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Mephedrone-Related Fatalities in the United Kingdom: Contextual, Clinical and Practical Issues

John M. Corkery, Fabrizio Schifano and A. Hamid Ghodse
University of Hertfordshire & St George's, University of London
United Kingdom

1. Introduction

The misuse of mephedrone (4-methylmethcathinone) has been increasing greatly in Western countries over the last two years or so, especially in the club and dance scenes. This period has also been marked by claims that the substance has been implicated in a rising number of deaths in the USA and Western Europe, especially the United Kingdom (UK).

This chapter explores the context(s) and evolution of mephedrone use in the UK, and the circumstances in which these fatalities occurred. Particular attention is paid to the settings in which these incidents took place, their symptomatology and physical characteristics; intervention/treatment opportunities; and toxicological and pathological findings. These results are related to the known pharmacological facts regarding mephedrone, its possible interactions with alcohol and other psychoactive drugs, and suggested clinical interventions and treatment(s).

The relationship between mephedrone, other methcathinones, and other emerging novel psychoactive substances, as well as established stimulants is also examined. These developments are important as novel substances used for recreational use become more globally accessible through the use of the Internet.

2. Recreational use

Mephedrone (4-methylmethcathinone; 'Plant Food', 'Meow Meow', 'Miaow', 'Drone', 'Meph', 'Bubbles', 'Spice E', 'Charge', 'M-Cat', 'Rush', 'Ronzio', 'Fiskrens' and 'MMC Hammer') (Schifano et al, 2011) is the most popular of the cathinone derivatives, which also include butylone, flephedrone, MDPV, methedrone, methylone, pentylone, and other compounds (ACMD, 2010; Morris, 2010). It has been readily available for purchase both online and in head shops as a 'legal high', and more recently as a 'research chemical'; its circulation has been promoted by aggressive web-based marketing (Deluca et al., 2009). Mephedrone elicits stimulant and empathogenic effects similar to amphetamine, methylamphetamine, cocaine and MDMA (Winstock et al., 2010). However, as we write, relatively few formal related papers and experimental/clinical data have been published (Dargan et al., 2010; Winstock et al., 2010; Winstock et al., 2011).

The synthesis of mephedrone was first described over 80 years ago (Saem de Burnaga Sanchez, 1929). However, the first Internet reference to it occurred reportedly in May 2003 (Power, 2009), but both its availability for purchase online (Camilleri et al., 2010; Roussel et al., 2009) and its related popularity only started in 2007 (Deluca et al., 2009). Data collected by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) indicate that during the first quarter of 2010, there were detections in some 20 EU Member States, with most of them reporting small- to medium-sized seizures (Europol-EMCDDA, 2010). During the second quarter of 2009, the UK Forensic Science Service received submissions of three times as many samples of mephedrone for analysis than it had in the previous 12-month period (ACMD, 2010; Ghodse et al., 2010). Since mephedrone appeared comparatively recently on the market, it does not feature in most drug use household surveys, and it is uncertain how many people present with a history of mephedrone misuse. Most available data originate from self-reported surveys and small focus group research.

The main settings for mephedrone use appear to be nightclubs, parties and people's homes (Newcombe, 2009). A survey of readers of the dance magazine 'Mixmag' found that 41.7% of respondents had ever tried mephedrone and 33.2% had used it during the previous month (Winstock et al., 2011). Dargan et al. (2010) assessed both the prevalence and frequency of use of mephedrone by students in Tayside (Scotland) in February 2010. Some 20.3% reported previous use of mephedrone; 23.4% reported using only using mephedrone on one occasion previously and 4.4% reported daily use. A total of 48.8% of users had sourced mephedrone from street-level dealers and 10.7% from the Internet. Heightened awareness and interest in mephedrone was reflected by a rise in the number of both telephone inquiries and visits to both the TOXBASE and FRANK web sites (ACMD, 2010; James et al., 2010). The 2011 sweep of the British Crime Survey, which covers households in England and Wales, found that 4.4% of adults aged 16 to 24 years had used mephedrone in the last year, compared to only 0.6% of those aged 25 to 59 years (Smith & Flatley, 2011). The rate for the younger age-group is similar to that for cocaine. The majority of respondents who had taken mephedrone in the last year had also taken another drug. It is, therefore, likely that it is existing users of drugs that are taking mephedrone rather than new users drawn to drug taking.

The emergence of mephedrone on the UK recreational drug scene may be linked to decreasing purity in the UK of both MDMA (ecstasy) and cocaine (Mulchandani et al., 2010; Fleming, 2010; Measham et al., 2010; NTA, 2010). As a consequence, drug users may have switched to mephedrone, as it was seen as cheaper and more powerful than the currently available 'traditional' stimulants (Deluca et al., 2009). Its availability over the Internet and its status as a 'legal high' (and therefore presumed not to be harmful) may have boosted its appeal (Daly, 2010; Ramsey et al., 2010).

3. Legal status

Mephedrone is not scheduled under the 1971 United Nations Convention on Psychotropic Substances. In Australia, New Zealand, and the USA mephedrone is considered as an analogue of other illegal substances already and can be controlled by laws similar to the Federal Analog Act. In March 2010, the EMCDDA and Europol submitted a joint report on mephedrone to the Council of the European Union, the European Commission and the European Medicines Agency (EMA), presenting the case for a formal risk assessment of the

drug (Europol-EMCDDA, 2010). The risk assessment report, which was submitted to the European Commission and the Council of the European Union on 26 May 2010, examined the health and social risks of the drug, as well as information on international trafficking and the involvement of organised crime. Furthermore, the report considers the potential implications for placing the drug under control in the EU. On the basis of this report – and on the initiative of the European Commission – on 2 December 2010, the Council decided that mephedrone is to be subject to control measures (EMCDDA, 2011).

In the UK, where mephedrone had been attracting great attention from both the mass media and the Government, the Advisory Council on the Misuse of Drugs (ACMD) submitted a report to the Home Office on the cathinone derivatives, recommending their inclusion in the Misuse of Drugs Act 1971 as a Class B drug (ACMD, 2010). The Home Office announced on 30 March 2010 that this recommendation would be enforced from 16 April 2010 (Home Office, 2010).

4. Chemistry

Mephedrone is a semi-synthetic compound belonging to the chemical class of cathinone derivatives (or substituted cathinones). Cathinone is a natural amphetamine-like alkaloid found in the fresh leaves and stems of the African shrub Khat (*Catha edulis*) (Kalix, 1992). The systematic name of mephedrone is 2-(methylamino)-1-(p-tolyl)propan-1-one(2S)-2-(methylamino)-1-(4-methylphenyl)propan-1-one, in accordance with the International Union of Pure and Applied Chemistry. The structure of mephedrone differs from cathinone by methylation of the amino group and the benzene ring present (Gustaffsson and Escher, 2009; Osorio-Olivares et al., 2003). The cathinones are beta-keto derivatives of phenethylamines, and hence analogues of amphetamines (Chemspider, 2010). Since they are mainly synthetic in origin, beta-keto amphetamines are also known as 'bk designer drugs'. It is relatively easy to produce mephedrone in nonprofessional laboratories via bromination of 4-methylpropiophenone followed by reaction with methylamine or by oxidation of 4-methylephedrine (Archer, 2009; Europol-EMCDDA, 2010).

