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Drugs of abuse

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Abstract

Toxicity related to drug misuse is a common reason for hospital presentation. The recent emergence of substantial numbers of novel psychoactive substances has made management more challenging because the exact constituents of branded products containing these may not be known and, when it is, the information available about clinical features and the management of toxicity is limited. Drugs of misuse are usefully classified by their primary clinical effects. Depressants including opioids, benzodiazepines and gamma-hydroxybutyrate cause sedation with depressed tendon reflexes. Commonly encountered stimulants are cocaine, amphetamines, methylenedioxymethamphetamine ('ecstasy'), cathinones (e.g. mephedrone), piperazines, piperidines and NBOMe compounds. Typical effects include tachycardia, hypertension, mydriasis, agitation and seizures. Examples of hallucinogens are synthetic cannabinoid receptor agonists, tryptamines (e.g. alpha methyltryptamine) and ergolines (e.g. lysergic acid diethylamide); some of these also have stimulant effects. The arylcyclohexamines ketamine and methoxetamine have dissociative actions. As well managing acute toxicity, blood-borne infections, sepsis and thrombosis arising from parenteral drug use should be treated. Longer term interventions are also needed to address drug use and the social and mental health issues that commonly co-exist.

Keywords Cannabis; cocaine; drugs of abuse; gamma-hydroxybutyrate; ketamine; methylamphetamine; methylenedioxymethamphetamine; opioids; piperazines; toxicity

Introduction

Drug misuse is important because of its prevalence and associated clinical and societal effects. It may cause acute toxicity or complications associated with administration methods such as blood-borne infections, sepsis and thrombosis after parenteral administration. There are also risks associated with intoxication, including accidents, sexually transmitted infections and unwanted pregnancies. Illicit drug use may compromise employment, education and personal relationships, culminating in financial hardship, homelessness and criminal behaviour such as theft, prostitution, drug dealing and violence. This article describes the acute toxicity that may occur after recreational drug use.

A recent important change in the pattern of illicit drug use is the emergence of novel psychoactive substances (NPS), sometimes erroneously referred to as 'legal highs' or 'research chemicals'.[1] These are psychoactive drugs that have recently become available as substances of misuse. They are not prohibited by United Nations Drug Conventions but may pose a public health threat comparable to that posed by substances that are prohibited.[2] NPS are often similar to traditional drugs of misuse, but with alterations made to the chemical structure so that the new compound is no longer captured by control of drugs legislation. Examples are shown in Table 1, alongside corresponding traditional drugs. The rapid emergence of substantial numbers of NPS continues to present a significant challenge to health services, not least because of the difficulty in identifying the chemicals involved in branded products and lack of information about clinical effects and appropriate management.

While traditional drugs of misuse have generally been obtained from street-level dealers, newer drugs that are often not initially subject to legal controls may be obtained from head shops and especially the internet. There has also been increasing recognition of the importance of prescription medicine abuse, including diversion and illicit supply.

Epidemiology

According to the 2012/13 crime survey for England and Wales, 8.2% of the adult (16–59 years) population reported illicit drug use in the last year, including 2.8% reporting use of a class A drug. The most common substances involved were cannabis (6.4%), nitrous oxide (2.0%), powder cocaine (1.9%), ecstasy (1.3%) and amyl nitrite (0.8%). A higher proportion (16.3%) of younger adults (aged 16–24 years) reported use of an illicit drug in the last year. Overall, however, illicit drug use has been declining in the UK over the last decade for many substances.[3] In the USA, 15.9% of the population over 12 years of age reported illicit drug use in the last year, including cannabis (12.6%) and cocaine (1.6%), while in the European Union the proportions o of those aged 15–34 years using a recreational drug in the last year were 11.7% for cannabis and 1.9% for cocaine, with substantial differences between countries.[4,5] While many people may experiment with illicit drugs, only a minority will develop addiction; the most problematic substances in this respect are opioids, cocaine and gamma-hydroxybutyrate (GHB).

