Novel Psychoactive Treatment UK Network

NEPTUNE

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

The Health Foundation
Inspiring Improvement

Club Drug Clinic/CAPS
Central and North West London NHS Foundation Trust (CNWL)
69 Warwick Road
Earls Court
SW5 9HB

http://www.Neptune-clinical-guidance.com

http://www.Neptune-clinical-guidance.co.uk

The guidance is based on a combination of literature review and expert clinical consensus and is based on information available up to March 2015. We accept no responsibility or liability for any consequences arising from the use of the information contained in this document.

The recommended citation of this document is:

Abdulrahim D & Bowden-Jones O, on behalf of the NEPTUNE Expert Group. *Guidance on the Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances*. Novel Psychoactive Treatment UK Network (NEPTUNE). London, 2015.

NEPTUNE is funded by the Health Foundation, an independent charity working to improve the quality of health care in the UK.

Editorial production and page design by Ralph Footring Ltd, http://www.footring.co.uk

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 methylenedioxypyrovalerone (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-methylenedioxypyrovalerone 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 buproprion 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±3.67%). Animal and human studies showed that mephedrone is metabolised by different phase I reactions (i.e. demetylation, 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 have others 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 Survey[23] 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 smell[37] 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 g[55] 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 features[49] 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 euvolaemic 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 methaemogloninaemia, 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 toxocity[45] 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, paracetemol, 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 UKindicate 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 series[45] 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 criteria[98] 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 olanzapine[98] 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 risperodone, 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]

References

1 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *EU Drug Market Report: A Strategic Analysis*. 2013. http://www.emcdda.europa.eu/publications/joint-publications/drug-markets (accessed 3 July 2013).

2 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *European Drugs Report 2014. Trends and Developments*.

3 United Nations Office on Drugs and Crime (UNODC) Laboratory and Scientific Section. Details for Synthetic Cathinones. https://www.unodc.org/LSS/SubstanceGroup/Details/67b1ba69-1253-4ae9-bd93-fed1ae8e6802 (accessed 2 April 2014).

4 Warfa N, Klein A, Bhui K, Leavey G, Craig T, Alfred Stansfeld S. Khat use and mental illness: a critical review. *Soc Sci Med*. 2007 Jul;65(2):309–18.

5 Fleckenstein AE, Volz TJ, Riddle EL, Gibb JW, Hanson GR. New insights into the mechanism of action of amphetamines. *Annu Rev Pharmacol Toxicol.* 2007;47:681–98.

6 Cozzi NV, Sievert MK, Shulgin AT, Jacob P 3rd, Ruoho AE.. Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. *Eur J Pharmacol.* 1999 Sep 17;381(1):63–9.

7 Coppola M, Mondola R. Synthetic cathinones: chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as 'bath salts' or 'plant food'. *Toxicol Lett*. 2012 Jun 1;211(2):144–9. doi: 10.1016/j.toxlet.2012.03.009.

8 Carroll FI, LewinAH, Mascarella SW, Seltzman HH, Reddy PA. Designer drugs: a medicinal chemistry perspective. *Ann NY Acad Sci*. 2012;1248:18–38.

9 Iversen L, White M, Treble R. Designer psychostimulants: pharmacology and differences. *Neuropharmacology*. 2014 Dec;87:59–65. doi: 10.1016/j.neuropharm.2014.01.015.

10 Hadlock GC, Webb KM, McFadden LM, Chu PW, Ellis JD, Allen SC, Andrenyak DM, Vieira-Brock PL, German CL, Conrad KM, Hoonakker AJ, Gibb JW, Wilkins DG, Hanson GR, Fleckenstein AE. 4-Methylmethcathinone (mephedrone): neuropharmacological effects of a designer stimulant of abuse. *J Pharmacol Exp Ther*. 2011 Nov;339(2):530–6. doi: 10.1124/jpet.111.184119.

11 Martínez-Clemente J, López-Arnau R, Carbó M, Pubill D, Camarasa J, Escubedo E. Mephedrone pharmacokinetics after intravenous and oral administration in rats: relation to pharmacodynamics. *Psychopharmacology (Berl)*. 2013 Sep;229(2):295–306.