Although mainly sold in powder and crystal forms, mephedrone may be commercially available in tablets and included within vegetable-based capsules. It has been reported that mephedrone is sometimes sold in some countries as either ecstasy or 'synthetic' cocaine (Deluca et al., 2009; Schifano et al., 2011). Furthermore, it may be found mixed with adulterants, such as caffeine, paracetamol and even cocaine, amphetamine and ketamine (Camilleri et al., 2010), as well as with other methcathinones (as revealed by information supplied to the National Programme on Substance Abuse Deaths by coroners – see below).

5. Pharmacology

Given the affiliation of cathinone derivatives to beta-keto amphetamines, mephedrone would be expected to act as a Central Nervous System stimulant. In vitro studies on the effects of the cathinone derivatives methcathinone and methylone confirm that the main mechanism of action is very similar to that of amphetamine, being characterised by a predominant action on plasma membrane catecholamine transporters (Cozzi et al., 1999). The presence of the ring substituent on the phenethylamine core modifies the

pharmacological properties by giving the compound some MDMA-like effects (Europol-EMCDDA, 2010). Cathinones' potencies are mostly lower than those of amphetamines as beta-keto amphetamines show a reduced ability to cross the blood-brain barrier due to the presence of the beta group (Nagai et al., 2007; Gygi et al., 1996).

N-demethylation to the primary amine, reduction of the keto moiety to the respective alcohol, and oxidation of the tolyl moiety to the corresponding alcohols and carboxylic acid is the major metabolic pathway for mephedrone, followed by N-dealkylation.

6. Routes of administration, dosage, use in combination with other drugs, effects

The most common routes for recreational use include insufflation (snorting) and oral ingestion. Because of its solubility in water, mephedrone is reportedly used by rectal administration or injected intravenously. Other typical methods of intake include oral ingestion as capsules or tablets; swallowing mephedrone powder wrapped up in cigarette paper (bombing); or mixed with water. Insufflation is likely to be the most common modality as, when snorted, mephedrone elicits its effects within a few minutes, with the peak being reached in less than 30 min followed by a rapid comedown. According to online users, the mephedrone dosage for snorting may range between 25 and 75 mg, with a lower threshold at 5–15 mg and levels in excess of 90 mg considered a high dosage (Sumnall and Wooding, 2009). Dosing is more frequent when taken intranasally; this route is allegedly associated with greater abuse liability than the oral route (Winstock et al., 2010, 2011). On average, the most common oral dosages are higher than the snorting ones (Sumnall & Wooding, 2009), in the range 150 to 250 mg.

Time of onset may be from 45 min to 2 h and may vary in association with the amount of food in the stomach. Because of this, users suggest taking mephedrone on an empty stomach. Psychoactive effects may last longer (up to 2–4 h) with oral ingestion; side-effects might be milder and the need to re-dose less urgent. Some users employ both insufflation and oral ingestion in combination to obtain faster onset and long-lasting effects (Deluca et al., 2009). Users report that rectal administration is characterised by faster onset of the effects and requires lower doses, e.g. 100 mg on average than oral ingestion (Deluca et al., 2009). Although not typically advised, because this may increase the drug's addictive liability levels (Deluca et al., 2009), mephedrone may also be injected either intramuscularly (Wood et al., 2010a) or intravenously, at one half or two-thirds of the oral dose (Deluca et al., 2009). According to online user fora, mephedrone may be taken in combination with a number of stimulants, sedatives and psychedelics (Deluca et al., 2009; Schifano et al., 2011).

As mephedrone has the capacity to induce tolerance on repeated dosing, an increasing number of user reports have stated a quick progression to either regular drug use and/or uncontrolled bingeing behaviour (known as 'fiending'), with 1–4 g of mephedrone consumed in a session to prolong the duration of its effects (Deluca et al., 2009; Europol-EMCDDA, 2010; Dargan et al., 2010). A recent survey carried out by a drug-related web site has unveiled an average monthly use of 11.16 g for each mephedrone consumer (Drugs-forum, 2010). Although withdrawal symptoms are not commonly reported, users often display strong cravings for mephedrone (Newcombe, 2009).

The effects of mephedrone have been compared by users variously to those of cocaine, amphetamine and MDMA. Self-reported subjective effects may include (Winstock et al., 2011; Deluca et al., 2009): intense stimulation and alertness, euphoria; empathy/feelings of closeness, sociability and talkativeness; intensification of sensory experiences; moderate sexual arousal; and perceptual distortions (reported with higher dosages only).

7. Adverse effects

Dargan et al. (2010) report that some 56% of those who had used mephedrone may complain of at least one unwanted effect associated with mephedrone use. These may include (ACMD, 2010; Deluca et al., 2009; James et al., 2010; Wood et al., 2009, 2010b): loss of appetite, nausea, vomiting and stomach discomfort; tremors, headache (very common), dizziness/light-headedness, seizures, nystagmus, pupil dilation, blurred vision, numbness of tactile sensitivity (reported at higher dosages); anxiety, confusion, dysphoria, aggression, depression, long-lasting hallucinations, paranoid delusions, short-term psychosis, short-term mania, insomnia and nightmares, impaired short-term memory, poor concentration, tachycardia, elevated blood pressure, respiratory difficulties, chest pain. Possibly due to vasoconstriction, users have anecdotally described cold/blue fingers. Of particular interest are recent reports of clinical significance: severe refractory left ventricular failure (Chhabra et al., 2010); and acute myocarditis (Nicholson et al., 2010). Further unwanted effects may include: difficulties in urination, possible nephrotoxicity, anorgasmia; changes in body temperature regulation, with hot flushes and sweating; immunological toxicity (vasculitis, infections and ulcerations); posterior reversible encephalopathy syndrome (Omer & Doherty, 2010); and finally serotonin syndrome (Garrett & Sweeney, 2011).

Most of the above untoward effects seem to be similar to those already documented for amphetamine, methylamphetamine and MDMA (Schifano et al., 2010), implicitly supporting a sympathomimetic activity of mephedrone. Conversely, symptoms of depression and anhedonia could be tentatively associated to a putative depletion of serotonin and dopamine as a consequence of drug use (ACMD, 2010), similarly to what may occur with other stimulants (Schifano, 1996). It is impossible to determine a 'safe' dose for mephedrone since negative side-effects may present in association with any dosage taken. Furthermore, similar dosages may have dramatically different consequences in different individuals (Dickson et al., 2010).

8. Fatalities

During the last few months of 2009 and the first few months of 2010, the UK media were constantly reporting fatalities allegedly related to mephedrone consumption, but only a proportion of them had by that time been formally confirmed. A report on a mephedrone-related fatality first appeared in Sweden, referring to an 18-year-old female death which occurred in December 2008. No other drugs, apart from mephedrone, were identified by the toxicological screenings (Gustaffson & Escher, 2009). Previously, a Danish teenager found in possession of mephedrone died in May 2008, although toxicology reports were inconclusive (Campbell, 2009). The first mephedrone-related death in the USA involved the combined use of mephedrone and heroin (Dickson et al., 2010). More recently, the first cases from the Netherlands (Lusthof et al., 2011) and the Republic of Ireland (EMCDDA, 2011:85) have been reported.

Given the potentially large numbers of consumers involved in the use of mephedrone across both the EU and the UK (EMCDDA, 2011), the main aims of this study were to report and analyse information relating to the socio-demographics and clinical circumstances of all recorded mephedrone-related deaths for the whole of the UK, both when the index drug was taken on its own and when in combination with other drugs. The rationale for doing this is to make accessible a corpus of material which will help inform treatments and interventions so as to reduce deaths associated with the use of this drug and other methcathinones.

