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Mephedrone (4-methylmethcathinone): What is new in our understanding of its use and toxicity

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ABSTRACT

Mephedrone (4-methylmethcathinone) is a synthetic cathinone that has been used as a recreational drug in Europe and elsewhere in the world since 2007. In addition to published scientific papers there are a number of different data sources available which provide information on the sources, availability and prevalence of use of mephedrone. Whilst there are no formal human studies to determine the acute toxicity of mephedrone, there is a range of different levels of data available which describe the acute toxicity of mephedrone. These include user Internet discussion fora, sub-population level surveys of user previous experiences of acute toxicity and individual case reports and case series of toxicity related to both self-reported and analytically confirmed mephedrone use. In this review article we describe how through the process of data triangulation using a combination of these different sources, it is possible to develop an understanding of the acute toxicity of mephedrone. This demonstrates that mephedrone has a pattern of acute toxicity that is similar to other stimulant drugs such as MDMA, amphetamine and cocaine.

1. Introduction

'Mephedrone', the synthetic cathinone 4-methylmethcathinone, has been available on the European recreational drug scene since 2007 (Dargan and Wood, 2010; Dargan et al., 2011). Although it was initially legally available throughout Europe, it was controlled as a Class B substance under the Misuse of Drugs Act, 1971 in the UK in April 2010 and in December 2010, The European Council adopted a decision on submitting mephedrone to control measures across the European Union (Council Decision, 2010). It was also controlled in 2011 under the Controlled Substances Act in the US (DEA, 2011). In this review article, we will provide a background to introduce what mephedrone is, and then discuss what is new in the prevalence of use of mephedrone and our understanding of the toxicity related to its use.

Abbreviations: ED, Emergency Department; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EWS, Early Warning System; GC–MS, Gas-chromatography mass-spectrometry; LC–MSMS, Liquid chromatography with mass-spectrometry mass–spectrometry; MDMA, Methylenedioxymethamphetamine; NMR, Nuclear magnetic resonance; NPIS, National Poisons Information Service; UPLC–QTOF–MS, ultra performance liquid chromatography–quadrupole time of flight-mass spectrometry.

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2. Background

2.1. What is mephedrone?

Mephedrone is usually purchased by/sold to users in powder form in small sealed plastic bags which are marked as 'not for human consumption' or 'research chemical' (Dargan and Wood, 2010; Dargan et al., 2011; Newcombe, 2009; Psychonaut 2009; Schifano et al., 2011). It is marketed under a number of brand names, including 'plant feeder', 'plant food' and 'bath salts', and of note in Europe it was more commonly sold as mephedrone or 'plant food', but in the US was more commonly sold as 'bath salts' (Dargan and Wood, 2010; Newcombe, 2009; Prosser and Nelson, 2012; Psychonaut, 2009; Schifano et al., 2011; Spiller et al., 2011). Despite these brand names, mephedrone has no proven use as a plant food or as a bath/cosmetic product. Although the majority of mephedrone is sold in powder form, it is available in tablet or encapsulated forms (Dargan et al., 2011). Use is predominately by nasal insuffulation, although some users report that this is associated with significant unwanted nasal effects, and therefore some individuals may dissolve it in water/other drinks or swallow the powder wrapped in paper (known as 'bombing') (Dargan et al., 2011; Dargan and Wood, 2010; Measham et al., 2010).

2.2. Sources of mephedrone

Mephedrone has been reported to be available from street-level drug dealers, high-street retail outlets known as 'head shops' and the Internet (Dargan et al., 2011; Dargan and Wood, 2010; Dargan et al., 2010; Drugs

Forum; EMCDDA, 2010; EMCDDA, 2011; Erowid; Measham et al., 2010; Newcombe, 2009). The European Monitoring Centre for Drugs and Drug Addiction, using their 'snapshot' Internet survey techniques, demonstrated that there was a significant increase in the number of Internet sites selling mephedrone between December 2009 and March 2010, when there were increasing reports of mephedrone use, and that the majority of these were UK based (Dargan and Wood, 2010; EMCDDA, 2010; EMCDDA, 2011; Hillebrand et al., 2010). They typically were mephedrone specific websites, and would ship mephedrone to any country on request. After the control of mephedrone in the UK in April 2010, not only was there a significant decrease in the number of internet sites selling mephedrone, the majority of sites were no longer UK based and a significant proportion had changed to selling other 'legal highs', which may in fact be mephedrone being sold covertly under different brand names (Brandt et al., 2010a, 2010b; Dargan and Wood, 2010). This puts the individual purchaser at risk of potential criminal conviction, since inadvertently they may be purchasing a substance that is controlled in the country where it is being supplied to.

