Designer Drugs on the Internet: a Phenomenon Out-of-Control? The Emergence of Hallucinogenic Drug Bromo-Dragonfly

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Abstract

Based on the material available in both the scientific literature and on the web, the present paper provides an updated pharmacological, chemical, toxicological and behavioural overview of Bromo-Dragonfly (1-(8-bromobenzo[1,2-*b*;4,5-*b'*]difuran-4-yl)-2-aminopropane; 'B-fly'). B-Fly is a powerful, long lasting, LSD-like, hallucinogenic drug, which has been associated with a number of acute intoxications and fatalities in a number of countries. A critical discussion of the potential of misuse of B-fly but also of the methodological limitations, which are intrinsically associated with the analysis of online, non-peer reviewed, material, is presented. It is concluded that the availability of online information on novel psychoactive drugs, such as B-fly, may constitute a public health challenge. Better international collaboration levels may be needed to tackle this novel and fast growing phenomenon.

Key words

ABDF, Bromo-Dragonfly, FLY-compounds, Internet monitoring, phenethylamines, Psychonaut project, ReDNet project, research chemicals

Introduction

A new generation of psychoactive drugs related to the phenethylamines' group, known as the 'FLY' drugs, emerged in the last few years as a new recreational drug misuse trend. The most common FLY compounds are:

- 2C-B-FLY: 1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b′*]difuran-4-yl)-2-aminoethane hydrochloride
- 3C-B-FLY: 1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-*b*;4,5-*b′*]difuran-4-yl)-2-aminopropane hydrochloride
- Bromo-Dragonfly: 1-(8-bromobenzo[1,2-*b*;4,5-*b′*]difuran-4-yl)-2-aminopropane

They are called 'FLY' because their molecular structure resembles the insect: the body of the fly will be the benzene ring; the two wings are the furan or dihydrofuran rings; the head is the bromine atom and the tail is the isopropylamine [1].

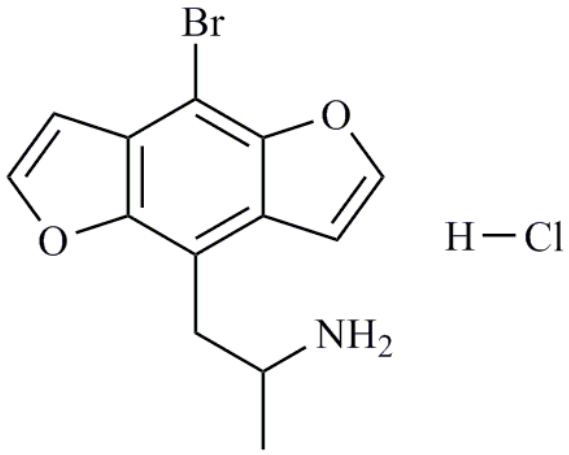

Figure 1

1-(8-bromobenzo[1,2-*b*;4,5-*b'*]difuran-4-yl)-2-aminopropane hydrochloride (Bromo-Dragonfly)

In particular, Bromo-Dragonfly was first synthesized by Matthew A. Parker at Purdue University in 1998 and used as a novel brain research chemical with rats [2-5]. Although structurally and chemically it is related to phenethylamines, the phenyl ring of this molecule is bound between two dihydrofuran rings, giving it more potency and much longer duration of action than most other phenethylamines [6]. Its effects can last up to 1-3 days [1]. A procedure based on liquid chromatography-mass spectrometry (LC-MS) has been described to identify a number of phenethylamines [7], including some of the 'FLY' drugs such as 2C-B-Fly, in the urines of consumers using 3,4 methylendioxypropylamphetamine (MDPA) as internal standard. Its mechanism of action is mediated primarily by agonist activity at the serotonin 5-HT2A receptors as well as to some degree at 5-HT1 receptor [2, 8]. It has been speculated that the interaction with both these receptors is likely to be responsible for the hallucinogenic effects [9-11]. Apart from 5-HT2A receptors, there is evidence from both biochemical [12] and behavioural [13-14] studies that the 5-TH2C receptors' subgroups, in both rodents and humans, are involved as well in the pharmacodynamics of B-Fly [13-16].

