

The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone)

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Mephedrone (4-methylmethcathinone) is a synthetic cathinone that is used as a recreational drug. It has been available since 2007 but its availability and use increased significantly during 2009 and 2010. In this review article we will summarize the available literature on the sources, availability, and prevalence of the use of mephedrone. We will also discuss the pharmacology of mephedrone, the patterns of acute toxicity associated with its use, the reports of fatalities associated with its use, and the potential for mephedrone dependence. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: Mephedrone; 4-methylmethcathinone; poisoning; recreational drugs; toxicity

Introduction

'Mephedrone' is the name more commonly used for the synthetic cathinone, 4-methylmethcathinone (Figure 1). It is a synthetic ring-substituted cathinone closely related to the phenethylamine family, differing only by a keto functional group at the beta carbon.^[1] The systematic (International Union of Pure and Applied Chemistry, IUPAC) name for mephedrone is (*RS*)-2-methylamino-1-(4-methylphenyl) propan-1-one. There are a number of additional chemical names for mephedrone including *N*-methylephedrone, β -keto-(4,*N*-dimethylamphetamine), 4,*N*-dimethylcathinone, *p*-methyl-methcathinone and 2-aminomethyl-1-tolyl-propan-1-one. In this review article we will refer to this compound as mephedrone.

Mephedrone is one of a group of synthetic cathinones that are used recreationally. There have been over 30 synthetic cathinones reported to the Early Warning System at the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).^[2] In addition to mephedrone, these include methedrone (4-methoxymethcathinone), methylone (3,4-methylenedioxy-*N*-methylcathinone) and flephedrone (4-fluoromethcathinone).

Mephedrone has been available in Europe since 2007 with increasing reports of seizures by law enforcement authorities, reports of its recreational use from Internet drug discussion forums, and reports of toxicity associated with its use both on Internet discussion forums and in the medical literature during 2009 and 2010.^[3–9] The growth in the interest in mephedrone was rapid, particularly in the UK in the last quarter of 2009 and first quarter of 2010.^[10] Mephedrone was controlled as a Class B substance under the Misuse of Drugs Act, 1971 in the UK in April 2010 and is also controlled in a number of other European countries. In December 2010, The European Council adopted a decision on submitting mephedrone to control measures across the European Union.^[11]

In this review article, we will review the currently available published literature on mephedrone and summarize the prevalence of its use, sources of supply, its pharmacology, and the patterns of acute and chronic harm, including reported fatalities, associated with the use of mephedrone.

Physical form, sources, and prevalence of use

Physical form

Mephedrone is typically sold to users in powder form and is generally described as being a white crystalline powder with a light yellow hue/colour.^[3,12] Some users report that mephedrone has a distinctive unpleasant odour.^[13] Mephedrone powder is readily soluble in water, and therefore can easily be dissolved prior to oral/rectal use or injection. There are also reports of mephedrone powder being supplied either as tablets pressed from the powder or in capsules containing the powder.^[12,14] Mephedrone powder is often sold in small plastic sealed bags labelled 'not for human consumption', 'research chemical' or 'not tested for hazards or toxicity' under a number of brand names including 'plant feeder', 'plant food' and 'bath salts'.^[12,13] It has no proven use as a plant food or as a bath/cosmetic product. Prior to the control of mephedrone under recreational/illicit drug legislation such as the UK Misuse of Drugs Act, 1971, it was often sold labelled 'not for human consumption', to circumvent national medicines legislation, such as the UK Medicines Act (1968). In addition to this labelling to circumvent existing legislation, the information provided to users in terms of dosing was often cryptic in nature. For example, some 'plant food' products were sold with information in terms of dosing in relation to 'an average size plant' or a '70 kg plant'.

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Conflicts of Interest DW and PD have acted as scientific advisers to the UK Advisory Council on Misuse of Drugs (ACMD) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

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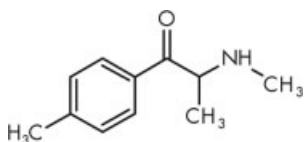


Figure 1. Chemical structure of mephedrone.

Sources of mephedrone

It appears from user discussion forums and surveys of users that mephedrone is readily available from a number of different sources.^[3,5,7,12,14–17] These include street-level drug dealers, high-street retail outlets (headshops), and from Internet suppliers.

Work undertaken by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has looked at Internet sites selling mephedrone and other 'legal highs'/novel psychoactive substances, using 'snapshot' survey techniques.^[3,16–18] In the survey carried out in March 2010, 77 websites were selling mephedrone and the majority of these (97%) were based in the UK.^[3,17] This was almost double the number of websites that were selling mephedrone in December 2009. Sixty-five percent of websites did not place restrictions on the country that they would deliver to. Interestingly, unlike many other Internet sites offering legal highs for sale which often offer a variety of different products and other drug-related paraphernalia, 96% of the Internet sites identified were mephedrone alone or mephedrone and other cathinone suppliers only. After the change in UK legislation to control mephedrone on 16 April 2010, there was a significant decrease in the number of Internet sites selling mephedrone with a number of sites now selling other replacement 'legal highs'. Work described below, has demonstrated that these replacement products in a number of cases may in fact still contain mephedrone and/or other controlled cathinones without declaring this to the purchaser.^[19–21] A proportion of the previous UK Internet sites have now moved overseas and openly advertise that 'the UK legislation does not affect the shipping and processing of orders'. However, they typically do not warn purchasers that they would be at risk of a potential criminal conviction should they be found in possession of products containing mephedrone.

There was often no limit on the amount of mephedrone that could be purchased, and indeed there were discounts for 'bulk purchases' in kilogram quantities. Whilst the websites were based in the UK, the mephedrone being sold largely originated from China and bordering countries in South East Asia.^[3,4] In addition, there is some anecdotal evidence that mephedrone shipped to Europe by air freight is being labelled as other chemicals by suppliers potentially due to their misconception that it is illegal in the country it is being shipped to.^[3] Customers who purchased bulk quantities of mephedrone would also be offered the option of repackaging in Europe into smaller quantities (typically 1g single-session amounts) for individuals to then sell on to others.

