness of how to dose with powder.⁹¹

A naturalistic study of Australian users found that doses consumed in a session usually fell in the 50–150 mg range, but rose as high as 280 mg. Users took 0.5–5 tablets and these varied in dose from 0 mg to 245 mg.⁹⁸ American adolescent users in one study rarely took more than one pill per session.¹⁰² Evidence from a web survey suggests that the dose users choose is linked to their level of experience. None of the 109 novice users (<10 lifetime uses) reported taking more than one or two tablets in one session, but 38% of 37 experienced users (>100 lifetime doses) described doing this.⁸⁶ When asked what their record highest ever intake was, heavy users in one sample had taken an average highest ever dose of 10.9 tablets,¹⁰³ but this may say more about variability in tablet quality,²⁷ as the same heavy user sample took 3.7 tablets during an average session.¹⁰³

In audits of emergency department presentations in Switzerland and London, 15.4% and 20% of patients respectively had taken more than two tablets.¹⁰⁴ In a small American sample, three-quarters of users took just one dose in a session, usually between 8pm and 2am on a Friday or Saturday night. A minority took a further dose, usually within the first 2 hours, suggesting the additional dose constitutes a top-up if the initial effects are not satisfactory, rather than a typical stimulant dosing pattern of extending the high and avoiding the come-down.⁹⁰

10.8. Desired effects for recreational use

The unique combination of desired effects elicited by ecstasy has been roughly summarised as the '3 Es' – energy, euphoria and empathy.¹⁰⁵ MDMA's continued presence as the key ingredient in ecstasy pills has been ascribed to its singular properties, combining unique desired effects with relatively low adverse effects at optimal doses.⁶⁸ MDMA topped a novel 'net pleasure index' among a large self-selected sample (22,000 people). In this index, subjective ratings of adverse effects were subtracted from ratings of desired effects to give a mean score that could be used to rank a range of drugs.¹⁰⁶ MDMA was also considered the best value drug overall by its users.¹⁰⁶

Questionnaire evidence from people currently on ecstasy in a naturalistic party setting allowed ter Bogt and Engels to identify a hierarchy of motives for taking ecstasy.⁷⁷ Energy and euphoria were the leading motivations for a majority of users (as captured by users endorsing statements like 'dance all night' and 'feel absolutely great'). These were followed by sociability and flirtatiousness (e.g. 'flirting easier'), sexiness (e.g. 'sex better') and coping (e.g. 'forget my problems'); conformity (e.g. 'be cool') was the least important motivating factor.⁷⁷ When they contain MDMA, 'ecstasy' tablets are a relatively reliable producer of subjective pleasure.⁶⁸ Commonly reported positive effects, such as 'calmness', however, contrast sharply with paradoxical adverse effects that clinicians may encounter, such as agitation and anxiety.³⁵

Pure MDMA usually elicits highly 'liked' effects, even in the research environment. However, in keeping with its intermediate position between typical stimulants (where positive mood change occurs reliably) and psychedelic hallucinogens (where setting powerfully mediates mood changes), positive effects may fail to appear in a context that is particularly uncondusive to them (as observed in a research setting which was poor in social stimulation).¹⁰⁷

Increased sensual awareness, love, feeling of connection, desire, sexual intensity and satisfaction are also reported,⁷⁷ but paradoxically this may be coupled with erectile dysfunction in men and delayed orgasm in both sexes.^{108,109} It has been hypothesised that this is due to release of prolactin and oxytocin, such that ecstasy mimics the emotionally close but sexually impaired features of the post-orgasmic refractory period.¹¹⁰ Female heterosexual ecstasy users, interviewed in one study, did not generally think that ecstasy increases the likelihood of high-risk sexual activities, although noted that they sometimes chose to engage in behaviours such as anal sex while intoxicated which they otherwise may not have engaged in.¹⁰⁹ Roger et al.'s systematic review, which includes a meta-analysis, shows that ecstasy use is linked to small to moderate increases in sexual risk.²³ However, ecstasy is not one of the drugs most linked to 'chemsex' and associated risks.¹¹¹

Ecstasy was found in one case to give temporary dramatic relief from the symptoms of Parkinson's disease;¹¹² this discovery, corroborated in animal studies, has led to drug development.¹¹³

Although not widespread, it has been reported that some individuals may use ecstasy in an attempt to self-medicate, for example to manage current stresses and lifetime traumas,¹¹⁴ including PTSD symptoms.⁸⁰ In the US, there appears to be some 'underground' use of ecstasy for therapeutic purposes.¹¹⁵

Some NPS have been reported to produce similar subjective effects to those reported by MDMA users,^{13,116} especially an 'entactogenic syndrome',² but evidence from studies in humans is limited. In combination with animal research, some anecdotal evidence supports the existence of subtle¹⁸ to significant differences, with some entactogens producing the empathogenic effects and serenity associated with ecstasy but with less of the stimulant and euphoriant effect.¹¹⁷

Whereas many NPS are selected by users because they wish to experience a new drug, this is not necessarily the case with PMMA and PMA, as these are typically not

taken deliberately as such. For example, none of the 22 people seen with PMA toxicity in an Australian emergency department reported deliberately taking the drug; rather, they had all intended to take ecstasy.⁴⁷

In fact, there is no evidence that PMA and PMMA have any prominent desired effects,^{68,118} although their serotonergic pharmacology suggests that they could have 'entactogenic' effects. A study linking the pharmacological content of a tablet consumed and its subjective effects on users reported that desired effects were nearly absent with tablets containing MDMA adulterated with PMMA (odds ratio of 0.05 relative to desired effects from MDMA-only tablets).⁶⁸

10.9. Unwanted effects

The use of MDMA is associated with a number of unwanted effects. For example, a study reported that typical side-effects as experienced by more than half of a sample of users included jaw clenching (trismus, 'gurning'), dry mouth, tachycardia and sweating, with a minority having experienced urinary retention, dizziness, nausea and vomiting, and decreased libido.¹¹⁹

It has been argued that common side-effects, such as nystagmus, trismus, mild confusion and feeling hot, are the low end of a spectrum of serotonergic overactivity that has at the higher end serotonin syndrome and death.¹²⁰ Other adverse reactions include feeling cold and shivering.¹²⁰

Unwanted effects could be associated with MDMA and/or adulterants and other compounds found in tablets sold as ecstasy. In one study, adverse drug effects were reported by 16% of 924 users who had handed in 'ecstasy' for testing by the Dutch recreational drug testing service, DIMS.⁶⁸ The testing revealed that where adulterated or counterfeited 'ecstasy' had been handed in, a much greater proportion of users had complained of adverse effects. Products containing MDMA alone (at widely varying doses) were reported to have been associated with adverse effects 8% of the time and desired effects 74% of the time. Adverse effects reported from tablets containing MDMA included nausea (most common), headache, hallucinations, dizziness, 'allergic reactions' (note, however, that this term may not have been used by users in its medical sense) and, more rarely, palpitations, hyperthermic seizures, agitation and abdominal cramps.⁶⁸

In addition to unwanted acute side-effects, MDMA may have long-lasting effects. Users have described 'mid-week blues' appearing three to five days after the use of ecstasy. These 'blues' appear to increase in intensity and incidence¹²⁰ as users persist with the drug.¹¹⁹ Novice users may suffer fatigue, depressed mood and decreased appetite in the days after use. The majority of experienced users have experienced additional symptoms, such as nightmares and difficulty with memory and concentration.¹¹⁹ The subacute effects are associated with depleted serotonin, so the worsening effects in experienced users,⁸³ especially when not associated with higher doses,¹¹⁹ may indicate chronic serotonergic dysfunction, with heightening sensitivity to depletion.¹²¹ Depressed mood following use is not universally found

after administration of MDMA and other entactogens in a therapeutic or research setting, and a positive mood change may even occur, as seen in a study with MDEA,³ suggesting that the combined effect of the drug and environmental and behavioural stressors in typical use is important.¹²²

One study of Dutch 'ravers', including 103 women, suggested that females may suffer a greater incidence of adverse effects, such as nausea, headache, dizziness and feeling faint.⁷⁷

PMA and PMMA seem to have pronounced unwanted effects. The Dutch testing service found that tablets containing MDMA adulterated with PMMA had caused adverse effects in the majority of users (56% vs. 8% for MDMA-only tablets).⁶⁸ There is limited evidence on the detail, but self-experimentation by Shulgin and Shulgin et al. found that PMA (called 4-MA in their book) produced a sudden robust rise in blood pressure at 60 mg, and a feeling of 'druggedness' rather than a 'high' at 70 mg.¹²³ PMMA was not liked either, as it produced tachycardia, eye-muscle twitch and compulsive yawning, and no enjoyable subjective effects.¹²⁴ The relative lack of desired ecstasy-like effects combined with a slow onset is thought to lead to users believing they have taken weaker ecstasy, taking more and suffering greater toxicity.¹¹⁸

10.10. Mortality

In England and Wales, MDMA or ecstasy was mentioned on the death certificate in 43 cases in 2013,¹²⁵ representing a steep year-on-year rise from a recent low of 8 in 2010, but a fall from a peak of 58 in 2005. There have been concerns about the recent availability of some 'super-strength' formulations, with reports of MDMA content 2–2.5 times higher than the 'standard' dose.¹²⁶

PMA and PMMA have been associated with a significant number of deaths. Compared with MDMA, they appear to have a high potential to cause life-threatening toxicity.⁴⁷

The emergence of PMA⁴⁷ and PMMA⁴⁴ on the ecstasy market internationally dates as far back as 1973, when PMA appeared in Canada, leading to fatalities.¹²⁷ In the UK, the number of PMA-associated deaths was 1 in 2011 but then 20 in 2012. In 2013, PMA or PMMA was mentioned on 29 death certificates in total, on 14 as the sole drug and on 2 with alcohol.¹²⁵ PMA-related deaths in the UK at first seemed to be concentrated in Scotland, but more recently clusters have also been reported in Suffolk and eastern England more generally.¹²⁸

Deaths in England and Wales related to other NPS are not listed separately, but several fatalities associated with substances with entactogenic effects (e.g. MDAI,⁵⁶ 5-APB and 6-APB¹⁷) have been reported from the UK and internationally in recent years.

10.11. Acute harms

A minority of users of ecstasy will present to hospitals from 'raves'¹²⁹ or nightclubs.¹³⁰ In a retrospective review of patients from nightclubs attending a hospital emergency

department between 1997 and 1998, ecstasy was the second most common drug cause of presentation, after alcohol.¹³¹

There is no clear fatal blood concentration level of MDMA. One study showed that the levels recorded at autopsy in 13 deaths by ecstasy toxicity alone overlapped considerably with MDMA levels recorded from 24 cases where the drug was detected post-mortem but trauma was the cause of death.¹³²

There are difficulties in disaggregating the harmful effects specific to MDMA toxicity from the confounding effects of analogues, co-intoxicants and environmental and individual factors.¹³³ It is not yet clear how much of the overall ecstasy-related harm is attributable to the toxicity of MDMA in isolation.²³

As with other club drugs, mixed intoxications (from deliberate poly-drug use, alcohol or from ecstasy adulteration) are typical in general use and in presentations to acute clinical settings.¹³⁰ Poly-drug use appears to be associated with life-threatening outcomes at lower blood concentrations, as shown by a study which reported a mean post-mortem MDMA blood concentration of 2.90 mg/l in 22 ecstasy poly-drug deaths, whereas it was 8.43 mg/l in 13 cases where only MDMA was found.¹³⁰

There is evidence that some adverse side-effects may be gender-specific. A study reported that women experienced more intense psychological effects, while men showed a greater increase in physiological measures, particularly systolic blood pressure. Although body weight may play a part, it also appears that there are pharmacokinetic and/or pharmacodynamic differences between genders.¹³⁴ Adverse effects may be dose-dependent as well as gender-specific. In the analysis of clinical studies by Lietchi et al., increasing dose was correlated with greater self-reporting of hallucinogen-like perceptual effects, in women in particular, and with greater reported dysphoric states in women alone. However, increasing dose was not associated with increases in measures of desired effects.¹³⁴

10.11.1. Features of acute ecstasy toxicity

Table 10.4 provides information on acute MDMA toxicity. In addition, MDMA (as well as NPS such as PMA and PMMA) causes severe serotonin syndrome and sympathomimetic effects. Death can follow sudden collapse and cardiac arrest, or can result from disseminated intravascular coagulation, protracted seizures and multiple organ failure. Many of these result from extreme hyperthermia.

When acute toxicity has occurred following the use of other NPS, patterns of harms are similar to the broad spectrum of acute harm associated with MDMA and are described below.^{18,47,135} However, the severity of symptoms may tend towards the higher or lower end of the spectrum seen with MDMA.

PMA and PMMA are particularly associated with severe and life-threatening symptoms, such as seizures and coma.^{23,45} A study from Norway, for example, reported 12 fatalities and 22 recoveries from a series PMMA intoxications.⁴⁴

Table 10.4. Features of acute ecstasy toxicity

Reported effects associated with 'ecstasy' or MDMA	Other NPS with similar reported effects
CNS, neurobehavioural and psychiatric	
Dilated pupils, mydriasis ¹³⁶ Common ^{104,130}	bk-MDMA (methylone), bk-MBDB (butylone), ⁷ 5-APB, 6-APB ⁹⁷
Feeling unwell/weak/dizzy Common ¹⁰⁴	
Restlessness Common ⁷⁴	MDEA, ³ PMA/PMMA ¹³⁷
Nystagmus	bk-MDMA (methylone), ¹³ 4-MTA, ²⁰ PMA/ PMMA ⁴⁵
Euphoria	bk-MDMA (methylone), bk-MBDB (butylone) ⁷
Anxiety ¹³⁶	5-APB, 6-APB, ¹³⁸ MDEA ³
Panic ¹⁰⁴	MDEA ³
Agitation ¹³⁶ Common ^{74,104,129}	6-APB, ¹³⁹ MDEA ¹⁴⁰
Disorientation/confusion ¹³⁶ Common ^{74,104}	Bk-MDMA (methylone), ¹³ 4-MTA ²⁰
Psychosis ¹³⁶	6-APB, ¹³⁹ MDEA ³
Paranoid ideation, delusions ¹³⁶	6-APB, ¹³⁹ MDEA ³
Delirium	PMA/PMMA ¹⁴¹
Sleepiness	PMA/PMMA ¹⁴¹
Collapse, loss of consciousness Common ^{74,104}	PMA/PMMA ^{44, 137}
Self-injury	6-APB ¹³⁹
Convulsions, seizures ¹³⁶ Common ¹²⁹	bk-MDMA (methylone), bk-MBDB (butylone), ⁷ 4-MTA, ⁴⁹ PMA/PMMA ^{137,141}
Amnesia (one case without analytic confirmation ¹⁴²)	4-MTA ²⁰
Hallucinations ¹³⁶	4-MTA, ⁴⁸ MDEA, ^{3,140} PMA/PMMA ⁴⁵
Coma ⁷⁴	bk-MDMA (methylone), bk-MBDB (mutylone), ⁷ PMA/PMMA ¹⁴¹
Trism, bruxism, ¹⁴³ increase in jaw/facial tension	Bk-MDMA (methylone), ¹³ MDEA, ³ PMA/ PMMA ⁴⁵
Thirst ¹⁰⁴	4-MTA ²⁰
Headache ¹³⁶ Common ^{74,104}	
Brian oedema ⁷⁴	
Cardiovascular effects	
Tachycardia Very common ^{104,129,130,144}	5-APB, 6-APB, ^{97,138} bk-MDMA (methylone), bk-MBDB (butylone), ⁷ MDEA, ³ PMA/PMMA ⁴⁵
Hyperthermia Common ^{74,104}	bk-MDMA (methylone), bk-MBDB (butylone), ⁷ 4-MTA, ^{20,49} MDEA, ¹⁴⁰ PMA/ PMMA ^{44,45}
QT prolongation ^{145,146}	5-APB, 6-APB ¹³⁸
Palpitations ¹⁰⁴	5-APB, 6-APB, ⁹⁷ MDEA ³
Hypertension Common ^{74,104})	bk-MDMA (methylone), bk-MBDB (butylone), ⁷ 5-APB, 6-APB, ^{97,138} PMA/ PMMA ⁴⁵
Disseminated intravascular coagulation (DIC) ¹⁰⁴	bk-MDMA (methylone), bk-MBDB (butylone), ⁷ MDEA, ^{135,140} PMA/PMMA ¹³⁷
Arrhythmias ¹⁴⁷ (atrial fibrillation ¹⁴⁸)	MDEA ³
Myocardial infarction ¹⁴⁹	
Cyanosis secondary to methaemoglobinaemia, one report ¹⁵⁰	