12 Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, et al. Involvement of CYP2B6 in n-demethylation of ketamine in human liver microsomes. *Drug Metab Dispos*. 2001;29:887–90.

13 Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. *Drug Metab Dispos*. 2002,30:853–8.

14 Advisory Council on the Misuse of Drugs (ACMD). *Consideration of the Cathinones*. Home Office, 2010.

15 Measham F, Moore K, Newcombe R, Welch Z. Tweaking, bombing, dabbing and stockpiling: the emergence of mephedrone and the perversity of prohibition. *Drugs Alcohol Today.* 2010;10(1):14–21.

16 Measham F, Wood DM, Dargan PI, Moore K. The rise in legal highs: prevalence and patterns in the use of illegal drugs and first- and second-generation 'legal highs' in South London gay dance clubs. *J Substance Use.* August 2011;16(4):263–72.

17 Brunt TM, Poortman A, Niesink RJ, van den Brink W. Instability of the ecstasy market and a new kid on the block: mephedrone. *J Psychopharmacol*. 2011 Nov;25(11):1543–7. doi: 10.1177/0269881110378370.

18 Measham F, Moore K, Østergaard J. Mephedrone, 'Bubble' and unidentified white powders: the contested identities of synthetic 'legal highs'. *Drugs Alcohol Today*. 2011;11(3):137–46.

19 Winstock A, Mitcheson L, Marsden J. Mephedrone: still available and twice the price. *Lancet.* 2010;376:1537.

20 Dybdal-Hargreaves NF, Holder ND, Ottoson PE, Sweeney MD, Williams T. Mephedrone: Public health risk, mechanisms of action, and behavioural effects Eur J Pharmacol. 2013 Aug 15;714(1–3):32–40. doi: 10.1016/j.ejphar.2013.05.024.

21 Wood DM, Greene SL, Dargan PI. Emergency department presentations in determining the effectiveness of drug control in the United Kingdom: mephedrone (4-methylmethcathinone) control appears to be effective using this model. *Emerg Med J.* 2013;30:70–1.

22 Office for National Statistics. *Drug Misuse Declared: Findings from the 2011/12 Crime Survey for England and Wales* (2nd edition). Home Office, July 2012.

23 Guardian online. Which drugs do you take? US and the UK compared by the Global Drug Survey. http://www.guardian.co.uk/society/datablog/2012/mar/15/global-drug-survey-us-uk#data (accessed 24 July 2013).

24 Archer JRH, Dargan PI, Hudson S, Wood DM. Analysis of anonymous pooled urine from portable urinals in central London confirms the significant use of novel psychoactive substances. *Q J Med*. 2013; 106:147–52.

25 National Poisons Information Service (NIPS). *Annual Report 2010/11*. Health Protection Agency, 2011.

26 National Poisons Information Service (NIPS). *Annual Report 2011/12*. Health Protection Agency, 2012.

27 Wood DM, Measham F, Dargan PI. 'Our favourite drug': prevalence of use and preference for mephedrone in the London night-time economy 1 year after control. *J Substance Use.* 2012;17(2):91–7.

28 Welsh Government. *Working Together to Reduce Harm. Substance Misuse Annual Report 2013*.

29 Moore K, Dargan PI, Wood DM, Measham F. Do novel psychoactive substances displace established club drugs, supplement them or act as drugs of initiation? The relationship between mephedrone, ecstasy and cocaine. *Eur Addict Res*. 2013;19(5):276–82.

30 Winstock A, Mitcheson L, Ramsey J, Davies S, Puchnarewicz M, Marsden J. Mephedrone: use, subjective effects and health risks. *Addiction*. 2011;106(11):1991–6.

31 Carhart-Harris RL, King LA, Nutt DJ. A Web-based survey on mephedrone. *Drug Alcohol Depend.* 2011;118:19–22.

32 Wood DM, Greene SL, Dargan PI. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emergency Med J.* 2010;28:280–2. doi 0:10.1136/emj.2010.092288.