It has been observed that the synthesis of this substance is complicated by the fact that the molecule can form two distinct chiral or optical isomers and that originally 5 other related synthetic molecules are also called FLY [17]. Although Bromo-Dragonfly is a research chemical and as such not for human consumption, in recent years it has been increasingly abused recreationally. Anecdotal evidence of this epidemic of misuse has emerged from an increased number of fatalities and hospitalizations [18-19], but also from the Internet. Indeed, hundreds of websites advertise the drug for sale and an increasing number of discussions and videos related to the substance are posted online on a regular basis [10-23]. B-Fly is currently not legislated for under the UK Misuse of Drugs Act and is legally available in the UK, US and in most of Europe. Conversely, it is a controlled substance in Denmark, Sweden, Norway and Romania.

We aimed at providing here a comprehensive overview of both the peer reviewed and the anecdotal online data on Bromo-Dragonfly.

Material and Methods

The literature on Bromo-Dragonfly was searched in three databases, PsychInfo, Pubmed and MedScape. Key words used to carry out the database searches included: '1-(8-bromobenzo[1,2-*b*;4,5-*b'*]difuran-4-yl)-2-aminopropanehydrochloride', 'Bromo-Dragonfly, 'B-fly' and 'ABDF'. Considering the limitation of peer reviewed, scientific, data results were integrated with a multilingual qualitative assessment of a range of websites, drug-forums and other online resources (e-newsgroups, chatrooms, mailing lists, e-newsletters, and bulletin boards). This was carried out using the Google search engine in 7 languages from a number of collaborating countries (UK, Finland, Norway, Belgium, Germany, Italy and Spain; see http://www.psychonautproject.eu). The online assessment was carried out over the period of one year (February 2009 - 2010) and involved the close monitoring of 203 websites. Of these, 108 were considered to be relevant for the present exercise and as such were monitored on a regular basis i.e., daily (n= 21), weekly (n= 32), or monthly (n= 53), depending on their relevance. The remaining 95 websites were considered not to bear any interest for the present study and thus were no longer monitored. Once the Bromo-Dragonfly was identified on these websites, further specific searches were carried for narratives focusing on the following issues: (a) the nature of its effects on users, including adverse reactions; (b) motivations behind its recreational use and possible trends of misuse, with particular attention to polydrug misuse/idiosyncratic combinations; (c) any other relevant information in the original language of the narratives. The full content of posts/sites of particular interest were also saved and copied onto a dedicated server using a specific programme [24]. This was carried out primarily for historical archiving and for allowing a more thorough and flexible content search using both MacOSX10.6 server built-in search capabilities [25] as well as a third-party search application [26]. Data collected were stored in a password-protected online database located within the coordinating centre (St. George's, University of London, UK) and a technical folder with all the available information on the effects of the drug, including various toxicological data, was also created. For the purpose of reporting results in this paper, any data collected from online forums, such as usernames and complete URLs for specific threads that were considered personal identifiable, were

anonymised. The study was cleared for ethical approval by the Wandsworth Local Research Ethics Committee, London, UK.

Results

Information on B-Fly online availability, consumption and manufacture

Although the first reported case of recreational B-Fly abuse can allegedly be traced back to 2001 [23] but, according to Google Insights for Search [27], the web search activity associated with the substance has started to gradually increase only in 2005. Bromo-Dragonfly was then formally identified in 2008 as a new emerging trend of drug abuse during the web monitoring activities of the Psychonaut Web Mapping Project following warnings from a number of EU countries, including Italy, Norway, Belgium, and Finland. 'B-Fly' is typically sold online as blotter papers, liquid and less commonly as pills. According to most online reports, its primary route of administration is oral. After ingestion, the onset of its effects can be delayed for up to 6 hours. This delay has often led recreational users to ingest another dose of the substance thinking that the first dose was inadequate. Alternatively, additional drugs may be ingested while waiting for the psychoactive effects to appear [20, 27, 21, 22]. Although the exact dosage is still unknown, a 'typical' dose is reported by users to be in the region of 200 to 800 μg [20]. There are two, or possibly more, types of B-Fly available on the Internet. The first one, called the 'European Batch' (active at dose of 200 to 500 μg) and a less potent one, called the 'American Batch' (active at 800 to 1800 μg) [17]. The average price for 1 gr of Bromo-Dragonfly is about 300 euros/420USD, while a single dose (blotter paper) is around 10-30 euros/14-42USD. Other items such as blotters sheets with various artworks are also widely available online [29].

