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### Mini review

## Drugs for youth via Internet and the example of mephedrone

I. Vardakou, C. Pistos\*, Ch. Spiliopoulou

Department of Forensic Medicine and Toxicology, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias Str., Athens 115 27, Greece

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### ABSTRACT

Recently a new class of “designer drugs” has emerged on the drugs abuse market, known as “legal highs”. Such drugs are legal to use and possess, and legal to supply. Mephedrone, a central nervous system stimulant, is the most widely experienced “legal high”.

This review presents any available information about psychoactive properties, safety profile, clinical data, and legislation of the new “legal high” and emphasizes the role of Internet with mephedrone’s expansion. Available data were collected by various literature search engines and World Wide Web. All valuable information about psychoactive properties, safety profile and clinical data for mephedrone and its use as “legal high” were managed to spot and summarise.

Internet plays a significant role for the distribution of “legal highs”, becoming one of the major “drug market”. Adolescents and young adults who are curious about drugs may search on the Internet and thereby become exposed to thousands of sites that expound upon the positive effects of drugs and downplay or deny any negative effects. Use of mephedrone is mainly a youth phenomenon. The hazardous side-effects are strong desire to re-dose, uncomfortable changes in body temperature and heart rate, hallucinations and psychosis.

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### 1. Introduction

In recent years, a dramatic increase has been observed in the sale of “legal highs” via Internet. “Legal highs” are drugs which are neither controlled by the 1971 Misuse of Drugs Act, nor licensed for legal use (like alcohol and tobacco). The “legal highs” phenomenon encompasses a wide range of products, varied advertising strategies, and different patterns of use (EMCDDA, 2009). Such drugs are legal to use and possess, and legal to supply as long as they are sold for purposes other than human consumption (Newcombe, 2009).

“Legal highs” plant materials have been mixed with either plant extracts or synthetic chemicals, as seen with “Spice” (Vardakou et al., 2010).

Mephedrone – the most widely experienced “legal high” (EMCDDA, 2009) – and mephedrone-containing products have been aggressively marketed by online suppliers (Winstock et al., 2010) and in “head shops” (Newcombe, 2009) or street-level drug dealers (EMCDDA, 2010a). Mephedrone is advertised on the Internet as a “research chemical”, “bath salts”, “for botanical research”, “plant food”, “plant feeder” and even “hoover freshener”, often with a note indicating that it is “not for human consumption” in order to circumvent potential control mechanisms. However, several online shops are more explicit about its actual usage (EMCDDA, 2010b). Overall, Internet and social networking sites play a signifi-

\* Corresponding author. Tel.: +30 210 7462433; fax: +30 210 7716098.  
E-mail address: [cpistos@med.uoa.gr](mailto:cpistos@med.uoa.gr) (C. Pistos).

cant role in the marketing, sale and distribution of the drug (ACMD, 2010).

Use of mephedrone is predominantly a youth phenomenon, in particular of 15–24 years old with rates of drug use higher in males than in females, predominantly from urban areas, frequent in clubs, discos and dance events (EMCDDA, 2010b). Furthermore, there are reports which clarify that mephedrone is used by very young people at the age of 12–14 years old (<http://www.aolnews.com>). Adolescence living in families with high levels of parental conflict, poor family relationships and discipline or where parents themselves have drug or alcohol related problems are at greater risk of drug abuse. Young people who are homeless, who have been excluded from school or who have stopped attending school, young offenders and young people who have been in institutional or foster care are more likely to experiment with drugs at an early age and to develop drug-related problems. These factors are highly interconnected and are best understood as a “web of causation” (EMCDDA, 2003).

This review provides a systematic overview of both literature and online available information on mephedrone, a summarisation of any information about its availability, psychoactive properties, safety profile, clinical data and legislation, while it reveals the correlation between Internet and the expansion of mephedrone among adolescence.

## 2. Mephedrone

In recent years, a new class of designer drugs has appeared on the drugs of abuse market in many countries, namely beta-keto (bk) designer drugs such as mephedrone (Meyer et al., 2010). Mephedrone (4-methylmethcathinone) is a pharmacologically active alkaloid, a phenethylamine beta-ketone that is structurally similar to methcathinone (Psychonaut Web Mapping Research Project, 2010), and can be extracted from the leaves of the khat plant (*Catha edulis*) (Wood et al., 2010).