9. Methodology for identifying potential mephedrone-related fatalities

In the UK and Islands all sudden, unexpected or violent deaths - as well as deaths in custody - are formally investigated by Coroners (or their equivalent in the Islands), or Procurators Fiscal in the case of Scotland. Most drug-related deaths are subject to these processes, typically by way of a coronial inquest (Corkery, 2002).

Since its establishment in 1997, the National Programme on Substance Abuse Deaths (np-SAD) has been regularly receiving coroners' information on drug-related deaths amongst both addicts and non-addicts in the UK, the Channel Islands and the Isle of Man. The average annual response rate from coroners in England and Wales to np-SAD has been between 89% and 95% (Ghodse et al., 2010). Since 2004, information has also been received from the Scottish Crime & Drug Enforcement Agency and the General Register Office for Northern Ireland. To date, details of some 25,000 deaths have been received. The information reported here on deaths associated with mephedrone consumption are based on all relevant cases recorded in the Special Mortality Register of the np-SAD based at St George's Hospital Medical School, University of London.

To be recorded in the np-SAD database as a drug-related death, at least one of the following criteria must be met: (a) presence of one or more psychoactive substances directly implicated in death; (b) history of dependence or abuse of drugs; and (c) presence of controlled drugs at post-mortem. Full details of the np-SAD data collection form and its surveillance work can be found in the Programme's annual report (Ghodse et al., 2010). Ethical approval is not required in the UK for studies whose subjects are deceased. However, confidentiality arrangements are in place with each of the respective data providers.

A range of documents are contained in coronial inquest files, although the variety differs from case to case. Typically, the coroner has access to: statements from witnesses, family and friends; General Practitioner records (if the deceased is registered with one); reports from ambulance, police or other emergency services; hospital Emergency Department and clinical ward reports; psychiatric and substance abuse team reports; as well as post mortem and toxicology reports. Internet searches of toxicological as well as newspaper and other media websites revealed information on further cases. The media reports available for some cases were used to supplement the information provided on the np-SAD data collection form, especially where access to the full coronial files was not possible.

In addition to its routine surveillance activities, the Programme also provides real-time information on the emergence of novel substances or new ways of taking existing substances to the UK Early Warning System and the Advisory Council on the Misuse of

Drugs (ACMD). This information comes both from notifications of deaths and from 'alerts' or other information provided by the various agencies and networks, national and international, with which the Programme maintains contacts. Regular searches of media reports are also undertaken.

Through these channels (including coroners, forensic toxicologists – principally the London Toxicology Group, Drug & Alcohol Action Teams, and the Scottish Crime & Drug Enforcement Agency) the Programme became aware of the emerging issue of the use of methcathinones, especially mephedrone, and similar substances (including chemicals), and of their potential adverse health consequences. It was decided to take a pro-active approach to monitor the situation especially in respect of the potential role of these new substances in causing or contributing to death. For those cases not formally reported to the Programme, contact was made with the relevant coroners to request the submission of an np-SD form so as to obtain the appropriate information. Information on these cases was added to the database when forms were received by the Programme team.

The np-SAD database was searched using the terms 'mephedrone' and '4-methylmethcathinone' to identify potentially relevant cases. The database fields searched were those holding data on: drugs present at post-mortem; drugs implicated; cause(s) of death; accident details; and 'other relevant information'. The data presented here relate to all concluded cases for which forms had been submitted to the Programme by 31 August 2011. Details of some of these cases have previously been published (Torrance & Cooper, 2010; Wood et al., 2010b; Maskell et al., 2011; EMCDDA, 2011:78-85).

Analyses were performed using IBM® SPSS® Statistics, version 18 for Windows™. Demographic details, risk factors, and categorical data were expressed as frequencies and percentages within groups; ages were compared using Levene's Test for Equality of Variances (two-tailed). The results for statistical tests were regarded as significant at or below the 5% probability level.

10. Results

A total of 125 alleged or suspected mephedrone-associated fatalities have been identified by the np-SAD team (Fig. 1). However, in 25 cases (20.0%) mephedrone was not found at post mortem and for 13 cases (10.4%) the toxicology results are still pending. For those 87 cases (69.6%) where mephedrone was identified at post mortem, inquests have been concluded in 60 cases. These were considered as confirmed fatalities meeting the above inclusion criteria, and on which the present analysis will focus.

10.1 Demographics

The mean age of the sample was 28.7 years (SD 11.3), range 14-64 years old. The mean age for males was 28.9 years compared to 28.0 years for females; this difference was not statistically significant ($t = 0.27$ (two-tailed for equality of means) $p = 0.79$ (95% CI = -5.87 to +7.72). Where known, most victims were described as 'White' (Table 1). Where place of birth was given, 39 were born in the UK and Islands and 8 overseas. Many were in employment ($n = 25$), but one-quarter ($n = 16$) were unemployed, and 11 were students.