Acute toxicity after recreational drug use is a common reason for hospital presentation, with 13,917 admissions to hospitals in England with a primary diagnosis of illicit drug poisoning in the 2013/14 reporting year, a 77% increase since 2003/04.[6] Many more illicit drug users are discharged from emergency departments without hospital admission. There were 2955 deaths registered as due to drug poisoning in England and Wales in 2013, with 1957 associated with drug misuse.[7] For the latter, heroin/morphine, methadone and other opioids were most commonly implicated and a recent change has been the increasing the numbers of deaths associated with tramadol (Figure 1).

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Classification for drugs of misuse

Primary effect	Chemical group	Examples	
		Traditional	**Novel**
Depressants	Opioids	Heroin Morphine Methadone	Desomorphine MT-45 AH-7921
	Benzodiazepines	Diazepam Temazepam	Etizolam Phenazepam
	Benzodiazepine-like	Zopiclone Zolpidem	
	Barbiturates		
	GHB/related	GHB GBL 1,4-Butanediol	
Stimulants	Cocaine	Cocaine	Dimethocaine Flourotrapococaine
	Amphetamines	Amphetamine MDMA Methylamphetamine PMA, PMMA Methiopropamine	
	Cathinones	Khat	Mephedrone Methylone MDPV α-pyrrolidinovalerophenone (α-PVP)
	Piperazines	1-Benzylpiperazine	Trifluoromethylphenylpiperazine (TFMPP)
	Benzofurans and difurans		5-(2-aminopropyl)benzofuran (5-APB) Bromo-DragonFLY
	Aminoindans		2-Aminoindane (2-AI) 5-Iodo-2-aminoindane (5-IAI) 5,6-Methylenedioxy-2-aminoindane (MDAI)
	D-Series	Dimethoxybromoamphetamine (*DOB*) Dimethoxymethylamphetamine (DOM)	
	2C-series	2C-B, 2C-E	
	NBOMe compounds		25I-NBOMe
	Piperidines	Methylphenidate	Desoxypipradrol Diphenylprolinol Ethylphenidate
	Thiophenes		Methiopropamine
Hallucinogens	Cannabinoids	Cannabis	JWH-018, AM-2201, AM-1220, RCS4, UR-144, XLR-11, APICA, STS-135, BB-22, LY2183240

(*continued on next page*)

Table 1 (*continued*)

Primary effect	Chemical group	Examples	
		Traditional	**Novel**
	Arylcyclohexamines	Ketamine Phencyclidine (PCP)	Methoxetamine
	Ergolines	lysergic acid diethylamide (LSD)	
	Tryptamines	dimethyltryptamine (DMT) 4-Hydroxy,N,N-dimethyltryptamine (psilocin)	AMT
Volatile substances	Anaesthetics	Nitrous oxide	
	Solvents	Toluene	
	Volatile nitrites	Amyl nitrite Isopropyl nitrite	