Effects and adverse reactions

Some users describe the effects of Bromo-Dragonfly as 'a ride to the moon' because they 'last too long and leave you drained' [20]. Accounts of experiences lasting 2-3 days after the consumption of a single dose (blotter paper) seem to be fairly common [20-21]. Some users report however that B-Fly is 'definitely not for everyone, just too powerful' [21-

22]. The drug can allegedly induce profound hallucinations (mainly visual distortions, such as geometric patterns and lights), sound alterations, but also other effects such as the sense of connection/belonging with other realities, sense of peace and well-being, emotional stimulation and meeting with entities, which are also common features of the so-called near-death experience [30].

The level of toxicity associated to Bromo-Dragonfly may well be a reason of concern, as recently revealed by a series of hospitalizations and fatalities. For instance, a case of death was recorded in 2008 in a Swedish hospital, where the patient had convulsions, respiratory problems, liver and kidney failure and lost several fingers and toes. This incident was associated with the oral assumption of an allegedly very large amount of B-Fly [18, 31]. Another fatality was recorded in Denmark after the ingestion of around 1ml of 'LSD-like liquid', later identified as Bromo-Dragonfly [32]. The autopsy findings included oedema of the lungs, slight oedema of the brain, enlargement of the spleen, irritation of the mucous membrane in the stomach and ischaemic changes in the kidney [32]. Further fatalities have been recorded in Finland, Denmark, the UK, Norway and the US [18,19]. Common adverse reactions may include: nausea and vomiting, headache, tachycardia, elevated blood pressure, lung collapse, gastrointestinal disturbances, muscle tension, tremor, body temperature fluctuations, anxiety, panic attacks, arrhythmias, heart murmurs, slight pupil dilation, convulsions, stomach tightness, hallucinations, flashbacks, memory disturbances, confusion, and paranoid ideation [19, 33].

Motivations for B-Fly intake and polydrug misuse issues

Most users may approach Bromo-Dragonfly due to its 'psychedelic' properties, which seem to be similar, but of longer duration, to those of lysergic acid diethylamide (LSD) [20, 28, 34]. Other observations are however consistent with the misuser need of enhancing his/her physical sensations (e.g. taste, touch, hearing) and/or to prolong the sexual excitement/pleasure [18]. Other reasons for taking B-Fly have been outlined in Table 1.

Bromo-Dragonfly is often used in combination with a variety of other drugs, generally to enhance or prolong the duration of action of their effects. These polydrug misuse experimentations have led to a range of cases of acute intoxication; particularly worrying

seems to be the combination of B-Fly with ketamine, with severe agitation, hallucinations and tonic-clonic seizures having been reported [19, 35].

Table 1: Overview of the alleged reasons for taking B-Fly

Reasons	**Description**
Hallucinogenic/psychedelic effects	'I nearly died from taking a £ 5 hit', claimed an 18-year old user, when he was promised a 'mellow hit, similar to acid but more enjoyable' [36]. Effects of Bromo-Dragonfly can include visual distortions, such as geometric patterns and lights, sense of belonging\connecting with other realities, and sense of unity with the cosmos among many others [28, 22, 20].
Experimenting with a new substance and/or with novel combinations	B-Fly is reportedly often taken in combination with other compounds in order to try a different 'high' [23, 22, 28], such as: • Alcohol • Prescribing drugs: alprazolam • Illicit/recreational drugs: hashish/marijuana; cocaine; amphetamines; LSD; ketamine • 'Legal highs', including: Salvia divinorum; and Kratom (*Mytragina speciosa*)
By mistake	Large numbers of users have tried B-Fly thinking it was LSD, especially because both substances are available in the form of