Use of the internet to source mephedrone in the UK prior to its control appeared to be less common amongst younger aged users; it was felt that this was due to the limitation of appropriate banking facilities to purchase on line and/or a secure delivery address away from parents/guardians (Dargan et al., 2010). These users were more likely to source their mephedrone from street-level drug dealers or friends. There is some suggestion that there has been a shift to greater sourcing of mephedrone from street-level drug dealers amongst all users; for example in one survey of 150 individuals who had used mephedrone prior to the UK control, 95 (63%) had continued to use it after its control and the proportion who had sourced from street-level drug dealers increased from 41% to 57% (Dargan and Wood, 2010; Measham et al., 2011a; Winstock et al., 2010).

2.3. Analytical techniques to detect mephedrone

There are currently no 'field tests' for mephedrone and it does not give a colour reaction with the Marquis Field test (this is a spot field test used to detect MDMA, amphetamine and other structurally related drugs). Detection of mephedrone and its metabolites is possible using techniques that have been developed for gas-chromatography mass-spectrometry (GC–MS), liquid chromatography with mass spectrometry–mass spectrometry (LC-MSMS), ultra performance liquid chromatography–quadrupole time of flight-mass spectrometry (UPLC-QTOF-MS), microcrystalline identification and nuclear magnetic resonance (NMR) (Bell et al., 2011; Brandt et al., 2010a; Camilleri et al., 2010; Elie et al., 2012; Gibbons and Zloh, 2010; Jankovics et al., 2011; McDermott et al., 2011; Meyer et al., 2010; Power et al., 2011; Reitzel et al., 2011; Santali et al., 2011; Sørensen, 2011). However, it should be noted that some of these techniques do not distinguish between the different methyl-methcathinone isomers, although this is possible through the use of nuclear magnetic resonance spectroscopy (NMR), where these facilities are present (Gibbons and Zloh, 2010; Meyer et al., 2010).

Hair analysis has previously been used to detect chronic use of recreational drugs such as cocaine and amphetamine. This type of analytical technique has also been extrapolated to mephedrone (Martin et al., 2012; Petróczi et al., 2011; Shah et al., 2012). These studies have demonstrated that it is not only possible to detect mephedrone in hair samples, but also two of its metabolites — 4-methylephedrine and 4-methylnorephedrine. The concentration of mephedrone and its metabolites in hair appear to be in the pg/mg hair to ng/mg hair range, similar to that with other recreational drug incorporation.

3. Prevalence of use

Information on the prevalence of use is available from data on seizure at both border and local law enforcement level and population or subpopulation level surveys.

3.1. Border and law enforcement seizure data

Within the European Union, information on detection of drugs such as mephedrone is collated through the EMCDDA Early Warning System (EWS) (EWS, 2007). The first reported seizure of mephedrone was in 2007 in Finland of capsules containing mephedrone and in 2008 it was detected in the UK and other Scandinavian countries (Sweden, Norway and Denmark) (Dargan and Wood, 2010; Dargan et al., 2011; EMCDDA-Europol, 2010). By the end of 2010 it had been detected in 31 European and neighbouring countries, suggesting widespread availability throughout Europe.

3.2. Population and sub-population use prevalence data

Collection of population prevalence of use of mephedrone was not undertaken by any EU country until the British Crime Survey included questions relating to the use of mephedrone in the 2010/2011 survey (Home Office Statistical Bulletin, 2011). Overall the prevalence of use in 16–59 year olds in the last year was 1.4%, which was the same reported prevalence for ecstasy. However, the prevalence of use was higher in those aged 16–24 at 4.4%, compared to 0.6% in those aged 25–59 years; the prevalence of use in those aged 16–24 was the same as the reported prevalence of cocaine use in this age range.