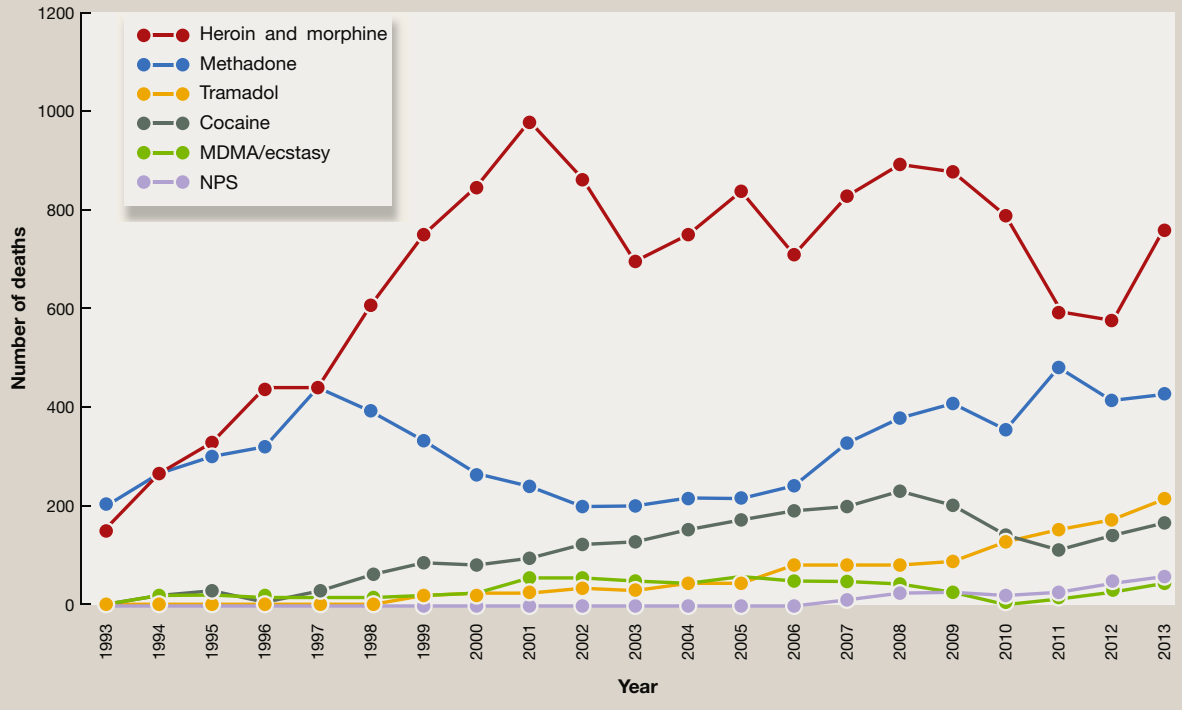
AMT, alpha methyltryptamine; GBL, gamma-butyrolactone; GHB, gamma-hydroxybutyrate; MDMA, 3,4 methylenedioxymethamphetamine; MDPV, methylenedioxypyrovalerone; PMA, paramethoxyamphetamine; PMMA, paramethoxy-N-methylamphetamine.

Table 1

Classification

Drugs of misuse can be classified according to their structures, pharmacology and primary effects (Table 1). The classification used here categorizes drugs according to their anticipated major clinical effects ('toxidrome') into depressants, stimulants, hallucinogens and volatile substances. Note, however, that several drugs have actions in more than one of these categories. This is

Numbers of deaths where selected substances were mentioned on the death certificate, England and Wales, 1993–2013[7]



Examples of potential drugs of misuse and their classification under UK Misuse of Drugs legislation (For abbreviations see Table 1)

Schedule[a]	Class[b]	A	B	C
		Most harmful	**Intermediate**	**Least harmful**
1	No recognized medical use. Possession prohibited without Home office licence	Ecstasy LSD Methamphetamine NBOMe compounds	Cannabis Methoxetamine	Khat
2	Recognized medical use. Subject to special prescription and safe custody requirements and the need to maintain registers	Morphine Diamorphine Methadone Cocaine Benzofuran compounds	Amphetamines Methylamphetamine Dihydrocodeine Codeine Ketamine	
3	Subject to special prescription, although not safe custody requirements.		Barbiturates	Temazepam Flunitrazepam Tramadol
4 (Part 1)	No prescription or safe custody requirements.			Other benzodiazepines Zolpidem Zopiclone Zaleplon GHB Ketamine
4 (Part 2)	No prescription or safe custody requirements.			Anabolic steroids
5	Preparations that, because of their strength, are exempt from most of the controlled drug requirements.			Cough medicines, antidiarrhoeals

[a] Misuse of Drugs Regulations, 2001 (and subsequent amendments).
[b] Misuse of Drugs Act, 1971.

Table 2

the most useful classification for clinicians because the substance involved may not be known by the user, especially if NPS are involved and the clinical features observed determine appropriate management.

Legal classification varies according to jurisdiction and changes with time; a summary of current UK legislation is shown in Table 2. Penalties are greatest for class A drugs and higher for supplying controlled drugs than for possession.

Clinical assessment

Those presenting with suspected toxicity relating to illicit drug use require careful clinical assessment. Where possible, a history of the substances taken should be obtained, including apparent dose, route used and timing of exposure, as well as adverse effects experienced. Use of 'street' names for drugs can cause difficulty as the same name may refer to more than one substance. Also, users of branded products may be unaware of their chemical composition, which may not be as advertised on packaging and may change with time.