The synthesis of mephedrone, mentioned as “toluyl-alpha-monomethylaminoethylketone”, was first described in 1929 by Saem de Burnaga Sanchez. Alternative synthetic methods, though more cumbersome, have been described in the literature (EMCDDA, 2010b). First online mention of mephedrone synthesis seems to appear around 2003, but forum chatter about it as a recreational drug seems to have really begun in 2007. In 2007 it appeared as capsules made by the company Neorganics in Israel (Psychonaut Web Mapping Research Project, 2010). Colloquially known as “Miaow”, “4-MMC”, “Meow meow”, “Meph”, “TopCat”, etc. (Winstock et al., 2010) today is the fourth most commonly used drug after cannabis, ecstasy and cocaine (EMCDDA, 2010b).

Mephedrone is a central nervous system (CNS) stimulant, which due to its chemical similarity to amphetamines or methcathinone and the use as alternative to these drugs, a similar stimulant effect of the bk-designer drugs could be postulated (Meyer et al., 2010). There are no formal pharmacokinetic and pharmacodynamic studies on mephedrone and no published formal studies assessing the psychological or behavioural effects in humans (Psychonaut Web Mapping Research Project, 2010). Therefore psychological and behavioural effects related to mephedrone use are based on users' reports and clinical reports of acute mephedrone toxicity. Additionally, there are no animal studies on which to base an extrapolation of potential effects (EMCDDA, 2010b).

The desired effects after mephedrone use are euphoria, empathy, stimulation, mood enhancement, mental clarity and hallucination (Psychonaut Web Mapping Research Project, 2010). On the other hand, the adverse effects reported by users of mephedrone include tachycardia, nasal irritation secondary to insufflation of the powder, restlessness, and bruxism. Periph-

eral vasoconstriction and severe anxiety/agitation have been also related to mephedrone consumption (Early Warning System, 2010d).

Mephedrone is expected to act as a central nervous system stimulant by promoting the release of monoamine neurotransmitters norepinephrine, serotonin, dopamine and likely inhibiting their reuptake. It is possible that mephedrone's metabolism involves a reduction of the keto-function into a hydroxy-group, as well as N-dealkylation/deamination, or hydroxylation of the methyl-substituent on the phenyl-ring (Psychonaut Web Mapping Research Project, 2010).

To the authors knowledge, only Meyer and colleagues, managed to identify and characterise the metabolites of mephedrone in rat and human urine using GC–MS techniques. This study revealed that the new designer drug was metabolized via three phase I pathways by rats and humans. The chromatographic analysis allowed the detection of mephedrone and its metabolites in urine of rats treated with doses corresponding to those reported for abuse of amphetamines. The detected metabolites in rat urine were nor-mephedrone, nor-dihydro mephedrone, hydroxytolyl mephedrone, and nor-hydroxytolyl mephedrone. Studying the human urine samples, a further metabolite, 4-carboxy-dihydro mephedrone was detected (Meyer et al., 2010).

## 3. Availability via Internet

Up to now, new products that purportedly contain mephedrone appear in the online market on a regular basis (Psychonaut Web Mapping Research Project, 2010). Although it is difficult to measure consumption or sales, the drug's popularity has grown rapidly in a short period. In March 2009, there were less than ten online vendors of the drug. By June, as the drug became better known, Internet's advertising service for website owners was throwing up dozens of adverts for online stores, with new sites opening every week (Druglink, 2010).

Although the provenance of the substance is often not clear, several suppliers source mephedrone from China. Intelligence from Australia Customs and Border Protection Service has identified China and the UK as being the principal source of mephedrone. However, it is likely that in the case of the UK, this represents transit of the drugs and not necessarily production in the apparent country of origin (ACMD, 2010).

Despite the lack of scientific reports regarding mephedrone in the published literature, the situation is very different on the World Wide Web (www), where information about the drug is “just a click away”.

Tracking the www, it is clear that mephedrone is generally used by teenagers and young people, who are interested in using “legal drugs”. Recorded data have been found which make clear that mephedrone has started to replace ecstasy (<http://www.aolnews.com>).

Although it is easy to purchase a number of “legal highs” from different Internet suppliers, there are time periods when not all the products are available for purchase (Davies et al., 2010). It is difficult to determine what users of mephedrone will do when they were unable to purchase their “usual” product. They may decide to purchase alternative products. Considering that particularly young people have lack of experience in using drugs, there is the risk of exposure to different active drugs and this could increase the hazard of unwanted effects or lead to acute toxicity due to a difference in the relative amounts of active drug ingredient(s). Another reason leading to acute toxicity is that youth like to experiment with new drug products. Experimenting with drugs is becoming an increasingly common aspect of adolescent behaviour (EMCDDA, 2003). The easy drug availability through Internet directs young people

who experiment with drugs to become intensive drug users and develop serious drug-related health problems.