	blotter paper [20, 22]. In 2009 there have been reports of users taking B-Fly by mistake thinking it was '2CB-fly' due to a mislabel batch sold online [22, 36, 39]. 'Thankful I am alive', said one these messages posted by a 23-year-old man: '*I was in a nearly catatonic state, unable and not wanting to move. Eyes closed the whole time. I couldn't keep them open (...). It was 23°C outside, yet I was freezing. I was under all of the covers in my bed, yet I began sweating immensely. I couldn't tell if I was awake or sleeping. Conscious or unconscious. It seemed I was somewhere in between the two. This scared me a bit. (After 50 hours) I still don't feel normal. I hope I do soon"* [20] .
Favourable legality status	B-Fly remains a legal substance in a number of countries, although bans have recently been made in Denmark, Sweden, Norway and Romania.
Online availability	B-Fly is easy to purchase over the Internet, often at a discounted rate [29, 20, 22].

Discussion

The present work provided a review of the current state of knowledge of Bromo-Dragonfly in the peer reviewed literature. To the best of our knowledge, it also provided

for the first time a critical analysis of the information from and for web surfers/users relating to B-Fly psychoactive effects, adverse reactions and use in combination with other drugs. It seems from here that reasons behind Bromo-Dragonfly increase in popularity include: its powerful a long lasting, LSD-like, hallucinogenic effects; its favourable legal status; and its affordability. Indeed, B-Fly is at times promoted with special offers. Online popularity of B-Fly may have increased as a result of technical facilities such as: 'alerts' about novel psychoactive products via text messages and/or instant messaging; and 'e-mail this product to a friend' [37, 38].

Young/vulnerable individuals might be encouraged by a range of widely available online comments/messages/videos relating to the B-Fly intake experiences. This may be an issue of concern, if one considers that an estimated 61% of young European people aged between 15-24 years typically quote the Internet as a potential source of information on illicit drugs [39]. Furthermore, it appeared from here that only a minority of drug selling websites were allegedly limiting access to the relevant links to under age individuals.

At the time of writing, B-Fly remains legal in most of the EU countries. This may be an intriguing issue, given its chemical structure similarity with other, already controlled, phenethylamines such as 4-bromo-2,5dimethoxyphenethylamine (2C-B) and 4-bromo-2,5-dimethoxyamphetamine (DOB). The current legal status of B-Fly may arguably facilitate the increasing levels of popularity of the drug, but might affect as well the users' perception of risks associated with its consumption. In fact, the idea that legality can equate with safety still remains well grounded amongst some recreational users [37, 40, 41].

Most of the novel psychoactive compounds available online, such as B-Fly, share a number of characteristics that may constitute a public health challenge, including: (a) not being approved for human consumption; (b) their intake possibly being associated with a number of unknown side effects/adverse reactions); (c) very few related pharmacological/toxicological data being available in the peer reviewed, scientific, literature, with the limited knowledge being mostly restricted to pre-clinical studies; (d) rapidly appearing in always more sophisticated forms and remaining unregulated for a long period of time; (e) being most often synthesized in underground laboratories simply modifying the molecular structure of remaining controlled drugs (e.g. amphetamines;

tryptamines), hence raising further concerns in terms of presence of contaminating agents; (f) being largely available online and thus 'just a click' away from our homes and potentially available to everyone; (h) being increasingly accepted as part of a 'trendy' lifestyle, because the internet may arguably act as an enabler for niche activities to develop into social norms.

A possible limitation of the present study could be given by the fact that only publicly available websites, forums and similar were monitored. Conversely, to improve the coverage of the study not only the web pages but also more private ways of communication (including newsgroups, chatrooms, mailing lists, newsletters, and bulletin boards) were here considered. A further limitation may be given by the fact that the present findings do rely mostly on what reported by users. In particular, we did not have any possibility here to understand if the substance the online B-Fly misusers were taking was indeed B-Fly.

One could conclude that a constant level of web monitoring activities with respect to drug-related issues is a necessary step to better understand the level of the diffusion of novel psychoactive substances, such as B-Fly. From this point of view, better international collaboration levels may be needed to tackle this novel and fast growing phenomenon. Finally, it is suggested that the use of technological tools could be successfully incorporated in specific prevention programmes for novel compounds in the field of eHealth, as currently piloted by the Recreational Drugs European Network (ReDNet; http://www.rednetproject.eu) [41].