Drug misuse commonly involves more than one substance, and alcohol use may also complicate the clinical picture. Adverse effects may also occur because of adulterants or 'cutting' agents, which may result from unintentional contamination (e.g. lead, strychnine) or use as bulking agents (e.g. talc, lactose, paracetamol), to mimic the taste or effects of the drug being sold (e.g. caffeine, procaine, paracetamol, quinine) or to enhance or prolong the desired effects (e.g. levamisole).

Hospital or primary care records should be checked for information about past history, currently prescribed medicines and blood-borne virus status. In unconscious or uncooperative patients, clues to the diagnosis may include needle tracks or the presence of drug paraphernalia at the scene or in the patient's belongings.

Recreational drugs are commonly used in acts of self-harm and there is a high prevalence of mental health disorders in recreational drug users. A careful history is therefore needed to identify these so that appropriate assessment and management can be performed.

Depressants

The major risks from use of drugs with depressant effects are respiratory depression and airway compromise, progressing to aspiration pneumonia and respiratory arrest. Pressure damage to skin and muscles may result in blistering, pressure sores or rhabdomyolysis.

Appropriate supportive care is essential, including adequate airway management and oxygenation together with frequent monitoring of pulse, blood pressure, oxygen saturation and conscious level. Arterial blood gases should be checked when respiratory depression is suspected. When specific antidotes are unavailable or ineffective, endotracheal intubation and intermittent positive-pressure ventilation may be needed in more severely affected patients, together with appropriate bladder care for patients with prolonged coma.

Head trauma may have occurred in patients presenting with intoxication, and appropriate imaging is needed to exclude serious intracranial pathology in those patients where there is evidence of head injury, the cause of unconsciousness is uncertain or there are localizing neurological signs.

Opioids

Opium has been smoked for centuries, and the semi-synthetic opioid heroin (diamorphine), usually smoked or injected intravenously, has been prevalent in recent decades. Others commonly misused, usually by the oral route, include methadone, oxycodone, dihydrocodeine and tramadol, with diversion of prescription medicines a major source. All these drugs are full agonists at opioid receptors; buprenorphine is a partial agonist. Novel opioids (Table 1) are currently rarely encountered in the UK but have caused serious toxicity in other countries. Opioids provide euphoric effects but are addictive.

Characteristic clinical features of opioid intoxication are shown in Table 3. Drowsiness may progress to respiratory depression and respiratory arrest. Cardiovascular collapse, rhabdomyolysis, renal failure, aspiration pneumonia and non-cardiac pulmonary oedema may also occur. Life-threatening intoxication is more common after use of high doses, purer drug product or a period of abstinence (e.g. after a time in prison), as well as with co-ingestion of sedatives such as alcohol or benzodiazepines.

In addition to typical opioid effects, methadone also causes dose-related cardiac repolarization delay, resulting in prolongation of the QT interval on the electrocardiogram (ECG) and the polymorphic ventricular tachycardia torsades de pointes.[8] Repolarization delay has also been reported with oxycodone.[9]

Opioid effects can be reversed rapidly by the competitive antagonist naloxone, preferably administered intravenously. Access via this route, however, may be difficult in intravenous drug users; the intramuscular and intratracheal routes are also effective but effects may be delayed. The aim of treatment is to restore an adequate airway and ventilation, rather than completely reverse the opioid effects. Excessive dosing may provoke withdrawal symptoms, sometimes accompanied by aggressive behaviour. This may result in self-discharge against medical advice, but there is a risk of recurrent toxicity, as naloxone is much shorter acting than almost all abused opioids. Care is also needed to avoid excessive doses of naloxone in those with opioid intoxication in the context of pain control, for example in those receiving palliative care, because of the severe breakthrough pain that may ensue.