There have been two surveys of school/university aged children (Dargan and Wood, 2010; Dargan et al., 2010; Dargan et al., 2011). In a survey of 1006 Scottish school and college/university students undertaken prior to the control of mephedrone in the UK, 205 (20.3%) reported that they had used mephedrone on at least one occasion previously (Dargan et al., 2010). 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 subsequent survey 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 (Dargan and Wood, 2010).

There have been two studies undertaken in South London 'gay friendly' nightclubs, one in 2010 approximately three months after the UK control of mephedrone and one in 2011 over a year after mephedrone's control (Measham et al., 2011a; Wood et al., 2012). In the 2010 survey of 308 clubbers, 54% reported life-time use of mephedrone and 52% reported use within the last year (Measham et al., 2011a). There was continuing popularity of mephedrone in the 2011 survey, with 41% reported that at the time of the survey they had already taken mephedrone and/or were planning on taking mephedrone later that evening (34% had already taken it and 35% were planning to take it later) (Wood et al., 2012). Respondents were also asked to name their favourite drug in this survey; mephedrone was the most commonly reported favourite drug (20.4%) of those surveyed. A third convenience sample of 207 bargoers in the night-time economy of Lancaster, a town in Northern England, showed approximately 5% of those surveyed reported use of mephedrone in the last month (Measham et al., 2011b). This study reported that mephedrone was being added to existing drug repertoires, rather than displacing other established drugs.

The self-reported prevalence of mephedrone use in same-sex attracted adults in Sydney, Australia was lower than in the UK (Lea et al., 2011). In an online survey of 572 same-sex attracted men and women aged 18 to 25 years, who lived or regularly spent time in Sydney, life-time prevalence of mephedrone use was 4.0% of those surveyed; 2.1% had used in the preceding 6 months and 1.4% in the preceding month. In a study of 693 regular ecstasy users in Australia, 28% reported that they had previously used an emerging psychoactive substance in the last six months (Bruno et al., 2012). Mephedrone was the most commonly used emerging psychoactive substance,

both from a stimulant and hallucinogenic perspective; 21% reported having ever used it and 17% reported use within the last six months.

Data is available from the annual MixMag surveys, which collect information from individuals who associated themselves with the MixMag magazine and its associated on-line Internet survey site. MixMag is a monthly print magazine, with the associated Internet site, that is targeted at individuals who are interested in clubbing and the clubbing scene. It is not solely available in the UK, and this is reflected by the international respondents that complete the annual MixMag drug surveys. In the 2009/10 survey, life-time and last month use of mephedrone were 41.7% and 33.6% (Dick and Torrance, 2010). Analysis of the 2295 UK respondents, reported that 41.3% had ever used mephedrone; 38.7% had used in the last year and 33.2% in the last month (Winstock et al., 2011a). Mephedrone was the sixth most frequently used drug in the last month after tobacco, alcohol, cannabis, cocaine and MDMA. In the 2010/2011 MixMag survey, life-time use had increased to 61% of those surveyed and use within the last year was 51% (Winstock, 2011). A greater proportion of younger individuals had used mephedrone in the last year: 58% of 18–20 year olds and 53% of 21–30 year olds 53%, compared to 37% of those aged over 30 years.

4. Acute toxicity

The information on the acute toxicity (harm) related to the use of mephedrone is available from a number of different data sources: i) user reports on Internet based discussion fora; ii) sub-population user surveys of unwanted effects; iii) information on reports to regional and national poisons information services; and iv) Emergency Department case reports and case series (Brunt et al., 2011; Dargan et al., 2010; Dick and Torrance, 2010; Drug Forum; Erowid; Hägerkvist et al., 2010; James et al., 2011; Nicholson et al., 2010; Psychonaut, 2009; Sammler et al., 2010; Schifano et al., 2011; Winstock et al., 2011b; Wood et al., 2010a; Wood et al., 2011; Wood et al., 2010b). The main limitation of a number of these data sources is that they are based on self-reported mephedrone use, and therefore there is the potential that whilst the individual believes that they have used mephedrone, they may in fact have used a different compound (Brandt et al., 2010a, 2010b; Davies et al., 2010; Ramsey et al., 2010; Spiller et al., 2011). In addition, mephedrone use may be part of a poly-drug repertoire, and therefore there is the potential that some/all of the described unwanted effects may be due to the other drug(s) rather than the mephedrone. Therefore, caution should be used when considering these data sources, but it is possible to combine the information from the number of different data sources mentioned above to build an overall summary of the acute toxicity associated with the use of mephedrone.