Even though mephedrone is often advertised as being of “high purity” (ACMD, 2010), reports of impurities identified by differences in colour, odour, etc. in commercially available mephedrone, has led some online users to label it a “dirty drug” (Psychonaut Web Mapping Research Project, 2010). Reports suggest varying prices around £10–15/g (Druglink, 2010; ACMD, 2010). Although the price is a predictor of the likely active ingredient(s) (Davies et al., 2010), youngsters prefer using cheap products and that raise the risk of adverse effects. Some vendors are offering same-day delivery services by car or motorbike courier, charging premium prices. One firm offers a minimum 5 g delivery service within 90 min to any address in London, 24 h a day, at a cost of £95. Users have to sign a disclaimer that they will not consume the drug (Druglink, 2010).

#### 4. Patterns of use

Mephedrone is usually available as a powder or tablets so it can be used orally, by nasal insufflation, intramuscular/intravenous injection and rectal insertion. Because of its physical characteristics (instability), mephedrone is not suitable for smoking. The powder can also be dissolved in water (EMCDDA, 2010b) or may also be swallowed—often after wrapping in tissue paper. The powder may be snorted by keying (sniffing a dose of a powdered drug from the thin end of a key) approximately 5–8 keys per gram (ACMD, 2010).

There are reports that mephedrone is sometimes used in conjunction with alcohol or controlled substances; co-abused substances include heroin (EMCDDA, 2010b), cocaine, cannabis, ketamine and MDMA (ACMD, 2010), either to heighten the effects or ameliorate the come-down (Newcombe, 2009). It is also reported that mephedrone is taken in combination with a variety of other compounds including: methylone, methylenedioxypropylvalerone (MDPV), butylone, GBL, Kratom (*Mitragyna speciosa*), CNS depressants such as benzodiazepines and many others (Psychonaut Web Mapping Research Project, 2010).

Mephedrone users report that dosages are 200 mg or more or “re-dosing” to prolong the euphoric experience, leading to the consumption of 1–2 g/session (ACMD, 2010). Furthermore, there are reports of upwards of 4 g being taken over an entire session (Psychonaut Web Mapping Research Project, 2010). Reports from hospital emergency units show that mephedrone is taken in staggered doses (Wood et al., 2010).

#### 5. Effects related to mephedrone use

Internet forums for mephedrone users reveal that desired effects are typically seen within 15–45 min after an oral ingestion. Following nasal insufflation, onset is reported by users to be within a few minutes and with peak effects within 30 min. The effects last approximately 2–3 h and therefore users may consume multiple doses during a session to prolong the duration of the desired effects. Reports from intravenous mephedrone users suggest that the high lasts approximately 10–15 min with an overall duration of desired effects of approximately 30 min (EMCDDA, 2010b).

In December 2009 Lifeline Publications & Research was commissioned to investigate mephedrone use in Middlesbrough. The research focused in three groups with a total of ten mephedrone users (nine men and one woman). All ten users were over eighteen years of age and polydrug users (mainly cannabis, alcohol and amphetamine). Most participants also mentioned being users of cocaine and ecstasy in the past, but generally indicated that they had ceased or reduced their use of these two drugs because of their low purity (which partly explains their increased interest in “legal highs”). The main adverse effects of mephedrone were reported

to be nose-bleeds, dilated pupils, blurred vision, dry mouth/thirst, hot flushes, palpitations, muscular tension in the jaw and limbs, and shrunken genitals (men only). The main mental effects were euphoria, unlimited energy, talkativeness, and time distortions – with heavier users also reporting visual hallucinations. The main residual effect was insomnia. The after-effects were similar to speed come-downs, involving fatigue, dizziness, and depression. Most users regarded mephedrone’s effects as superior to those of cocaine and ecstasy (Newcombe, 2009).

Reported clinical symptoms after mephedrone use are palpitations, seizure and vomiting, sweating, headache, discoloration of the skin, hypertension and hyper-reflexia. The most severe self reported side effects of mephedrone are strong desire to re-dose, uncomfortable changes in body temperature and heart rate, serious vasoconstriction in extremities and cold or blue fingers. Furthermore, high doses of mephedrone can cause hallucinations and psychotic episodes (ACMD, 2010).

Winstock et al. (2010) reported that people with underlying cardiac, neurological, and psychiatric conditions, especially those on medication, are likely to be at greatest risk of serious adverse events. Additionally, mephedrone induced increase in libido and may lead to risky sexual behaviour (Winstock et al., 2010).