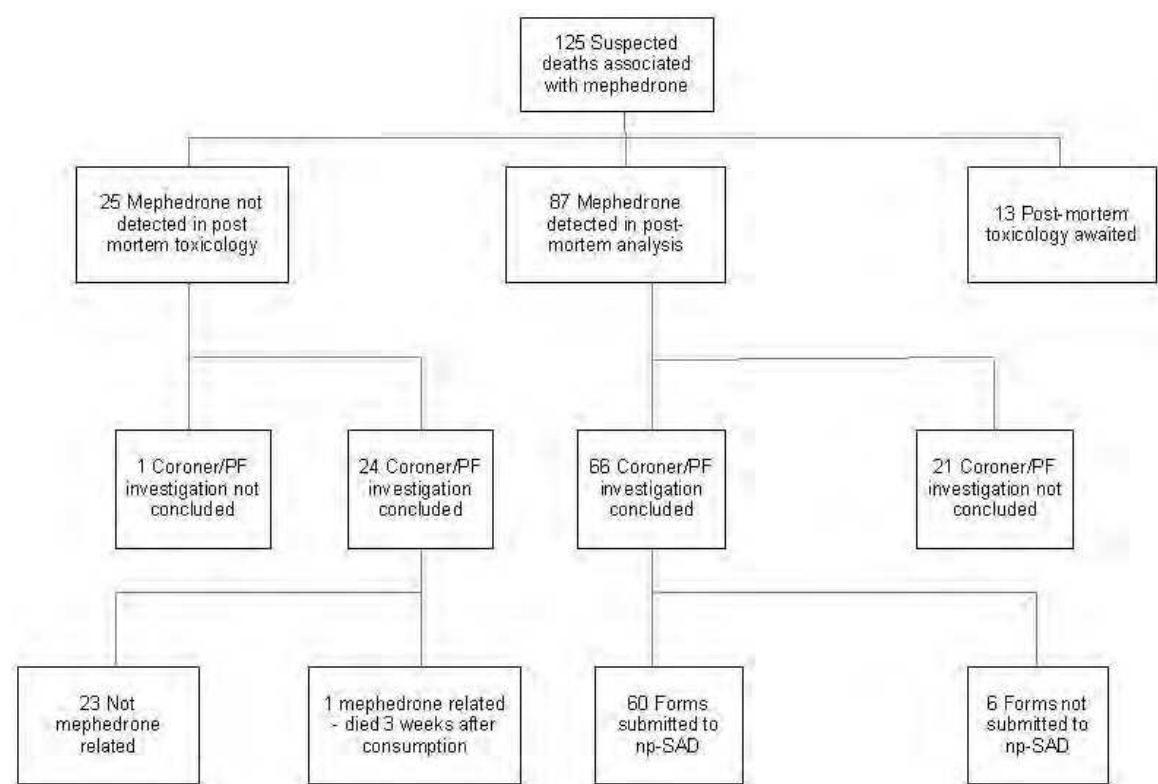


Fig. 1. Flow-chart of UK deaths associated with mephedrone

Demographic variable	Characteristics
Age (years): male (n=45) female (n=15) all (n=60)	mean = 28.9, median = 24.9, minimum = 17.1, maximum = 63.8, range = 46.8, SD = 11.1. mean = 28.0, median = 24.9, minimum = 14.8, maximum = 55.1, range = 40.3, SD = 12.2. mean = 28.7, median = 24.9, minimum = 14.8, maximum = 63.8, range = 49.0, SD = 11.3.
Age-group (years)	< 15 = 1; 15-24 = 30; 25-34 = 16; 35-44 = 6; 45-54 = 5; 55-64 = 2; >64 = 0.
Ethnicity	White = 50; Black = 0; Asian = 1; Other (Filipina) = 1; Not known = 8.
Country of birth	England = 32, Wales = 2, Scotland = 1, Northern Ireland = 2, Guernsey = 2; overseas = 8; unknown/unavailable = 13.
Employment status	non-manual = 9; manual = 14; unemployed = 16; self-employed = 2; invalidity/sickness = 1; student = 11; housewife = 0; unknown = 7.
Living arrangements	alone = 11; with parents = 20; with partner = 14; with partner and children = 2; with friends = 4; no fixed abode = 2; self & children = 1; Other = 1; unknown = 5.
Addict status	non-addict = 10; addict/drug abuser = 27; unknown = 23.

Table 1. Socio-demographics of 60 UK deaths associated with mephedrone reported to np-SAD

Just over half (33) died in their home or that of a friend and 12 in hospital (Table 2). The verdict/conclusion returned by the coroners or procurators fiscal in 35 instances was accidental death or misadventure; (non-dependent) abuse of drugs in 5 cases, suicide in 10 cases, homicide in one case, natural causes in one case, and an open verdict in 8 cases. Forty-four of these deaths occurred in England; nine in Scotland, four in Northern Ireland, two on Guernsey, and one in Wales.

Twenty-seven were known to be as 'addicts' (either dependent on or misusing drugs), and 10 were not addicts; for 23 cases the information was not known. Only 11 of the deceased were known to have been prescribed psychoactive drugs: these included diazepam, antidepressants, antipsychotics, antiepileptics, methadone, and opioid analgesics, often in combination.

Demographic variable	Characteristics
Place of death	at home = 28; friend's home = 5; hospital = 12; open space/ woodland/ river = 7; other = 7; unknown = 1.
Country of death	England = 44; Wales = 1; Scotland = 9; Northern Ireland = 4; Guernsey = 2; Jersey = 0; Isle of Man = 0.
Day of week of death (this is not necessarily day of consumption)	Sunday = 13; Monday = 12; Tuesday = 10; Wednesday = 8; Thursday = 2; Friday = 5; Saturday = 10.
Month of death	Sep 2009 = 1; Oct 2009 = 1; Nov 2009 = 1; Dec 2009 = 5; Jan 2010 = 7; Feb 2010 = 7; Mar 2010 = 9; Apr 2010 = 6; May 2010 = 3; Jun 2010 = 1; Jul 2010 = 7; Aug 2010 = 2; Sep 2010 = 0; Oct 2010 = 2; Nov 2010 = 2; Dec 2010 = 0; Jan 2011 = 0; Feb 2011 = 2; Mar 2011 = 0; Apr 2011 = 2; May 2011 = 2; Jun 2011 = 0; Jul 2011 = 0; Aug 2011 = 0.
Verdict (legal conclusion)	accident/ misadventure = 35; (non-dependent) abuse of drugs = 5; open/ undetermined = 8; suicide = 10; killed unlawfully = 1; other = 1.
Manner of death (intentionality)	natural = 1; accidental = 41; suicidal = 11; homicidal = 1; undetermined = 6.

Table 2. Circumstances of 60 deaths associated with mephedrone reported to np-SAD

The first known death in the UK occurred in September 2009. The number steadily rose to 7 both in January and February 2010, peaked at 9 in March, falling to 6 in April, and declining in the next couple of months to one in June. However, there was a further peak of 7 cases in July, followed by two deaths in August and another 2 in both October and November. There then followed a period of a few months without any reported fatalities, but the most recent deaths occurred in April and May 2011 (Fig. 2). There were twice as many deaths on Saturdays, Sundays, Mondays and Tuesdays (n = 45, average 11.2 per day) compared to the other days of the week (n = 15; average of 5.0 per day). It should be noted that the day of death was not necessarily the day that mephedrone was consumed, as in a few cases death occurred several days later in hospital – in one case three weeks after the event.