In terms of information from the US on "mephedrone-related toxicity" presenting to the Emergency Department, these reports typically are of toxicity related to the use of "bath salts" (Adebamiro and Perazella, 2012; CDC, 2011; Kasick et al., 2012; Spiller et al., 2011). Whilst some of these products may have contained mephedrone, a significant proportion will contain other novel psychoactive substances. Therefore it is not possible to extrapolate the data from these reports to incorporate in our wider assessment of the toxicity of mephedrone.

4.1. User discussion fora and surveys

Often the first sources of information on the acute toxicity related to the use of any novel psychoactive substance are reports on Internet-based user discussion fora (Drugs Forum; Erowid). The reports may also be augmented by sub-population surveys of users, which collate information on the unwanted effects described (Dargan et al., 2010; Dick and Torrance, 2010; Psychonaut, 2009; Schifano et al., 2011; Winstock, 2011; Winstock et al., 2011a, 2011b). In addition to the limitation that both of these data sources are based on self-reported non-confirmed mephedrone use, the sub-population surveys often use pre-defined unwanted effects to collect information, which may limit collection of information on the overall adverse effect profile. Overall, however, 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, discolouration of extremities and joints, elevated heart rate, tremors and convulsions, headaches, bizarre behaviour, anxiety, agitation, insomnia and/or nightmares, hallucinations and delusions.

There is the potential in sub-population level surveys to look at the reported frequency of unwanted effects. In a survey of 900 UK clubbers, individuals who self-reported mephedrone use provided information on the frequency of a number of pre-defined unwanted effects experienced: sweating (67.2% of users); headache (50.7%); palpitations (43.4%); nausea (37.0%) and cold blue fingers/toes (15.3%) (Winstock et al., 2011a). In the Scottish student survey, 56% of those who had previously used mephedrone reported experiencing at least one adverse effect associated with its use (Dargan et al., 2010). The frequency of the pre-defined adverse effects in this survey were: 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 an Internet based survey of 1506 previous/current mephedrone users, 20% reported a significant negative reaction related to mephedrone use in themselves and 28% reported that a friend had had a significant negative reaction whilst using mephedrone (Carhart-Harris et al., 2011). Only skin discolouration/blotches was asked about specifically; 21% reported experiencing this related to using mephedrone.

Telephone interviews were conducted using individuals who had previously been in online research into mephedrone to investigate further the qualitative effects of mephedrone (Winstock et al., 2011b). 100 individuals, of the 218 who had previously expressed an interest in being involved in follow-up research were recruited. Individuals were asked about both positive and negative subjective effects related to the use of mephedrone, and the investigators attempted to standardise for frequency of the effect and the severity of the effect with a frequency-intensity effect product with a maximum score of 9. In terms of unwanted effects related to the use of mephedrone, the highest frequency–intensity effect was bruxism (frequency–intensity effect product 5.1). Other physical features of mephedrone toxicity included: body sweats (4.4), heart racing (3.8), overheating (2.8), tremor (2.6), shortness of breath (1.9), headache (1.4) and chest pain (0.8). The highest frequency neuro-psychiatric symptom was forgetting things (frequency–intensity effect product 3.5); others included restlessness/anxiety (3.3), paranoia (1.4), panic (1.2), agitation (1.4), visual hallucinations (0.8), auditory hallucinations (0.5) and aggression (0.2). Similar to other user surveys, there was reporting of cold/numb extremities (0.9), blue/red skin (0.5), skin rashes (0.3), although the frequency–intensity effect product was lower than for the majority of the other unwanted effects.