Gastrointestinal effects	
Nausea, vomiting ¹⁰⁴	bk-MDMA (methylo), ¹³ 4-MTA, ^{20, 49} MDEA, ³ PMA/PMMA ¹³⁷
Stomach cramps	4-MTA ⁴⁹
Dry mouth	MDEA ³
Respiratory effects	
Tachypnoea ¹³⁰	bk-MDMA (methylo), bk-MBDB (butylo), ⁷ MDEA 'hyperventilation' ³
Pneumomediastinum, causing subcutaneous crepitation, ¹⁵¹ emphysema with neck/chest swelling ^{152,153} (3 reports)	
Shortness of breath, dyspnoea, breathing difficulty ^{104,151,153}	4-MTA, ⁴⁹ MDEA ¹⁴⁰
Chest pain ^{104,151}	
Respiratory failure, acute respiratory distress	MDEA, ³ PMA/PMMA ⁴⁴
Musculoskeletal effects	
Rhabdomyolysis ⁷⁴	bk-MDMA (methylo), ¹³ MDEA, ¹⁴⁰ PMA/PMMA ¹³⁷
Hyperreflexia	bk-MDMA (methylo), bk-MBDB (butylo) ⁷
Shivering ^{105, 130}	bk-MDMA (methylo), bk-MBDB (butylo), ⁷ 5-APB, 6-APB, ⁹⁷ 4-MTA, ^{20,48}
Shaking Common ⁷⁴	4-MTA ^{48, 49}
Tremor ^{104,136}	bk-MDMA (methylo), bk-MBDB (butylo), ⁷ 5-APB, 6-APB ⁹⁷
Muscle spasms	MDEA, ¹⁴⁰ PMA/PMMA ⁴⁵
Myoclonus ¹⁰⁴	bk-MDMA (methylo), bk-MBDB (butylo) ⁷
Increased muscle tone, muscle rigidity	Bk-MDMA (methylo), bk-MBDB (butylo), ⁷ PMA/PMMA ⁴⁵
Inability to stand	4-MTA, ⁴⁹ MDEA ¹⁴⁰
Collapse	4-MTA ⁴⁹
Hyperactivity ('hrashing around')	PMA, ^{127,154} 4-MTA ¹⁵⁵
Other effects	
Metabolic acidosis	bk-MDMA (,ethylone) ¹⁵⁶
Sweating, diaphoresis,	bk-MDMA (methylo), bk-MBDB (butylo), ⁷ 5-APB, 6-APB, ⁹⁷ 4-MTA, ^{20,48,49} MDEA ¹⁴⁰
Fever	5-APB, 6-APB ⁹⁷
Foaming at the mouth	4-MTA, ⁴⁹ MDEA ¹⁴⁰
Acute kidney injury/ acute kidney failure ¹⁵⁷	

Data from the National Poisons Information Service (NIPS) provides some information about harms in the UK. In 2012/13, among telephone enquiries relating to psychoactive illicit drugs, those about MDMA were the second highest in number (131), after cocaine, and in terms of the number of times the NIPS's TOXBASE® website was accessed (4778), it came third, after cocaine and mephedrone.¹⁵⁸

The majority of presentations are managed in hospital emergency departments; they are mild or moderate in severity and self-limiting.^{23,130} In a recent Australian study, the median duration of stay in the emergency department was 3 hours.⁷⁵

Studies from accident and emergency units show that the most common presentations after consuming ecstasy include collapse and/or loss of consciousness, as well as 'feeling 'unwell', 'strange', 'weak' or 'dizzy'; nausea, vomiting and palpitations are also common.^{23,130} Most of those presenting have come from a club, rave or party; among a series of presentations to a London emergency department, 67% had co-used other substances.^{104,130} Similar and higher rates of co-intoxication were found in more recent reviews internationally, with alcohol, amphetamines and cocaine being common co-intoxicants.^{23,104}

Severe acute harm following use of ecstasy usually falls into the categories described below,^{105,159} although the clinical picture is often complicated by concomitant drug use,¹⁰⁴ and a single case may have symptoms from more than one category:

- hyperthermia/hyperpyrexia and secondary manifestations;
- serotonin syndrome (a cause of hyperthermia¹⁰⁵);
- dilutional hyponatraemia and hyponatraemic encephalopathy. Hyponatraemia is particularly a cause of ecstasy fatalities in women;¹²⁹
- acute psychiatric presentations, including symptoms of anxiety, panic or psychosis;
- other isolated physiological syndromes, including cardiac events, liver failure and pneumomediastinum.

It has been suggested that hypoglycaemia, hyperkalaemia¹⁶⁰ and QRS elongation⁴⁷ may be features specific to PMA poisoning. However, all these signs have been observed occasionally in cases of severe ecstasy toxicity not linked to PMA.¹⁶¹⁻¹⁶³

10.11.2. Hyperpyrexia/hyperthermia and consequences

Ecstasy use can promote the development of hyperthermia in two principal ways:¹⁰⁵ by adding to heat load and by reducing heat dissipation. It promotes a hypermetabolic state pharmacologically,¹⁶² and behaviourally, often leading to muscular exertion through hours of dancing.¹⁰⁴ Moreover, hot, overcrowded dance floors are a typical setting for its use.^{164,165} Heat dissipation can be impaired by peripheral vasoconstriction, at least in rats,¹⁶⁶ or by dehydration. Many ecstasy-using dancers who suffer adverse effects display typical symptoms of heat illness, such as feeling unwell and collapsing in an exhausted state.^{104,130,165} Some will move to a 'chill-out' room to recover at the dance venue, or be treated on site. Some will present to hospital, mostly with self-limiting symptoms, requiring minimal intervention beyond correcting dehydration and allowing rest. However, more severe symptoms have been reported.¹³⁰

The overheating associated with ecstasy use can produce harms across a spectrum of severity; a minority of patients present with a severe hyperpyrexia that will not resolve spontaneously with rest in a cooler environment. This has been attributed

to an idiosyncratic drug reaction causing a pharmacologically mediated central and peripheral thermogenesis.^{23,167}

Hyperpyrexia associated with MDMA can appear across a broad dosage range.²³ A vicious cycle of positive feedback from agitation, clonus and seizures can all contribute to heat generation. The hyperpyrexia and serotonin syndrome seen in association with MDMA and related serotonergic drugs are clinically distinct from malignant hyperthermia and neuroleptic malignant syndrome.^{105,168,169}

Hyperpyrexia is one of the predominant life-threatening adverse reactions to ecstasy and is the underlying cause of many acute ecstasy-related deaths. It is also a cause of severe chronic harm resulting from secondary complications such as liver failure and brain damage.^{23,167} Compartment syndrome has been reported as a complication at least twice,¹⁷⁰ and was in one further case associated with ecstasy injection in the absence of hyperpyrexia.¹⁷¹

There may be considerable overlap between serotonin syndrome and this form of acute ecstasy-related toxicity. Serotonin syndrome can be a trigger for uncontrolled hyperpyrexia, but hyperpyrexia can also occur without serotonin syndrome.¹⁰⁵ Acute kidney injury occurs as a consequence of the myoglobinuria seen with rhabdomyolysis, but may be compounded by a number of factors, which include a direct toxic effect of the drug in the kidney and volume depletion from dehydration.¹⁵⁷

10.11.3. Serotonin syndrome/serotonin toxicity

MDMA is a powerful releaser of serotonin and as such is linked to serotonin syndrome. Further information on the features and management of serotonin toxicity can be found in Chapter 7.

Ecstasy can be a cause of serotonin syndrome alone, or in combination with other factors that increase serotonin to toxic levels, including many recreational and pharmaceutical drugs,¹⁷² such as MAOIs, SSRIs, tricyclics, tramadol and linezolid (see TOXBASE®). In one Australian study, some ecstasy users reported deliberately taking these and other pharmaceuticals to magnify the effects of MDMA.¹⁷³

The risks of serotonin syndrome associated with MDMA are boosted by several classes of serotonergic drug.^{53,174} A recent fatality was associated with 6-APB and mirtazapine.²² Some NPS entactogens inhibit monoamine oxidase.

PMA/PMMA poses a particular threat of severe serotonin toxicity.⁴⁴ It has been suggested that it may simultaneously promote serotonin toxicity in several ways – by causing serotonin release, inhibiting reuptake and inhibiting CYP2D6 metabolism.⁴⁵ Symptoms commonly seen in reports of severe PMA and PMMA toxicity are consistent with serotonin syndrome and hyperthermia. Serotonergic and sympathomimetic features may include bruxism, agitation, confusion, convulsions, rhabdomyolysis, coagulopathy, organ failure, coma and death.^{47,160,175} One case series of eight fatal PMMA intoxications showed different presentations depending on dose; those with lower blood concentrations of the drug had delirious hypertalkativity and convulsions, but higher blood concentrations were associated with drowsiness and coma,¹⁴¹ symptoms consistent with severe serotonin syndrome.

10.11.4. Dilutional hyponatraemia and hyponatraemic encephalopathy

Ecstasy has been described as causing a 'perfect storm' of effects that can precipitate dilutional hyponatraemia. Women make up more than 85% of symptomatic cases in the literature, despite more males being users of MDMA.^{129,157,176} MDMA has the potential to directly affect water balance via a syndrome of inappropriate anti-diuretic hormone (SIADH) secretion, at least in women.¹⁷⁶

The drug and the typical contexts of use promote exertion and sweating (resulting in loss of sodium). Hyponatraemia can occur when these effects are combined with the consumption of excessive quantities of low-electrolyte fluids such as beer and water.¹⁴³ The psychoactive effects of ecstasy may encourage this, perhaps promoting obsessional repetitive behaviour, and masking awareness of emerging symptoms of hyponatraemia, such as confusion.^{23,177} Furthermore, mistaken, or misunderstood, harm-reduction information has allegedly led to excessive drinking of water to avoid dehydration and heatstroke.¹⁷⁷

Mild, asymptomatic hyponatraemia has recently been shown to be a common effect of ecstasy use in a typical electronic dance music context. Women are more vulnerable than men, as they are more likely to have lower serum sodium levels before MDMA use. They are more likely to become mildly hyponatraemic while using, more likely to develop symptomatic hyponatraemic encephalopathy, and more likely to die as a result.²³ Fatalities are almost exclusively in women under 21, although men have suffered hyponatraemia so the possibility of male cases should not be ignored.²³

In contrast to other acute syndromes caused by ecstasy, dilutional hyponatraemia often follows a uniform course, with symptoms mostly resulting from the progression of cerebral swelling. Initial headache, vomiting and disturbed mental state are followed by seizures, drowsiness, disorientation and muteness, progressing to coma, hypoxia and death, often due to tentorial herniation.²³ Patients may already be comatose upon admission to hospital.¹⁷⁸

Relatively low doses, including single tablets, are not unusual in cases of hyponatraemia.²³ Also, the excess water intake required to cause symptomatic hyponatraemia, in the context of ecstasy intoxication, is not extreme; 1700 ml and 1200 ml have been cited in case reports;^{157,178} 3500 ml was drunk in a case related to bk-MDMA (methylone) and ethcathinone.¹³ Genetic variation in the function of alleles coding for the CYP2D6 enzyme and the COMT enzyme may predispose some individuals to ecstasy-induced hyponatraemia.

10.11.5. Acute psychiatric presentations

Anxiety and panic are common presentations among users seeking medical help.²³ Ecstasy is an ATS, and is widely used, yet evidence linking it to psychosis is limited to a relatively small number of case reports and case series.²³ Collectively, these suggest that ecstasy does occasionally act as a stressor that precipitates acute psychosis, but at a much lower rate than amphetamine, its molecular relative.¹³⁶

Psychotic symptoms can result from poly-drug use involving ecstasy or, on occasion, from ecstasy alone, particularly in vulnerable individuals.^{23,136} No single characteristic pattern emerges from the evidence base; putative cases include previously healthy people experiencing sudden onset of psychosis after taking a single pill,¹⁷⁹ as well as chronic poly-drug users with complex vulnerabilities taking up to four tablets of ecstasy *daily* before admission with acute symptoms.⁷⁹ As with psychosis linked to other drugs, the prognosis varies from rapid resolution within hours (perhaps in those with a low intrinsic propensity to psychosis) to months or years as an inpatient (perhaps in those with a high vulnerability).^{23,180}

The evidence base includes several cases where there is no toxicological evidence of ecstasy consumption^{29,179} and, in most cases, deliberate or unintended co-intoxication with other drugs linked to psychosis cannot be excluded as a factor.⁷⁹ It remains unclear whether the tendency for ATS to precipitate psychosis is more a direct pharmacological action or toxicity, or more an indirect product of severe psychological stress, such as that caused by sleep deprivation and bingeing behaviour.^{180,181} In either case, ecstasy is an exception among ATS, with lesser effects on dopamine and use typically confined to weekends, rather than multi-day binges, as may occur with methamphetamine and cocaine. Two cases of ecstasy-induced psychosis occurred in individuals who were 'spiked' with the drug without their knowledge and consent.^{23,181} This may indicate a substantial influence of psychological 'set' in determining the response to intoxication. A case control study in a subacute population of males undergoing treatment for their first-episode psychosis found that those who had a recent history of ecstasy use showed significantly different symptoms from those who had not used ecstasy, including shorter hospitalisation, less blunting of affect but increased hostility.¹⁸²

10.11.6 Suicidal ideation and suicide

Ecstasy users have an increased risk of suicide attempts,¹⁸³ but it is uncertain how much of this association is causal, how much may relate to acute use and how much to chronic effects. Recent ecstasy use has been linked to suicidal thoughts and behaviour, in some case reports in the context of acute psychosis as described above, or subacutely, possibly triggered by the ecstasy 'come-down' (for example one case followed a three-day session of injecting ecstasy).²³ Ecstasy overdose has been employed as a mechanism of suicide or suicide attempt,^{184,185,186} as has bk-MDMA (butylone).¹⁸⁷

10.11.7. Acute and subacute cardiac events

Ecstasy alone, and in mixed intoxication, has been associated with acute cardiac events, including myocardial ischaemia and infarction.^{23,188} It can also unmask underlying cardiac dysfunction. Myocardial infarction probably results from coronary artery spasms, similar to those observed in cocaine users. A series of three cases of acute coronary syndrome and ST elevation myocardial infarction (STEMI) demonstrates that, as with cocaine-induced heart problems, they may emerge long after plasma

drug concentrations have peaked.¹⁸⁸ Hyperkalaemia could also contribute to cardiac arrhythmias. There is a single case report of severe dilated cardiomyopathy accompanying hepatic damage.¹⁸⁹

Cardiac arrests occasionally occur without being precipitated by hyperpyrexia or serotonin syndrome.¹⁰⁴ When patients present with chest pain and other symptoms, concomitant use of other drugs should be considered, especially cocaine, which is well known for provoking cardiac dysfunction.²³

10.11.8. Pulmonary harms: pneumothorax, pneumomediastinum

One study has reported that ecstasy has been associated (through uncertain mechanisms) with at least 23 cases of pneumomediastinum,¹⁵² and a smaller number of pneumothorax cases are also reported in the systematic review by Rogers et al.²³ Patients usually present with pain of the chest and neck and shortness of breath, but subcutaneous emphysema and resultant swelling may also be apparent.¹⁵² Sometimes presentations may be delayed, days after consumption. It is hypothesised that the muscle tension caused by ecstasy, combined with exertion from dancing, jumping or sex,^{153,190} could lead to air pressure against a closed glottis, similar to the Valsalva manoeuvre, raising alveolar pressures and causing ruptures.¹⁵² This can result in air being forced out into spaces in the mediastinum.¹⁹¹ One case with an alternative mechanism featured a tear in the oesophagus, allowing air into the mediastinum.¹⁰⁵

10.11.9. Intracranial haemorrhage

Ecstasy use has been associated with intracranial haemorrhage, even in the apparent absence of co-intoxicants.^{23,192} Pre-existing aneurysms, or arteriovenous malformations, may rupture as a result of the acute surge in blood pressure caused by ecstasy, similar to the mechanisms seen with cocaine.