33 Zuba D, Byrska B. Prevalence and co-existence of active components of 'legal highs'. *Drug Test Anal.* 2013 Jun;5(6):420–9. doi: 10.1002/dta.1365.

34 Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, Davey Z, Corkery J, Siemann H, Scherbaum N, Farre' M, Torrens M, Demetrovics Z, Ghodse AH; Psychonaut Web Mapping; ReDNet Research Groups. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. *Psychopharmacology (Berl)*. 2011 Apr;214(3):593–602. doi: 10.1007/s00213-010-2070-x.

35 Marinetti LJ, Antonides HM. Analysis of synthetic cathinones commonly found in bath salts in human performance and postmortem toxicology: method development, drug distribution and interpretation of results. *J Anal Toxicol.* 2013 Apr;37(3):135–46. doi: 10.1093/jat/bks136.

36 McElrath K, O'Neill C. Experiences with mephedrone pre- and post-legislative control: perceptions of safety and sources of supply. *Int J Drug Policy.* 2011;22:120–7.

37 Deluca P, Schifano F, Davey Z, Corazza O, Di Furia L; the Psychonaut Web Mapping Research Group. *Mephedrone Report*. Institute of Psychiatry, King's College London, London, 2009. http://www.psychonautproject.eu (accessed 19 August 2010).

38 Van Hout MC, Bingham T. 'A costly turn on': patterns of use and perceived consequences of mephedrone based head shop products amongst Irish injectors. *Int J Drug Policy.* 23;2012:188–97.

39 Karila L, Reynaud M. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Test Anal.* 2011;3:552–9.

40 Colfax G, Santos GM, Chu P, Vittinghoff E, Pluddeman A, Kumar S, et al. Amphetamine-group substances and HIV. *Lancet*. 2010;376:458–74.

41 Wood DM, Davies S, Greene SL, Button J, Holt DW, Ramsey J, et al. Case series of individuals with analytically confirmed acute mephedrone toxicity. *Clin Toxicol.* 2010;48:924–7.

42 DrugScope. DrugScope street drug trends survey highlights growing problems with mephedrone, 22 November 2012. http://www.drugscope.org.uk/Media/Press+office/pressreleases/DrugScope+Street+Drug+Trends+Survey+highlights+growing+problems+with+mephedrone (accessed 2 March 2015).

43 McNamara S, Stokes S, Coleman N. Head shop compound abuse amongst attendees of the Drug Treatment Centre Board. *Int Med J.* 2010;103(5):134–7.

44 Kirby T, Thornber-Dunwell M. High-risk drug practices tighten grip on London gay scene. *Lancet*. 2013;381(9861):101–2. doi:10.1016/S0140-6736(13)60032-X.

45 Dargan PI, Wood DM. Annex 1 to the risk assessment report *Technical Report on Mephedrone*. EMCDDA contract CT.10.EPI.057. Guy's and St Thomas' NHS Foundation Trust, London, UK, July 2010. http://www.emcdda.europa.eu (accessed 14 June 2011).

46 Global Drug Survey. http://globaldrugsurvey.com/about/drug-prices (accessed 1 July 2013).

47 James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, Thomas SH; National Poisons Information Service. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. *Emerg Med J.* 2011 Aug;28(8):686–9. doi: 10.1136/emj.2010.096636.

48 Winstock AR, Mitcheson LR, Deluca P, et al. Mephedrone, new kid for the chop? *Addiction*. 2011;106(1):154–61.

49 Wood DM, Davies S, Puchnarewicz M, et al. Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. *J Med Toxicol.* 2010;6(3):327–30.

50 Newcombe R. *Mephedrone: Use of Mephedrone (M-Cat, Meow) in Middlesbrough*. Lifeline, Manchester, 2009.

51 Winstock AR, Marsden J, Mitcheson L. What should be done about mephedrone? *BMJ*. 2010;340:c1605.

52 Dargan PI, Sedefov R, Gallegos A, Wood DM. The pharmacology and toxicology of the synthetic cathinonemephedrone (4-methylmethcathinone). *Drug Test Anal.* 2011 Jul–Aug;3(7–8):454–63. doi: 10.1002/dta.312.