In addition to the availability of mephedrone from Internet-based suppliers, there are a number of reports that mephedrone was available from street-level drug dealers prior to its control in the UK.^[5,7,12] In particular, there was some evidence that the sourcing of mephedrone from these street-level drug dealers was greatest amongst the younger aged users.^[5] It has been postulated that this may be because younger individuals do not have access to credit/debit cards to be able to order online and/or because they are living at home with their parents they do not have an address that they are happy to have the mephedrone delivered to. Since

the classification of mephedrone in the UK in April 2010, it appears that users are increasingly sourcing mephedrone from street-level dealers.^[7,22] In one study that surveyed 150 individuals who were mephedrone users before the classification of mephedrone, 95 (63%) continued to use mephedrone two months after its classification in June 2010; with 52 (55%) of these saying they would continue to use the same amount.^[22] Eighty-five (57%) had purchased mephedrone from a dealer after its classification compared to 41% of those surveyed prior to its classification.

Availability of mephedrone

The detection of mephedrone in seizures, at both customs and law enforcement levels, provides some information on its availability. In the European Union and neighbouring countries, these data are collated on a national level through the 'national focal point' and then collated by the EMCDDA through the Early Warning System.^[2,23] The first reported seizure of mephedrone was in 2007 in Finland of capsules containing mephedrone; in 2008, there was a small number of other reports of seizures of mephedrone, both powder and powder within capsules from the UK and the other Scandinavian countries (Sweden, Norway, and Denmark).^[3,4] By July 2010, there were reports of detection of mephedrone in law enforcement/customs seizures and/or *ad hoc* test purchases from 28 European and neighbouring countries; at that time, however, there had been no reports of detection of mephedrone in seizures from Greece, Spain, or Portugal.^[3] By the end of 2010, mephedrone had been also encountered in those countries. Similar to the initial reports of detection of mephedrone, the majority of reports are detection of mephedrone in powder form, tablets, or capsules containing mephedrone. Interestingly, in 2009, there were reports of seizures of tablets containing mephedrone from a number of countries, some of which had logos and/or markings similar to those used for other 'classical' recreational drugs such as MDMA (ecstasy) and amphetamine.^[3,4] In the Dutch Drug Information and Monitoring System (DIMS), there was a decrease in the proportion of ecstasy tablets sold to users that contained MDMA from >90% in 2008 to less than 50% in 2009.^[24] During 2008, the most common drug found in these tablets was *meta*-chlorophenylpiperazine (*m*CPP). However, during 2009, mephedrone was increasingly detected in these tablets sold to users as MDMA and all of the 995 'MDMA tablets' analyzed in one batch during 2009 contained mephedrone. The quantity of mephedrone base varied from 96 to 155 mg per tablet.

In reports from 11 countries to the Early Warning System at the EMCDDA, mephedrone was detected in powder and/or tablet seizures in combination with one or more pharmacologically active compound(s).^[3] A range of different compounds were detected in these samples, including 'classical recreational drugs' (cocaine, MDMA, amphetamine and ketamine), other cathinones (butylone, ethylcathinone, methylenedioxypropylvalerone (MDPV), methylone, fluoromethcathinone, ethcathinone and methoxymethcathinone), piperazines (*meta*-chlorophenylpiperazine (*m*CPP) and *para*-methoxyphenylpiperazine (MeOPP)), local anaesthetics (lidocaine and benzocaine) and other stimulants (caffeine and phenethylamine).

A number of studies have reported on the analysis of legal highs purchased from Internet suppliers for delivery to the UK since the control of mephedrone and the other cathinones on 16 April 2010.^[19–21] In one study, analysis of six products purchased after the UK control of cathinones, five (83.3%) still contained a cathinone (mephedrone, 4-fluoromethcathinone or

3-fluoromethcathinone); additionally, two of the products sold as legal and not containing mephedrone in fact contained mephedrone.^[19]

In a further study, a total of 24 products were purchased from 18 different Internet sites in the six weeks following the UK control of the cathinones.^[20,21] On analysis of these products 17 (70.8%) contained one or more cathinones that had been controlled under the UK Misuse of Drugs (1971).

Prevalence of use

There is no formal collection of data on the prevalence of use of mephedrone at population level through the national surveys that report to European (EMCDDA) and International (United Nations Office on Drug and Crime, UNODC) bodies that produce and publish annual reports on the prevalence of recreational drug use. Currently, the only data available on the prevalence of use of mephedrone are from smaller surveys that have collected data from discrete geographical areas and have focused on specific sub-populations (e.g. school/university students, those who attend nightclubs and discotheques, individuals in drug treatment programmes).

A survey of 1006 Scottish school and college/university students undertaken in February 2010 reported that 205 (20.3%) had used mephedrone on at least one occasion previously.^[5] Of those who reported that they had previously used mephedrone, 23.4% reported that this was on one occasion only. Self-reported 'occasional use', defined as on more than one occasion but not more than once a week, in this study increased with increasing age. Regular daily use was reported by 4.4% of those who had used mephedrone, with the highest daily use rates occurring in the younger aged individuals, particularly those under the age of 21.

A survey undertaken of 154 pupils aged 14–15 in Northern Ireland in May 2010, after the control of mephedrone in the UK, reported that 40% of those interviewed had used mephedrone on at least one occasion in the past.^[3] Interestingly those interviewed reported that '70% of their friends had tried mephedrone'. Use appeared to be higher amongst males and also those who used cannabis. There was confusion amongst the students between mephedrone and methadone (an opioid) and also whether all 'plant foods' contained mephedrone.

The use of recreational drugs, including novel psychoactive substances such as mephedrone, is typically higher amongst those who attend nightclubs and other night-time economy venues. In a survey of just over 2295 UK clubbers undertaken towards the end of 2009, 41.3% reported that they had used/tried mephedrone on at least one occasion, 38.7% had used it within the last year, and 33.2% reported they had used mephedrone in the last month.^[25] The 'last month' use rate of 33.2% is comparable to that reported for other more classical recreational drugs such as ketamine (32.4%), ecstasy (48.4), and cocaine (47.4%).^[26] The life-time prevalence use rate of mephedrone, defined as having tried mephedrone on at least one occasion, was lower than that for the more classical recreational drugs such as ketamine (67.8%), ecstasy (91.0%), and cocaine (86.7%).^[25,26] The lower life-time prevalence use rate for mephedrone probably reflects the difference in time that it has been available on the recreational drug scene, which is much shorter than that for the established classical recreational drugs.