10.11.10. Liver failure

Ecstasy may cause liver failure in two ways. According to a review of the evidence, one group develop acute liver failure secondary to a severe hyperthermic reaction to ecstasy. The other group appear to suffer, isolated hepatotoxicity without any hyperthermia. This is generally a subacute effect which may emerge over the days following use, in contrast to the rapid onset of organ failure in the hyperthermic patients.²³ Despite its rarity, this constitutes one of the more common causes of liver failure in this young age group. Patients may present in a critical condition, with hepatic encephalopathy, and some will require transplantation.¹⁹³ It has been suggested that ecstasy may cause a greater amount of 'silent' liver damage than is recognised.²³

10.11.11. Diabetic ketoacidosis

A small number of case reports demonstrate that people with diabetes can suffer ketoacidosis and associated symptoms following ecstasy use combined with exertion.^{194,195}

10.11.12. Poly-drug use and drug interactions

As discussed above, MDMA is commonly used with other psychoactive drugs and this can increase harm. For example, cocaine co-ingested with ecstasy seems to increase the risk of severe anxiety. In an audit of 52 acute ecstasy-related admissions, 13 with co-use of cocaine, 4 of the 7 patients who suffered panic reactions were among the 13 cocaine users.¹⁰⁴ When MDMA is co-ingested with stimulants in general, the potential for toxicity is likely to be raised.¹⁹⁶ Co-intoxication with caffeine increases the risk of hyperpyrexia in rats.¹⁹⁷ PMMA and PMA produce greater toxicity in combination with stimulants.⁴⁵

Poly-drug use commonly confuses the clinical picture of ecstasy intoxication, and can lead to paradoxical features that are not those expected from intoxication with ecstasy alone. In a Swiss emergency department audit, hypothermia was, paradoxically, one of the most commonly recorded features, and bradycardia, coma, pupil constriction and hypotension were also noted.¹⁰⁴ These were associated with the co-use of substances, including GHB and opiates.²³ Consuming alcohol with ecstasy is associated with a higher rate of harm. Concomitant alcohol use was implicated in 75% of cases of ecstasy-related presentations in an Australian emergency department.⁷⁵

In terms of drug interactions, MDMA and related drugs are substrates and inhibitors of CYP2D6, so combining them with other drugs or pharmaceuticals which compete for, inhibit or block CYP2D6 may cause greater unwanted effects or toxicity. For example, people taking the antiretroviral drug ritonavir are likely to be at particular danger from ecstasy toxicity.¹⁹⁸ Similar reactions may be possible with any drug sharing ritonavir's capacity to compete with MDMA as a substrate of CYP2D6 and inhibit the enzyme. Other drugs linked to apparent cases of adverse interactions include dextromethorphan (DXM), fluoxetine, paroxetine and moclobemide.^{18,43} Drugs which could theoretically cause similar problems include haloperidol, thioridazine and quinidine.¹⁸ CYP3A4 is also involved in the metabolism of MDMA and its derivatives, and co-ingestion of ritonavir has been linked with several cases of toxicity.¹⁸ There may be risks associated with many other substances which affect CYP3A4.^{18,199}

Importantly, MDMA is metabolised by CYP2D6 and inhibitors of this metabolic pathway may therefore increase its level and consequently toxicity. Among the antiretrovirals, the new booster cobicistat (used to optimise concentrations of the integrase inhibitor elvitegravir or of the protease inhibitors atazanavir and darunavir) has been reported to be a CYP2D6 inhibitor.^{200,201} While ritonavir at low doses (as administered to boost HIV protease inhibitors) is not a CYP2D6 inhibitor but is a strong CYP3A4 inhibitor, its role may be important if CYP2D6 metabolisers use CYP3A4 as a compensative metabolic pathway of MDMA, as the latter would be inhibited and lead to increase concentrations of MDMA and toxicity. This would add to the already discussed wide inter-individual variability in responses to MDMA.

For up-to-date guidance on the management of ecstasy/MDMA acute toxicity, 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/M-Products/MDMA2/>

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

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

10.12. Clinical management of acute toxicity

Admissions following ecstasy use often occur at peak times and therefore put pressure on resources.⁷⁵ PMA and PMMA may account for many cases of severe 'ecstasy' toxicity encountered in an emergency department.^{44,47}

In an Australian emergency department, 14% of people presenting to hospital after ecstasy consumption required admission.⁷⁵ The most common interventions required are clinical monitoring, observation and reassurance, and symptomatic treatment, including fluids.¹⁰⁴ The average duration of hospital stay reported by the Australian study was three hours.⁷⁵ TOXBASE® recommends observation of asymptomatic patients for at least four hours.

Dehydration should be addressed. Following ecstasy-related presentation to a hospital emergency department, intravenous fluids were administered to 31% of patients in a UK study,¹³⁰ and to 71% of cases in a Swiss study,¹⁰⁴ but it is important to note that symptoms following ecstasy use range from severe dehydration to severe hyponatraemia; the latter patients require fluid restriction, so it is dangerous to give hypotonic fluids or normal saline to patients prior to proper assessment.^{143,157}

There is no evidence to support gastric decontamination with activated charcoal, but it may be appropriate for cases of presentation within 1 hour of ingestion. Gastric lavage was used in a case with a positive outcome following an attempted suicide with 30 tablets.¹⁸⁴

10.12.1. Hyperpyrexia and hyperthermia

Patients presenting with body temperatures above 39°C need aggressive cooling measures, such as icebaths or internal cooling, and benzodiazepine sedation. It has been suggested that dantrolene may be considered when hyperthermia persists. However, this has been contested by some. No clinical trials have been conducted but a review has reported better survival rates for patients with temperatures above 40°C who received dantrolene, with minimal adverse effects.²⁰² However, a 2011 evaluation of options in MDMA-induced hyperthermia recommended against the use dantrolene and antipyretics.²⁰³

10.12.2. Acute psychiatric presentations

The most of the common features observed in acute patients can be at least partially attributable to anxiety, agitation and panic (e.g. dizziness, palpitations, hyperthermia, hypertension). Some features (e.g. tachycardia) act as internal stimuli to anxiety and panic attacks through positive feedback. TOXBASE® notes that controlling agitation with benzodiazepines may relieve hypertension.

Many cases are resolved in a preclinical setting, or upon reassurance during the initial assessment. Agitation, anxiety and panic can be managed as they would be in the absence of a drug trigger, but cardiac monitoring is a higher priority.¹³⁰ Reassuring patients that they are not likely to be in physical danger may be sufficient, but benzodiazepines are the first-line pharmacological treatment. One study reported that they were administered to a quarter of all patients presenting following ecstasy use at a Swiss emergency department.^{104,105} Some suggest that haloperidol is contraindicated as a second-line option, because of possible dangerous interactions with MDMA and related drugs.¹⁸

10.13. Harms associated with chronic use

While the association between ecstasy consumption and several types of acute harm is relatively clear, current understanding of the chronic harm caused by ecstasy use is limited, due to incomplete and disputed evidence.

Chronic use of ecstasy has been linked to serotonergic neurological damage and dysfunction, which some researchers have suggested may be responsible for a broad range of neuropsychiatric symptoms and cognitive impairments. A meta-analysis shows these to be predominantly small, subclinical effects.²³ Significant trends indicating impairment are typically not identified in samples of ecstasy users who have taken the drug on fewer than 50 occasions.²⁰⁴

Other harmful chronic consequences that have been attributed to use of ecstasy include cardiovascular damage, particularly serotonergic valvular heart disease.

Evidence of long-term effects of NPS use is not available, and so the potential for each of these to cause harm remains unknown. Chronic use of an NPS product (called 'Pink Panthers') containing MDAI and 2-AI (the latter of which appears to be more amphetamine-like than MDMA-like) has been linked to one case of cyanosis caused by methemoglobinaemia. Such effects may also result from chronic use of the many NPS products containing benzocaine as a cutting agent.²⁰⁵

10.13.1. Neurotoxicity

Differences in the serotonergic function of ecstasy users, compared with controls, have been observed in neuroimaging studies.²⁰⁶⁻²¹¹ Observed differences in markers of serotonergic function have been interpreted as indicating the degeneration and loss of serotonergic neurons and their terminals, i.e. 'neurotoxicity'.²⁰⁹ Correlations have been demonstrated between presumed markers of toxicity seen in users and

functional deficits in memory.^{212,213} This supports the hypothesis that serotonergic neurotoxicity is the cause of the cognitive deficits and worsened neuropsychiatric status of ecstasy users.²⁵

The idea that MDMA is neurotoxic in typical human users is supported by some animal research,²⁰⁶ but some experts do not consider the evidence to be conclusive.^{27,214} Some have argued that the observations in such studies may be consistent with changes and loss of serotonergic markers, without loss of the neurons themselves (i.e. serotonergic dysfunction occurs but this may or may not amount to 'neurotoxicity').^{215,216} Other authors highlight limitations in the predominantly retrospective and non-randomised studies supposedly indicative of 'neurotoxicity', claiming that current evidence is insufficient to exclude non-causal explanations,²¹⁴ such as pre-existing lower levels of serotonergic markers in the brains of ecstasy users.^{27,217} While poly-drug use in virtually all ecstasy users has been cited as a confounding factor, recent investigations comparing ecstasy users with LSD users²¹⁸ and other poly-drug users²¹⁹ add weight to the evidence for ecstasy-specific neurotoxicity.

High lifetime intake may not necessarily be required for neurotoxicity to occur. One prospective study found evidence indicative of some brain changes in new users with an average lifetime intake of only six tablets. These changes did not, though, include losses in serotonin transporter density, which is the marker of toxicity most commonly observed. The authors concluded that it is possible that MDMA is neurotoxic even in small quantities.⁷⁶

Studies have found evidence consistent with some recovery²²⁰ and adaptation of the altered serotonin system,²¹¹ but, conversely, other results indicate the persistence of serotonergic dysfunction following cessation of ecstasy use.²⁰⁷

The degree of any lasting dysfunction or neurotoxicity caused by MDMA is thought to be a function of the bioenergetic stress undergone during acute intoxication.²²¹ This theory has led to the hypothesis that there are mediating factors for the bioenergetic stress experienced, and thus the vulnerability or resilience an individual may have to neurotoxicity, beyond the MDMA dose per session and frequency of use. These factors include: ambient temperature and level of exertion (increases of each may promote neurotoxicity), poly-drug use (with stimulants likely to promote neurotoxicity^{222,223}) and others ranging from users' genetics and nutritional status to how well rested they are.²²⁴

A recent study suggests that people's age when they first used ecstasy may be strongly linked to brain changes brought about by ecstasy, with those first exposed while their brains were still developing showing greater apparent deficits. The authors suggest that these age-related differences may reflect differences in the maturation stage of the 5-HT projection fields at the time of first exposure and enhanced outgrowth of the 5-HT system due to 5-HT's neurotrophic effects.²²⁵

Some entactogenic NPS, for example 4-MTA,⁴⁹ have been referred to in the literature as 'non-neurotoxic' analogues of MDMA,^{226,227} and some were developed for this purpose.²²⁸ However, these assessments were based on pre-clinical evidence, and evidence from long-term human use is not available to confirm that these drugs do

not cause serotonergic neurotoxicity. Animal and in vitro evidence suggests that among MDMA-like drugs, some are likely to be more neurotoxic (e.g. MDA) and some less neurotoxic (e.g. MDEA) than MDMA.¹⁸

10.13.2. Cognitive deficits

A number of studies have compared the performance of community samples of ecstasy users (current or past) against that of matched controls on many standard tests of cognitive performance. Weaker performance in certain domains has been identified in the ecstasy users, with the greatest and most consistent effects seen on aspects of memory and recall,²³ such as verbal memory²¹³ and visual paired associate learning.²²⁹

One explanation for the poorer performance of the ecstasy users is typically considered to be serotonergic neurotoxicity associated with the drug (see above). However, there is no consensus on this,²⁶ with many findings open to alternative, non-causal, interpretations, such as confounding cannabis use, or tendencies towards impulsivity and boredom leading to both ecstasy use and poorer performance on tests.²³⁰

The weaker performance of ecstasy users remains within 'normal' limits, according to some,²³⁰ and deficits appear to be specific to certain domains rather than general, with one meta-analysis finding general intelligence unaffected and no impairments seen in simple cognitive functions like basic attention and reaction times.²³

Deficits in verbal memory have been identified, whereas deficits in executive function and visual memory have been identified in some studies but not others.²³⁰ The performance of users typically overlaps substantially with the performance of controls, and uncertainty and controversy remain over the clinical significance and real-world impact of the apparent deficits identified in these samples.^{25,27}

A relatively high intensity of use may be necessary to produce significant deficits. In one study, which excluded anyone with significant poly-drug or alcohol use from the ecstasy-user sample, and which used controls who also shared the 'rave' lifestyle, no marked deficits were found. The authors argued that the confounding influences of poly-drug use and lifestyle may lead to overestimation of the harm associated with ecstasy.²³¹ However, in response it has been argued that this study was nonetheless consistent with the serotonergic neurotoxicity of ecstasy causing cognitive deficits, since it was not highly powered enough (with fewer than 50 users) to show subtle deficits associated with an average lifetime history of use.²⁰⁴

10.13.3. Psychiatric symptoms and harms

Community samples of current or past ecstasy users have been compared with matched controls on measures of psychiatric and psychological health. A study has shown poorer results among ecstasy users on several of these indices.²³² MDMA acutely increases cortisol levels, especially when the bioenergetic stress is magnified by behaviour and environment, but recent studies have also associated ecstasy use with more chronic increases in cortisol and related dysfunction of the

hypothalamic–pituitary–adrenal axis. This in turn has been linked in chronic users to symptoms of distress, anxiety, aggression²³³ and impaired coping.^{234,235}

A meta-analysis in 2005 of 25 studies found a small but significant link between ecstasy use and depressive symptoms. However, the authors noted several methodological limitations and showed that publication bias may have occurred. They concluded that any effect of ecstasy on depression is unlikely to be clinically significant.²³⁶ More recently, in a sample of 3880 disadvantaged Canadian adolescents, those who self-reported ecstasy use were more likely to have elevated depression symptoms one year later (odds ratio 1.5) and those who used MDMA with methamphetamine had even higher rates (odds ratio 1.9).²³⁷ However, studies have shown that circumstances such as a deprived home environment can provide a partial or even complete explanation for the higher incidence of depressive symptoms in ecstasy users.^{238,239}

A US study using a national sample reported that suicide risk appears to be elevated among adolescent users of ecstasy, almost twice that of users of other illicit drugs and nine times the risk among non-users.¹⁸³

A number of factors may be associated with long-term harms. A study by Soar et al. found that the 57 people who reported their ecstasy use as having caused them problems (such as increased depression, somatisation and anxiety) did not differ from those who reported no harm in the duration of their use of ecstasy. However, those who reported problems also reported higher doses, in a pattern the authors call ‘binge consumption’, without further defining this.²⁴⁰

Concomitant use of other drugs is a confounding factor¹³³ that may explain much of the apparent heightened prevalence of various markers of psychopathology, such as depression and anxiety experiences.²⁴¹ Cannabis use, for example, has been found to mediate this relationship.²⁴² Early onset of cannabis use,²³⁹ and tobacco use, have been shown to correlate with greater anxiety among ecstasy users, where neither lifetime nor recent ecstasy use did.²³⁹ However, in one sample of 30 users, the users were not more likely than controls to report pre-existing depression or anxiety symptoms.²⁴³

The come-down period after ecstasy use is characterised by low mood and serotonin depletion, and it is possible that, for people vulnerable to depressive symptoms, this could exacerbate symptoms or cause suicidality.²³

In an experimental set-up, 12 male ecstasy users performed a laboratory task involving monetary rewards. They were more ‘aggressive’ and ‘irritable’ than controls towards fictional co-players. It is not possible to exclude personality factors that pre-existed ecstasy use, and it is uncertain how this ‘aggression’ would translate to real-world face-to-face interactions.²³³

In addition to this evidence of poorer mental health in samples of ecstasy users, mostly relating to subtle, subclinical differences, there is evidence from case reports of more profound psychiatric disturbances and disorders in individual users. One paper detailed two case studies of severe obsessive-compulsive disorder developing in chronic heavy users of ecstasy, leading, in one case, to depression with psychotic features, and, in the other, to psychosis.²⁴⁴ The former patient (a 16-year-old female

who took four or five tablets per week for a year) was judged to have vulnerabilities to mental disorder, but the second patient did not (a 23-year-old male who took one or two tablets a week for more than two years). Both cases resolved with treatment. The authors conclude that causation cannot be determined, but is suggested by the case histories.

10.13.4. Dependence and withdrawal

While ecstasy is generally considered to have some potential for dependence,³ use is often self-limiting and focused around weekend activities.³ Reasons suggested for the low dependence potential include the relatively long period of recovery after one dose.²⁴

It has been argued that although the physiological basis of MDMA dependence is relatively weak in comparison with some other drugs, other factors related to the behavioural and psychological aspects of reward and dependence may have a relatively greater contribution to dependence for ecstasy than for other drugs.²⁴⁵

Users may fulfil dependence criteria,²⁴⁶⁻²⁵¹ develop problematic chronic use patterns, have concerns about their use and seek treatment.²⁴⁵ Several studies have demonstrated some features of dependence among ecstasy users, such as worrying about use, thinking use was out of control and finding it difficult to abstain.^{245,247}

A number of studies have shown that approximately one in five users have been found to be potentially dependent,^{73,249,252,253} although studies which carried out detailed investigation of withdrawal symptoms have shown higher rates, as much as 43% in a US study of adolescents and young adults,^{248,250} and as high as 64% in a study using DSM-IV criteria for amphetamines dependence.²⁵³

Some studies have suggested that how ecstasy is used, rather than how often, may be of key importance in ecstasy dependence, with 'binge' use and higher doses being associated with dependence.²⁴⁷ Users who 'binge', who use ecstasy more frequently, and who experience more social and physical harm are more likely to become dependent users.⁹⁶

Ecstasy 'craving' does not tend to follow the pattern typical with other drugs, as a symptom of dependence, but instead resembles anticipation of an enjoyed activity, typically being low during the week, but rising in the hours before weekend use.⁹⁰

A withdrawal syndrome with ecstasy has been reported. However, it has been argued that the wide between-study variations in the incidence of withdrawal symptoms indicate the need for improved distinction between the short- and the long-term effects of MDMA in standardised assessment tools, despite recent advances. As with other stimulants, the period following acute use is marked by a number of phases: an initial dysphoric 'crash', followed, in chronic users, by an extended 'withdrawal' phase, marked by anhedonia and anergia.²⁵⁴ It has been argued that the application by some studies of withdrawal criteria related to the ecstasy come-down may have led to inflation of estimates of rates of potential dependence and withdrawal.²⁵⁵ While 'true' withdrawal symptoms lead to users taking more of the drug to relieve them, adverse

effects following an episode of ecstasy use have been seen as one reason why heavy users sometimes spontaneously quit ecstasy.⁸³

Some animal studies have shown that chronic use can lead to ecstasy acting increasingly like an addictive stimulant. If chronic use of MDMA causes significant serotonergic damage but little or no dopaminergic damage (as supported by brain imaging²¹²), then the dopaminergic effects may become more prominent than the serotonergic ones, similar to amphetamines with greater addictive potential.²⁵⁶ This is partially supported by user experiences; many report 'losing the magic'⁸³ of the serotonergic effects with overuse and, outside the academic literature, users of drugs fora note how, after overuse, MDMA feels more typically amphetamine-like.²⁵⁷

Ecstasy dependence presents unique features.²⁴⁷ In an online survey promoted to users of a dance-music website, ecstasy users were *more* likely than users of cocaine, ketamine or mephedrone to endorse three or more DSM-IV criteria, yet reported less harm, more pleasure and less desire to seek help than users of these other club drugs.²⁴⁶

Ecstasy is rarely reported as an individual's principal problem drug,²⁴⁷ with 201 people presenting to drug treatment services in England (fewer than 0.1%) in 2013/14 citing ecstasy as the main problem drug they used.⁸⁴ Although ecstasy is rarely a primary problematic drug, users of ecstasy are more likely than other drug users to have experienced substance use disorders in the past year involving drugs other than ecstasy.²⁵⁸ This was the case for 7 out of 10 ecstasy users in an American population sample.²⁵⁸

10.13.5. Sleep problems

A history of ecstasy use has been linked to poorer sleep in some studies but other studies have found no differences.^{23,259,260} Dysfunctional sleep processes may be involved in the memory deficits associated with ecstasy use.²⁶¹

10.13.6. Vascular problems

The typical surge in blood pressure that ecstasy causes may, over time, damage the blood vessels, in particular the walls of aneurysms and arteriovenous malformations.²³ This could lead to haemorrhage.²⁶² Therefore, patients with aneurysms, or any other history of vascular disorders, should be strongly advised of the risks from any drug with a hypertensive effect.