53 Freeman TP, Morgan CJ, Vaughn-Jones J, Hussain N, Karimi K, Curran HV. Cognitive and subjective effects of mephedrone and factors influencing use of a 'new legal high'. *Addiction*. 2012 Apr;107(4):792–800. doi: 10.1111/j.1360-0443.2011.03719.x.

54 Motbey CP, Clemens KJ, Apetz N, Winstock AR, Ramsey J, Li KM, Wyatt N, Callaghan PD, Bowen MT, Cornish JL, McGregor IS. High levels of intravenous mephedrone (4-methylmethcathinone) self-administration in rats: neural consequences and comparison with methamphetamine. *J Psychopharmacol*. 2013 Sep;27(9):823–36. doi: 10.1177/0269881113490325.

55 Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow…and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *J Med Toxicol*. 2012 Mar;8(1):15–32. doi: 10.1007/s13181-011-0202-2.

56 Wood DM, Dargan PI. Mephedrone (4-methylmethcathinone): what is new in our understanding of its use and toxicity. *Prog Neuropsychopharmacol Biol Psychiatry.* 2012 Dec 3;39(2):227–33. doi: 10.1016/j.pnpbp.2012.04.020.

57 Dick D, Torrance C. Drugs survey. *MixMag*. 2010;225:44.

58 Van Hout MC, Brennan R. 'Bump and grind': an exploratory study of mephedrone users' perceptions of sexuality and sexual risk. *Drugs Alcohol Today.* 2012;11(2):93–103.

59 Semple SJ, Patterson TL, Grant I. Motivations associated with methamphetamine use among HIV men who have sex with men. *J Substance Abuse Treatment.* 2002;22:149–56.

60 Frohmader KS, Pitchers KL, Balfour M, Coolen LM. Mixing pleasures: review of the effects of drugs on sex behavior in humans and animal models. *Hormones Behavior.* 2010;58:149–62.

61 Pfaus JG. Pathways of sexual desire. J Sex Med. 2009;6:1506–33.

62 Raj A, Saitz R, Cheng DM, Winter M, Samet JH. Associations between alcohol, heroin, and cocaine use and high risk sexual behaviors among detoxification patients. *Am J Drug Alcohol Abuse*. 2007;33:169–78.

63 Mitcheson L, McCambridge J, Byrne A, Hunt N, Winstock A. Sexual health risk among dance drug users: cross-sectional comparisons with nationally representative data. *J Drug Policy*. 2008;19:304–10.

64 Rhodes T, Quirk A. Drug users' sexual relationships and the social organization of risk: the sexual relationship as a site of risk management. *Soc Sci Med.* 1998;46(2):157–69.

65 Dargan PI, Albert S, Wood DM. Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. *QJM*. 2010;103(11):875–9.

66 Schifano F, Corkery J, Naidoo V, Oyefeso A, Ghodse AH. Comparison between amphetamine/methylamphetamine and ecstasy (MDMA, MDEA, MDA, 4-MTA) mortality data in the UK (1997–2007). *Neuropsychobiology*. 2010;61:122–30.

67 Dickson AJ, Vorce SP, Levine B, Past MR. Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. *J Analytic Toxicol.* 2010;34:162–8.

68 Corkery JM, Schifano F, Ghodse AH. Mephedrone-related fatalities in the United Kingdom: contextual, clinical and practical issues. In: Gallelli L, ed. *Pharmacology*. InTech, 2012. http://www.intechopen.com/books/pharmacology/mephedrone-related-fatalities-in-the-united-kingdom-contextual-clinical-and-practical-issues.

69 Schifano F, Corkery C, Ghodse AH. Background: suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone, 'meow meow') in the United Kingdom. *J Clin Psychopharmacol.* 2012 Oct;32(5):710–4. doi: 10.1097/JCP.0b013e318266c70c.