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References

[1] Reed EC, Kiddon GS. The characterization of three FLY compounds (2C-BFLY, 3C-B-FLY, and BromoDragonFLY). DEA Microgram Journal 2007; 5: 4-12.

[2] Parker MA, Marona-Lewicka D, Lucaites VL, Nelson DL, Nichol DE. A novel (benzodifuranyl)aminoalkane with extremely potent activity at the 5-HT2A receptor. J Med Chem 1998; 41: 5148-9.

[3] Monte, AP, Marona-Lewicka D, Parker MA, Wainscott DB, Nelson DL, Nichols DE. Dihydrobenzofuran analogues of hallucinogens. J Med Chem 1996; 39: 2953-61.

[4] Chambers JJ, Kurrasch-Orbaugh DM, Parker MA, Nichols DE. Enantiospecific synthesis and pharmacological evaluation of a series of super-potent, conformationally restricted 5-HT2A/2C receptor antagonists. J Med Chem 2001; 44: 1003-10.

[5] Anonymous. “Bromo-Dragonfly” (bromo-benzodifuranyl-isopropylamine) in Ashland, Oregon. Microgram Bulletin 2007; 40:78.

[6] Shulgin A, Shulgin A. PIHKAL A Chemical Love Story. Transform Press; Berkeley, CA 1998.

[7] Pichini S, Pujadas M, Marchei E, Pellegrini M, Fiz J, Pacifini R, Zuccaro P, Faree’ M, de la Torre R. Liquid chromatography-atmospheric pressure ionization electrospray mass spectrometry determination of "hallucinogenic designer drugs" in urine of consumers. J Pharm Biomed Anal 2008; 47: 335-42.

[8] Fiorella D, Rabin RA, Winter JC. The role of the 5-HT2A and 5-HT2C receptors in the stimulus effects of hallucinogenic drugs I: Antagonist correlation analysis. Psychopharmacol 1995; 121: 347-56.

[9] Titeler M, Lyon RA, Glennon RA. Radioligand binding evidence implicates the brain 5-HT2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. Psychopharmacol 1988; 94: 213-6.

[10] Glennon RA. Do classical hallucinogens act as 5-HT2 agonists or antagonists? Neuropsychopharmacol 1990; 3: 509-17.

[11] European Monitoring Centre for Drugs and Drug Addiction: Report on the risk assessment of 2C-I, 2C-T-2 and 2C-T-7 in the framework of the joint action on

new synthetic drugs. Office for Official Publications of the European Communities, Luxembourg 2004.

[12] Sanders-Bush E, Burris KD, Knoth K. Lysergic acid diethylamide and 2,5-dimethoxy-4-methylamphetamine are partial agonists at serotonin receptors linked to phosphoinositide hydrolysis. J Pharmacol Exp Ther1988; 246: 924-8.

[13] Marek GJ, Aghajanian GK. LSD and the phenethylamine hallucinogen DOI are potent partial agonists at 5-HT2A receptors on interneurons in rat piriform cortex. J Pharmacol Exp Ther 1996; 278: 1373-82.

[14] Gewirtz JC, Marek GJ. Behavioral evidence for interactions between a hallucinogenic drug and group II metabotropic glutamate receptors. Neuropsychopharmacol 2000; 23: 569-76.

[15] Vollenweider FX. Advances and pathophysiological models of hallucinogenic drug actions in humans: a preamble to schizophrenia research. Pharmacopsychiatry 1998; 31: 92-103.

[16] Backstrom JR, Chang MS, Chu H, Niswender CM, Sanders-Bush E. Agonist-directed signaling of serotonin 5-HT2C receptors: differences between serotonin and lysergic acid diethylamide (LSD). Neuropsychopharmacol 1999; 21: 77S-81S.

[17] Bromo-Dragonfly & the DEA Microgram Bulletin. Addiction Education Blog. http://www.cnsproductions.com/drugeducationblog/drug-information/24/ (Accessed March 16, 2011).

[18] Andreasen MF, Telving R, Birkler RI, Schumacher B, Johannsen M. A fatal poisoning involving Bromo-Dragonfly. Forensic Sci. Int. 2009; 183: 91-6.