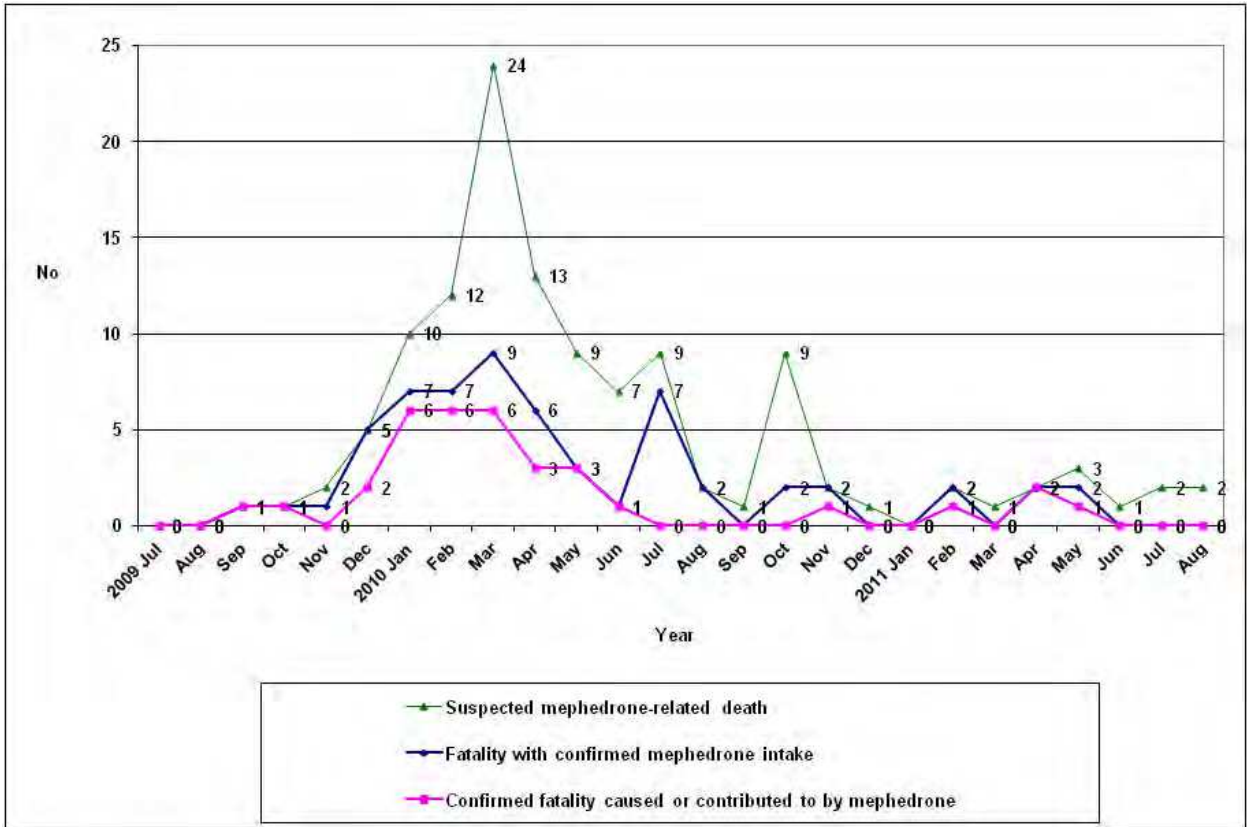


Fig. 2. Evolution of suspected deaths (n = 125) and cases with confirmed positive toxicology for mephedrone submitted to np-SAD as at 31 August 2011 (n = 60)

10.2 Events leading to death

As might be expected given the typical purpose of using mephedrone to experience its psychoactive effects, many deaths occurred following recreational consumption of the drug (Table 3), often in the deceased’s or another’s home. However, some deaths (road traffic collisions, drowning, hypothermia, etc.) occurred as the result of accidents through impaired judgement due to mephedrone use. In two cases, the deceased had been engaged in sexual activity.

There was a significant number (n = 18) of deaths involving violent means, and especially hanging (13 cases). In several of these cases, mephedrone was considered by the pathologist/coroner/Procurator Fiscal to have played a role although it was not being specifically mentioned in the cause of death field. Mephedrone withdrawal was considered a contributory factor in one suicide by hanging. There were also three fatal road traffic accidents following consumption of mephedrone (and other drugs), and one homicide when the deceased was killed for his supply of mephedrone (about 500 g).

10.3 Cause(s) of death

The effects (‘adverse’, poisoning, intoxication, toxicity) of mephedrone, including other substances, were recorded in the cause of death for 24 cases (Table 4). Consumption of mephedrone led to a seizure in one case, and cardiac arrest in another. In a further case,

cardiac arrest was caused by multiple drug toxicity (including mephedrone) and/or excited delirium. In two cases the ingestion of mephedrone with other drugs led to hypoxic brain injury (one with cerebral oedema). Health issues were present in a number of cases. These, along with mephedrone (and other substances) contributed to death; for example, cardiovascular conditions - 4, bronchopneumonia - 3.

Found unresponsive/ dead after taking mephedrone (and other substance) - 14
Found hanging after paranoiac/ suicidal behaviour - 6
Found hanging following depression relationship broke up - 1
Found hanging following row with girlfriend over his drug misuse - 1
Self-suspension when intoxicated with alcohol and cocaine - 1
Found hanging after no apparent untoward behaviour - 1
Found dead after cutting own throat - 1
Suicide by gun-shot following consumption of mephedrone, other methcathinone(s) and cocaine - 1
Had consumed mephedrone and other substances, jumped from bridge where relative had previously committed suicide - 1
Committed suicide by drug overdose, including mephedrone - 2
Following family argument, took fatal levels of amitriptyline and methadone, consumed mephedrone - 1
Reported missing after argument with partner, found dead next day on running track with suicide note, had consumed prescribed medications and mephedrone - 1
Had taken mephedrone, but was stabbed and his large supply of mephedrone was stolen, bled to death - 1
Took drugs (including mephedrone and cocaine), started behaving bizarrely, aggressively and abusively; police tried unsuccessfully to calm him down and had to arrest him; collapsed whilst under restraint and suffered cardiac arrest - 1
Attended party, collapsed with cardiac arrest, died in hospital - 1
Attended party, collapsed with breathing difficulties, died in hospital - 1
Attended party, took mephedrone 'bomb', collapsed with very high temperature which prevented blood from clotting, causing abdominal haemorrhages, never regained consciousness - 1
Took mephedrone and other substances, collapsed with chest pains - 2
Took mephedrone and other methcathinones, together with cocaine, which caused fatal heart attack - 1
Took cocaine and mephedrone at party, collapsed and died following day - 1
Had consumed mephedrone but died from heroin and alcohol toxicity - 1
Found dead after consuming Datura, dihydrocodeine, alcohol and mephedrone - 1
Had consumed mephedrone and other stimulants, attempted to swim across river but drowned - 1
Had taken mephedrone and other drugs, driving vehicle involved in fatal road traffic accident - 3
Following consumption of alcohol and mephedrone, felt sick, collapsed, died in hospital - 1

Took alcohol and mephedrone, collapsed and unrouseable, died in hospital - 1
Collapsed after taking mephedrone, died in hospital 3 weeks later from acute liver failure - 1
Attended party where took mephedrone and heroin, collapsed died in hospital 3 weeks later - 1
Died in hospital after taking mephedrone - 1
Indulged in sexual activity, self-injected mephedrone, had seizure and collapsed - 1
Had taken large amounts of methcathinones, engaged in auto-erotic asphyxiation with plastic bag over head, but accidentally suffocated - 1
Consumed amphetamine & mephedrone, vomited, felt cold & sleepy; taken to hospital where, despite treatment, suffered liver problems & multi-organ failure - 1
Found unresponsive in bed, death certified at scene; had been feeling unwell, on medication for chronic abdominal & back pain - 1
Admitted to Emergency Department previous day with drug overdose, had been partying but later found hanging - 1
Aspirated blood following mixed drug (including mephedrone) intoxication - 1
Had consumed GHB and mephedrone; found dead beside bed at home by a friend - 1
Not known - 2

Table 3. Events leading to death

1a Hanging - 10
1a Hanging; 2 Mephedrone withdrawal - 1
1a Hanging; 2 alcohol and mephedrone use - 1
1a Hanging; 2 using mephedrone - 1
1a Shotgun wound to head; 2 Use of mephedrone, methylone and cocaine - 1
1a Blood loss following fatal stabbing to thigh [inflicted by third party] - 1
1a Exsanguination; 1b Neck laceration cutting left jugular vein [self-inflicted] - 1
1a Multiple injuries; 1b Blunt force trauma; 1c Vehicular collision (driver) - 1
1a Ruptured inferior vena cava with haemorrhage in abdominal cavity & cervical spine fracture; 1b Road traffic accident; 2 Cirrhosis of liver & misuse of drugs - 1
1a Multiple injuries [road traffic accident] - 1
1a Multiple injuries [fall from height] - 1
1a Drowning; 2 Multiple drug overdose - 1
1a Hypothermia; 1b Drug overdose [quetiapine, lorazepam, venlafaxine, mephedrone] - 1
1a Adverse effects of mephedrone - 1
1a Poisoning by mephedrone - 1
1a Mephedrone toxicity - 1
1a Mephedrone poisoning; 2 Coronary artery disease - 1
1a Adverse effects of mephedrone; 2 Atherosclerotic coronary artery disease; myocardial fibrosis - 1
1a Mephedrone intoxication - 2
1a Cardiac arrest following ingestion of mephedrone - 1