Individuals who reported that they were mephedrone users in an initial telephone survey in early 2010 were subsequently

followed-up by a further telephone survey after the control of mephedrone under the UK Misuse of Drugs Act, 1971.^[22] Ninety-five (63%) of the 150 individuals continued to use mephedrone; 52 (55%) stated that they intended to continue to use the same amount of mephedrone.

In a study of 209 urine samples submitted for 'drugs of abuse' screening in the Republic of Ireland, 13.9% were positive for mephedrone.^[27] There was limited clinical information available apart from that 46 samples were from individuals in a drug treatment clinic (37.0% positive for mephedrone) and 163 were samples randomly selected from other samples submitted for routine drugs of abuse screening (7.4% positive for mephedrone). Additionally, those samples positive for a 'head shop' product, which included additional novel psychoactive substances and not purely mephedrone, were also positive for opiates. Therefore this would suggest that in this sub-population study that 'head shop' products were being used by a population of individuals also using opiates. However, it is not possible to determine whether the opiate positive ones were positive for mephedrone or another novel substance.

Pharmacology of mephedrone

Synthesis

Mephedrone was first synthesized in 1929.^[28] The main pathway that is used for the synthesis of mephedrone is relatively straightforward and the underlying processes are similar to that for the synthesis of MDMA (3,4-methylenedioxymethamphetamine, ecstasy) and amphetamine. This involves initial alpha-bromination of the precursor 4-methylpropiofenone, followed by reaction of the resulting 4-methyl-2-bromopropiofenone with methylamine hydrochloride and triethylamine with an acidic scavenger environment to produce 4-methylmethcathinone hydrochloride. Ultimately this final reaction is then 'quenched' with gaseous or aqueous hydrogen chloride and the resultant hydrochloride salt is then recrystallized.^[1,29] There is a report from the Netherlands Drug Information and Monitoring Service (DIMS) of 7 samples analysed in 2010 that contained the precursor, 4-methylpropiofenone, in combination with mephedrone in the products purchased by users, suggesting that the conversion of the precursor to mephedrone and/or purification of the finalized product had been incomplete.^[3] 4-methylpropiofenone, the main precursor of mephedrone, is available to purchase from Internet suppliers however, there are no reports to date of this occurring in Europe.^[4]

There are other potential pathways for the synthesis of mephedrone, including the oxidation of the substituted ephedrine analogue (4-methylephedrine) with potassium permanganate or potassium dichromate in diluted sulfuric acid. This synthetic pathway is similar to the primary pathway used for the synthesis of methcathinone (the resultant product of which is often referred to as the 'Russian Cocktail'). The synthesis of methcathinone by this permanganate process requires adequate purification to remove any potential contamination by manganese and there were numerous reports in the literature of Parkinsonism-like movement disorders developing in users of methcathinone, which were due to inadequate purification and resultant manganese toxicity.^[30–36] However, not only is there no evidence that this pathway is used for the synthesis of mephedrone, there are also no reports to date of similar toxicity developing amongst regular long-term mephedrone users.

Analytical detection

Recently, 'field tests' have been developed for mephedrone, including portable infra-red and Raman spectrometers. However, these are only reliable for 'relatively pure' mephedrone and mephedrone does not give a colour reaction with the Marquis Field test. Detection of mephedrone and its metabolites is possible using techniques that have been developed for both gas chromatography-mass spectrometry (GC-MS) and liquid chromatography with tandem mass spectrometry (LC-MS/MS).^[1,29,37] However, it should be noted that these mass-spectrometry techniques do not distinguish between the different methyl-methcathinone regioisomers in the absence of reference standards. This is possible through the use of nuclear magnetic resonance spectroscopy (NMR), where these facilities are available.^[1,37]

Pharmacokinetics

The only published information on the pharmacokinetics of mephedrone, relates to its metabolism.^[37] Currently, therefore, the majority of information on the likely pharmacokinetics of mephedrone comes from user self-reports on websites, user surveys and clinical reports of toxicity associated with the use of mephedrone.^[7–9,12,13,15,38,39]

Mephedrone is used by the oral route, nasal insufflation ('snorting'), intramuscular injection, intravenous injection, and rectal insertion.^[7–9,12,13,15,38,39] The majority of users typically use mephedrone either by nasal insufflation or oral ingestion, or a combination of both.^[8,9,25,26] In a survey of 947 UK clubbers who reported mephedrone use, 65.9% reported that nasal insufflation was their primary route of use.^[25] However, as noted in the acute toxicity section, a large proportion of users report that nasal insufflation is associated with significant nasal irritation, which can lead to some users switching to oral ingestion instead.^[26,38] Oral ingestion of mephedrone is by swallowing the powder directly, tablets 'pressed' from the powder, or capsules containing the powder. As users report that the powder has an unpleasant taste, it may be swallowed either dissolved in water or by wrapping it in cigarette papers ('bombing').^[7,12]

Users report that 'single-use' doses of mephedrone are between 15 and 250 mg for oral ingestion and between 5 and 125 mg for nasal insufflation.^[40] Since use by other routes (rectal, intravenous injection, and intramuscular injection) is less common, there is no reliable information or reports on the amounts used by these routes. In a focus group of mephedrone users, the majority reported that they started initially with low amounts of mephedrone (typically 50–75 mg), but that both within single-use sessions and over time, they rapidly increased the amounts used to hundreds of milligrams per dose.^[12] Typically users report using between 0.5 and 1 g per single-use session, although in a survey of UK clubbers using mephedrone, 22.3% used more than 1 g in a typical session.^[25] The quantity of mephedrone in ecstasy tablets mis-sold to users in the Netherlands was found to be between 96 and 155 mg per tablet.^[24] This would suggest that for users to use between 0.5 and 1 g of mephedrone per single-use session, they would need to use up to 10 pills. Users in one survey reported that the average duration of a single-use session of mephedrone was approximately 10 h, and that there was a correlation between the total amount of mephedrone used and the duration of the use session.^[25]

The absorption of mephedrone is dependent on the route of use, with the onset of desired effects typically occurring within

a few minutes of nasal insufflation or intravenous injection and within 15–45 min of oral ingestion.^[6,38] Some users report a delay in that onset of the desired effects following oral ingestion if it is taken after food, suggesting that absorption is delayed in the presence of food. The duration of the desired effects lasts up to 2–3 h following nasal insufflation or oral ingestion (although shorter for nasal insufflation compared to oral ingestion) and 15–30 minutes following intravenous injection.^[6,38] The majority of users will repeatedly re-dose within a single-use session to maintain the desired effects, irrespective of the route of use and may combine routes of use within a single-use session.