10.13.7. Heart disease

A link between heavy, chronic MDMA use and valvular heart disease has been proposed, due directly to its serotonergic effects.^{263,264} Activation of the 5-HT_{2B} receptor in heart valves by (now obsolete) serotonergic pharmaceuticals such as fenfluramine and ergotamine have been demonstrated to cause cell proliferation, fibrotic thickening and valve dysfunction.²⁶⁵ There is some limited evidence that ecstasy may be capable

of causing such reactions in chronic, heavy users. A blinded study using echocardiography to identify abnormalities reported that MDMA may lead to mild to moderate valvular heart disease and valvular strands.²⁶⁴

A 33-year-old male smoker with an exceptionally high level of lifetime ecstasy use (several pills per week since the age of 17)²⁶⁶ reported shortness of breath and chest pain. He had severe mitral valve disease, with fibrotic thickening of the leaflets and resulting severe regurgitation, necessitating a valve replacement. It was suggested that the lack of reports of similar cases may be explained by the typically short 'ecstasy career' of most users, and the potential reversibility of the valve damage.²⁶³

In addition to valvular heart disease, chronic ecstasy use has been linked to cardiomyopathy more generally,²⁶³ although the evidence remains inconclusive. A retrospective analysis of autopsy records shows that the hearts of people who had MDMA in their bodies at post-mortem were more likely to have enlarged hearts, consistent with myocardial hypertrophy, as seen in users of cocaine and methamphetamine. However, this study did not appear to be controlled in a way that could exclude the confounding factor of poly-drug use.²⁶⁷ A single case study of dilated cardiomyopathy associated with ecstasy has been reported.¹⁸⁹

10.14. Management of chronic harms

10.14.1. Treatments for harmful use and dependence

As with other ATS, the treatment of harmful ecstasy use is primarily psychosocial. No specific guidelines for psychosocial intervention have been described and validated for chronic ecstasy users, but for general guidance on treatment options see Chapter 2.

In most cases, chronic ecstasy users will be poly-drug users, and existing interventions would be unlikely to focus on ecstasy in isolation. For example, an intervention in the form of 45–60 minutes of structured motivational discussion was trialled in young stimulant users, most of whom had recently used ecstasy and cocaine, and most of whom were also regular users of cannabis and alcohol.²⁶⁸ This discussion included exploration of the individual's pattern of use, 'good' and 'bad' effects of use, plans for behaviour change, likely outcomes of this and, for users with no immediate plans to change behaviour, reflection on what future scenarios would lead to a change (boundary setting).²⁶⁸ In this study, the majority (59%) of participants did report making efforts to reduce or cease their stimulant use following the intervention, but 41% of the control group did as well. Average number of days with ecstasy use in the previous 90 days fell from around 18 at baseline to around 8 at 6-month follow-up, and average dose fell from more than 2 tablets per session to around 1.5, with no significant difference seen between intervention and control groups.²⁶⁸ Both the intervention and the control groups participated in baseline self-assessment and read health information, so the authors speculate that while there was no additional benefit from the intervention, contact with personnel and actions that focus attention on substance use may be enough to change behaviour.²⁶⁸

Similar results were found in a trial aiming to reduce ecstasy use among Australian university students. A 50% reduction in use and a 20% reduction in reported severity of harm were recorded 24 weeks after 'motivational enhancement therapy', but the same changes followed the control condition, a 15-minute information session.²⁶⁹ Another brief intervention for regular users did not produce significant reductions in quantity or frequency of use compared with the control condition (assessment only), but did significantly reduce reported symptoms of dependence, and a greater proportion (16%) achieved abstinence, although the study was underpowered to show whether this was statistically significant.²⁷⁰

It has been noted that ecstasy users may not always accurately assess the harm that their drug use may be causing. The degree of apparent subclinical cognitive impairment in users appears to correlate not with the users' own assessments of how problematic their use is, but with the cumulative dose.²⁷¹

However, most ecstasy users are aware that there are risks associated with the drug, and will have reflected upon, contextualised and rationalised that risk.^{272,273} Reducing risk of harm by encouraging ecstasy users to cease use (especially early in their career²⁶⁸) may be difficult because acute harm may be perceived as rare, and chronic harm too subtle to motivate behavioural change.²⁷⁴

Consequently, it has been suggested that the best approach to reducing the risk of harm may be to encourage users to minimise their intake as much as possible.²⁷⁴ This can be attempted by exploring users' experiences of the common unpleasant side-effects during and following use, and the disruption to other areas of life.²⁷⁴

This approach may be supported by sharing the evidence that lighter users tend to maintain the positive effects from ecstasy, without the negative effects increasing much over time, whereas heavy users tend to find that the positive effects reduce sharply and unpleasant effects rise over time, to the point where they outweigh the enjoyment.⁸³ Furthermore, typical user ratings of the positive effects from MDMA, as a function of dose, peak at around 100 mg (matching the content of a single average pill, as of 2012). Doses higher than one average pill, or equivalent, are more likely to decrease the positive effects, with adverse effects rising steeply above 120 mg.^{66,68}

10.14.2. Treatment of depression in the context of MDMA use

It is recommended that clinicians prescribing antidepressants ask about recreational drug use and discuss the risk of drug interactions with those who use MDMA.⁵³

One study has reported that citalopram strongly reduces the desired effects of MDMA, and other SSRIs would be likely to act similarly.²⁷⁵ Despite this reduction in enjoyment, it is possible that SSRIs or SNRIs could increase the risks of MDMA toxicity.^{53,172} In rats, some effects of MDMA, including hyperthermia, are not diminished by citalopram, suggesting that if human users attempt to compensate for diminished enjoyment with higher doses, the risk of acute harm could be increased.²⁷⁶ Furthermore, the pharmacological effects of these drugs involve multiple actions on serotonin release and reuptake, and this complexity may allow for unexpected interactions, including serotonin syndrome.

MAOIs are strictly contraindicated in those who are unlikely to be able to abstain from ecstasy, because the combination has a high risk of causing serotonin syndrome.

10.15. Public health and harm reduction

Taking precautions and limiting dose were not found to be associated with experiencing a lower rate of adverse effects in a sample of 159 ecstasy poly-drug users, although most of this sample did not associate their use with adverse effects.²⁷⁷

Ecstasy users sometimes believe that MDMA itself is virtually risk-free when it is 'clean',²⁷⁸ i.e. that adulteration is responsible for most or all of the adverse effects, minor and severe. It may be beneficial to tell patients that while adulteration certainly does contribute to the risks, pure MDMA can cause harm and death,²⁷⁸ especially in high doses and in environments that contribute to overheating and overexertion.⁹⁹

The principles for the reduction of the harms of ecstasy are similar to those for the reduction of ATS harms in general. In addition:

- Ecstasy users should be made aware that not all ecstasy pills contain the same dose, and that some tablets sold as ecstasy may contain other drugs, like PMA, which can be stronger, take longer to take effect and have higher risks.
- Users should be advised to start with a small dose (half or quarter of a tablet) to test a tablet to make sure there are no bad effects. They should be made aware that taking more than one pill at once might not increase the effect, but can make a come-down worse and increase the risk.
- Users should be advised take regular breaks from dancing and be sensitive to the possibility of exhaustion or overheating.
- Users should be advised to stay hydrated, but not to over-drink. It is best to take regular small sips of water and to drink no more than one pint per hour if dancing in a hot environment and half a pint if not dancing.
- Users should be advised to avoid mixing ecstasy with alcohol and other drugs, as this increases the risks.
- Users should be aware that serotonin syndrome is dangerous and that they should watch out for anyone who looks red hot and rigid and call 999 immediately. A person on antidepressants who also takes ecstasy pills will be at greater risk of serotonin syndrome.

10.16. Benzofurans

Other substances used for their 'emphathogenic', and well as their stimulant effects, include benzofurans, principally 6-(2-aminopropyl)benzofuran (6-APB) and 5-(2-aminopropyl)benzofuran (5-APB), but also the other substances listed in Table 10.5.

Benzodifurans include a group also known as the 'fly' drugs (for example, bromo-dragon fly, 2C-B-fly). They are hallucinogens and are discussed in Chapter 12.

Table 10.5. *Benzofuran derivatives*¹⁷

Chemical name	Street names or product brands (other names may be used locally)	
5-(2-aminopropyl)benzofuran	5-APB ¹⁹	Benzofury
6-(2-aminopropyl)benzofuran	6-APB ¹⁹	Benzofury
5-(2-aminopropyl)-2,3-dihydrobenzofuran	5-APDB	Benzofury
6-(2-aminopropyl)-2,3-dihydrobenzofuran	6-APDB	Benzofury
1-(benzofuran-5-yl)-N-methylpropan-2-amine	5-MAPB	Benzofury
1-(benzofuran-6-yl)-N-methylpropan-2-amine	6-MAPB	Benzofury
1-(benzofuran-5-yl)-N-ethylpropan-2-amine	5-EAPB	Benzofury
<i>Indanylalkylamine derivative</i> ¹⁹		
5-(2-aminopropyl)-2,3-dihydro-1H-indene	5-APDI IAP ¹⁹	
<i>Aminoindane derivatives</i> ²⁷⁹		
5,6-methylenedioxy-2-aminoindane	MDAI	Sparkle, Mindy ⁵⁶
5-iodo-2-aminoindan	5-IAI ¹¹⁶	

In 2013, temporary legislation was passed relating to a number of benzofurans, indanylalkylamines and some 'NBOMe' compounds. Then in 2014, benzofurans were classified as Class B drugs under the 1971 Misuse of Drugs Act.

Benzofurans are ring-substituted amphetamine derivatives. Similar compounds have also appeared on the market in recent years, including 5- and 6-APB and their *N*-methyl derivatives. It was found that when these two materials were subjected to standard analytical techniques, it was not possible to distinguish between them. It is therefore very unlikely that those selling these drugs will know which form they are selling.²²

Benzofurans were initially sold as 'legal highs', initially sometimes as 'legal ecstasy'. They were also sold as psychoactive substances in their own right, as 'Benzofury'. A study of internet sites showed that when mephedrone became controlled, the vendors aggressively promoted the sale Benzofury, as well as other new compounds (e.g. NRG-1 and NRG-2).²⁸⁰ It has been reported that after the temporary drug order on these two substances, some websites no longer offered them, but described the ethyl analogue 5-EAPB (1-(benzofuran-5-yl)-*N*-ethylpropan-2-amine) as a legal alternative to 5- or 6-APB.²²

The term Benzofury was originally applied to 6-APB; however, the name was later used interchangeably for 5-APB and 6-APB, as differentiation of the two isomers even in laboratory analysis is difficult.

10.16.1. Pharmacology

Understanding of benzofurans remains limited. Both 5- and 6-APB are phenethylamine-type materials and are related to methylenedioxyphenethylamines, such

as MDMA and MDA.²² They are potent inhibitors of the reuptake of noradrenaline, dopamine and serotonin with a potency on monoamine transporters similar to that of MDMA.²⁸¹ An animal study has shown that 5-APB and 6-APB are potent full agonists at 5-HT_{2B} receptors.²⁸²

10.16.2. Patterns of use, modes of ingestion

It is not possible to determine the prevalence of use of benzofurans in the UK, but there was confirmation of its use in 2012, through analyses of pooled urine from London and north-west England.^{283,284} There are also police reports of the use of 5- and 6-APB across north Scotland, with anecdotal evidence that they are more prevalent in remote areas. Their use in open prisons was reported by Avon and Somerset police. The 2013 report from the Advisory Council on the Misuse of Drugs (ACMD) refers to anecdotal evidence that they were one of the most popular products sold in 'legal high' shops.²² However, there was no evidence of significant use from the 2013 Global Drug Survey (only 3.2% of UK respondents reported use at some point in their lives and 2.4% use in the past year). Enquiries to the NPIS about benzofuran compounds are also infrequent.⁹⁷

Similarly, in a personal communication from Professor F. Measham to the ACMD, she suggests that the prevalence of 5- and 6-APB use is very low in surveys conducted in night clubs and festivals.²²

As with other substances, benzofurans are used as part of a wider drug repertoire. Information about 5 and 6-APB toxicity collected by the NPIS (prior to the ban) found that co-used substances (9 cases) included aMT (alpha-methyltryptamine, a tryptamine), etizolam (a thienodiazepine currently not controlled nor licensed as a medicine in the UK), 5-iodo-2-aminoindane (5,IAI) and 5,6-methylenedioxy-2-aminoindane (MDAI) (phenethylamines; aminoindane derivatives⁹⁷).

Benzofurans are typically sold as a white powder, or in the form of pellets.²⁸⁵ The ACMD review reports that in 2013 it was claimed by sellers on the web that pellets contained a 120 mg dose (sold at approximately £10 a pellet, with reductions for multiple purchases), while powder was sold for approximately £35 per gram.²²

There are reports from police seizures from around the UK, as well as from the Serious Organised Crime Agency (SOCA) in 2011 and 2012, that many of the 'Benzofury' products did not in fact contain benzofurans, but rather piperazines, cathinone derivatives, benzocaine, D2PM or caffeine.²²

10.16.3. Desired effects

Users report that the effects of 5-APB and 6-APB are comparable to those of MDMA but more intense.²⁸⁶ and that they have mood-enhancing, empathogenic and stimulant effects; they suggest that 5-APB is stronger than 6-APB.²²

10.16.4. Clinical uses

A patent application has been made for benzofuran compounds and their use as antidepressants and anxiolytics. The compounds inhibit serotonin reuptake, exhibit serotonin agonistic and antagonistic properties and are claimed to be suitable as antidepressants, anxiolytics, antipsychotics, neuroleptics and/or antihypertensives.²⁸⁷

10.16.5. Mortality

Analysis of data collected by NPSAD from 1977 to 2012 showed that there were 10 cases in 2011 and 2012 in which 'Benzofury' was identified at post-mortem, with the drug directly implicated in eight of these deaths. In nine cases, other drugs were also detected at post-mortem.²⁸⁸

10.16.6. Acute harms

Very little information has been published on the acute harms of benzofuran. It is suggested that such compounds produce clinical features similar to those of amphetamine, MDMA and mephedrone. Acute toxicity is characterised by serotonergic and sympathomimetic toxidrome, with nausea, agitation, anxiety, dizziness and hyperthermia.²⁸⁹

Adverse effects include nausea, sympathomimetic stimulation and agitation.²⁸⁶ Stimulant features of acute intoxication with benzofurans are most common, followed by mental health disturbances.⁹⁷ A study of NPIS patient-specific telephone enquiries and user sessions for TOXBASE® from March 2009 to August 2013 was conducted, focusing on (2-aminopropyl)-2,3-dihydrobenzofurans. These data were compared with those of mephedrone collected over the same period. Ingestion of benzofuran was associated with similar toxic effects to those of amphetamines and cathinones. However, mental health disturbances and stimulant features were reported more frequently following reported ingestion of benzofuran compounds than after ingestion of mephedrone. However, there are limitations to these findings, resulting from a number of factors, including lack of analytical confirmation.⁹⁷

Comparing the 57 patients who reported ingesting benzofuran compounds alone with 315 patients ingesting mephedrone alone, benzofurans were more often associated with stimulant features, including tachycardia, hypertension, mydriasis, palpitation, fever, increased sweating and tremor (72% v. 38%) and mental health disturbances (58% v. 38%). Other features reported after benzofuran compound ingestion included gastrointestinal symptoms (16%), reduced level of consciousness (9%), chest pain (7%) and creatinine kinase elevation (5%).⁹⁷

One case report describes agitation and paranoia, but as a number of other drugs were ingested it is possible that another substance – or all – contributed to acute psychosis.¹³⁹

It has been argued that the serotonin agonism of benzofuran raises the possibility that chronic use of this compound could be associated with valvular heart disease similar to that caused by fenfluramine and ergoline derivatives.^{290,291}

For up-to-date guidance on the management of benzofuran acute toxicity, 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/B-Products/Benzo-Fury/>

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

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

10.16.7. Management of acute harms

A case with severe psychotic symptoms after use of 6-APB was successfully managed with benzodiazepines alone.¹³⁹

10.16.8. Harm reduction

The harm reduction advice given for ATS and for MDMA is applicable here.