Benzodiazepines and related compounds

These drugs are widely available via diversion of prescription medicines and increasingly via internet sales (e.g. etizolam) and are commonly misused. They act by binding to a specific benzodiazepine receptor on the gamma-aminobutyric acid (GABA) complex in the central nervous system, augmenting the increase in chloride permeability induced by GABA and reducing neuronal excitability. Clinical effects include drowsiness, unsteadiness, nystagmus and slurred speech, progressing to coma associated with reduced tendon reflexes. Life-threatening toxicity is uncommon from pure benzodiazepine intoxication, unless there are underlying neurological or respiratory disease or if alcohol or other sedative agents have been co-ingested.

Management is largely supportive. The specific benzodiazepine antagonist flumazenil can increase level of consciousness, but this may be at the expense of adverse effects including convulsions, especially in those with a history of seizures, if proconvulsants (e.g. tricyclic antidepressants) have also been taken or in the context of acute withdrawal. Use of small doses, titrating up as needed, may be appropriate in the absence of these contraindications, if the patient would otherwise require intubation and ventilation. Flumazenil has a short half-life and careful monitoring is needed, with administration of further doses as needed.

Gamma-hydroxybutyrate and related compounds

GHB is a GABA agonist originally developed as an anaesthetic agent. gamma-butyrolactone (GBL) and 1,4-butanediol are GHB precursors and have similar actions.

Early features of toxicity include headache, agitation, ataxia, hypersalivation and gastrointestinal disturbances, progressing to confusion and agitation with drowsiness, urinary incontinence, tremor and myoclonus. Coma with reduced tendon reflexes and respiratory depression may develop, especially if alcohol or other sedatives are involved. Other features include bradycardia, hypotension, metabolic acidosis, hypernatraemia, hypokalaemia and hyperglycaemia. Abrupt recovery from coma is characteristic. Chronic use can lead to dependence, with rapid escalation of dose requirements. A GHB withdrawal syndrome may occur after cessation of regular use. Features may be prolonged and include initial insomnia, tremor, confusion and vomiting progressing to agitation associated with tachycardia, hypertension, hallucinations, myoclonus and seizures.

Management of GHB intoxication is largely supportive, including appropriate airway management and support of respiration as needed. There is no specific antidote; extreme agitation or convulsions may require a benzodiazepine, although this may worsen respiratory depression. Atropine may reverse bradycardias and intravenous fluids may prevent renal injury if there is evidence of rhabdomyolysis.

Clinical features of toxicity with selected drug groups (see Table 1 for examples)

Group		Depressants		Stimulants		Hallucinogens	
Subgroup	**Opioids**	**Benzodiazepines**	**GHB/related**		**SCRAs**	**Arylcyclohexamines**	**Tryptamines[a]**
General	Hypothermia Needle tracks Piloerection	Hypothermia	Hypothermia Urinary incontinence Hypersalivation	Euphoria Sweating Hyperthermia Anorexia	Dry mouth	Hyperthermia	Hyperthermia
Neurological	Meiosis Sedation Confusion Hallucinations Coma	Sedation Confusion Hallucinations Ataxia Coma	Headache, sedation Confusion, amnesia, Coma Seizures	Mydriasis Agitation/psychosis Confusion Trismus[b] Seizures[c]	Agitation Panic Confusion Hallucinations Hypertonia Myoclonus Seizures Somnolence	Sedation Blurred vision Ataxia Agitation/psychosis Seizures	Mydriasis Hallucinations Seizures Myoclonus
CVS	Hypotension Bradycardia (relative)	Hypotension	Bradyarrhythmia, Hypotension	Tachycardia Hypertension, Arrhythmias[c]	Tachycardia Chest pain ECG changes	Hypertension Tachycardia	Hypertension Tachycardia
Respiratory	Respiratory depression	Respiratory depression	Respiratory depression		Dyspnoea	Respiratory depression	
Abdominal	Nausea/vomiting, Ileus		Nausea/vomiting		Nausea/vomiting	Nausea/vomiting	
Muscle	Ataxia Reduced muscle tone/reflexes Rhabdomyolysis	Ataxia Reduced muscle tone/reflexes	Tremor, Myoclonus Reduced muscle tone/reflexes	Tremor Rhabdomyolysis			
Laboratory			Metabolic acidosis, Hypokalaemia, hyperglycaemia, hypernatraemia	Hyponatraemia[b] Metabolic acidosis[c]	Hypokalaemia Renal dysfunction		Creatine kinase increased