4.2. Regional and national poisons centre data

There are published reports on calls to local and/or regional poisons information services in the UK and Sweden (James et al., 2011; Hägerkvist et al., 2010). Of the 150 calls to the Swedish Poisons Centre concerning cathinones in 2008/2009 (100 were mephedrone related) the clinical features reported by the clinicians calling included tachycardia (present in 54% of these cases), restlessness (37%), mydriasis (25%), hypertension (14%) and anxiety (14%) (Hägerkvist et al., 2010). In 131 telephone calls to the UK National Poisons Information Service (NPIS) relating to lone mephedrone and/or mephedrone and ethanol use (26 additional calls were excluded as the

caller mentioned other co-used substances), the most commonly reported by clinicians calling were: agitation/aggression (24% of calls); tachycardia (22%); anxiety (15%); confusion or psychosis (14%); chest pain (13%); palpitations (11%); nausea (11%) (James et al., 2011). Less commonly reported unwanted effects 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 occurred in only 4% of cases and myoclonus in 2%. The duration of the symptoms in the UK NPIS dataset appeared to be prolonged, with 45% having symptoms for more than 24 h and 30% having symptoms for more than 48 h post-exposure to mephedrone (James et al., 2011). Data on the pattern of unwanted effects of a novel psychoactive substances from regional or national poisons information services need to be interpreted with some degree of caution; not only does it require clinicians to contact the poisons information service, but it also requires them to volunteer the information on the unwanted effects involved. However, despite this, the pattern of unwanted effects reported in these datasets appears to be similar to that from users described above and from Emergency Department presentations described below.

4.3. Emergency Department presentation data

There are a number of case reports/series relating to individuals presenting to healthcare facilities with acute mephedrone toxicity (Lusthof et al., 2011; Nicholson et al., 2010; Sammler et al., 2010; Wong and Holt, 2011; Wood et al., 2010a; Wood et al., 2011; Wood et al., 2010b). The first reported case of analytically confirmed acute toxicity was an individual who presented following oral ingestion and intramuscular injection of mephedrone powder, who subsequently developed sympathomimetic clinical features (Wood et al., 2010a). There is a case of a fatality in The Netherlands in an individual who was initially found with extreme agitation and aggression, who was described as “having injured himself severely by smashing windows in a rage of fury” (Lusthof et al., 2011). There was post mortem analytical confirmation of mephedrone use (femoral blood 5.1 mg/L post mortem), although “traces” of cocaine, MDMA and oxazepam were also detected. Finally, there is also a report of an individual with Type 1 diabetes who presented with ketoacidosis following mephedrone use (Wong and Holt, 2011).

There is a report from the Republic of Ireland of an individual who developed myocarditis related to the unconfirmed use of mephedrone (there was analysis of the plant food reported to have been ingested, but no biological sample analysis) (Nicholson et al., 2010). One report was of presumed “mephedrone-induced euvolaemic 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 used only mephedrone (Sammler et al., 2010).

We have previously published information on a total of 72 patients presenting to our Emergency Department acutely unwell following self-reported use of mephedrone (Dargan and Wood, 2010; Dargan et al., 2011; Wood et al., 2011). Information on the unwanted effects in these individuals was extracted from the routine Emergency Department and Medical notes, rather than using a proforma with pre-defined unwanted effects. The most common unwanted effect on presentation to the ED was agitation (38.9% of patients); other common effects were palpitations (25.0%), vomiting (13.9%), chest pain (12.5%), self-limiting pre-hospital seizures (6.9%) and headache (7.2%). In particular there were no reports of skin discolouration or cool/cold peripheries in this series. A number of physiological markers of potentially severe toxicity were pre-defined prior to data analysis: 13.9% had significant hypertension (systolic blood pressure of $\geq$160 mm Hg); 8.3% had (significant tachycardia $\geq$140 bpm); 0% had significant hyper-pyrexia (temperature of $>$38.5 °C). Serum sodium concentrations were measured in 34 (47.2%) individuals, and were normal in 33 (97.1% of those measured). One patient who died following analytically confirmed mephedrone use had hyponatraemia with a sodium concentration of 125 mmol/L on presentation to the ED; subsequent review at the coroner's inquest and of the medical notes suggests that this was secondary to excess fluid intake and water intoxication.

Of this case series, biological samples were collected at the time of review from nine individuals and subsequently analysed to determine whether mephedrone had in fact been used (Wood et al., 2010b). Mephedrone use was confirmed in seven individuals, and it was felt in the remaining two that they had presented too long after use for it to be detected in the biological matrix analysed (blood/serum). 4 (57.1% of those where mephedrone was detected) had used only mephedrone; the other drugs co-used with the mephedrone in the remaining 3 patients were cocaine (2 patients) and butylone/MDPV (1 patient). Unwanted effects on or before presentation to the ED were similar to the larger self-reported group described above: agitation (57.1% of those with confirmed mephedrone use), palpitations (28.6%); chest pain (28.6%); self-limiting pre-hospital seizures (14.3%); and headache (14.3%). No patients had any skin discolouration or cool/cold peripheries and no patients reported vomiting. In this subset of patients, 42.9% had clinically significant hypertension, 14.3% had a significant tachycardia and again no patients had significant hyperpyrexia.