There is one published study that has tried to determine the metabolites of mephedrone, and the potential pathways involved in the metabolism of mephedrone in both a rat model and in human users.^[37] Rats were administered a single 20 mg/kg dose of mephedrone orally through gastric intubation, and their urine was then collected over the subsequent 24-h period. The total urine collected over the 24-h period was analyzed and the following metabolites were detected in addition to mephedrone: nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone, and nor-hydroxytolyl mephedrone. In the urine samples submitted for routine drug screening from users who admitted to oral use of mephedrone, in addition to detection of mephedrone and the same metabolites listed above in the urine, there was also a 4-carboxy-dihydro mephedrone metabolite detected. This suggests that a proportion of the mephedrone 'orally ingested' in both the rat model and in humans is excreted unchanged in the urine, with the remainder being metabolized by a number of different pathways. However, it should be noted that it is not possible to determine from these studies either how long mephedrone and its major metabolites are detectable in urine or the time course over which the different metabolites are excreted. Additionally, to date, there are no studies that have investigated the time course of detection of mephedrone and its major metabolites in blood.

A number of overlapping pathways for the metabolism of mephedrone have been postulated on the basis of the results of the above study in rats and humans.^[37] These pathways can be summarized as follows:

- *N*-demethylation to the primary amine (responsible for forming the nor-mephedrone, nor-dihydro mephedrone and nor-hydroxytolyl mephedrone metabolites);
- reduction of the keto moiety to the respective alcohol (responsible for forming the nor-dihydro mephedrone and 4-carboxy-dihydro mephedrone metabolites); and
- oxidation of the tolyl moiety to the corresponding alcohol (responsible for forming the hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone metabolites); the authors further postulated that these hydroxytolyl mephedrone and nor-hydroxytolyl mephedrone metabolites are partly excreted in the urine as glucuronide and sulfate conjugates.

Pharmacodynamics

There are no formal studies in humans or animal models investigating the pharmacodynamics of mephedrone. The desired effects reported by users on discussion forums and in surveys appear to suggest that mephedrone has similar stimulant, sympathomimetic effects to MDMA (ecstasy) and cocaine.^[6,7,13,15,25,26]

The desired effects, both psychological and behavioural, reported by users of mephedrone include euphoria, general stimulation, enhanced appreciation of music, elevation of

mood, reduced hostility, improved mental function, and mild sexual stimulation.^[6,7,15,22,25] Sixty percent of UK clubbers using mephedrone reported that they experienced some degree of increased sex drive following the use of mephedrone, and 8.4% reported that this was occurred every time they used mephedrone.^[25]

In a recent survey of 947 UK clubbers who reported use of mephedrone, users were asked specifically how they thought the desired effects associated with the use of mephedrone compared to those associated with the use of cocaine;^[25] 54.6% reported that the high associated with the use of mephedrone was better than that with cocaine and 65.2% reported that the high was longer-lasting with mephedrone compared to cocaine. Although those who used mephedrone orally were more likely to report that the duration of the high was longer than those who used it by nasal insufflation, the route of use was not associated with any perceived difference in the quality of the high.^[25]

Acute toxicity

There are no formal human or animal studies to determine the prevalence of adverse effects associated with the use of mephedrone. Currently, the available information is from user self-reports on Internet discussion forums, surveys of users, information from poisons information services, and case reports/case series of individuals presenting to healthcare facilities with acute toxicity related to the use of mephedrone.^[5,6,8,9,13,15,25,24,39,41–44] It should be noted that in the majority of cases, these are based on self-reported mephedrone use, because routine toxicological screening is not undertaken in patients presenting with acute recreational drug toxicity to the Emergency Department as the results are typically not available in a time-frame to alter an individual patient's management. Furthermore, even if screening is undertaken, many standard analytical libraries do not contain mephedrone and the other cathinones, and therefore unless the samples are analyzed in a specialized toxicological laboratory, a negative result for mephedrone would not exclude its use. There have been a small number of case reports and case series which are analytically confirmed.^[9,39,43] In addition, the majority of use of mephedrone is part of an overall drug use repertoire, and therefore some of the unwanted effects reported by users may relate to the concomitant use of other drugs, including alcohol, ketamine, gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL), and/or other stimulant drugs such as MDMA (ecstasy), amphetamine, or cocaine.

Mephedrone has a similar-sounding name to other synthetic cathinones (e.g. methedrone and methylone) and also to non-cathinone drugs such as methadone. This similarity in their names has led to confusion, not only amongst users, but also amongst healthcare professionals and law enforcement agencies.^[3,5] There is the potential that some of the earlier cases of mephedrone toxicity were recorded as other drugs, including methadone, before healthcare professionals were aware of mephedrone's use as a recreational drug.^[3]

Users report 'head rushes', inability to concentrate, inability to visually focus, memory problems, altered conscious level, nasal irritation and nose bleeds, increased body temperature (often referred to as 'mephedrone sweat'), chest pain, nausea and vomiting, discoloration of extremities and joints, elevated heart rate, tremors and convulsions, headaches, bizarre behaviour, anxiety, agitation, insomnia and/or nightmares, hallucinations and delusions

as the most common undesired psychological and behavioural effects associated with the use of mephedrone.^[5,6,13,15,24–26,38] Anecdotally, the risk of more severe unwanted effects appears to be associated with either high dose and/or prolonged use of mephedrone. In addition, users of intravenous mephedrone also report paracitosis, leading to scratching and gauging of the skin particularly of the face, neck, and arms; paranoia; suicidal ideation; and severe insomnia particularly after prolonged periods of use [Callum McVean, Guernsey, pers. comm.³].