(*continued on next page*)

Table 3 (*continued*)

Group		Depressants		Stimulants		Hallucinogens	
Subgroup	**Opioids**	**Benzodiazepines**	**GHB/related**		**SCRAs**	**Arylcyclohexamines**	**Tryptamines**[a]
Complications	Respiratory failure Aspiration pneumonia Pulmonary oedema	Respiratory failure Aspiration pneumonia	Respiratory failure Aspiration pneumonia	Circulatory collapse, Pulmonary oedema[c] Myocardial ischaemia/infarction[c] Intracerebral haemorrhage Cerebral infarction[c,d] Disseminated intravascular coagulation and multi-organ failure[b]		Chronic cystitis	

[a] Also prominent stimulant effects.
[b] Especially MDMA.
[c] Especially cocaine.
[d] Especially amphetamines.

Table 3

GHB withdrawal can be difficult to manage. Benzodiazepines (GABA-A receptor agonists) can be used but very high doses are often needed. Regular baclofen (GABA-B receptor agonist) therapy may also be beneficial.

Stimulants

These drugs act by enhancing the central release and inhibiting the reuptake and metabolism of catecholamines and serotonin, resulting in increased concentrations of norepinephrine, epinephrine, dopamine and/or serotonin within the synaptic cleft. This may produce stimulation, entactogenic effects such as relaxation, euphoria and increased sociability, or hallucinations. The balance of these effects and the toxicity that may occur depend on the pattern of neurotransmitter effects. Clinical features of the stimulant toxidrome are shown in Table 3.

Cocaine

Powder cocaine, the water-soluble hydrochloride salt, is the most common form used and is generally administered by nasal insufflation ('snorting'). 'Crack' cocaine is the insoluble free base that, unlike the hydrochloride salt, vaporizes at high temperature and can be smoked, giving a more rapid and intense effect.

Stimulant effects occur rapidly after use (Table 3) and cardiovascular effects are common, especially chest pain, which in about 6% of cases results from myocardial ischaemia or infarction due coronary artery spasm or thrombosis, coupled with increased myocardial oxygen demand resulting from hypertension, peripheral vasoconstriction and tachycardia. Aortic or coronary dissection, intracerebral or subarachnoid haemorrhage and cerebral infarction are also complications of cocaine use. Levamisole, a veterinary antihelminthic, is a common adulterant of cocaine preparations. This may be added because the metabolite of levamisole, aminorex, has its own psychostimulant effects[10] which may be more prolonged than those of cocaine. Exposure to high or repeated doses of levamisole, however, may cause agranulocytosis or vasculitis.

Management of cocaine intoxication is generally supportive. Hypertension and chest pain often respond to administration of benzodiazepines, although intravenous nitrates are occasionally required. Aspirin should be administered and coronary angiography considered in patients with suspected acute coronary syndromes.[11] The benefits of thrombolysis are uncertain because of an increased risk of intracerebral haemorrhage. Hyperpyrexia may be life-threatening and should be treated with active cooling measures, with ice bath emersion in severe cases.

Amphetamines and related compounds

There are an increasing number of compounds available to recreational drug users that are structurally similar to amphetamine, having the same phenethylamine backbone. Established drugs include 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and methamphetamine ('crystal meth'), but more recently emerging compounds include the 2C and D series ring-substituted phenethylamine compounds, piperazines and piperidines, cathinones, benzofurans and difurans, aminoindans and NBOMe compounds. These may all produce features of the stimulant toxidrome (Table 3), but the pattern of clinical effects

varies, with some, for example NBOMe compounds, having more prominent hallucinogenic effects.

These compounds are generally taken by ingestion, nasal insufflation ('snorting') or injection, with the latter two routes providing more rapid and intense effects. There is considerable individual variation in response and tolerance develops in habitual users. Acute effects are commonly followed by fatigue and depression, encouraging further dosing.