Reports from a case study of mephedrone use (Linell, 2010) suggest that users can become regular users rapidly, although they are generally not in a “state of dependency”. However, this conclusion contrasts with the same report whereby users knew people who became daily users. Some users have reported developing cravings for mephedrone after use. It is likely that mephedrone use carries a risk of dependency. Dargan and Wood (2010) report a single case of dependency on mephedrone where the individual had been using the drug for 18 months. Emergent research with mephedrone users suggests that they may appear to develop tolerance quickly and as a consequence tend to consume higher doses more frequently (Dargan and Wood, 2010).

#### 6. Case reports related to mephedrone use

Mephedrone was first highlighted by the UN Office on Drugs and Crime after the death of an 18-year-old Swedish woman, reported in December (2008) in which mephedrone was the only substance detected post mortem (Morris, 2010). In the UK (2010) the substance has received substantial media attention after reportedly being linked to a number of deaths (Johnson, 2010), among them two teenagers at the age of 18 and 19 died after taking the drug (Dyer, 2010). One death in Scotland has been confirmed as the result of the “adverse effects of mephedrone and methadone” (ACMD, 2010). In Sweden, mephedrone was involved in about 100 enquiries (EMCDDA, 2009).

Deaths have been also reported in Romania press potentially related to mephedrone, however, these have not been confirmed (EMCDDA, 2009). Seven other mephedrone related fatalities have been reported, but is not certain whether or not death was directly caused by mephedrone consumption: a teenager in Denmark (2008) (<http://www.guardian.co.uk>), a Swedish woman in Stockholm (2008) – reportedly taken in combination with cannabis (<http://www.thelocal.se>), a teenager (14 year-old, female) in the UK (2009) – reportedly taken in combination with ketamine (<http://www.setox.org>), a second teenager (18 years old, male) in the UK (2010) (<http://www.dailymail.co.uk>), a woman (49 years old) in the UK in January 2010 (<http://www.heraldsotland.com>), a male (46 years old) in the UK (2010) and a female (20 years old) in the UK (2010) (<http://www.independent.co.uk>).

Furthermore, an accidental death (as the case characterised by medical examiner) caused by the combined use of “mephedrone and heroin” has been reported. Routine toxicological analysis

detected morphine in the decedent's blood at 0.06 mg/L. Additionally, 6-acetylmorphine, morphine, codeine, and doxylamine were detected in urine. Mephedrone was confirmed in the decedent's blood and urine at 0.50 and 198 mg/L, respectively (Dickson et al., 2010). Mephedrone has been also linked to the death of an 18-year-old girl who had taken "mephedrone and smoked cannabis". Forensic autopsy showed severe brain swelling, preceded by respiratory and circulatory arrest (Gustavsson and Esher, 2009). A likely that other drugs and/or other medical conditions or trauma may have contributed to or been responsible for death. The inquests into the deaths are pending for the majority of these cases therefore it is not possible at this time to determine the contribution of mephedrone (EMCDDA, 2010c).

## 7. Mephedrone and designer drugs

New pharmacologically active chemicals are often created when a structural or functional group is added to or removed from a chemical with demonstrated pharmacological activity (Camilleri et al., 2010). New or novel chemicals with central nervous system (CNS) activity are known to consumers as "research chemicals" and in the popular media as "designer drugs" (<http://www.jackshafer.com>).

Synthetic cathinones are increasingly being reported to the EMCDDA and Europol via the European early-warning system (EWS) on new psychoactive substances. These "designer" compounds, are derivatives of the parent compound cathinone, which is structurally related to amphetamine. Fifteen synthetic cathinones, including mephedrone, are currently being monitored through the EWS (EMCDDA, 2009).

Nowadays the stimulant has been banned in a number of countries. Only months after the statutory instrument controlling mephedrone under the Misuse of Drugs Act 1971, the press is already reporting on the "new killer drug" naphyrone, known to users as NG1 or Rave (Eastwood, 2010). In a sensationalist report based on no real evidence except for an interview with an apparent drug dealer identified as "chemist Dave", the Sun (U.K.) reports that Britain is about to be "hit" with a new synthetic drug. "Chemist Dave" states that naphyrone is <Britain's worst nightmare> and makes mephedrone <look like a baby powder>. "Chemist Dave" also declared about naphyrone <It will wreck hundreds of live and kill many times more than meow meow – and far more horrifically. It juices the brain, causing cerebral burn-out of a degree not seen before> (<http://www.thepoisonreview.com>).

It is expected that by the time that naphyrone is controlled, its successor will already have been designed and be ready for export (Eastwood, 2010).