Some of the larger user surveys have reported on the frequency of different unwanted effects related to the use of mephedrone. However, as these are often small sub-population surveys, it is not possible to extrapolate these data to an overall prevalence of unwanted effects amongst mephedrone users. In a survey of 900 UK clubbers, individuals who self-reported mephedrone use provided information on the frequency of unwanted effects experienced.^[25] Clubbers were asked to comment on specific unwanted effects and indicate whether they had experienced these in association with mephedrone use. Therefore it is not possible to determine the pattern of unwanted effects, but simply the reported frequency with which specific pre-determined unwanted effects occurred. These unwanted effects were: excessive sweating (67.2% of users); headache (50.7%); palpitations (43.4%); nausea (37.0%); and cold blue fingers/toes (15.3%). Fifty-six percent of those who had previously used mephedrone in the Scottish student survey reported experiencing at least one adverse effect associated with the use of mephedrone.^[5] Similar to the UK clubber survey, those surveyed were asked to indicate whether they had experienced any of a predetermined list of unwanted effects in relation to the use of mephedrone. The frequency of experiencing these unwanted effects was: bruxism (28.3% of users); 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%). In this study, a significant proportion of users reported local irritant effects related to the nasal insufflation of mephedrone, such as sore nasal passages and nose bleeds.

There are also a number of case reports and case series relating to individuals presenting to healthcare facilities with acute mephedrone toxicity.^[8,9,39,41,43] The first reported case of confirmed acute toxicity related to the use of mephedrone was an individual who presented following both oral ingestion and intramuscular injection of mephedrone powder, and developed typical sympathomimetic clinical features.^[39] Analysis of a serum sample obtained on presentation to the Emergency Department confirmed that he had used mephedrone and no other recreational drugs were detected. We have previously published a case series of 15 patients who presented to our Emergency Department in London during 2009 with acute toxicity related to self-reported mephedrone use.^[8] Subsequent to these cases in 2009, we have seen a number of other patients presenting with acute toxicity following mephedrone use. Data were submitted to the EMCDDA as part of the risk assessment process on mephedrone in 2010 on a total of 72 patients that we had seen until the middle of June 2010.^[3] There were no patients with acute recreational drug toxicity who reported the use of mephedrone prior to the beginning of 2009.^[8]

The mean \pm SD age was 27.8 ± 8.7 years (range 16–54 years) and 81.9% were male; this high proportion of males may reflect that in the local vicinity of our Emergency Department is a large number

of nightclubs and night-time venues that cater for men who have sex with men (gay) community. Information was available on the route of use in 35 (48.6%) presentations: nasal insufflation (54.3% where route of use was specified) was the most common route of use, followed by oral ingestion (34.3%); combined nasal insufflation/oral ingestion (8.6%); and combined oral ingestion/IM injection (2.9%). The amount of mephedrone used prior to the presentation in the Emergency Department was reported in mass (mg/g) quantities by 21 (29.2%) individuals and in these cases the mean \pm SD (range) total amount used was 1.9 ± 2.0 (0.3–7.0)g.

Nine patients presented with self-reported lone mephedrone use and in the remaining 63 patients the mean \pm SD number of co-used substances was 1.6 ± 0.9 . The most commonly co-used substance was gamma-hydroxybutyrate (GHB)/gamma-butyrolactone (GBL) in 44% of those reporting use of other substances; other self-reported co-used substances included: ethanol (41.3%); cocaine (17.5%); MDMA (ecstasy) (15.9%); ketamine (14.3%); cannabis (6.3%); methamphetamine (4.8%); and volatile nitrites (4.8%). Additionally, two patients reported the use of methylone, a cathinone, and three reported the use of another unspecified 'legal high'.

The most common clinical symptom and/or sign prior to or on presentation to the Emergency Department was agitation (38.9% of patients). Other commonly reported features on presentation were palpitations (25.0%), vomiting (13.9%), chest pain (12.5%), self-limiting pre-hospital seizures (6.9%), and headache (7.2%). There were no reports of skin discolouration or cool/cold peripheries in this series. Baseline physiological parameters on arrival were: mean heart rate 93.1 ± 26.1 (range 50–158) beats per minute; mean systolic blood pressure 141.1 ± 23.7 (range 99–210) mmHg; and mean temperature 36.0 ± 1.0 (range 33.0–38.1) $^{\circ}$ C. In terms of markers of severity, 13.9% had clinically significant hypertension (pre-defined prior to analysis of the data as a systolic blood pressure ≥ 160 mmHg), 36.1% of had a tachycardia (heart rate of ≥ 100 bpm), and 8.3% had a severe tachycardia (≥ 140 bpm). No patients had clinically significant hyperpyrexia. Serum urea and electrolytes were measured in 34 (47.2%) and were normal in 33 (97.1% of those measured). There was one patient with hyponatraemia (serum sodium concentration of 125 mmol/l); this patient died following presentation to hospital and is discussed in more detail in the mephedrone-related fatalities section below. Serum creatinine kinase was measured in 18 (25.0%) and was raised in 10 of these patients (55.6% of those in whom it was measured), ranging from 296–4134 IU/L (upper limit of normal 229 IU/L).

The majority (61; 84.7%) of patients were discharged either directly from the Emergency Department or from the short-stay observation ward. Of the 11 (15.3%) patients who were admitted to hospital, 8 (11.1%) were admitted for observation/management on a general internal medicine ward and 3 (4.2% of all presentations) required admission to the intensive care unit. Ten (13.9%) patients required the use of benzodiazepines (oral or intravenous) for the management of ongoing agitation at or after the time of presentation to hospital. Overall, 71 (98.6%) survived to discharge from hospital with no long-term sequelae at the time of discharge and the mean length of stay following presentation to hospital was 6.7 ± 7.3 (range 0.3–30.0) h.