70 Nicholson PJ, Quinn MJ, Dodd JD. Headshop heartache: acute mephedrone meow myocarditis. *Heart*. 2010;96:2051.

71 Sammler EM, Foley PL, Lauder GD, Wilson SJ, Goudie AR, O'Riordan JI. A harmless high? *Lancet*. 2010;376:742.

72 Benzie F, Hekman K, Cameron L, Wade DR, Miller C, Smolinske S, Warrick B. Emergency department visits after use of a drug sold as 'bath salts' – Michigan, November 13, 2010–March 31, 2011. Michigan, November 13, 2010–March 31, 2011. *MMWR Morb Mortal Wkly Rep*. 2011 May 20;60(19):624–7.

73 Wood DM, Dargan PI. Understanding how data triangulation identifies acute toxicity of novel psychoactive drugs. *J Med Toxicol.* 2012;8:300–3. doi: 10.1007/s13181-012-0241-3.

74 Prosser JM, Nelson LS. The toxicology of bath salts: a review of synthetic cathinones. *J Med Toxicol*. 2012;8:33–42.

75 Gustavsson D, Escher C. [Mephedrone – Internet drug which seems to have come and stay. Fatal cases in Sweden have drawn attention to previously unknown substance.] [Article in Swedish.] *Lakartidningen*. 2009 Oct 21-27;106(43):2769–71.

76 Omer TA, Doherty C. Posterior reversible encephalopathy syndrome (PRES) complicating the 'legal high' mephedrone. *BMJ Case Rep*. 2011 Aug 29;2011. pii: bcr0220113904. doi: 10.1136/bcr.02.2011.3904.

77 Kolli V, Sharma A, Amani M, Bestha D, Chaturvedi R. 'Meow meow' (mephedrone) and catatonia. *Innov Clin Neurosci*. 2013 Feb;10(2):11–12.

78 Maan ZN, D'Souza AR. Spontaneous subcutaneous emphysema associated with mephedrone usage. *Ann R Coll Surg Engl.* 2012 Jan;94(1):e38-40. doi: 10.1308/003588412X13171221499108.

79 Ahmed N, Hoy BP, McInerney J. Methaemoglobinaemia due to mephedrone ('snow'). *BMJ Case Rep*. 2010 Oct 22;2010. pii: bcr0420102879. doi: 10.1136/bcr.04.2010.2879.

80 Garrett G, Sweeney M. The serotonin syndrome as a result of mephedrone toxicity. *BMJ Case Rep.* 2010 Sep 20;2010. pii: bcr0420102925. doi: 10.1136/bcr.04.2010.2925.

81 Mugele J, Nañagas KA, Tormoehlen LM. Serotonin syndrome associated with MDPV use: a case report. *Ann Emerg Med*. 2012 Jul;60(1):100–2. doi: 10.1016/j.annemergmed.2011.11.033.

82 Wong ML, Holt RI. The potential dangers of mephedrone in people with diabetes: a case report. *Drug Test Anal*. 2011 Jul–Aug;3(7–8):464–5. doi: 10.1002/dta.316.

83 Chhabra JS, Nandalan S, Saad R. Mephedrone poisoning – a case of severe refractory left ventricular failure. Poster Presentation 33. In: *The State of the Art Meeting*, London, 13–14 December 2010, pp. 74-5.

84 Brandt SD, Sumnall HR, Measham F, Cole J. Second-generation mephedrone. The confusing case of NRG-1. *BMJ*. 2010;341:c3564

85 Davies S, Wood DM, Smith G, et al. Purchasing 'legal highs' on the Internet – is there consistency in what you get? *QJM*. 2010;103(7):489–93.

86 Camilleri A, Johnston MR, Brennan M, Davis S, Caldicott DG. Chemical analysis of four capsules containing the controlled substance analogues 4-methylmethcathinone, 2-fluoromethamphetamine, alpha-phthalimidopropiophenone and N-ethylcathinone. *Forensic Sci Int* 2010;197:59–66.