## 8. Legal status

Mephedrone is controlled in a number of countries, including, Italy (16th June 2010), Belgium (13th June 2010), France (11th June 2010) (EMCDDA, 2010a), UK (16th April 2010) (<http://www.legislation.gov.uk>, No. 1144), Romania (10th February 2010) (EMCDDA, 2010b), Germany (22nd January 2010), Estonia (27th November 2009), Sweden (25th May 2009), Denmark (21st December 2008), Israel (January 2008) (Dickson et al., 2010), and Norway (30th June 1978). In Ireland the legislation will come to effect in June 2010 while in Croatia, mephedrone is controlled under precursors control legislation since 4 January 2010 (EMCDDA, 2010b). In Lithuania, mephedrone was included in the first list in the list of "Narcotic drugs and psychotropic substances prohibited for medical use" on June 2010 by the ministerial order No. V-540 (EMCDDA, 2010c). Furthermore, mephedrone is illegal in the USA under vague, catch-all analogue laws that ban chemical

compounds "substantially similar" to illegal substances (Druglink, 2010).

Mephedrone has no established or acknowledged medical value or use (human or veterinary) in the European Union. There is no marketing authorisation (existing, ongoing or suspended) for mephedrone in the European Union or in the Member States. There is no information that mephedrone is used for the manufacture of a medicinal product or an active pharmaceutical ingredient (API) of a medicinal product in the European Union. There remains a theoretical possibility that mephedrone could be used for the synthesis of some API of veterinary or human medicinal products (e.g. ephedrine, pseudo-ephedrine and pyrovalerone). No data exists to suggest that this is currently the case but it should be noted that there is no European Union database on the synthetic routes of all registered medicinal products (EMCDDA, 2010c).

In the European Union (EU), a risk assessment on mephedrone carried out by the extended Scientific Committee of the EMCDDA. The Council of the EU, has adopted the following decisions:

### Article 1

Member States shall take the necessary measures, in accordance with their national law, to submit 4-methylmethcathinone (mephedrone) to control measures and criminal penalties as provided for under their legislation by virtue of their obligations under the 1971 United Nations Convention on Psychotropic Substances.

### Article 2

This Decision shall enter into force on the day following that of its publication in the Official Journal of the European Union.

## 9. Conclusion

In this article, author's effort was focused at all available data regarding the availability, pharmacological properties and the current worldwide legislation status about the new "designer drug" mephedrone.

At present, mephedrone seems to be the most popular of the synthesized cathinone stimulants. It seems to be trendy among young clubbers, but is also used by a wider population of older adolescents and young adults. Concern also exists that mephedrone may be taken by young people with little previous experience of drug use (Winstock et al., 2010).

Mephedrone's rapid rise in popularity has been linked to its psychoactive effects, cheapness, and legality. Another significant factor for its widespread use is that mephedrone is not detected in standard drug tests (Psychonaut Web Mapping Research Project, 2010). Furthermore, recently surveyed mephedrone users reported that the drug gives a better "high" than cocaine. Some researchers have suggested that mephedrone's popularity reflects, in part, dissatisfaction with the purity and consistency of available cocaine and ecstasy among regular stimulant users, who now seek out mephedrone instead (Winstock et al., 2010). Above all the main reason for mephedrone's expansion is the simple availability via Internet. It is important to note that youngsters freely surf the Internet, most likely without the pressures of parental control or authority (Tsitsika et al., 2009). Adolescents and young adults have become the largest segment with drug-related Internet activity. Through www even the novice user has easy access to all the information needed to purchase, sell, or use any drug.

Chemists are staying one step ahead of drug laws by toying with the chemical make-up of illegal stimulants such as ecstasy, speed and methylamphetamine (crystal meth) to make an increasingly popular range of "legal highs" (Druglink, 2010). As there are a vast number of potentially active compounds, it is generally not feasible for controlled substance legislation to list each and every chemical variant explicitly. This is particularly problem-



atic when there is no documented evidence of pharmacological activity or previous abuse. This lack of legislative control provides entrepreneurial individuals and companies with the opportunity to attempt to exploit or circumvent legislation and create pharmacologically active chemicals that are not explicitly controlled, and in some instances, market them as “legal” alternatives (Camilleri et al., 2010).

Research community must remain alert, as various new products containing mephedrone continuously appear and are easily obtainable. As almost nothing about neurotoxicity or the long term effects of mephedrone's use is known, educational and risk assessment about this drug are urgently needed.

### Conflict of interest statement

The authors declare that there are no conflicts of interest.

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