We have previously reported a case series of nine individuals who presented with acute recreational drug toxicity and self-reported mephedrone use in whom comprehensive toxicological screening was undertaken.^[9] Mephedrone use was confirmed in 7 (77.8%) of these patients; it is presumed that mephedrone was not detected in the other two patients as they presented more than

24 h after mephedrone use. 4 (57.1% of those where mephedrone was detected) had used only mephedrone; the other drugs co-used with the mephedrone in the remaining three patients were cocaine (two patients) and butylone/MDPV (one patient). The patients were of similar age (24.6 ± 6.5 years (range 16–36 years)) and had used mephedrone by similar routes (oral ingestion (2, 33.3% where route of use was specified), combined nasal insufflation and oral ingestion (2, 33.3%), nasal insufflation (1, 16.7%) and combined oral ingestion and intramuscular injection (1, 16.7%)) and in similar amounts (2.1 ± 2.3 (range 0.3–5.0) g) as the cases described above where toxicological screening was not undertaken. The clinical symptoms on or before presentation to the ED were similar: agitation (4 patients), palpitations (2 patients); chest pain (2 patients); self-limiting pre-hospital seizures (1 patient); and headache (1 patient) (14.3%) who had a self-limiting pre-hospital seizure and 1 (14.3%) who had a headache. No patients had any skin discolouration or cool/cold peripheries and no patients reported vomiting. In terms of physiological parameters on presentation to the ED, 42.9% had clinically significant hypertension (systolic blood pressure ≥ 160 mmHg), 71.4% of had a tachycardia (heart rate of ≥ 100 bpm) and 14.3% had a severe tachycardia (≥ 140 bpm); no patients had clinically significant hyperpyrexia.

There has been one other large case series describing the pattern of toxicity seen in patients presenting to an Emergency Department in Aberdeen, Scotland.^[45] There were 89 presentations between 1 December 2009 and 16 April 2010 of patients with recreational drug toxicity and self-reported use of mephedrone. There was no toxicological screening in this study to confirm use of mephedrone and/or exclude the use of other drugs. Thirty (33%) presented after self-reported use of mephedrone alone, 27 (30%) had used alcohol in addition to mephedrone and 32 (35%) had also used other drugs. There were no data in the paper on the other drugs used and no information was included on the clinical features seen in these patients who had co-ingested other drugs. The following clinical features were recorded in more than 10% of the 57 patients with self-reported mephedrone and self-reported mephedrone and alcohol use: anxiety/agitation ($n = 23$, 40.4%), chest pain (14, 24.6%), paraesthesiae (14, 24.6%), palpitations (12, 21.1%), dyspnoea (10, 17.5%), confusion (10, 17.5%), collapse (8, 14.0%), and 'oral symptoms' (7, 12.3%). In these 57 patients, the mean \pm SD (range) heart rate was 110.6 ± 6.7 (68–184) beats per minute and systolic blood pressure was 137.0 ± 4.5 (88–184) mmHg. A tachycardia (defined as HR > 90 beats per minute) was present in 79% and 74% of patients had a systolic BP > 130 mmHg. Twenty patients had a blood sample taken for creatinine kinase and this was above the normal range (the authors did not state what the normal range for their laboratory was) in all but one case. The mean creatinine kinase in these 20 patients was 335 IU/L (95% confidence intervals 219–451, range 99–923). Of note, 14 patients had chest pain and a troponin was measured in 6 patients and was negative; however, it was not stated whether this was a troponin I or T or what time relative to the chest pain the troponin was taken.

In addition to the expected sympathomimetic effects related to mephedrone use, there have been case reports of more unusual adverse effects related to the use of mephedrone.^[41,43] There is a report from the Republic of Ireland of an individual who developed myocarditis related to the use of mephedrone.^[41] Although analysis of the reported 'plant food' that was ingested confirmed that this contained mephedrone, there was no analysis undertaken of biological samples obtained from the patient to confirm that the patient had actually used mephedrone and that

the features seen were related to mephedrone. Additionally, there is one case report of presumed 'mephedrone-induced euvoalaemic hypo-osmotic hyponatraemia with encephalopathy and raised intra-cranial pressure' in a 15-year-old girl following oral ingestion of mephedrone, with analytical confirmation that she had only used mephedrone.^[43]

There are reports on calls to poisons information services in the UK and Sweden, which have also reported on the frequency of unwanted effects.^[42,44] There were 150 calls to the Swedish Poisons Centre concerning cathinones in 2008/2009, and mephedrone was the cathinone involved in 100 of these (82 in 2008 and 18 in 2009).^[44] Clinical symptoms/signs reported by the clinicians calling the poisons centre included tachycardia (present in 54% of these cases), restlessness (37%), mydriasis (25%), hypertension (14%), and anxiety (14%). In a report from the UK National Poisons Information Service (NPIS), there were 157 calls relating to mephedrone between March 2009 and February 2010.^[42] In this study, the authors only commented on calls to the UK NPIS where the clinician reported that the patient who they were treating had used mephedrone alone or in combination with ethanol; those with co-use of other recreational drugs were excluded – data were reported on 131 telephone enquiries. However, given the high rate of polysubstance use reported in other studies,^[3,8,9] there is the potential that in a proportion of the cases included, the patient may have also used one or more recreational drug (either the clinician calling had not asked about other drug use or did not volunteer this information to the poisons service). The most commonly reported clinical features reported in the calls included were: agitation/aggression (24% of calls); tachycardia (22%); anxiety (15%); confusion or psychosis (14%); chest pain (13%); palpitations (11%); and nausea (11%). Clinical features occurring in 5–10% of calls included fever/sweating, dizziness, peripheral vasoconstriction, mydriasis, headache, skin changes/rash, hypertension, abdominal pain, insomnia, and reduced level of consciousness. Convulsions were reported to have only occurred in 4% of cases and myoclonus in 2%. Interpretation of the frequency of unwanted effects in both of these studies needs to be with caution; as noted, the recording of a particular clinical feature related to acute mephedrone toxicity is dependent on the clinician calling the poisons information service volunteering this information. Additionally, this also applies to co-used drugs which in some cases may be more likely to have been related to the clinical features reported. However, despite these caveats, the types of clinical features reported and the frequency of their occurrence seems comparable to the studies collecting data from the Emergency Department and from user reports/surveys.^[5,6,8,9,13,15,25,39] In a proportion of calls to the UK NPIS, the symptoms appeared to be prolonged in duration: 45% had symptoms for more than 24 h and 30% had symptoms for more than 48 h post-exposure to mephedrone.