1a Seizure; 1b Effect of mephedrone - 1
1a Cardiac arrest, cause unascertained between multiple drug toxicity [mephedrone, MDPV, fluoromethcathinone] and/or Excited Delirium - 1
1a Aspiration of blood; 1b Mixed drug intoxication [inc. mephedrone] - 1
1a Adverse effects of methadone and mephedrone - 1
1a Overdosage of mephedrone (meow meow) compounded by cocaine; 2 Cocaine abuse - 1
1a Mixed MDMA and mephedrone toxicity - 1
1a Combined toxic effects of amphetamine and mephedrone - 1
1a Patchy bronchopneumonia & pulmonary oedema; 1b Cardiac ischaemia, contributed to by mephedrone, citalopram and diazepam - 1
1a Ischaemic heart disease; 1b Illicit use of cathinones - 1
1a Toxic effects of drugs [inc. mephedrone] - 1
1a Fatal drug intoxication [inc. mephedrone] - 1
1a Mixed drug toxicity [inc. mephedrone] - 1
1a Hypoxic brain injury; 1b Mixed drug overdose [inc. mephedrone] - 1
1a Hypoxic brain injury; 1b Cerebral oedema; 1c Ingestion of psychoactive drug [inc. mephedrone] - 1
1a Toxic effects of alcohol and cocaine - 1
1a Heroin and alcohol toxicity - 1
1a GHB intoxication - 2
1a Acute alcohol poisoning - 1
1a Morphine (heroin) toxicity - 1
1a Morphine toxicity (on balance of probability) - 1
1a BZP and TFMPP toxicity - 1
1a Illicit methadone misuse - 1
1a Combined effects of alcohol and GBL intoxication - 1
1a Combined toxic effects of alcohol, dihydrocodeine and atropine/hyoscine (from Datura Stramonium) together with postural asphyxia - 1
1a Systemic sepsis, resulting in cardiac arrest; 1b Bronchopneumonia; 1c Beta haemolytic Streptococcal Group A infection - 1
1a Medication toxicity; 2 Acute & chronic debilitating back pain, early stage bronchopneumonia - 1
1a Combined methadone and alcohol overdose - 1
1a Amitriptyline/Methadone overdose - 1
1a Asphyxia [plastic bag suffocation] - 1
(Where cause of death sections of the death certificate specifically mentioned mephedrone or where it was included in verdict. Mephedrone was implicated on its own in 18 cases, with other substances in 18 cases. In many of the hanging causes, mephedrone was considered to have played a contributory role although not recorded in the cause of death.)

Table 4. Cause of deaths associated with mephedrone reported to np-SAD

10.4 Drugs implicated

Mephedrone was specifically mentioned as being present at post-mortem in 59 cases. The drug was formally included in the cause of death in 18 cases and implicitly (e.g. polydrug toxicity given in the cause of death without specifying particular drugs, but mephedrone was found in post-mortem analysis or mentioned by the pathologist as contributing to death) in 10 further cases. In a further case, the drug was not mentioned either as being present at post-mortem (death occurred 3 weeks after mephedrone consumption) or in the cause of death although stated by witnesses to have been consumed.

Where details of the drugs present at post-mortem (or ante-mortem) were given, mephedrone alone was used on eight occasions, solely with alcohol in four cases, and in combination with further substances in 18 cases (Table 5). In 15 cases mephedrone was ingested with stimulants, and with diazepam in 13 cases. It is noteworthy that other newly emerging psychoactive substances were also here identified, including: GBL/GHB, ketamine, and piperazines, as well as other methcathinones (n = 8), especially MDPV. Prescribed medications were also present: opioids including methadone; hypnotics/sedatives; antidepressants; antipsychotics; and antiepileptics.

(Mephedrone was present in 59 cases, including 2 ante-mortem. It had been consumed in all cases in the period leading up the incident causing death.)	
Mephedrone sole mention -	8
Mephedrone with alcohol -	4
Mephedrone and alcohol and other drugs -	18
Mephedrone with cannabis -	4
Mephedrone with stimulants -	15
Mephedrone with diazepam -	13
Mephedrone with opiates -	12
Mephedrone with piperazines -	7
Mephedrone with GBL/GHB -	5
Mephedrone with ketamine -	2
Mephedrone with other methcathinones -	8
Mephedrone with antidepressants -	5
Mephedrone with antipsychotics -	2
Mephedrone with antiepileptics -	1
Mephedrone with hypnotics/sedatives (exc. Diazepam) -	3

Table 5. Summary of drug combinations and positive toxicological findings for deaths associated with mephedrone reported to np-SAD

10.5 Toxicology

Full details of mephedrone levels are given in Table 6; actual levels were quantified in 36 cases (Table 6). Overall: (n = 36) mean = 1.586mg/l, range = <0.01 - 22.0mg/l; mono-mephedrone cases (n = 10) mean = 1.996mg/l range = <0.01 - 12.15mg/l; combined mephedrone cases (n = 26): mean = 1.429mg/l; range = 0.03 - 22.0mg/l. These figures exclude one combined mephedrone case with a level of >2000mg/l.

Case No.	Mephedrone present	Mephedrone levels	Second drug present	Third drug present	Fourth drug present	Fifth drug present	Sixth drug present
1	Yes	bl 0.04mg/l	methadone	diazepam	olanzapine	chlorpromazine	
2	Yes	bl <0.01mg/l ur +					
3	Yes	bl 0.76mg/l	alcohol	GBL	diazepam & metabolites		
4	Yes	bl 1.3mg/l ur +					
5	Yes	bl 0.07mg/l, 0.15mg/l ur 16mg/l	alcohol	diazepam			
6	Yes	bl 0.41mg/l, 0.42mg/l	diazepam	citalopram			
7	Yes	bl +	alcohol	cocaine & metabolite	lignocaine		
8	Yes	bl 16ug/l	alcohol				
9	Yes	bl detected	alcohol	cocaine	cocaethylene	levamisole	lignocaine
10	Yes	bl 2.1ug/ml	alcohol				
11	Yes	bl 0.21ug/ml ur +	GBL	TFMPP	ketamine	methylamphetamine	diazepam
12	Yes	bl 2.24mg/l, ur +	TFMPP	alcohol			
13	Yes	bl 1.0mg/l	MDMA				
14	Yes	bl 0.32mg/l					
15	Yes	bl 0.88mg/l, ur +, stomach +	paracetamol				
16	Yes	bl 22mg/l	alcohol	amphetamine	diazepam		
17	Yes	bl 0.04mg/l, 0.19mg/l, ur 64.8mg/l, stomach 2.65mg/l					
18	Yes	bl 0.108mg/l, 0.08mg/l	alcohol	diazepam			
19	Yes	bl 3.3mg/l, stomach +, hair 4.2ng/mg, 4.7ng/mg					
20	Yes	bl > 2.0mg/ml	ampheta- mine	BZP	TFMPP	chlorpheni- ramine	
21	Yes	bl 9.01ug/ml, ur 0.01ug/ml, stomach +	morphine	cannabis			

