Novel Psychoactive Treatment UK Network

NEPTUNE

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

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Inspiring Improvement

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Chapter 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 phenyl-ethan-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 metham-phetamine – 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 methylone (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 1960s[17] 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 para-methoxyamphetamine (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 euphorigenic 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).

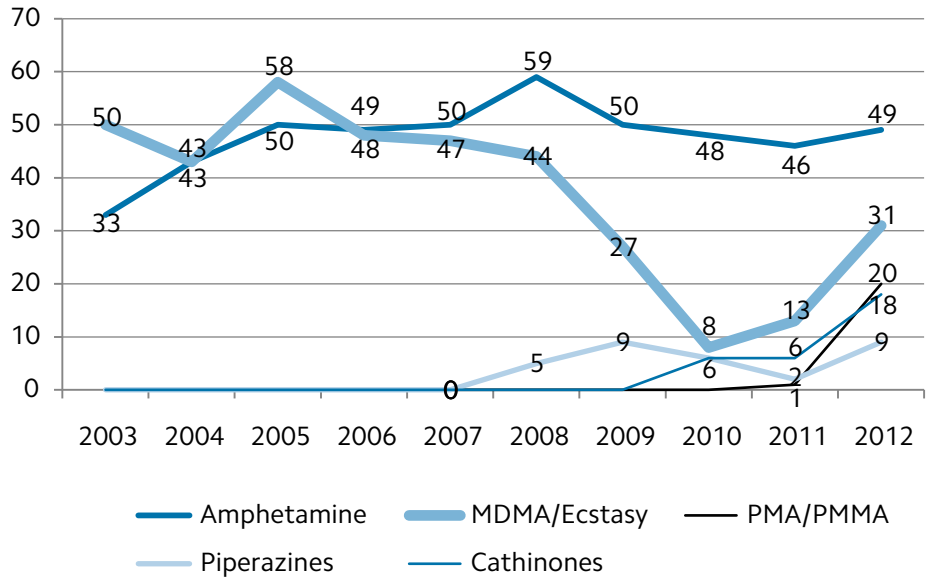

Figure 7.1. *Numbers of drug-related deaths where stimulants were mentioned in the death certificate, England and Wales death registered between 2003 and 2012*

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 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 toxity, 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)
Tricyclic antidepressants
Selective serotonin reuptake inhibitors (SSRIs; also called serotonin-specific reuptake inhibitors)
Opiate analgesics
Tramadol
Over-the-counter cough medicines
Antibiotics
Weight-reduction agents
Antiemetics
Antimigraine agents
Herbal products

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 aferbile. 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 methylenedioxypyrovalerone MPDV[47,64–66] mephedrone, methylenedioxypyrovalerone (MDPV),[67,68] butylone, methylone[68] 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. phenelezine, 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 withdrawal[80] (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 ATS[78] 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 HIV[32] 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 dependence[90]

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 ATS[90] 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	*Personal care activities:* 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 *primary health-care* 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 *drug dependence clinical care*: 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 review[91] 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 2[78] 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 review[88] 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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