MDMA is probably still the most commonly used amphetamine-like drug in the UK and is generally taken orally. Some users may develop hyponatraemia because of inappropriate antidiuretic hormone secretion coupled with excessive water drinking. Jaw clenching (bruxism) is also common. Severe complications are uncommon but hyperpyrexia, metabolic acidosis, rhabdomyolysis, acute renal failure, disseminated intravascular coagulation, hepatocellular necrosis, acute respiratory distress syndrome and cardiovascular collapse have all been described.

Recreational use of piperazine compounds such as benzylpiperazine, triflouromethylphenylpiperazine (TFMPP) and 1-(meta-chlorophenyl)piperazine (mCPP) has been common in some countries, with benzylpiperazine used commonly in New Zealand, for example. Some tablets sold as ecstasy have been found to contain benzylpiperazine on analysis. Piperazines are usually taken orally, but intravenous use has been reported. Clinical effects of piperazines are similar to those of amphetamines and MDMA, although may be less marked.

Synthetic cathinones such as mephedrone, methylone and methylenedioxypyrovalerone (MDPV) are structurally related to cathinone, a natural compound found in the khat plant (*Catha edulis*), which is commonly chewed by people originating from countries around the horn of Africa. Initially not controlled under drug misuse legislation, synthetic cathinones were easily available via the internet and head shops, described as 'bath salts' and 'plant foods' but intended for recreational use. Presentations with synthetic cathinone toxicity became very common from 2009 until legal control was enacted in the UK in 2010. Subsequently the numbers of hospital presentations and poisons centre enquiries[12] fell, although mephedrone toxicity is still commonly encountered. Administration is usually by mouth or nasal insufflation, although the latter is painful for some compounds. Parenteral use has also been reported. Clinical effects of cathinone use are similar to those of amphetamines and include agitation, hypertension and convulsions.

The piperidines pipradrol, desoxypipradrol (2-DPMP) and diphenylprolinol (D2PM), are structurally related to methylphenidate. Use has been associated with prolonged and extreme agitation and psychosis, with stimulant features also common. These drugs are now uncommonly encountered. More recently, use of the structurally related substance ethylphenidate has been associated with stimulant features with bizarre and violent behaviour.[13] Tissue necrosis and *Streptococcus pyogenes* infection has been reported after parenteral use.[14]

There has been recent concern provoked by deaths caused by the ring substituted amphetamine derivatives paramethoxyamphetamine (PMA, 'Death') and paramethoxymethamphetamine (PMMA). Hyperthermia is a prominent feature of toxicity, probably arising from their potent serotoninergic affects coupled with monoamine oxidase inhibition.

Management of stimulant toxicity is supportive and is summarized in Table 4.

Management of complications caused by stimulant use

Complication	Notes on management
Confusion, behavioural disturbances	Diazepam or lorazepam
Tachyarrhythmias	Avoid treatment unless cardiovascular compromise Correct hypoxia, pH and electrolytes Diazepam or lorazepam if associated with agitation Avoid β blockade because of risk of hypertension and coronary spasm (unopposed α stimulation) Ventricular arrhythmias may respond to sodium bicarbonate, with lidocaine reserved for non-responders
Hypertension	Diazepam or lorazepam If severe hypertension persists consider glyceryl trinitrate infusion
Seizures	Diazepam or lorazepam
Acidosis	Correct with sodium bicarbonate
Hyperpyrexia	Physical cooling methods. Consider dantrolene if these are ineffective
Rhabdomyolysis	Intravenous fluids Urinary alkalinization Monitor renal function and potassium Dialysis for renal failure or severe hyperkalaemia

Table 4

Hallucinogens

Cannabinoid receptor agonists

Hallucinations are a common clinical effect of this group of drugs, although early stimulant and later depressant effects are also observed with synthetic cannabinoid receptor agonists, making classification difficult.

Cannabis: as detailed above, cannabis (marijuana) remains the most widely used substance of misuse. It contains the active substance Δ^9-tetrahydrocannabinol (Δ^9-THC), which is a partial agonist at CB_1 and CB_2 cannabinoid receptors.