Case No.	Mephedrone present	Mephedrone levels	Second drug present	Third drug present	Fourth drug present	Fifth drug present	Sixth drug present
22	No	-	morphine				
23	Yes	AM serum 0.042mg/l, ur +					
24	Yes	bl 12.15mg/l, ur +					
25	Yes	ur +	cocaine	methylone			
26	Yes	ur +	alcohol	pyrovalerone	BZP	FTMPP	
27	Yes	bl 0.31ug/ml	cannabis				
28	Yes	bl trace	morphine	quetiapine			
29	Yes	bl 0.07mg/l	alcohol				
30	Yes	bl +	alcohol	BZP	TFMPP	paracetamol	citalopram
31	Yes	bl +	alcohol	paracetamol	citalopram	zopiclone	
32	Yes	AM bl +					
33	Yes	bl 0.08ug/ml	methylone	MDPV	GBL		
34	Yes	bl +	methadone	alcohol	cocaine		
35	Yes	bl + recent use	alcohol	benzocaine			
36	Yes	bl + recent use	alcohol	benzocaine			
37	Yes	bl 0.03ug/ml	cannabis				
38	Yes	bl + ur +	diazepam				
39	Yes	bl low level	diazepam	cannabis			
40	Yes	bl +	ampheta- mine				
41	Yes	ur +	alcohol	cocaine & metabolites			
42	Yes	bl 6.2mg/l	diazepam & metabolites	gabapentin	oxycodone		
43	Yes	bl +	alcohol	cannabis	diazepam		
44	Yes	bl 0.05mg/l	GHB	alcohol	ampheta- mine	cocaine & metabolites	methadon e
45	Yes	bl 0.033ug/ml, bile 0.05ug/ml, ur 0.24ug/ml					
46	Yes	bl 1.7mg/l	BZP	TFMPP	codeine	diazepam	
47	Yes	bl <0.05mg/l, ur 11.67mg/l	alcohol	venlafaxine	quetiapine	halperidol	lorazepam
48	Yes	bl 0.51mg/l	alcohol				
49	Yes	bl <0.3125, ur +	alcohol	MDPV	cocaine	levamisole	quinine

Case No.	Mephedrone present	Mephedrone levels	Second drug present	Third drug present	Fourth drug present	Fifth drug present	Sixth drug present
50	Yes	bl 0.17mg/l	MDPV	MDMA	MDA	cocaine	diazepam
51	Yes	ur +	methy-lam-phetamine	amphetamine	GHB	ketamine	
52	Yes	n/k	alcohol	morphine	cocaine	fluoxetine	
53	Yes	bl 0.04mg/l, ur +	alcohol	dihydroco-deine	atropine	hyoscine butylbromide	diazepam
54	Yes	bl <0.005mg/l	morphine	nitrazepam	buprenor-phine	mirtazapine	
55	Yes	bl 0.21mg/l	cocaine	levamisole	alcohol		
56	Yes	n/k	methadone	amitriptyline	nitrazepam		
57	Yes	ur <0.005mg/l	flephedrone	MDPV	ibuprofen	unidentified compounds	
58	Yes	n/k	MDPV	MDPBP	pentylone	cocaine metabolites	
59	Yes	bl 0.05mg/l, ur 0.05mg/l	MDPV	fluoromethcat hinone	diazepam		
60	Yes	bl 1.94mg/l	BZP	TFMPP	diazepam		

Table 6. Combinations of post mortem drugs in deaths associated with mephedrone (levels) reported to np-SAD

11. Discussion

The existence of the Special Mortality Register maintained by the National Programme on Substance Abuse Deaths fulfills several major roles: it provides a unique UK-wide historic repository of unparalleled detailed information on drug-related deaths and deaths of drug addicts since 1997; the provision of a nation-wide surveillance capability for monitoring substance-related deaths; and the provision of information on the epidemiology of such events.

This paper contributes to the knowledge-base on mephedrone by providing supplementary/complementary information on the epidemiology of its use in the UK through the provision of centralised collation of post mortem toxicological results. Furthermore, this report has provided an analysis of the only UK-wide, mephedrone-specific mortality dataset. Although not all cases have yet been fully investigated, to the best of our knowledge this is the most comprehensive and detailed study of deaths associated with mephedrone in the literature.

11.1 User profile

One in five of ‘mephedrone fatalities’ turned out here not to be actually related to mephedrone, since the drug was actually not identified at post mortem. This might be understood in the context of the high levels of both media attention and public concerns surrounding the unprecedented rapidity of the appearance of mephedrone in the UK recreational drug market (Davey et al., 2010). However, some of these cases turned out to involve other methcathinones such as MDPV.

Typical mephedrone victims in this study were young (78% under 35 years of age); male (75%); White (96% where ethnicity was known); either in full time employment,

unemployed or students; and with a previous history of drug misuse (73% where known). With an average age of 29 years and nearly four-fifths under the age of 35, the age profile of this dataset is much younger than cases typically reported to np-SAD (Ghodse et al., 2010).

Mephedrone misuse in the UK is likely to have started as early as 2007 (Davey et al., 2010), and the first mephedrone-related fatality recorded on the np-SAD database occurred in September 2009. Although further studies are needed to confirm present observations, it seems from the information presented here that reports of mephedrone fatalities dropped in the months following the announcement by the Home Office on 30 March 2010 that the chemical, together with other related substances, was going to become a Controlled Drug. However, there was a further peak in July 2010, as well as additional deaths occurring in February, April and May 2011. This suggests that mephedrone, as well as other illegal methcathinones, are still being consumed in the UK.

The excess number (doubling) of observed mephedrone-associated fatalities between Saturdays and Tuesdays, compared to other days of the week, might be explained by its more frequent intake over the weekend, confirming once again its recreational drug profile.

An issue of particular concern and, to the best of our knowledge, something previously unreported is that 16 victims (about 1 in 3 cases of the current sample) either hanged themselves (13 cases), or used particularly violent means to terminate their own lives. In 10 cases, the coroner gave a verdict of suicide and in 8 further cases an open verdict was returned. In most of these cases, mephedrone was considered to have played a contributory role. Although a full psychiatric history is not typically made available to np-SAD, it is worth emphasizing that, out of the whole sample, antipsychotics were here identified at post mortem in 2 cases and antidepressants in 5 cases. Therefore, it can be postulated that mephedrone (either on its own, or in a polydrug misuse combination) has the potential to cause and/or exacerbate psychosis and/or depression, thus facilitating the occurrence of bizarre behaviour/self harm with particularly violent means. In one instance, the possibility of Excited Delirium was recorded. Although the present report comments on only 60 cases, the suicide rates in our other UK studies of stimulant-related fatalities were quantitatively less significant, being in the range of 3-6%: amphetamine-type drugs (Schifano et al., 2010); MDMA/ecstasy (Schifano et al., 2010; Schifano et al., 2003b); cocaine (Schifano & Corkery, 2008). The rate for khat-related fatalities was about 31% (sample size = 13) (Corkery et al., 2010).

Contributory clinical (e.g. sepsis; bronchopneumonia; pre-existing atherosclerotic cardiovascular conditions) and environmental (e.g. involvement in traffic accidents, drowning, hypothermia) factors were here identified at post mortem in respectively 5 and 5 mephedrone fatalities. These observations are overall consistent with the existing literature on stimulant misuse and may reflect the sympathomimetic actions of mephedrone and the accident-proneness or risk-taking behaviour of stimulant, including mephedrone, misusers (Schifano et al., 2011).

Mean mephedrone blood levels at post mortem were of either about 1.43mg/l (in polydrug cases) or 2.00mg/l (mono-intoxication fatalities), which is broadly in line with previous, small scale, anecdotal observations (Dickson et al., 2010; Lusthof et al., 2011).