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Chapter 11

Pipradrols and pipradrol derivatives

Pipradrols and pipradrol derivatives are a group of amphetamine-type substances (ATS) structurally related to methamphetamines. In recent years, 2-DPMP (desoxy-pipradrol, also known as 2-diphenylmethylpiperadine) and D2PM (diphenylprolinol) have appeared on the recreational drug market, initially as so-called legal highs.

2-DPMP was first sold as 'Ivory Wave', but there is some evidence that D2PM has since replaced 2-DPMP in Ivory Wave products. Brand names for these substances also included 'Head Candy' and it was also sold as a 'research chemical'. As with other 'legal highs', brand names can be misleading in identifying drug content and associated harms. Ivory Wave is a good example, inasmuch as it was shown have contained methylenedioxypropylvalerone (MDPV) and lidocaine,¹ in addition to 2-DPMP and D2PM.²

2-DPMP and related compounds D2PM and diphenylmethylpyrrolidine are Class B under the Misuse of Drugs Act.

11.1. Brief summary of pharmacology

Desoxypipradrol (2-DPMP) is a long-acting noradrenaline–dopamine reuptake inhibitor originally developed as a treatment for narcolepsy and attention deficit hyperactivity disorder (ADHD). 2-DPMP is thought to increase the release of dopamine and decrease dopamine reuptake, similar to the effects of cocaine.³ There is some evidence that 2-DPMP is more potent than cocaine in stimulating dopamine release and in inhibiting its reuptake.⁴ It is also comparable to amphetamine and methamphetamine in its potential to cause acute toxicity. 2-DPMP has particularly long-lasting effects and a long half-life.² The substance is capable of inducing agitation, which may last for several days after a single dose.⁴

D2PM is a pyrrolidine analogue and 2-DPMP is a desoxy analogue of pipradrol. It has been argued that, based on published evidence, that the binding and activity of D2PM at the dopamine reuptake transporter are similar to those of cocaine, although it appears that D2PM has less biological activity.³ D2PM also has long-lasting effects, albeit shorter than those of 2-DPMP.

11.2. Patterns of use and routes of ingestion

Pipradrols are typically part of a drug-using repertoire and their use has been reported among a minority of users. For example, in a survey of individuals attending gay-friendly nightclubs in south-east London (July 2011), 0.6% of 315 individuals reported that they had used a pipradrol: 1.0% had used within the last year and 0.6% had used or

were planning to use a pipradrol on the night of the survey.⁵ Pipradrols were also detected in an analysis of anonymous pooled urine samples from stand-alone urinals.⁶

It is important to note that people who use 2DPM and D2PM do not necessarily know that they have consumed this drug. In a case series of five patients who presented to an emergency department (ED) in London, none of them knew that they had consumed it. They were sold it instead of the substance they had intended to buy.⁷

2-DPMP is sold as a hydrochloride salt or in free-base form. It is described by retail websites 'as a white crystal powder with not much smell' or 'a white coloured fine powder', with a purity of up to 99.9%.²

Oral ingestion is the most common route of administration of 2-DPM ('bombed' wrapped in a cigarette paper) or dissolved in water. However, the drug can also be insufflated, used rectally, smoked and intravenously injected.² Based on analysis of online fora, Corkery et al. reported that doses range from 1 mg to 10 mg according to mode of use, typical oral doses being 1–2 mg, but the optimum dose being thought of as 5–10 mg. The authors also reported that there is no information on whether the effects of 2-DPMP are dose-dependent or dependent on the mode of ingestion.² The elimination half-life is 16–20 hours.

The oral and insufflation of D2PM have been reported. The typical human active dose of D2PM is 2–5 mg, but reports on online drug user fora suggest that rectal doses range from 10 mg to 30 mg and oral doses from 35 mg to 50 mg.²

An analysis of user reports suggested that 2-DPMP effects are felt within 60 minutes of oral use, and may last up to 24 hours (or even 48 hours). The psychoactive effects of D2PM are similar to those of 2-DPMP but appear to occur 15 minutes after ingestion and may last up to 10 hours.²

Nasal irritation and epistaxis may occur after nasal insufflation. Analysis of user reports suggest that prolonged use of D2PM can cause craving and increased need to re-dose.²

11.3. Desired effects

Analysis of user reports of the desired psychoactive effects of 2-DPMP include prolonged euphoria, increased energy and alertness, sociability, and loquacity.² Other stimulant effects reported include sweating and bruxism.³ The desired psychoactive effects of D2PM are, similar to those of 2-DPMP, but as mentioned earlier, occur sooner and last for less time.²

11.4. Mortality

2-DPMP has been detected in three fatalities in the UK,² its role in these deaths has not yet been established. There have been no reports of deaths directly attributed to either D2PM or 2-DPMP.

11.5. Acute harms

Information on the acute toxicity related to both D2PM and 2-DPMP is very limited. Reports suggest the development of sympathomimetic features similar to those seen with other recreational drugs and other amphetamines in particular, such as MDMA. They also suggest that these compounds may be associated with significant neuropsychiatric symptoms, which can be prolonged in nature, in which respect they are different to other sympathomimetic compounds.³

The limited experience of the UK National Poisons Information Service (NPIS) suggests that their acute clinical effects include tachycardia, palpitations, convulsions, raised levels of creatine kinase, acute renal failure and chest pain (sometimes with ECG abnormalities). There is also a reported risk of serotonin toxicity.⁸ D2PM and 2-DPMP are related predominantly to neuropsychiatric symptoms.⁴

There is emerging evidence that they have sympathomimetic properties similar to cocaine.³ The initial pattern of acute toxicity is similar to that of other sympathomimetic drugs, with users describing a 'rush'.⁷ Prolonged and clinically significant neuropsychiatric symptoms have been reported following the use of the D2PM.^{3,7} A high risk of central nervous and cardiovascular system toxicity has been suggested.⁹ One case report of a presentation to a London emergency department associated with the use of D2PM (in addition to glaucine) described an individual who presented with acute onset of agitation and chest pain. The authors suggested that the D2PM was likely responsible for the ischaemic chest pain, as the acute toxicity of glaucine is more hallucinogenic in nature.¹⁰

There are two reports of acute harms associated with 2-DPMP (products sold as 'Ivory Wave' and 'Whack') from Scotland and Ireland,^{1,11} although both studies lack robust analytical confirmation or have none at all ('Whack' also contained fluorotropacocaine).

An analysis of 37 consecutive patients attending the Royal Infirmary of Edinburgh emergency department in July and August 2010 with self-reported Ivory Wave use was carried out. Over a similar time frame, enquiries regarding Ivory Wave' to the NPIS, by telephone and via the internet-based TOXBASE®, were analysed. Analysis of both sets of data showed a toxidrome which lasted several days, and included tachycardia (65%), tachypnoea (76%), dystonia (18%), rhabdomyolysis (96%), leucocytosis (57%), agitation (62%), hallucinations (50%), insomnia (32%) and paranoia (21%).¹

The use of D2PM and 2-DPMP is related to neuropsychiatric symptoms. There were 49 enquiries to the Irish National Poisons Information Centre relating to 'Whack'; these commonly described cardiovascular effects, including hypertension in 10 cases, and tachycardia. Neuropsychiatric effects were also reported, including agitation and psychosis, and these persisted for up to five days. However, this study was limited by the fact that fluorotropacocaine was also found in Whack and that there was no analysis of biological samples.¹¹

Similarly, 96% had neuropsychiatric features in a case series of acute intoxication related to Ivory Wave. Cases presented up to a week after use, with tachycardia,

dystonia, rhabdomyolysis, agitation, hallucinations and paranoia. A similar Ivory Wave product contained 2-DPMP in another study, but that was limited by the fact that in the majority of cases biological samples were not analysed.¹

A case series with analytical confirmation of D2PM in five individuals who presented to a London emergency department described patients showing the neuropsychiatric symptoms of agitation, anxiety and insomnia, lasting for 24–96 hours following the use of the D2PM.⁷

11.6. Chronic use

No information is available on the long-term effects of desoxypipradrol or of D2PM. Analysis of user reports suggest that, as with desoxypipradrol, prolonged use of D2PM leads to craving and a need to re-dose.²

11.7. Management of acute harms

The limited evidence on the acute toxic effects of 2-DPMP and D2PM suggests that the management of their harms is similar to the management of the harms from other stimulants and ATS.

Because of the particularly long-lasting effects of these drugs, the authors of a case series said that an important part of the management of presentations for acute intoxication was the reassurance of individuals that the prolonged neuropsychiatric symptoms will resolve.⁷

For up-to-date guidance on the management of pipradrol acute toxicity, 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/2-Products/2-DPMP/>

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

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

11.8. Harm reduction

For more information on the reduction of the harms of ATS, see Chapter x, bearing in mind the fact that 2-DPMP and D-2PM are potent amphetamine-type stimulants. 2-DPMP in particular is a long-acting drug, capable of causing severe agitation, which can last for several days after a single dose

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Part IV: Hallucinogens

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-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		
(6aR,9R)-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)
(6aR,9R)-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	
(6aR,9R)-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-[[[(2S,4S)-2,4-dimethylazetididin-1-yl]carbonyl]-6-methyl-9,10-didehydroergoline (lysergic acid 2,4-dimethylazetidide)	LSZ ⁹	
Tryptamines		
O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine	Psilocybin	'Magic mushrooms', 'Mushies' or 'Shrooms' contain psilocybin and related tryptamines 'Liberty caps' or 'Libs' are the most common wild UK species of magic mushroom, <i>Psilocybe semilanceata</i> . Also occurring in the UK are <i>Panaeolus cinctulus</i> and 'Wavy caps', <i>Psilocybe cyanescens</i> 'Cubes' or 'Boomers' are the most commonly home-cultivated species, <i>Psilocybe cubensis</i> 'Truffles' or 'Philosopher's stones' are cultivated nodular growths (technically 'sclerotia') from other <i>Psilocybe</i> species. They are sold online
4-hydroxy-N,N-dimethyltryptamine	Psilocin	
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-diisopropyltryptamine	5-MeO-DiPT	'Foxy Methoxy'
12-methoxyibogamine	Ibogaine	'Iboga' (<i>Tabernanthe iboga</i>) 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, tranquility and peace') was the original name for pills of DOM
Tetrahydrodifenyl 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
<i>Salvia divinorum</i>	<i>Salvia</i>	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 <i>Amanita</i> mushrooms		
<i>Amanita muscaria</i>		
<i>Amanita pantherina</i>	Fly agaric (<i>Amanita muscaria</i>) Panther cap (<i>Amanita pantherina</i>) 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* legal¹² 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-DALT¹³ and α MT,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' online¹⁴ 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' online¹⁴ 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-HT₂ serotonin receptors,² particularly 5-HT_{2A} and/or other 5-HT₂ 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-B²⁸ 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-HT₂ 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 LSD⁴⁰ and psilocybin⁴¹ 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 hallucinogens

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 <i>Salvia</i> use	0.5% in 2013/14, significantly up from 0.3 in 2012/13
16–24-year-olds reporting <i>Salvia</i> use	1.8% in 2013/14, 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

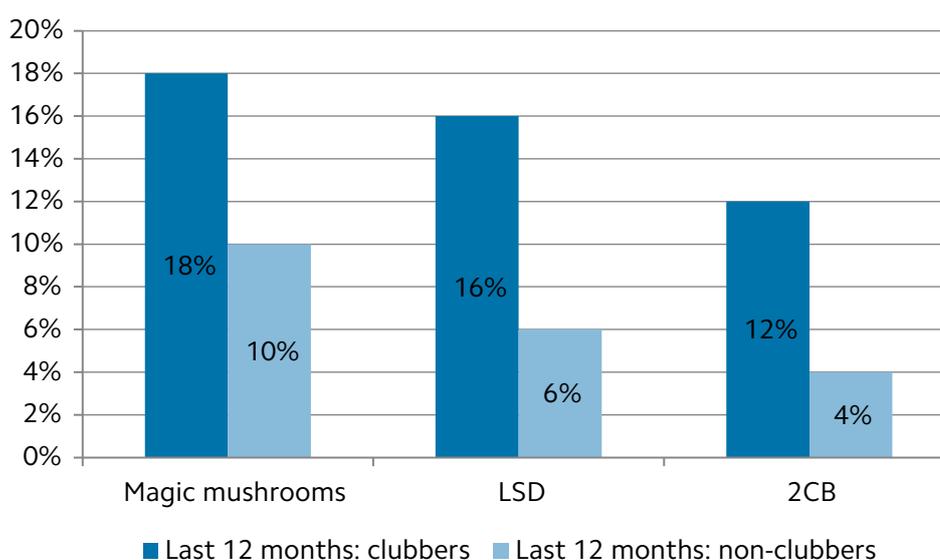


Figure 12.1. Drug use by frequency of visits to ‘clubs’ (Global Drug Survey 2012)

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 mescaline² (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 µg⁴⁷).

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 as 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, α MT 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 drug⁸²) 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. α MT⁸⁸); others drugs may more typically evoke symptoms of serotonin syndrome (e.g 5-MeO-DiPT³⁰).

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

CNS, neurobehavioural and psychiatric

Dilated pupils, mydriasis (common, psilocybin⁸⁹)
 Sensory distortions, visual, auditory illusions, synaesthesia^{8,90}
 Tactile hallucinations, e.g. formication⁹¹
 Affect lability
 Euphoria⁹²
 Dysphoria⁷⁴
 Acute panic⁸
 Paranoia, ideas of reference^{8,90}
 Depersonalisation^{8,90,93}
 Anxiety^{8,90}
 Disorientation⁹⁴
 Dissociation⁹⁴
 Agitation^{30, 33}
 Aggression, combativeness³⁰
 Delirium
 Depression, suicidal ideation, attempted suicide⁹⁵
 Psychosis, delusions, hallucinations^{96,97}
 Seizures³²
 Confusion^{33,98}
 Ataxia^{8, 90}
 'Bizarre behaviour'³³
 Lightheadedness^{8,93}
 Headaches⁸
 Paraesthesias,⁹⁴ abnormal sensations of heat and cold, chills⁸
 Restlessness, excitement^{30,98}

Cardiovascular

Tachycardia^{8,30}
 Hypertension⁸
 Musculoskeletal
 Myalgias⁸
 Twitching⁹³
 Muscle tension and jaw clenching³⁰
 Shaking⁸⁸
 Respiratory
 Tachypnoea^{30,93}
 Metabolic
 Metabolic acidosis³⁰

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}
 Rhabdomyolysis³⁰

Renal

Acute kidney injury/acute kidney failure⁸

Other symptoms

Hyperthermia^{8,30}
 Pyrexia⁹⁴
 Hypoglycaemia
 Flushing⁹³
 Sweating⁸⁸

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 salvia¹⁰⁶ 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-DALT¹¹¹ 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 mescaline¹²¹ 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 alkaloids¹²⁴). 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 fatal¹²⁵ 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'. Sympathetic⁸ non-judgemental¹³⁰ 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 diazepam¹³¹ (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 intravenous 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 atypical¹³⁵ 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 vapourisation (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, after-images, 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 mescaline¹⁴¹ 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 topimarat, ¹⁵⁶ trazodone, mirtazapine, nefazodone¹⁴⁵ and SSRIs¹⁵⁷ 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 psychotherapy¹⁴⁴ 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, lamotrigine¹⁴⁵ 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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Part V: Synthetic cannabinoids

Synthetic cannabinoids

Drug group: synthetic cannabinoid

Synthetic cannabinoids (SCs), also referred to as synthetic cannabimimetics or synthetic cannabinoid receptor agonists, are smokable drugs often used as legal alternatives to cannabis. They have a strong effect on the endocannabinoid system.

13.1. Street names

A variety of street names are used for synthetic cannabinoids. The term 'Spice', which is the brand name of one of the most common SC products sold in Europe, is often used as a generic term for all synthetic cannabinoids. They are often referred to as 'K2' in the US, and 'Kronic' in Australia and New Zealand.¹

A wide range of brands of herbal products containing synthetic cannabinoids have been available on the market. They include, but are not limited to, Spice, Black Mamba, Annihilation and Amsterdam Gold. New brands continue to emerge. Brand names are sometimes reminiscent of street names of strains of cannabis.