87 Pacifici R, Zuccaro P, Farre M, et al. Cell-mediated immune response in MDMA users after repeated dose administration: studies in controlled versus noncontrolled settings. *Ann N Y Acad Sci*. 2002;965:421–33.

88 Schifano F, Oyefeso A, Corkery J, et al. Death rates from ecstasy (MDMA, MDA) and polydrug use in England and Wales 1996-2002. *Hum Psychopharmacol Clin Exp.* 2003;18:519–24.

89 McGaw C, Kankam O. The co-ingestion of alcohol and mephedrone – an emerging cause of acute medical admissions in young adults and a potential cause of tachyarrhythmias. *West London Med J.* 2010;2:9–13.

90 Angoa-Perez M, Kane M, Briggs D, Francescutti D, Sykes C, Shah M, Thomas D, Kuhn D. Mephedrone does not damage dopamine nerve endings of the striatum, but enhances the neurotoxicity of methamphetamine, amphetamine and MDMA. *J Neurochem.* 2013;125:102–10.

91 Aromatario M, Bottoni E, Santoni M, Ciallella C. New 'lethal highs': a case of a deadly cocktail of GHB and mephedrone. *Forensic Science International.* 2012;223(1–3):e38–e41.

92 National Poisons Information Service (NIPS). *Annual Report 2012/13*. Health Protection Agency, 2013.

93 Shah AD, Wood DM, Dargan PI. Survey of ICD-10 coding of hospital admissions in the UK due to recreational drug toxicity. *QJM*. 2011 Sep;104(9):779–84. doi: 10.1093/qjmed/hcr074.

94 Regan L, Mitchelson M, Macdonald C. Mephedrone toxicity in a Scottish emergency department. *Emerg Med J*. 2011;28:1055–8.

95 Spiller HA, Ryan ML, Weston RG, Jansen J. Clinical experience with and analytical confirmation of 'bath salts' and 'legal highs' (synthetic cathinones) in the United States. *Clin Toxicol (Phil).* 2011;49(6):499–505. doi: 10.3109/15563650.2011.590812.

96 Woo TM, Hanley J. 'How do they look?' Identification and treatment of common ingestions in adolescents. *J Pediatr Health Care.* 2013 Mar–Apr;27(2):135–44. doi: 10.1016/j.pedhc.2012.12.002.

97 Baumann MH, Ayestas MA Jr, Partilla JS, Sink JR, Shulgin AT, Daley PF, Brandt SD, Rothman RB, Ruoho AE, Cozzi NV. The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology*. 2012 Apr;37(5):1192–203. doi: 10.1038/npp.2011.304.

98 Bajaj N, Mullen D, Wylie S. Dependence and psychosis with 4-methylmethcathinone (mephedrone) use. *BMJ Case Rep.* 2010 Nov 3;2010. pii: bcr0220102780. doi: 10.1136/bcr.02.2010.2780.

99 Winder GS, Stern N, Hosanagar A. Are 'bath salts' the next generation of stimulant abuse? *J Subst Abuse Treat*. 2013 Jan;44(1):42–5. doi: 10.1016/j.jsat.2012.02.003. Epub 2012 Mar 24.

100 Antonowicz JL, Metzger AK, Ramanujam SL. Paranoid psychosis induced by consumption of methylenedioxypyrovalerone: two cases. *Gen Hosp Psychiatry.* 2011 Nov-Dec;33(6):640.e5-6. doi: 10.1016/j.genhosppsych.2011.04.010.

101 Public Health England (PHE). *Adult Drug Statistics from the National Drug Treatment Monitoring System (NDTMS). 1 April 2013 to 31 March 2014.* PHE, 2014.

102 *Statistical Bulletin* PHIRB 3, October 2012.

103 Burch HJ, Clarke EJ, Hubbard AM, Scott-Ham M. Concentrations of drugs determined in blood samples collected from suspected drugged drivers in England and Wales. *J Forensic Leg Med*. 2013 May;20(4):278–89. doi: 10.1016/j.jflm.2012.10.005. Epub 2012 Dec 5.