11.2 Mephedrone use with other substances

Although mephedrone was here identified on its own in the cause of death in only one-third of cases ($n = 18$, 30%), this finding confirms some of the concerns recently expressed

regarding the acute toxicity potential of the drug itself (James et al., 2011; Maskell et al., 2011; Schifano et al., 2011; Torrance & Cooper, 2010; Wood et al., 2010; Regan et al., 2010). It could be argued that the fact there are such a relatively large number of deaths in a comparatively short period (two years) underlines the need to inform consumers of its potential to cause death on its own.

Conversely, most mephedrone victims died of polydrug, and especially alcohol, consumption. Anecdotally, it appears that alcohol is taken in association with stimulants to get a stronger/better 'high'. Similarly, other stimulants such as MDMA/ecstasy, whilst in the presence of alcohol, show more significant physiopathological effects (Pacifci et al., 2002; Schifano et al., 2003a). In 15 cases mephedrone was ingested with stimulants. Cocaine, amphetamines, other methcathinones and/or ecstasy tablets may be taken to maintain arousal and a state of alertness, since the stimulant desired effects of mephedrone fade away in a few hours (Schifano et al., 2011). However, co-ingestion of two stimulants could increase, in a synergic way, both the dopaminergic and serotonergic stimulation, and this is likely to increase mephedrone toxicity effects and harm potential (Schifano et al., 2011). In other cases, arguably to modulate its stimulant effects, mephedrone was associated in this study with opiates (12 cases) and/or diazepam (13 cases). This is likely to be consistent with the observation made here that, where known, about 3 out of 4 victims had a history of drug misuse. It is noteworthy that other newly emerging psychoactive substances (including: GBL/GHB, ketamine, piperazines, as well as other methcathinones) were also found in several cases in conjunction with mephedrone; this is in line with the literature (Deluca et al., 2009; Schifano et al., 2011). In all of these polydrug abuse cases, the precise role of mephedrone in causing fatality was due to simultaneous drug use and remains unclear. Conversely, the use of stimulants might afford some protective effects to those who overdosed with sedatives.

11.3 Treatment and prevention of fatalities

The patterns of drug use evidenced by post mortem toxicology results are similar to those reported by surveys and online users' fora; polysubstance use is common, especially the co-ingestion of alcohol, stimulants and other 'legal highs'. The pathologies (including psychopathologies) exhibited in many of these cases exhibit close similarities to those previous noted for amphetamine, cocaine, MDMA and khat. The implication of these findings is that similar advice to that already given for adverse events caused by other stimulants should be provided to clinicians, the emergency services and first-aiders. It is suggested that the treatment for more life-threatening conditions might be broadly similar to that for amphetamine poisoning. Individuals with less severe symptoms should be assessed and managed as for any psychoactive drug user; they may simply need reassurance, support and observation. People with underlying cardiac, neurological and psychiatric conditions, especially those on medication, are likely to be at greatest risk of serious adverse events (Winstock et al., 2010).

Although our knowledge of mephedrone's potential neurotoxicity or long-term consequences of its use is still very limited, it is sensible to offer the following advice: avoiding regular use to avoid developing tolerance; not using the drug in combination with other stimulants or large amounts of alcohol and other depressants; not injecting the drug; remaining well hydrated when using the drug; and avoiding becoming overheated. Brief

motivational interventions and appropriately adapted psychosocial intervention may be employed to treat mephedrone addiction (Winstock et al., 2010).

11.4 Limitations

A number of limitations need to be borne in mind in respect of this study: (a) not all suspected cases may have been identified; (b) remaining 'positive' cases are awaiting further inquiries or inquest; (c) the fact that mephedrone may have been involved in death cannot be confirmed until the relevant Coroner or Procurator Fiscal has concluded her/his inquest or other formal inquiry; (d) the presence of mephedrone in post mortem toxicology does not necessarily imply that it caused or contributed to a death; (e) not all completed cases have been formally notified to the Programme for recording. Hence, the number of identified cases reported here is likely to be an underestimation.

It is thought unlikely that the changes in fatality rates over time observed here are related to parallel changes in coroner methods, which would in turn affect surveillance. Data collection methods have remained unchanged. However, greater awareness of the phenomenon, improved case identification methods, and the development of new approaches in forensic toxicology and the range of substances now routinely screened for may have led to more potential cases being notified and registered.

Further limitations of the present report may include: lack of analytical attention to the role of the possible triggering environmental factors (i.e. overcrowding; hot settings etc); lack of total geographical coverage of coroner's jurisdictions; possible incomplete information relating to the prescription of psychoactive medications; and lack of information for some fatalities on the concentration of mephedrone detected in body fluids, so that some victims might have had only traces of the substance. Finally, since mortality rates (e.g. number of deaths out of number of mephedrone intake occasions) were not here calculated, it may be difficult to determine the true extent of risks associated with mephedrone consumption. However, in at least one case death occurred on the first use of mephedrone (albeit in combination with amphetamine).

12. Conclusions

This chapter has highlighted the dangers associated with mephedrone consumption, especially with regard to recreational use. This study represents the most detailed analysis to date of the largest number of mephedrone-related fatalities world-wide. It is hoped that it will thereby make a major contribution to the evidence-base being built up on this drug, and therefore, to reducing drug-related deaths.

Although identified on its own in only a minority of cases, present data confirm concerns regarding the acute toxicity potential of the drug. It is of concern that about 1 in 3 cases of the current sample used particularly violent means to terminate their own lives.

The number of mephedrone intake occasions was not calculated here, and so it may be difficult to determine the true extent of risks associated with mephedrone consumption. It may be possible to compare the lethality of mephedrone with other substances building on methods developed by King and Corkery (2010).

Further studies of a similar nature should be conducted in other countries, to see if the clinical and toxicity patterns associated with mephedrone use described here are confirmed. Notwithstanding the possible biases outlined above, the number of cases reported here may however suggest a significant level of caution when ingesting mephedrone for recreational purposes.

The limited information yet available on mephedrone underlines the need for basic pre-clinical and in-vitro research (and the necessary funding to carry it out) on the pharmacology, metabolism, etc. of methcathinones so as to provide evidence-based interventions and treatments.

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14. Conflicts of interest

No conflicts of interest are declared here which may have influenced the interpretation of present data. Please note the following: JC has been the UK Focal Point expert on Drug-Related Deaths for the European Monitoring Centre for Drugs and Drugs Addiction since 2000; FS is a full member of the UK Advisory Council on the Misuse of Drugs (ACMD); JC and FS are members of the ACMD Working Group on Novel Psychoactive Substances, the UK Early Warning System. All authors are members of the International Centre for Drug Policy (ICDP). AHG is current President of the International Narcotics Control Board (INCB). The views expressed here reflect only those of authors and not necessarily those of the Department of Health, Home Office, the ACMD, the ICDP, the EMCDDA, or the INCB.

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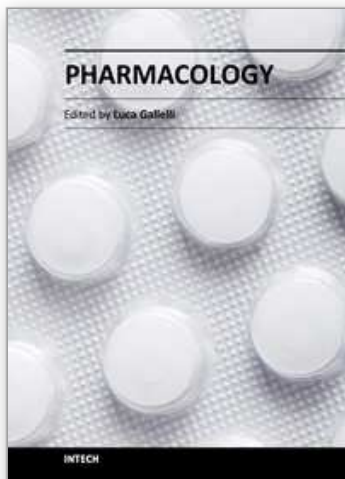
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The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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Phone: +385 (51) 770 447
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Phone: +86-21-62489820
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