13.2. Legal status

Some SC are Class B Schedule I drugs under the Misuse of Drugs Regulations (2001), under a generic definition. The cannabinoids targeted for control under these generic definitions are CB1 receptor agonists.² Products that contain other synthetic cannabinoids are currently legal to possess and include AM-694 and the Belarus compound.³

13.3. Quality of the research evidence

The research evidence on SCs is limited to case reports and case series, as well as retrospective toxicology surveys, human and animal laboratory studies, surveys and interviews with SC users. There are no longitudinal studies or randomised controlled trials.

13.4. Brief summary of pharmacology

Synthetic cannabinoids play an important part in the 'legal high' market. In Europe, it is the largest chemical group monitored by the European Union's early warning

system, with 30 new products reported in 2012 and 29 in 2013.⁴ Although they first appeared in Europe, they are now part of the drugs market in almost all developed countries throughout the world.⁵

SCs have been developed since the discovery of delta-9-tetrahydrocannabinol (Δ 9-THC or THC) cannabinoids. They are a large and chemically diverse group of molecules with some functional similarity to THC and other phytocannabinoids. Overall, SCs produce effects that have similarities to THC, although they are not the same and in particular are structurally dissimilar.^{6,7,8} Both SCs and phytocannabinoids (natural cannabis) bind CB1 and CB2 receptors.⁹ However, SCs have a much higher affinity for those receptors than natural cannabinoids and produce a stronger effect.¹⁰ Structure–activity relationship analyses reveal that SC compounds may indeed exhibit higher potency. In fact, SCs are full agonists on the endocannabinoid system, while THC is only a partial agonist.¹¹

THC has a dibenzofuran structure which is not present in the majority of SCs. Furthermore, a number of SCs contain nitrogen atoms in their scaffolds, which are not found in phytocannabinoids. While THC is a partial agonist and has psychotomimetic properties,¹² the second most prevalent cannabinoid in natural-grown cannabis, cannabidiol (CBD), seems to possess anxiolytic, antipsychotic and anticraving properties.^{13,14} These effects of CBD on THC in cannabis cannot be found in SCs.¹⁵

SCs were initially synthesised for biomedical research purposes,¹⁶ by scientists investigating the mode of action of cannabinoids on signalling pathways in the body or as therapeutic agents.⁴ This includes the analogues to THC (the classical cannabinoid) which were developed by Raphael Mechoulam at the Hebrew University (the 'HU' compounds) in the 1960s and include HU-210, which is structurally similar to Δ 9-THC, but more potent, and difficult to synthesise.

The cyclohexylphenols ('CPs'), referred to as non-classical cannabinoids, were developed by Pfizer in the 1970s. In the 1990s, John W. Huffman developed the 'JWH' series of synthetic cannabinoids which evolved from a computational melding of the chemical structural features of Δ 9-THC with previously developed aminoalkylindoles.¹⁷ Other indole-derived cannabinoids detected in products for recreational use are those synthesised by Alexandros Makriyannis (the 'AM' compounds).⁷

SCs fall into the major structural groups, based on their chemical structure.^{5,18} Many of the compounds incorporate indole-derived moieties, as components of the structure or as substituents.¹⁹ Indoles are groups structurally similar to serotonin, and so are active on 5-HT receptors, and they are typically identified in indoleamine hallucinogens such as dimethyltryptamine.²⁰ From this point of view, it could be argued that ingestion of indole SC compounds may be associated with particularly high levels of activation of serotonin receptors.^{21,22} Furthermore, it has been suggested that, at high doses, SC compounds may also possess some monoamine oxidase inhibitory properties.²³ This element may further increase the risk of serotonin syndrome in SC misusers (for serotonin syndrome see section 7.7.2).

There are currently 200 cannabinoid receptor agonists. Synthetic cannabinoids fall into seven major structural groups: naphthoylindoles (e.g. JWH-018, JWH-073 and

JWH-398); naphthylmethylindoles; naphthoylpyrroles; naphthylmethylindenes; phenylacetylindoles (i.e. benzoylindoles, e.g. JWH-250); cyclohexylphenols (e.g. CP 47,497 and homologues of CP 47,497) and classical cannabinoids (e.g. HU-210).

Over 80 compounds from 13 different chemical groups had been reported in Europe alone by June 2013,^{24,25} and a number of new scaffolds and substituents to produce new drugs have recently emerged on the market.²⁶

The large structural heterogeneity of the different SC compounds means that some are more potent than others. There are differences in terms of metabolism, toxicity and duration of effects. Generally speaking, the greater the affinity to the CB1 receptor, the higher is the pharmacological activity of the agonist compound.

The JWH series of cannabinoids were the most commonly used in Europe,^{27,28} although have become less available since legal control. Their chemical structure is markedly different from THC. In comparison with THC, the JWH class has a much greater affinity for and full agonism on cannabinoid receptors.^{29,30} The CP compounds are another commonly used group of cannabinoid receptor agonists and also lack the classical cannabinoid structure. CP-47,497, often found in herbal products, is up to 28 times more potent than THC.^{31,32} The HU compounds are structurally similar to THC but are 100–800 times more potent.³³ Benzoylindoles are a fourth group and the include AM-694 and RCS-4, which have only more recently been detected in herbal blends. Very little is known about this last group.^{34,35}

Synthetic cannabinoid receptor agonists do not give a positive result on routine urine screening tests for metabolites of delta-9-tetrahydrocannabinol (THC).³⁶ The forensic chemical detection of SCs remains complex,³⁷ not least because of continuously emerging compounds and the lack of reference samples in laboratories to identify them.

13.5. What are synthetic cannabinoid products?

In the pure state, SCs are either solids or oils. Smoking mixtures are usually sold in metal-foil sachets, typically containing dried vegetable matter to which one or more of the cannabinoids have been added. Sachets usually contain 0.5–3 g of finely ground plant material.⁵

Most synthetic cannabinoids are produced in China and exported, usually in powder form, using wrong declarations, such as 'polyphosphate', 'maleic acid', 'fluorescent whitening agent' or 'ethyl vanillin'.⁵ Once in Europe, the retail products are assembled by lacing inert herbal products with synthetic cannabinoids. Commonly used herbal bases for the active chemical ingredients are damiana (*Turnera diffusa*) and lamiaceae herbs, such as *Mellissa*, *Mentha* and *Thymus*. The synthetic chemicals are mixed with or sprayed onto the herbs, typically on an industrial scale, often using equipment like cement mixers and liquid solvents, such as acetone or methanol, to dissolve the powders. They are then dried and packaged for sale.⁴

Many of the 'herbal mixtures' are inhomogeneous with respect to the concentration of compounds contained. For instance, in one analysis the JWH-018 content ranged from 6.8 mg/g to 44.4 mg/g within a single product.³⁸ Furthermore, quite often more than one SC is added to the 'herbal mixture'.³⁹ In Japan, Kikura-Hanajiri et al.⁴⁰ detected an average of 2.6 SCs per product. The most detected in one mixture by the authors was 10.

Other substances identified in SC products include fatty acids and their esters (linoleic acid, palmitic acid), amide fatty acids (oleamide, palmitoylethanolamide), plant-derived substances (eugenol, thymol and flavours like acetyl vanillin), preservatives (benzyl benzoate) and additives (alpha-tocopherol).^{41,42} SC products may also contain high quantities of tocopherol (vitamin E), possibly to mask analysis of the active cannabinoids.³⁷ They are often contaminated with the beta₂-adrenergic agonist clenbuterol,⁴³ thus providing a basis for sympathomimetic-like effects (tremor, tachycardia, anxiety) often described in intoxicated patients presenting to emergency departments.^{44,45} Although the herbal blend that contains the SCs is most likely to be an inert product, the pharmacology and toxicology of the plant material in these blends is unclear.⁴⁶ The herbal material, which is used as a basis for the smoking of these mixtures, may contain toxicologically relevant substances, like pesticides.³⁹

Generally, herbal blends or mixtures that contain SCs but not tobacco or cannabis⁴⁷ are sold online and in so-called 'head-shops'. There are current reports of its sale in pubs, petrol stations and take-away food shops, especially in the north of England.⁴⁸ Like other NPS, SC products have on their label 'not for human consumption', and are instead advertised as incense or room deodoriser. However, they are usually in the form of herbal products for smoking. Pure compounds, not sprayed on inert herbal products, are also available for sale on websites, which users can mix with their own herbal mixture.²

Herbal products containing SCs first appeared around 2004.⁴⁶ The first SC detected in Europe as a so-called legal high was JWH-018, which was detected in Germany and Austria in late 2008.⁴ It has been noted that the popularity of these drugs increased significantly around 2008, as a result of numerous media reports that called them a 'legal' alternative to cannabis.⁵

SCs provide an example of how regulated psychoactive compounds can be easily replaced with equally effective homologues for the purpose of avoiding legal control. For instance, in January 2009, Germany banned the production, sale, acquisition and possession of the two specific psychoactive synthetic chemicals (CP 47,497-C8 and JWH-018). Within four weeks of this legal control, samples of 'Spice' obtained throughout Germany demonstrated replacement of those two recently banned compounds with JWH-073, a then unregulated chemical homologue.^{29,49} A study by the Poisons Information Centre in Freiburg, Germany, undertaken between September 2008 and February 2011, reported that, after January 2010, when JWH-073 and JWH-019 were added to the list of scheduled substances, there was an increase in emergency presentations associated with the extremely potent synthetic cannabinoids JWH-122 and JWH-210. The authors commented that early cases (i.e. patients presenting after taking JWH-018), symptoms were generally mild, but more

recent presentations, mainly due to the highly potent agonists JWH-081, JWH-122 or JWH-210, involved much more severe symptoms.⁵⁰

Elsewhere too, producers of these products have been quick to adapt to changes in legislation by using similar compounds that are yet to be controlled.⁵ Slight modifications are made to banned compounds and new derivatives continue to emerge as older ones are regulated. Chemists have synthesised similar compounds easily by the addition of a halogen, alkyl, alkoxy or other substitutes to one of the aromatic ring systems, or by making small changes in the length and configuration of the alkyl chain, for example.⁵

This has led to a rapid increase in the number of SCs in recent years. In 2012, out of the 73 new psychoactive substances reported in the EU to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 30 were SCs.⁴

Although the manufacturers of SCs and other so-called legal highs often try to circumvent the law by developing compounds slightly different from those banned, there is evidence that some of these products contain classified compounds and are therefore illegal under UK law.³ Similarly, a recent German study found products which contain compounds not banned in Germany, such as AM-2201 and MAM-2201, together with banned cannabinoids JWH-018 and JWH-122.⁵¹

The strength and purity of SC products vary. One US study looked at the purity of JWH-018 and JWH-073 from three online suppliers. Purity was determined using high-performance liquid chromatography with ultraviolet detection, and compared against validated standards obtained from a traditional research chemical supplier. The study found that products bought online were of comparable purity to validated standards, even though the products varied from each other in colour, texture and odour. There was no evidence of other compounds.⁵²

In terms of the herbal products laced with SCs, analytical tests have shown that the cannabinoid constituents and dosage vary greatly between products, batches and even within the same package, giving rise to what are known as 'hot spots'.⁵³ UK research has shown that there is significant variation in the content of 'legal high' products bought over the internet.⁵⁴⁻⁵⁷ Conversely, different brands on sale may contain the same compound. For example, AM2201 was identified in 'Black Mamba', 'Annihilation', 'Tai High', 'Hawaiian Haze' and 'Bombay Blue Extreme'.²

It has also been reported that SCs have been found recently in products that look like cannabis resin, as well as in samples of herbal cannabis. This may be to strengthen the potency of weak cannabis or to reduce the 'harvest time' and increase production rates by improving the poor potency of immature plants.

A recent trend has been reported whereby SCs have been detected in mixtures containing other psychoactive herbs and plants:⁵⁸

- benzodiazepines, such as phenazepam;
- tryptamines;^{59,60}
- phenethylamines/NBOMe compounds;⁶¹

- cathinones;
- opioid analgesics;⁶²
- benzocaine;⁶³
- diphenidine.^{4,60,64}

It is therefore not easy to determine the contents of each SC product or to predict its pharmacological and toxicological characteristics.⁶⁵

13.6. Clinical and other legitimate uses of synthetic cannabinoids

Synthetic cannabinoids have been developed for the past 40 years as potential pharmaceutical agents, often for pain management⁶⁶ or nausea. Those currently used include nabilone (Cesamet®), for the treatment of anorexia and for its antiemetic properties in cancer patients. Dronabinol (Marinol®) and nabiximol (Sativex®) are used in the management of multiple sclerosis and pain.^{5,37}

13.7. Prevalence and patterns of use

The use of SC herbal products in the UK seems to be limited, although over the last few years they have gained popularity, especially among adolescents and young adults⁶⁻⁸ and among prison populations.⁶⁷ This increase in popularity may be because the market is quasi-legal market and the products readily available, as well as affordable at about £10/12 per gram.⁶⁸

One of the main reasons for the misuse of SCs is the difficulty detecting consumption by analysis of biological samples. The non-detectability of these compounds makes them attractive for persons undergoing regular drug tests (e.g. patients of forensic or withdrawal clinics, people obliged to undergo workplace drug testing, and driving licence re-granting candidates, those working in law enforcement, fire fighting, the armed forces,⁶⁹ prisoners or clients on probation, mining workers, and athletes).¹⁵

SC products have been reported by the Avon and Somerset police as popular among inmates of their open prisons, again to circumvent the drug testing.⁷⁰ Similar findings have been reported in prison and probation services in Sweden.⁷¹

Questions on the use of 'Spice' were added to British Crime Survey in 2009 and asked for two consecutive years. In 2010/11, 0.2% of adults reported using them in the past year, with higher rates among adults aged 16–24 years than among those aged 25–59 years (0.4% and 0.1% respectively).⁷² In 2011/12, 0.1% of adults in general reported using 'Spice'.⁷²

Comparisons with other European and US studies are not possible because of different methods used, sampling frames and terminology, but findings shed light on patterns of SC use. In Europe, a 2010 Spanish survey of 25,000 people aged of 14–18

years reported 1.1% lifetime use, 0.8% use in the past 12 months and 0.4% in the last month.⁷³

The use of SCs may be significantly more prevalent in the US. A US study of 852 university students with an average age of 20.6 years (SD 5.1) reported use ever of 'K2' by 8% of the sample (in comparison with 36% who had used cannabis/marijuana). Just over 90% of those had also ever used cannabis. Use of 'K2' was significantly associated with age, gender, year in college and ever use of tobacco and cannabis. Use of SCs was more common among males than females, and more common among first-year and second-year students than among those in the third year or above.⁷⁴

The large US 'Monitoring the Future' survey looked at SC use in 2011 for the first time (45,400 pupils in 395 secondary schools in 2012). Among 12th-grade school students, 11.4% reported using in the past 12 months. Use in 2012, which followed its control in March 2011, remained unchanged at 11.3%, making it the second most used substance among this group, after natural cannabis. Among pupils in grades 8 and 10 in 2012, 4.4% and 8.8% respectively had used SCs in the previous year. Among the 8th-graders, it was the third most used illicit substance, after cannabis and inhalants.⁷⁵

The 'Monitoring the Future' survey carried out in 2013 among a similarly large number of young people in three grades reported a substantial drop in the use of SCs products, such as 'K2' and 'Spice', but an increase in the use of natural cannabis. The use of synthetic marijuana in the previous year dropped significantly, from 11.3% in 2012 to 7.9% in 2013 among 12th-graders, from 8.8% to 7.4% among 10th-graders, and from 4.4% to 4.0% among 8th-graders. It was noted that the drop in SC use among pupils in the 12th grade was highly statistically significant, and the drop for the three grades combined was also significant.⁷⁵

Generally speaking, it has been noted that the use of SC products is more prevalent among young people. It is also more prevalent among males than females.^{1,71,76,77} Although it is not possible to generalise, surveys have looked at SC users' social capital, with two-thirds of respondents to the Global Drug Survey who reported having used SC also reporting currently working (66.6%). Over half reported currently studying (53.3%) and only a minority of 8.8% reported neither working nor studying. One-third of the sample (36.4%) reported having completed a university degree.¹ An Australian survey of 316 SC users, recruited from the general population, also reported that respondents were mostly employed or studying.⁷⁸

Poly-drug use is common among SC users; for example, a study of young people in treatment for SC use found that those using these drugs were also more likely to use a range of other substances.⁶⁶ Similarly, among non-treatment-seekers, an internet survey of 168 users in 13 countries found that lifetime use included: alcohol (92%), cannabis (84%), tobacco (66%), hallucinogens (37%), prescription opioids (34%), MDMA (29%), benzodiazepines (23%), amphetamines (22%), cocaine (17%), *Salvia divinorum* (17%), heroin (7%), inhalants (7%), dissociative anaesthetics (6%), methamphetamine (3%) and miscellaneous other drugs (mephadrone, dextromethorphan, kratom; 12%). Spice was reported as the drug of choice among 21% of respondents, and 25% reported no plans for future Spice use.⁷⁹

Users of SC have been grouped in three main categories based on previous drug use: cannabis smokers; occasional drug users seeking to avoid legal complications; and drug-naïve curious experimenters.⁴⁶

The 'Monitoring the Future' survey carried out in 2013 (mentioned above) reported that a growing number of adolescents perceived the drug as dangerous in comparison to previous years, with fewer seeing natural cannabis as harmful.⁷⁵ Other studies have also shown that natural cannabis is generally preferred to synthetic cannabis, with natural cannabis rated as giving greater pleasurable effects.¹

Poly-substance use with SCs, especially alcohol and cannabis, has been described in case reports and series, online surveys and toxicology retrospective reviews.^{78,80–84} Poly-drug use of other novel psychoactive substances together with SCs has been described too.^{85,86}

13.8. Routes of ingestion and frequency of dosing

Based on user reports, and on the dosage forms of products, the primary route of administration of SCs is inhalation, either by smoking the 'herbal mixture' as a joint, or by utilising a vapouriser, bong or pipe.³⁹ Both oral consumption and snorting of the compounds have also been described.⁶³

There are also reports that SCs can be ingested as an infusion, although this is rare. There are no reports of parenteral use so far.⁵

The onset of the action of SCs is usually within minutes of smoking, like cannabis, because of the instant absorption via the lungs and redistribution into the brain and other organs, within minutes of use. There is a delay of absorption following oral consumption.⁵

The length of the effect of SCs varies. It has been reported that, within 10 minutes of inhaling a 0.3 g dose, users demonstrate mild to moderate cognitive impairment, as well as changes in perception and mood. Effects gradually diminish over 6 hours.³¹ Although there are no controlled studies in humans, there are reports that the duration of action for JWH-018 is 1–2 hours and for CP 47,497 is 6–8 hours.³¹ Compared with THC, the effect seem to be shorter for JWH-018 and longer for CP-47,497 (and its C8 homologues, the effects of which last 5–6 hours).