Mephedrone-related fatalities

During 2010, there was widespread media attention in the UK, as well as other countries, regarding potential deaths which have been 'linked' to the use of mephedrone.^[46–53] This coverage in the 'lay press' tends to occur shortly around the time of death, and is generally based on anecdotal reports of mephedrone use. Generally, at the time of death, when the media interest is maximal, there are no toxicological findings available to substantiate the claims that mephedrone was implicated in the death. Subsequent inquiries into the cause of death and toxicological screening of

ante- or post-mortem biological samples for mephedrone and other drugs takes time. It should be noted that in a number of cases in the UK, that either mephedrone was not detected or an inquest by the Coroner/Procurator Fiscal determined that mephedrone had not contributed to the death. In general, the subsequent media coverage stating that a death is not attributable to mephedrone has been less widespread and of lower profile than the initial coverage attributing death to mephedrone, and in some cases still makes reference to the initial media coverage about the death being related to mephedrone.^[3]

The data on potential mephedrone-related fatalities need, like all data on drug-related deaths, to be interpreted with caution. As already mentioned, the detection of mephedrone in either ante- or post-mortem biological samples does not necessarily mean that it is responsible for, or has contributed to, death. Additionally, the detection of mephedrone in ante- and/or post-mortem samples relies on the comprehensiveness of the analytical library used and whether the sample(s) were screened for mephedrone. Finally, at this time, the stability of mephedrone and its metabolites in post-mortem samples has not been determined, as well as the time course for their detection in human biological samples.

The first death attributed to lone mephedrone toxicity was in an 18-year-old female in Sweden.^[54] The individual had an out-of-hospital cardiorespiratory arrest following the reported use of mephedrone and cannabis. She was initially successfully resuscitated on arrival in the Emergency Department. Initial investigations in hospital showed hyponatraemia (serum sodium 120 mmol/L), a metabolic acidosis and cerebral oedema; no samples were taken to determine the aetiology of the hyponatraemia. Despite having been successfully resuscitated, she was declared brain dead on the intensive care unit 36 h after arrival in the Emergency Department. Subsequent toxicological screening of blood and urine revealed the presence of mephedrone only (the mephedrone concentration was not reported), with no other drugs or alcohol detected.

There have been a number of other deaths reported in the medical literature where mephedrone has been detected either ante-mortem or post-mortem.^[9,55,56] One report from a forensic science group in Scotland discussed the detection of mephedrone in post-mortem biological samples in four deaths.^[55] Toxicological screening was undertaken of post-mortem blood in all cases, urine in three cases and hair in one case. There was no clinical information included in these deaths, and the authors stated that 'various prescribed and illegal drugs' were detected on analysis in three of the cases. Therefore, as noted previously, it is not possible to determine the significance of the detection of mephedrone in these cases. The authors comment that 'investigations are ongoing in the four cases', but that mephedrone intoxication was recorded as the cause of death in two. Additionally, one of the remaining deaths was attributed to an abdominal stab wound.

We previously reported a death where mephedrone was detected in ante-mortem biological samples.^[9] A 29-year-old male was found collapsed and unwell in a local nightclub. An unlabelled zip-lock bag containing a white powder was found in his pocket; subsequent toxicological screening confirmed this white powder to be mephedrone. Similar to the Swedish death discussed earlier, he had evidence of significant cerebral oedema and hyponatraemia (serum sodium concentration 125 mmol/L). Plasma and urine osmolalities available later suggested that this was likely to be the result of water intoxication. Following a witnessed generalized seizure in the Emergency Department, a further CT headscan demonstrated that he had developed tonsillar herniation. He was admitted to the Intensive Care Unit for

ongoing supportive management; after discussion with the family treatment was withdrawn. Qualitative ante-mortem toxicological screening confirmed the presence of mephedrone. No other recreational drugs were detected on an extended screen of both the powder and ante-mortem biological samples from the patient. The coroner determined that the cause of death was 'hypoxic brain injury due to cerebral oedema following ingestion of a psychoactive substance'. The coroner felt unable to state on the information available that the psychoactive substance was mephedrone, as it was possible that other drugs may have been used which would not have been readily detectable at the time the biological samples were collected (e.g. gamma-hydroxybutyrate and/or gammabutyrolactone).

There is one further clinical report from Maryland, USA of a 22-year-old male who was found collapsed and unresponsive in his living quarters and who was unsuccessfully resuscitated. Subsequent urine toxicological screening by GC-MS was positive for 6-acetylmorphine, codeine, morphine, doxylamine and mephedrone (198 mg/l); mephedrone was also detected in a post-mortem blood sample at a concentration of 0.5 mg/l. The medical examiner reported the cause of death as 'accidental multiple drug toxicity'. It is not possible to determine from the data presented in this case report what role mephedrone played in this death.^[56]

Finally, in the UK, there is collation of data on all suspected substance abuse and/or recreational drug related deaths is undertaken by the UK National Programme on Substance Abuse Deaths (np-SAD). Information provided to np-SAD on these on these deaths from a number of different sources in the UK, and includes the forensic analytical services, law enforcement agencies, the coroner/procurator fiscal system, drug and alcohol treatment teams, and occasionally from the 'lay media'. As noted, there are caveats in interpretation of the data provided to np-SAD, particularly when there has not been the formal inquest. In its 2010 annual report, published at the beginning of October 2010, it reported that there had been 45 deaths where mephedrone has been potentially implicated to be related to mephedrone in England, 12 in Scotland, 1 in Wales, 1 in Northern Ireland, and 1 in Guernsey.^[57]

Data were collated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) on deaths related to and/or where mephedrone had been detected as part of the Risk Assessment of mephedrone carried out in July 2010.^[3] At that time, there were only deaths in Sweden and the UK where the death was determined to be directly related to the use of mephedrone. Additionally, in the UK, there were deaths where mephedrone had been detected and was thought to have contributed to the death (in combination with one or more other factors) and deaths where mephedrone had been detected analytically but was not determined to have contributed to the death. A number of other countries (Austria, Belgium, Denmark, Finland, France, Germany, Italy, Latvia, Lithuania, Luxembourg, the Netherlands, Poland, Slovakia, and Slovenia) at that time reported that there had been no deaths directly or indirectly related to mephedrone. However, both Greece and Lithuania commented in their response to the EMCDDA that, at that time, mephedrone was not included within their countries analytical libraries and therefore it was not possible to determine whether mephedrone had been implicated in any deaths.