There is one further case series of 89 presentations to an ED in Aberdeen, Scotland relating to self-reported mephedrone use (Regan et al., 2011). 30 (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. Unwanted effects were reported only for the 57 patients with self-reported lone mephedrone or mephedrone and alcohol use. The most common unwanted effects were: anxiety/agitation (40.4%), chest pain (24.6%), parasthesiae (24.6%), palpitations (21.1%), dyspnoea (17.5%), confusion (17.5%), collapse (14.0%) and ‘oral symptoms’ (12.3%). Based on the clinical data published, a proportion of patients in this group will have had potentially clinically significant hypertension or tachycardia based on our pre-defined criteria above, however this is based on the range rather than actual publication of the proportion with clinically significant findings (heart rate range was 68–184 bpm and systolic blood pressure range was 88–184 mm Hg).

5. Animal models of mephedrone effects and toxicity

There have been a number of recent publications describing the use of animal models to investigate the potential pharmacological mechanisms of activity and the mechanisms of acute toxicity of mephedrone (Angoa-Pérez et al., 2011; Baumann et al., 2012; Hadlock et al., 2011; Kehr et al., 2011; Martínez-Clemente et al., 2012; Meng et al., 2012; Motbey et al., 2012; Ramoz et al., 2012).

The effect of mephedrone on the uptake of serotonin (5-HT) and dopamine has been investigated using isolated rat synaptosomes (Martínez-Clemente et al., 2012). Overall these studies demonstrated that that mephedrone inhibited the uptake of both serotonin (IC50 value 0.31 ± 0.08 μM) and dopamine (IC50 value 0.97 ± 0.05 μM) and that mephedrone had affinity for both serotonin and dopamine membrane transporters and receptors (5-HT2 and D2 receptors). This uptake study suggests that mephedrone has a similar effect profile to that of other amphetamine-like compounds. In a rat model, using microdialysis of the nucleus accumbens, mephedrone administration resulted in an increase in both extracellular serotonin and dopamine concentrations, and the effect was greater for serotonin (Baumann et al., 2012). Although repeated administration resulted in hyperthermia similar to repeated MDMA administration, there were no long-term changes in striatal or cortical amine concentrations that are seen with repeated MDMA administration. A further microdialysis study in the rat nucleus accumbens, demonstrated that mephedrone and amphetamine had similar effects on increasing dopamine concentrations (496% increase and 412% increase respectively) whereas MDMA had a

more moderate effect (235% increase), whereas mephedrone and MDMA had similar effects on serotonin concentrations (941% and 911% respectively) compared to amphetamine (165% increase) (Kehr et al., 2011).

In an invertebrate model, mephedrone resulted in stereotypical movement, similar to that seen with other psychostimulant drugs, which could be attenuated by dopamine receptor antagonists (Ramoz et al., 2012). Mice given mephedrone in a human like binge use pattern, developed stimulant like hyperthermia and locomotor stimulation (Angoa-Pérez et al., 2011). However, it did not result in the expected lowering of striatal dopamine, tyrosine hydroxylase or dopamine transport activity that is seen with other sympathomimetic drugs such as amphetamine derivatives. A further study in rats again demonstrated that administration of mephedrone resulted in an increase in locomotor activity and a reduction in social preference (Motbey et al., 2012). Subsequent histological analysis of the rat brains, to determine the pattern of brain activation, demonstrated that this was comparable to the combined pattern seen in methamphetamine and MDMA use. The authors in this study concluded that mephedrone had a similar effect profile to an MDMA/methamphetamine hydrid. The cardiovascular effects of mephedrone have been studied both *in vitro* and *in vivo* (Meng et al., 2012). Application of mephedrone to *in vitro* guinea pig cardiac myocytes, demonstrated that mephedrone had no effects on the major voltage-dependent cardiac ion channels. However, subcutaneous and intravenous administration of mephedrone to rats resulted in dose-dependent increases in heart rate and blood pressure, as well as overall cardiac function (cardiac output, ejection fraction and stroke volume).