As many of the SC products are much more potent than THC, it has been postulated that the psychoactive dose may be less than 1 mg.⁷¹ It is possible that smaller doses of many SCs may produce the same effects as larger quantities of natural cannabis.⁶⁶ Apart from high potency, some of these substances could have long half-lives, and active metabolites,⁸⁷ potentially leading to a prolonged psychoactive effect.⁴ It has been noted that users mistakenly equate the safety and dosing profile of natural cannabis to that of SC herbal products.⁴⁶

13.9. Desired and undesired effects for recreational SC use

The desired effects of SCs are similar to those of cannabis intoxication:⁷⁹ relaxation, altered consciousness, disinhibition, a state of 'being energised' and euphoria.^{79,80,88}

A number of factors have been identified as contributing to the use of SC, including easy access, affordability and the fact that it is not detected by many commonly used urine drug tests.^{6,89,90} An Australian survey of 316 SC users reported reasons for first use included curiosity (50%), legality (39%), availability (23%), recreational effects (20%), therapeutic effects (9%), non-detection in standard drug screening assays (8%) and to aid the reduction or cessation of cannabis use (5%).⁷⁸

Castellanos et al. suggested that the effects cluster in four areas: cognitive impairment; behavioural disturbances; changes in mood; and sensory and perceptual changes.⁶⁶ Although they are related to THC (found in natural cannabis), SCs are five times more likely to be associated with hallucinations.⁷⁷

In one internet survey of 168 SC adult users from a number of countries, the majority of respondents (87%) reported having a positive experience after the use of Spice, although 40% also reported negative or unwanted effects. The quantities of SC products consumed did not vary significantly between those who had negative effects and those who did not. In addition, 11% reported that multiple use of the same brand or SC product results in variable and unpredictable effects.⁷⁹

A study of 11 adolescents aged 15–19 who had used SCs found that all the subjects reported a feeling of euphoria but 9 (82%) also reported negative mood changes, 4 irritability and 3 anxiety. All 11 respondents reported difficulties with memory, 1 described auditory perceptual disorders, 5 visual perceptual disorders and 2 described paranoid thoughts.⁸⁰

Reported subjective and physiological effects of SC products can vary greatly.^{8,91} There are some reports of sedation, while other users have reported agitation, sickness, hot flushes, burning eyes, mydriasis and xerostomia (dryness in the mouth). The most commonly reported unwanted physical effects are nausea and vomiting.^{31,92} There are some reports that the frequency of hallucinations is greater than for cannabis. For example, in a survey of 168 SC users by Vandrey et al., 28% reported hallucinations following SC use, which the authors describe as greater than what would be expected for cannabis consumption.⁷⁹

Similarly, in the Australian survey of 316 SC users, more than two-thirds (68%) reported at least one side-effect during their last session of use, including decreased motor coordination (39%), fast or irregular heartbeat (33%), dissociation (22%), dizziness (20%), paranoia (18%) and psychosis (4%). Four respondents reported seeking help. More side-effects were reported by males, respondents aged 18–25 years, those who had used water pipes and those who had concurrently used alcohol.⁷⁸

One study looked at the effects of inhaled versus ingested SCs and suggested that there was more abdominal pain with the ingestion route and more dyspnoea with the

inhalation route. Both routes of exposure resulted in similar degrees of neurological changes, including agitation, drowsiness and hallucinations.⁹³

Despite indicating that the effects of SCs are similar to those of cannabis, 54% of respondents to an internet survey reported that SCs produce subjective effects unique and discernible from other licit or illicit drugs.⁷⁹ Similarly, findings from the Global Drug Survey also suggest that, when products are smoked, users are able to differentiate between the effects of natural versus synthetic cannabis.¹

Although it cannot be assumed that this can be generalised, respondents to the Global Drug Survey reported a strong preference for natural over synthetic cannabis (it was preferred by 93% of users), with natural cannabis rated as giving greater pleasurable effects while leaving the user able to function better. SCs were given significantly higher scores for self-reported hangover effects and other negative effects than were given to natural cannabis. The survey also found that natural cannabis was used more frequently and more recently than SC. Only a small minority of users seem to have fully substituted natural for synthetic cannabis.¹

13.10. Mortality

A number of deaths have been related to SC ingestion, either on their own or in combination, in analytically confirmed reports.⁹⁴⁻¹⁰² Three completed suicides following a SC intake have been described.^{94,103,104}

13.11. Acute harms

A major health problem arises from the fact that mixtures are inhomogeneous with regard to their active ingredients.³⁹ As a consequence, it is not possible for the consumer to estimate the dose at all accurately. Two cigarettes or joints prepared from the same mixture could contain significantly different amounts of the drug, and this raises the risk of harm.

13.11.1. Acute toxicity

We do not yet know how much the different SC compounds vary in effects and harm. Variability may be due to the differences between the particular SC compounds, but could also be related to individual susceptibility to the effect of the drug or the dose, or it may be multifactorial.¹⁰⁵ It has been suggested that the effects of SCs are greater in individuals with less previous exposure to cannabis, and especially those who are drug naïve.⁵⁰

Little is known about the metabolism and toxicology of SCs in humans, but the consensus is that it cannot be assumed that the risks associated with their use will be comparable to those of THC. There are concerns that they may have a greater potential to cause harm. Again, the amount and type of SC may vary, within and between products,⁶⁶ and some may contain more than intended.^{9,41,49} In addition, SCs are also full agonists, with significantly higher potency than THC.⁹

Data on 1898 exposures to SCs were reported to the US National Poison Data System between 1 January 2010 and 1 October 2010 (1353 of which were single-agent exposures). Despite concerns that the adverse effects after exposure to SCs are significantly more severe than with cannabis, the majority of cases had self-limited signs and symptoms, and received only symptomatic treatment. Most symptomatic exposures to products marketed as SCs are associated with non-life-threatening clinical effects.⁷⁶

Similarly, a study of telephone enquiries to the Swedish Poisons Information Centre graded 145 enquiries relating to SC use; 74% were graded as mild ('Poisoning Severity Score', PSS, 1) and 26% as moderate poisoning (PSS 2). No severe or lethal cases (PSS 3 or 4) were registered.¹⁰⁶ And a case series of 13 SC smokers presenting to hospital emergency departments described the severity of poisoning as 'moderate' in 10 cases and as 'minor' in 3.¹⁰⁷

13.11.2. Features of acute intoxication

At least some SCs could lead to severe or even life-threatening intoxication when taken in sufficiently larger doses, particularly so in the case of compounds that act as a full agonists at the CB1 receptor, such as HU-210, CP-55,940 or WIN-55,212-2.^{108,109}

SC toxicity is characterised by the following:^{47,50,89,110,111,112,113,114}

- cannabis-like effects;
- psychosis;
- sympathomimetic effects, including seizures, tachycardia, hypertension, diaphoresis, hyperthermia, agitation and combativeness;
- the potential for other effects, including acute damage to the kidneys.

TOXBASE® summarises the features of acute SC toxicity as shown in Box 13.1.

Box 13.1. Summary of features of acute SC toxicity

Central nervous system

Agitation, tremor, anxiety, confusion, somnolence, syncope, hallucinations, changes in perception, acute psychosis, nystagmus, convulsions, coma

Cardiac

Tachycardia, hypertension, chest pain, palpitations, ECG changes

Renal

Acute kidney damage

Muscular

Hypertonia, myoclonus, muscle jerking, myalgia

Other

Cold extremities, dry mouth, dyspnoea, mydriasis, vomiting, hypokalaemia
Loss of eyesight and speech also reported

13.11.2.1. Cognitive, psychological and psychiatric effects

A number of studies have reported cognitive changes associated with SC use, including difficulty in thinking clearly, confusion, sedation and somnolence, disorganisation, thought blocking, or nonsensical speech or alogia, memory changes/problems, amnesia, increased focus and internal unrest.^{45,79,80,90,115–119} Studies have also reported a variety of behavioural disturbances, including a change of activity from decreased activity to excitability, agitation and restlessness. Aggression has been reported in a small number of subjects.^{45,80,82,90,116,117,120,121} Psychomotor retardation and nightmares were reported in one study.^{81,115}

Studies have reported changes in mood and affect. There are reports of subjective feelings of euphoric mood associated with intoxication,^{79,80} but reports of users experiencing negative mood changes are more common and typify intoxication associated with SCs rather than cannabis use.⁶⁶ Anxiety was reported most frequently across the studies reviewed,^{36,79,80,81,115,119,120,122,123} followed by irritability.^{80,116} There are also reports of inappropriate or uncontrollable laughter,^{36,79} anger and sadness,⁸⁰ with an odd/flat affect.⁸¹ A few subjects were reported to have suicidal ideation.^{81,82,124,125} Other problems associated with SC use include paranoid thoughts, combativeness, irritability,^{80,116,123} thought disorganisation,^{118,122} anxiety and panic attacks,^{80,116,123} depression and suicidal thoughts.^{82,105,125} Sensory and perceptual changes include paranoid thinking,^{79,80,82,90,118,119,122} delusions^{81,82,90,117,123} and auditory and visual hallucinations.^{79,81,90,119–121,126}

The use of SCs has been associated with psychosis and psychosis linked to SCs has been associated with more agitation than would be expected from cannabis alone.^{36,44,123,127} It has also been argued by some that there is a greater risk of psychosis with SCs than with cannabis. This is due to a combination of factors which may include the absence of cannabidiol (CBD), a naturally occurring product in cannabis which has antipsychotic properties.¹²³ The impact of the absence of CBD has been described in relation to natural cannabis with low cannabidiol content, such as skunk.¹²⁸

There are reports of SC-associated acute transient psychosis,^{50,83,120} as well as reports that some individuals may experience psychosis that persists for weeks after the acute intoxication.^{81,122–124} There is some evidence that SCs may precipitate psychosis in vulnerable individuals,^{36,44,50,117,118,123} including those with a history of psychosis.^{81,82,117–120,123,124}

There is also some evidence of new-onset psychosis in otherwise healthy people with no history of psychosis. This will be discussed in section 13.13, on the harms of chronic SC use.

13.11.2.2. Physiological effects

13.11.2.2.1. Cardiovascular

Although they are related to THC found in natural cannabis, SCs have been reported to be two or three times more likely to be associated with sympathomimetic effects such as tachycardia and hypertension.^{44,45,129} Case reports and case series have

described a range of cardiovascular problems, including bradycardia, chest pain and cardiac ischaemia.^{36,45,126,130} Cases of myocardial infarction have been reported in healthy adolescents, although this is of limited clinical application because of the lack of analytical confirmation.¹¹⁴ There is one case report of cerebrovascular accident (CVA) associated with the use of the synthetic cannabinoid K2.¹³¹

13.11.2.2.2. Neurological

Some neurological and neuromuscular effects linked to the use of SCs have also been reported and include tremors,^{115,116,121} numbness,^{80,115,121} tingling,¹²¹ light-headedness,^{79,126} and dizziness.⁷⁹ Also reported are pallor,^{116,121} tinnitus,⁷⁹ excessive sweating,¹¹⁵ diaphoresis¹¹⁹ and unresponsiveness.⁴⁴

Out of the 1898 exposures to SCs reported to the US National Poison Data System between January 2010 and October 2010, 52 seizures were reported; the majority (43) were single episodes, although two patients developed status epilepticus. The majority of all 1898 patients had minimal symptoms but the study identified 34 cases in which there were life-threatening effects associated with exposure, and more than half of these involved seizures.⁷⁶

Although seizures or convulsions associated with the use of (natural) cannabis seem to be unusual, there are some reports associated with SC use. These include a case report which describes a patient presenting to hospital with seizures after consuming a large quantity of analytically confirmed SC powder and alcohol, and reports of generalised convulsions occurring after SC use.¹³²⁻¹³⁶

Other reported adverse effects include hypokalaemia.⁴

13.11.2.2.3. Renal and gastrointestinal

Gastrointestinal effects of SCs include nausea^{79,115} and vomiting.^{79,115,121} Acute kidney injury (AKI) associated with SC use has also been described.^{89,137,138} A case series reports on four cases of oliguric AKI, associated with SC use, in previously healthy men.¹³⁹ The use of at least one compound, XLR-11, which is (1-(5-fluoropentyl)-1H-indol-3-yl) (2,2,3,3-tetramethylcyclopropyl)methanone, has been associated with AKI.¹⁴⁰

13.11.2.2.4. Other

Xerostomia, hyperglycaemia and hypokalaemia have been described in case reports.^{31,36,45} Nystagmus, conjunctival injection* and mydriasis were reported in a small number of cases.^{31,36} The loss of eyesight and speech has been reported.¹⁰⁶

13.11.2.3. Presentations for treatment for acute intoxication

In the UK, although enquiries about SC use to TOXBASE® ranked 17th in terms of all substances of misuse, it has been noted that there was a seven-fold increase in TOXBASE® in 2012/13 accesses in comparison with the previous year.¹⁴¹

* Conjunctival injection is the forcing of a fluid into the conjunctiva; it is common in cluster headaches, making the eye appear swollen and red.

In the US, the rise in the use of SCs was mirrored by a rise in the incidence of SC-related health problems. According to the American Association of Poison Control Centers, there was a rise from 53 calls related to use of K2 in 2009, to 2500 in 2010.¹⁴² Among the 1898 exposures to SCs reported to the US National Poison Data System between January and October 2010 the age and gender of patients mirrored those of SC users (median age 20 years; 74% were male). The majority of reported exposure were acute; 3.25% were chronic, 3% were acute on chronic and 5% unknown. The majority of cases reported had self-limited signs and symptoms. Only 7.3% of symptomatic exposures were coded by a poison centre specialist as potentially life-threatening. The most frequently reported cardiac effects were tachycardia (37.7%), hypertension (8.1%), chest pain (4.7%), syncope (2.1%), hypotension (1.3%) and bradycardia (1.3%). Reported central nervous system effects included agitation/irritability (23.4%), drowsiness/lethargy (13.5%), confusion (12%), hallucinations or delusions (9.4%), dizziness (7.3%) and respiratory depression (>1%). As mentioned earlier, seizures were reported in 3.8% of cases. Overall, and although the majority of cases had minimal symptoms, the study identified 34 cases in which there were life-threatening effects associated with exposure; more than half were seizures.⁷⁶

A case report of 21 patients presenting to an emergency department between November 2011 and October 2012, with analytically confirmed SC use, presents a broadly similar picture. The most frequent clinical symptoms were tachycardia (12 cases), nausea/vomiting (11), somnolence (9) and hyperglycaemia (9). Less frequent symptoms were hypokalaemia (4), syncope (4), dyspnoea (3), aggressive behaviour (3), amnesia (2), diplopia (2) and seizures (2). Acute psychosis in one individual lasted for five days. One patient with diabetes mellitus developed pronounced hyperglycaemia.⁵¹

A retrospective review of cases presenting to an emergency department during a three-month period, with chief complaint of SC use before arrival, reported that most such patients can be discharged after a period of observation (an average of 2.8 hours).¹⁰⁵

An Australian study of patients hospitalised in an acute psychiatric ward for problems associated with SC use from January to April 2013 found that they represented 13% of all admissions on the ward (17 patients with 21 admissions). For four patients, this was their first hospitalisation and these patients presented with new psychotic symptoms; 9 had a recurrence of a pre-existing disorders. Symptoms included psychotic symptoms, affective symptoms, disturbances and/or intense suicidal ideation/behaviour. The mean length of admission was 8.5 days, with significantly longer duration for those presenting with psychotic symptoms (13.1 days versus 4.4 days).¹⁴³

13.11.3. Acute withdrawal

For withdrawal, see section 3.14.