Chronic dependence liability

Given the pharmacology of mephedrone, it is unlikely that long-term use would be associated with a physical dependency and

withdrawal syndrome. However, similar to other classical and novel sympathomimetic recreational drugs, there is the potential that mephedrone could be associated with the development of psychological dependency. Mephedrone availability, and therefore use, has only been significant during 2009 and 2010, and therefore given its short history on the recreational drug scene, it is not possible to determine the true prevalence of dependency in chronic long-term users.

However, in a number of published reports there is the suggestion that users can develop 'cravings' for mephedrone.^[5,7,13] Of the 205 students in the Scottish school survey who had previously used mephedrone, 17.6% reported 'addiction/dependency' symptoms in relation to their mephedrone use.^[5] Seven hundred and ninety-seven of the UK clubbers reported use of mephedrone compared its addictiveness to cocaine, and 44.3% of them reported that it was 'as or more addictive' than cocaine.^[25] Additionally, those who used mephedrone by nasal insufflation were more likely than those who used it by oral ingestion to rate it as more addictive than cocaine. This may reflect the more rapid onset of the desired high and shorter duration of action following nasal insufflation compared to oral ingestion. The risk for the development of cravings for mephedrone is reported to be highest in those with frequent use of it.^[7,13] This potential for cravings associated with mephedrone use is reported by some users as the 'main problem associated with mephedrone use'.^[3] It is thought that the cravings occur due to the fact that the use of mephedrone is associated with the desired 'high' users require, but that it has a relatively short duration of action. This leads individuals to repeatedly 'dose' with mephedrone during a single use session. Additionally, users also report that they develop cravings for mephedrone between use sessions, and in some individuals this can be associated with an increased frequency of use.^[25]

In addition to the cravings associated with use, there is one case that was reported at a Scottish addiction conference in 2009 of an individual who developed dependence related to long-term use of mephedrone.^[58] The gentleman, with no previous history of psychiatric disease or drug/alcohol dependency, had been using mephedrone on a regular basis over an 18-month period. He presented to psychiatric services with transient psychosis, hallucinations, hypomania, and mood disturbance. He fulfilled ICD-10 criteria for a 'dependence syndrome' and required inpatient treatment for his clinical symptoms. There are also anecdotal reports of increasing numbers of individuals presenting to drug treatment services, either with problematic isolated mephedrone use or in combination with other classical and/or novel psychoactive substances.^[3]

Given that mephedrone is not likely to be associated with a physical dependency syndrome, there is unlikely to be any specific management in terms of a withdrawal syndrome. Users with psychological dependency may require medical treatment for their symptoms on discontinuation, but we would not recommend a routine withdrawal programme as for other drugs such as gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL), opioids, and ethanol. In those individuals with problematic use of mephedrone, there is likely to be the need for ongoing psychological support after discontinuation of use to prevent relapse.

Summary

Mephedrone has been available in Europe since 2007, and there was increasing evidence of its availability and use as a

recreational drug during 2009 and 2010. There is currently no systematic collection at a population level on the prevalence of use of mephedrone. However, data from surveys of subpopulation groups, including students and clubbers, suggest that mephedrone is widely used. Some of these studies suggest a similar prevalence of recent use (within the last month) to established recreational drugs such as cocaine and ecstasy (MDMA). There is some anecdotal evidence that whilst mephedrone use has continued, this has reduced from the peak rates of use seen in early 2010 following the control of mephedrone in the UK and some other European countries. Mephedrone is typically sold in powder form but is also available to users in tablet and capsule form. It is used predominantly by oral ingestion or nasal insufflation, although some users report that the severe nasal irritant effects associated with insufflation means that they switch to oral ingestion.

Prior to control, it was easily obtainable and widely available from street-level drug dealers, high-street head shops, and Internet suppliers. Since control, the number of Internet sites openly selling mephedrone has decreased and these have based themselves in countries where mephedrone remains legal. Additionally, a number of studies have shown that classified cathinones such as mephedrone are still available in Internet 'legal high' products, either sold transparently as mephedrone or mis-sold to users in products claiming not to contain mephedrone or other controlled substances.

Data on the pattern of acute toxicity associated with the use of mephedrone come from user self-reports on Internet discussion forums, surveys of mephedrone users, information from poisons information services and case reports/case series of individuals presenting to healthcare facilities with acute toxicity related to the use of mephedrone. Often these data are based on self-reported mephedrone use, although there have been a small number of analytically confirmed mephedrone cases reported where the pattern of acute toxicity is similar to that in the self-reported mephedrone use cases. These suggest that mephedrone causes similar sympathomimetic features to other stimulant drugs such as cocaine and ecstasy (MDMA). A number of reports suggest that mephedrone users can develop cravings for mephedrone and there are anecdotal reports of psychological dependence to mephedrone. There has been widespread media attention concerning 'potential' mephedrone related fatalities. However, whilst mephedrone has been detected in a number of deaths, there have only been a small number of cases in which the death was directly related to mephedrone.

Mephedrone was controlled as a Class B substance under the Misuse of Drugs Act (1971) in the UK on 16 April 2010 and in December 2010 the European Council recommended that mephedrone be submitted to control measures across the European Union. It is not currently clear what the potential effects of these control measures will be in terms of both the prevalence of mephedrone use and the acute harm related to its use. Some authors have already reported that as a result of the control of mephedrone in the UK, the price of mephedrone has increased alongside a decrease in its purity.

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