These *in vitro* and *in vivo* animal studies provide some useful insight into the potential mechanisms for both the desired effects of mephedrone and a potential explanation for the acute toxicity seen with its use. Overall, it would appear that mephedrone has similar pharmacological actions in terms of increasing extracellular serotonin (5-HT) and dopamine concentrations to a combined amphetamine/MDMA profile. Similarly, the neuro-behavioural and cardiovascular effects appear to be those of an amphetamine/MDMA like combination. Based on our experience from discussions with users, they typically describe that mephedrone has an effect profile that they would describe as being similar to a combination of amphetamine/MDMA.

6. Impact of control of mephedrone

Mephedrone was controlled in the UK in April 2010 and across Europe in December 2010. The impact of controlling any drug and in particular a novel psychoactive substance is always subject to debate as to whether this results in a reduction in use and/or the harm associated with the use of the substance. The prevalence data from the MixMag and South London gay-friendly nightclubs, along with the British Crime Survey 2010/2011 suggests that there is significant ongoing use of mephedrone in the UK despite its ban in April 2010 (Home Office Statistical Bulletin, 2011; McElrath and O'Neill, 2011; Measham et al., 2011a; Measham et al., 2011b; Winstock et al., 2010; Wood et al., 2012). There is a suggestion in fact that not only has mephedrone use increased, but also that it is now the "preferred drug" in some sub-population level surveys (Wood et al., 2012). In line with mephedrone no longer being legally available following its control, surveys suggest that after control there is a shift to greater reliance on "street-level" drug dealers as the main source of supply, rather than previously used legitimate sources such as high-street head shops and the Internet (McElrath and O'Neill, 2011; Winstock et al., 2010). Additionally, users report that an effect of control is that not only has the quality (perceived purity) of mephedrone decreased, but the price has also increased (Winstock et al., 2010). Despite these user-perceived negative effects of control and the data showing significant continued control of mephedrone, there has been a suggestion that the control of mephedrone in the UK has been associated with a reduction in the number of Emergency Department presentations with acute mephedrone-related toxicity (Wood et al., in press). Similarly there has been a reduction in contacts with the UK National Poisons Information Service (NPIS) relating to mephedrone and in the number of deaths in which mephedrone has been involved following its control (Dargan and Wood, 2010). It is not possible to extrapolate that these results are simply due to a reduction in usage and therefore a direct impact of control. Following the widespread media interest and increasing data available in the medical literature on mephedrone, more healthcare professionals will be aware of mephedrone and its effects, and therefore may not access poisons services for advice. There is the potential that whilst there is ongoing use a reduction in purity has meant that individuals are exposed to less actual mephedrone and therefore less at risk of acute toxicity. There is the need for more work to determine the true overall impact of the control of mephedrone both currently and over time.

7. Summary

Mephedrone, 4-methylmethcathinone, is a synthetic cathinone that has been available and used on the European recreational drug scene over the last five years. Recent surveys described above appear to suggest that the prevalence of use in Europe, and in particular in the UK, is comparable to other classical recreational drugs, despite its recent control. There is limited information on the prevalence of use outside of the UK and Europe, which is compounded by the recording of data in countries such as the US under the term "bath salts", which is a more colloquial user name for a range of novel psychoactive substances and not just mephedrone. Combination of the different available datasets that report information on the acute toxicity (harm) associated with the use of mephedrone, suggest that the pattern of acute toxicity is similar to that previously described for amphetamine/MDMA. Each of these datasets has its own limitations, but the process of combination and data triangulation reduces the impact of these limitations. The information from these different data sources is strengthened by an increasing number of *in vitro* and *in vivo* animal models which demonstrate that mephedrone has effects similar to an amphetamine/MDMA combination. There is a need for a targeted approach to identifying the most appropriate data sources to describe the pattern of acute toxicity with novel psychoactive substances such as mephedrone; this information can then be utilised to direct appropriate animal and laboratory studies to define the toxicity of an individual compound or class of compounds appropriately. Further work is needed to determine the true impact of the control of mephedrone to help legislative authorities and other interested bodies determine how to manage other emerging novel psychoactive substances in the future.

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