13.12. Management of acute harms

13.12.1. Identification and assessment

SCs cannot be detected by the screening tests for phytocannabinoid delta-9-tetrahydrocannabinol (THC). Although laboratory techniques have been developed to detect some compounds,^{92,144–146} there are currently no widely available tests. In addition, more than one SC can be found within the same mixture or product, and the regular appearance of new compounds poses another challenge.¹⁵

It has therefore been recommended that clinicians need to rely on clinical skills to detect SC use. This includes specifically asking about SC, being aware of the physiological effects, such as conjunctival injection, and having a high index of suspicion in the context of unexplained deterioration despite a negative urine screen.¹²²

13.12.2. Clinical management of acute toxicity

Symptoms of SC intoxication may be self-limiting and resolve spontaneously.^{66,76} Case reports suggest that, in emergency departments, hydration and monitoring may be enough for patients with mild to moderate intoxication.^{45,116,118,120,147} Benzodiazepines may be of benefit to patients who present with symptoms of anxiety, panic and agitation.^{45,82,90,116} Antipsychotic medication may be indicated for some patients, especially those who present with agitation or aggression, when the patient has a history of psychotic disorders, and when the psychotic symptoms do not remit spontaneously or with supportive care.^{81,82,123,124}

The management of SC toxicity is symptomatic and supportive, as no antidotes exist.⁸⁹ Supportive treatment is dependent on a patient's specific presentation. Only a few specific interventions have been described. Intravenous benzodiazepines have been reported for the management of seizures, and monitored observation for cases of SC-related psychosis.⁴⁴

The 2010 nine-month study of the National Poison Data System that reported 1898 SC exposures found that the majority had self-limited signs and symptoms and received only symptomatic treatment. The study also reported that the most common intervention for patients with a single-agent exposure was the administration of

For up-to-date guidance on the management of acute toxicity related to synthetic cannabinoids, 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/S-Products/Synthetic-Cannabinoid-Receptor-Agonists/>

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

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

intravenous fluids (25.3%), followed by benzodiazepine (16%), supplemental oxygen (5.8%) and anti-emetics (4.7%). The duration of clinical effect was recorded in 907 cases. Out of those, clinical effect lasted less than 8 hours in 78.4% of cases, between 8 and 24 hours in 16.6% and more than 24 hours in 4.9% of cases.⁷⁶

13.13. Harms associated with chronic use

13.13.1. Dependence

In an internet survey of 168 SC users, a subset of respondents met DMS-IV criteria for abuse (37%) and dependence (12%). The most commonly endorsed abuse criterion was use (of 'Spice') in a hazardous situation (27%). The most commonly reported dependence criteria were being unable to cut down or stop SC use (38%), experiencing symptoms of tolerance (36%), using for longer periods than originally intended (22%) and interference with other activities (18%). Reported withdrawal symptoms following cessation of SC use were rare, and more prevalent among frequent users. The most commonly reported withdrawal effects were headaches (15%), anxiety/nervousness (15%), coughing (15%), insomnia/sleep disturbance (14%), anger/irritability (13%), impatience (11%), difficulty concentrating (9%), restlessness (9%), nausea (7%) and depression (6%).⁷⁹

Some reports have described withdrawal symptoms following prolonged use,^{115,122} and preliminary reports suggest that the chronic use of SCs may be associated with tolerance.⁶⁶ For example, Zimmerman et al. presented a case report of an individual who began inhaling 1 g of SC daily, which, due to tolerance, increased rapidly to 3 g daily.¹¹⁵

SCs may have a higher addictive potential than cannabis, due to the quicker development of tolerance.^{115,148} A case report of an individual using for eight months mentions a potential withdrawal syndrome, with drug craving, nocturnal nightmares, profuse diaphoresis, nausea, tremor, hypertension and tachycardia.¹¹⁵

13.13.2. Other harms of chronic use

The long-term effects of the use of SCs are unknown. Although no experimental data are available, it is expected that these SCs, as lipophilic compounds, have high volumes of distribution. It is therefore likely that chronic use of them can lead to accumulation of the substances themselves and/or their metabolites in fat-containing compartments in the body.⁵ There is also speculation that some of these products, and particularly the aminoalkylindoles carrying a naphthyl moiety, may have carcinogenic potential.¹⁴⁹

There may also be gastrointestinal effects. One case report suggests that frequent habitual smoking of SCs can cause cannabinoid hyperemesis syndrome, which is mediated by cannabinoid receptors.¹⁵⁰ Xerostomia^{31,79} has been reported, as well as acidosis.^{31,36,45} There is one case report of pulmonary infiltrates associated with chronic SC use.¹⁵¹

Psychosis has also been reported among frequent users. One study describes new-onset psychosis in otherwise healthy young men.⁸¹ A case series reported on 10 patients admitted in the context of SC use, none of whom had a history of psychosis. All of the patients reported smoking SC on more than one occasion (ranging from four uses over a three-week period to daily use for a year and a half). The onset of psychotic symptoms varied from after the fourth use to after more than a year of use.

Presentations were characterised by paranoid delusions, ideas of reference and a disorganised, confused mental state. It was noted that a distinct, though waxing and waning, stuporous appearance was often present for weeks after last SC use. The affect of patients was described as generally flat, with most patients reporting significant depressive symptoms and 40% describing suicidal ideation. Hospitalisation generally lasted 6–10 days. Although psychotic symptoms did remit in most patients, 30% were noted to have persistent psychosis at 8-month follow-up.⁸¹

Three patients who presented to an emergency department with persistent psychosis, which did not resolve within 24–48 hours, required at least two weeks of hospitalisation. Two of the patients were treated with haloperidol and one with risperidone and, although the patients demonstrated improvements, none had their symptoms resolve completely and medication was prescribed upon discharge.⁸²

13.14. Management of harms related to chronic use

13.14.1. Clinical management of dependence and chronic use

The Global Drug Survey, carried out in 2011, investigated demand for treatment by 2513 SC users, including 980 individuals who had used it in the past 12 months. It found that 7% reported that they wanted to use less SC in the coming year and 1.8% reported that they would like help to reduce or stop their use of SC. Among those who had used SC in the past month, those who reported they would like to use less SC were those who were using it on significantly more days (median 6 days in past month) than others who also had used it in the past month (median 2 days). Similarly, those who reported use in the past month and also reported that they would like help to reduce or stop, used on significantly more days (median 27 days in last 30 days) than other 'last month' users (median 2 days).

13.14.1.1. Psychosocial interventions

See Chapter 2 on psychosocial interventions.

13.14.1.2. Pharmacological interventions

Psychopathological disturbances related to SC misuse may be managed with benzodiazepines and antipsychotics, with antidepressants being administered in case of concurrent depression.¹¹⁰ If faced with a psychotic disorder associated with chronic SC

misuse, it can be argued that the use of second-generation antipsychotics (SGAs) may be a rational approach. Indeed, with respect to first-generation antipsychotic, SGAs present with lower risk of increase in cravings¹⁵² and a more significant antagonism at 5-HT_{2A} receptors.¹⁵³ In cases of acute SC intoxication, it has been suggested that an to perform an electrocardiogram should be performed, because misusers may present with vomiting and associated hypokalaemia.¹⁵⁴

13.14.1.3. Aftercare and support

See Chapter 2 on psychosocial interventions.

13.15. Harm reduction and public safety

A study focusing on analytical results and signs of impairment documented by the police or the physicians who had taken the blood sample from suspects driving under the influence of SC reported that the use of SCs can lead to impairment similar to typical performance deficits caused by cannabis use. This includes the centrally sedating effects of SCs and impairment of the fine motor skills necessary for keeping the vehicle on track.¹⁵⁵

A study of drivers found that officers or drug recognition experts (DREs) reported that drivers suspected of using SCs were more confused and disoriented, and were involved in more motor vehicle crashes than were those suspected of using natural cannabis. DREs documented significantly more confusion (6/10) or disorientation (5/10) in the 'Spice' group versus those in the marijuana group (0/25). A significantly larger proportion of marijuana users had tremors (25/25) than those in the 'Spice' group (8/13).¹⁵⁶

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Appendix

Interactions of 'club drugs' with HIV medication

There are concerns about the effects of drugs used by HIV-positive individuals on antiretroviral medications because of issues relating to adherence as well as serious drug interactions (Table A1).^{1,2} Case studies have been published on severe problems caused by drug interactions³ and even death.⁴ Studies have also shown the immunosuppressant effect of substances.⁵⁻⁷ Recreational drug use has consistently been linked to lower rates of adherence to HIV medication,^{8,9} with especially low levels among poly-drug users.¹⁰ There is also some evidence of a dose-response relationship between the use of certain drugs and medication adherence which suggests that bingeing or heavy use may have a particularly detrimental effect on medication adherence,¹¹ although this needs to be investigated further.

A major concern is the interaction of GHB/GBL with antiviral medications for HIV-positive patients.¹ Romanelli et al. say that HIV-positive patients who use GHB/GBL must be warned about the potential dangers of a drug interaction with protease inhibitors (especially ritonavir). This is because clearance of GHB is mediated partially by systemic oxidation and partially by first-pass metabolism via the CYP450 system. In the case report described by Romanelli et al. the inhibition of the CYP450 system by ritonavir might explain this patient's exaggerated response to the GHB. It illustrates the potential adverse effects that may be seen when club drugs such as MDMA and GHB are co-administered with antiretroviral, particularly protease inhibitors with CYP450-inhibitive properties² and possibly efavirenz.¹

It has also been recommended that GHB/GBL be used with caution by HIV-positive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (e.g. toxoplasmosis, cryptococcal meningitis) as GHB/GBL may precipitate seizure-like activity. GHB/GBL use may also cause severe nausea, vomiting and gastrointestinal-tract irritation, which will adversely affect absorption of antiretroviral medication.² There are also concerns about compliance with HIV medication while intoxicated, especially during prolonged binges.²

The use of ketamine raises general issues of adherence to antiretroviral regimens and cardiovascular effects of the drug may be deleterious among patients with underlying heart disease or lipid abnormalities. As a substrate of the CYP450 system (specifically 3A4 and 2B6), ketamine may interact with certain antiretroviral medications, particularly protease inhibitors and their boosters (ritonavir and cobicistat) as they are characterised by CYP3A4- and CYP2B6-inhibitive properties.² On the other hand, non-nucleoside reverse-transcriptase inhibitors (NNRTIs) like efavirenz and nevirapine are inducers of CYP3A4 and 2B6 and lead to a decrease in ketamic effects. This may lead individual to inject ketamine to avoid first-pass metabolism and maintained the desired effects.

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Table A1. Potential for drug-drug interactions (DDI) between the most commonly used antiretroviral (ARV) agents and club drugs/psychoactive substances (CD/PS)

Antiretroviral drug	GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
CD/PS metabolism	First pass metabolism by CYP2D6 and CYP3A4; oxidation to succinic acid	First-pass metabolism by CYP3A4 (major), CYP2B6 (minor), and CYP2C9 (minor)	Nitrous oxide (N2O) is not metabolized in human tissues but is reductively metabolized by rat and human intestinal bacteria to molecular nitrogen (N2). Therefore the potential for DDI with ARVs is very low	First pass metabolism by CYP2D6	Potential involvement of CYP2D6 and CYP3A4 in mephedrone first pass metabolism; involvement of UDP-glucuronyltransferase as elimination pathways	First pass metabolism by CYP2D6 and CYP3A4 (minor)
Efavirenz	Potential DDI mechanism Efavirenz may reduce GHB systemic exposure by CYP3A4 induction	Efavirenz may reduce ketamine systemic exposure by CYP3A4 and CYP2B6 induction (but may also inhibit CYP2C9 and lead to mild increases in ketamine)	Unlikely to interact with ARVs	None	Efavirenz may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyltransferase induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
Hypothetical DDI outcome	Reduced effect of GBL/GBL	Reduced effect of ketamine	None	None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect
Comments	Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to interact	Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant

Antiretroviral drug	GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
Nevirapine	Potential DDI mechanism Nevirapine may reduce GHB systemic exposure by CYP3A4 induction	Nevirapine may reduce ketamine systemic exposure by CYP3A4 and CYP2B6 induction		None	Nevirapine may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyl-transferases induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
	Hypothetical DDI outcome Reduced effect of GBL/GHB	Reduced effect of ketamine		None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect
	Comments Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism		Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant
Etravirine	Potential DDI mechanism Etravirine may reduce GHB systemic exposure by CYP3A4 induction	Etravirine may reduce ketamine systemic exposure by CYP3A4 induction (but may also inhibit CYP2C9 and lead to mild increases in ketamine)		None	Etravirine may reduce mephedrone systemic exposure by CYP3A4 and UDP-glucuronyl-transferases induction	None or very mild reduction in MDMA systemic exposure by CYP3A4 induction
	Hypothetical DDI outcome Reduced effect of GBL/GHB	Potential reduced effect of ketamine (probably not as much as with efavirenz and nevirapine)		None	Reduced effect of mephedrone	Potential minor reduction of MDMA effect

Antiretroviral drug	Comments	GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
		Unlikely to be significant	Potential for ketamine to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism - impact of CYP2C9 inhibition versus CYP3A4 induction is unknown)		Unlikely to interact	Potential for mephedrone to be less effective and for subjects to inject it to increase effect and avoid first pass metabolism	Unlikely to be significant
Atazanvir/ritonavir	Potential DDI mechanism	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in GBL/ GHB exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized	Inhibition of CYP3A4, CYP2B6 and CYP2C9 by ritonavir may lead to increases in ketamine exposure		Atazanvir and low dose ritonavir are unlikely to affect CYP2D6 metabolism. However, CYP2D6 slow metabolizers, alternative metabolic routes (i.e. CYP3A4) may be utilized and the activity these is inhibited by atazanvir and ritonavir	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in mephedrone exposure; the role of ritonavir induction on UDP-glucuronyltransferases (mephedrone metabolite glucuronidation) remains unclear and this is counterbalanced by atazanvir inhibition of this metabolic pathway	Inhibition of CYP3A4 by atazanvir and especially ritonavir may lead to increases in mephedrone exposure; the role of ritonavir induction on UDP-glucuronyltransferases (mephedrone metabolite glucuronidation) remains unclear where alternative metabolic routes (i.e. CYP3A4) may be utilized
	Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS		Potential increased systemic exposure and toxicity of the CD/PS in CYP2D6 slow metabolizers	Increased systemic exposure and toxicity of the CD/PS	Potential increased systemic exposure and toxicity of the CD/PS

Antiretroviral drug	GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamine	Mephedrone	MDMA
Comments	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with GBL/GBH	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with ketamine		Clinical significance unclear	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with MDMA
Darunavir/ritonavir	Potential DDI mechanism Inhibition of CYP3A4 by ritonavir may lead to increases in GBL/GBH exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized	Inhibition of CYP3A4, CYP2B6 and CYP2C9 by ritonavir may lead to increases in ketamine exposure		Low dose ritonavir is unlikely to affect CYP2D6 metabolism. However, CYP2D6 slow metabolizers, alternative metabolic routes (i.e. CYP3A4) may be utilized and the activity these is inhibited ritonavir	Inhibition of CYP3A4 by ritonavir may lead to increases in mephedrone exposure; the role of ritonavir induction on UDP-glucuronyltransferases (mephedrone metabolite glucuronidation) remains unclear	Inhibition of CYP3A4 by ritonavir may lead to increases in MDMA exposure, especially in CYP2D6 slow metabolizers, where alternative metabolic routes (i.e. CYP3A4) may be utilized
Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS		Potential increased systemic exposure and toxicity of the CD/PS in CYP2D6 slow metabolizers	Increased systemic exposure and toxicity of the CD/PS	Potential increased systemic exposure and toxicity of the CD/PS

Antiretroviral drug	GHB/GBL	Ketamine (and methoxetamine)	Nitrous oxide	Metamphetamines	Mephedrone	MDMA
Comments	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with GBL/GHB	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with ketamine		Clinical significance unclear	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on ritonavir boosted protease inhibitors should be warned of the potential for DDI with MDMA
Elvitegravir/cobicistat	Potential DDI mechanism Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in GBL/GHB exposure	Inhibition of CYP3A4 and CYP2B6 (mild) by cobicistat may lead to increases in ketamine exposure		Inhibition of CYP2D6 by cobicistat may lead to increases in methamphetamine exposure	Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in mephedrone exposure	Inhibition of CYP2D6 and CYP3A4 by cobicistat may lead to increases in MDMA exposure
Hypothetical DDI outcome	Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS		Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS	Increased systemic exposure and toxicity of the CD/PS
Comments	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with GBL/GHB	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with ketamine		Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with methamphetamine	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with mephedrone	Although not clinically proven, individuals on cobicistat** should be warned of the potential for DDI with MDMA

Note: The nucleoside reverse transcriptase inhibitor (NRTI) class, the non-NRTI rilpivirine, the integrase inhibitors raltegravir and dolutegravir, and the CCR5 receptor antagonist maraviroc have not been included in the table because of the low potential for drug-drug interactions with club drugs/psychoactive substances.

**Cobicistat can be used as a booster for the integrase inhibitor elvitegravir and for the protease inhibitors atazanavir and darunavir