Severe toxic effects from cannabis use alone are uncommon, but longer term health effects may occur including lung damage

with bullae formation, a probable increased risk of lung cancer and an increased risk of cardiac ischaemia for a few hours after use. Cannabis has also been associated with psychosis after acute consumption, and there is a probable link between chronic psychosis and heavy cannabis use.[15] This may become more common because of the increasing use of intensively grown, un-pollinated female cannabis, termed 'skunk' or sinsemilla.

Synthetic cannabinoid receptor agonists (SCRAs): the use of SCRAs has become increasingly common as legal alternatives to cannabis and these substances are among the most common recreational drugs involved in enquiries to poisons centres. Many have greater binding potency for CB_1 and CB_2 receptors than Δ^9-THC and are full rather than partial agonists.[16] These chemicals are synthetic in origin, with the structure manipulated to avoid being captured by drug misuse legislation. Control of first-generation SCRAs such as JWH-018 and HU-210 under UK law in 2009 was rapidly followed by the emergence of second-generation agents such as AM-2201 and UR-144, which were subsequently controlled in 2013. Since then, however, third generation substances have emerged, with commonly encountered examples including PB-22, 5F-PB-22, 5F-AKB-48 and STS-135.

SCRAs are usually added to a base formed of plant material that is suitable for smoking and sold as 'branded' products with names including 'K2', 'Clockwork Orange', 'Annihilation', 'Pandora's Box', 'Black Mamba' and many more. They may be labelled as incense or room deodorizers, but are clearly intended for human use. More than one SCRA may be found in an individual product and the chemical constituents of these products may change with time. SCRAs have also been found in e-cigarette refills for use by 'vaping'.

Importantly, the pattern and severity of their toxicity differs from that of cannabis, with reported features including agitation, panic, confusion, hallucinations, changes in perception, tachycardia, ECG changes, hypertonia, dyspnoea, vomiting, convulsions, hypokalaemia and renal dysfunction.[17]

Arylcyclohexamines

Arylcyclohexamines are antagonists of the neuroexcitatory neurotransmitter glutamate at the N-methyl-D-aspartate (NMDA) receptor. They include phencyclidine, which is now rarely encountered, the veterinary and human anaesthetic ketamine and its *N*-ethyl derivative methoxetamine.

These drugs produce dissociative effects, accompanied by impaired consciousness, agitation and hallucinations. Long-term ketamine misuse is also associated with severe chronic cystitis, which may cause dysuria, frequency, urgency, haematuria and incontinence. There is increasing evidence that similar effects may occur with methoxetamine. Long-term high-dose users may also develop memory impairment and abnormal liver function tests. Management is supportive.[18]

Tryptamines

The tryptamines are agonists at a wide range of serotonin and other receptors and ion channels. Hallucinogenic properties relate to agonism at the (5HT2)a and 5HT1a receptors. Serotonin syndrome, including confusion, agitation, hallucinations, myoclonus, diarrhoea and fever, may occur with use of one or more serotoninergic agents.

Lysergic acid diethylamide (LSD) is a synthetic ergoline and highly potent hallucinogen via agonism of central 5HT2 receptors. Severe clinical toxicity is not common, although users may experience confusion and agitation and sometimes acute panic reactions or acute psychosis.

Physical injury and death may occur from accidents sustained while psychotic. Tachycardia, tachypnoea, hypertension, hyperthermia, twitching, flushing, lightheadedness, hyperreflexia, vomiting and diarrhoea may sometimes occur. Management is supportive and includes sedation as required.

The hallucinogenic effects of the natural tryptamines psilocin and psilocybin in 'magic mushrooms' and dimethyltryptamine (DMT) in ayahuasca brews have been recognized for centuries. Synthetic tryptamines, some with more prominent stimulant actions, have been developed more recently, such as alpha methyltryptamine (AMT). Hallucinations may be associated with agitation and confusion, as well as stimulant effects such as hypertension, tachycardia, sweating, anxiety, and headache.[19] ◆

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