[19] Wood DM, Looker J, Shaikh L, Button J, Puchnarewicz M, Davies S, Lidder S, Ramsey J, Holt D, Dargan PI. Delayed Onset of Seizures and Toxicity Associated with Recreational Use of Bromo-Dragonfly Clinical Toxicology, Guy's and St. Thomas' NHS Foundation Trust, London, UK. J Med Toxicol 2009; 5: 226-9.

[20] Erowid. http://www.erowid.org/ (Accessed on February 28, 2009).

[21] Cannabis Culture Forums. http://forums.cannabisculture.com/forums/ (Accessed February 28, 2009).

[22] Bluelight. http://www.bluelight.ru/vb/home.php (Accessed November 10, 2009).

[23] Bromo-DragonFLY Trip: You Tube videos. http://www.neurosoup.com/bromodragonfly.htm. (Accessed November 5, 2009).

[24] Blue Crab. http://www.limit-point.com/BlueCrab/BlueCrab.html (Accessed November 5, 2009).

[25] Spotlight™ and Search™. http://www.apple.com/macosx/what-is-macosx/ (Accessed November 5, 2009).

[26] Boolean Search™. http://www.limit-point.com/BooleanSearchServer/BSS.html (Accessed on November 5, 2009).

[27] Google Insights for Search analysis. www.google.com/insights/search (Accessed November 5, 2009).

[28] Drugs-forum. http://www.drugs-forum.com/index.php (Accessed February 8, 2010).

[29] eBay. http://www.ebay.com/ (Acessed November 18, 2009).

[30] Corazza O. Near-Death Experiences: exploring the mind-body connection. Routledge, London, NY 2008.

[31] Thorlacius K, Borna C, Personne M. Bromo-dragon fly--life-threatening drug. Can cause tissue necrosis as demonstrated by the first described case. (In Swedish only). Lakartidningen 2008; 105:1199-2000.

[32] Nyt stof har slået dansker ihjel. http://jp.dk/indland/aar/article1418250.ece (in Danish only). (Accessed October 30, 2009).

[33] Stolaroff MJ, Wells CW. Preliminary Results with New Psychoactive Agents 2C-T-2 and 2C-T-7. Yearbook Ethnomed 1993; 99-117.

[34] Anonymous. “Bromo-Dragonfly” in Queensland, Australia. DEA Microgram Bulletin 2008; 41: 16.

[35] Corazza O, Schifano F. Ketamine use: a prospective study on the emergence of near-death states among a group of 50 ketamine recreational users. Subst Use Misuse 2010; 45: 916-924.

[36] BBC News. I nearly died from taking a £5 hit. http://news.bbc.co.uk/1/hi/england/surrey/7315020.stm (Accessed February 8, 2010) .

[37] Schifano F, Corazza O, Deluca P, Davey Z, the Psychonaut group. Psychoactive

drug or mystical incense? Overview of the online available information on Spice products. International Journal of Culture and Mental Health 2009; 2: 137-44.

[38] Drogen-Forum. http://drogen-forum.us (Accessed March 17, 2011).

[39] Eurobarometer. Young people and drugs: Analytical report. http://ec.europa.eu/public_opinion/flash/fl_233_en.pdf. (Accessed November 17, 2009).

[40] Schifano F, Deluca P, the Psychonaut 2002 research group. Drugs on the web; the Psychonaut 2002 EU project preliminary results. Prog Neuro-Psychoph 2006; 30: 640-6.

[41] Corazza O, Davey Z, Deluca P, Demetrovics Z, Drummond C, Enea A, Moskalewicz J, Di Melchiorre G, Di Furia L, Farre' M, Flesland L, Scherbaum N, Siemann H, Skutle A, Torrens M, Pasinetti M, Pezzolesi C, Shapiro H, Sferrazza E, van der Kreeft P, and Schifano F. Le nuove potenzialità della prevenzione digitale in materia di nuove droghe: il ruolo del Recreational Drugs European Network. Dipendenze Patologiche/Addictive Behaviors, 43-46, 2010.

Novel Drugs, Novel Solutions: exploring the potentials of web-assistance and multimedia approaches for the prevention of drug abuse

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Objectives: Drug abuse has increased markedly in the last decade especially with the emerging of the unregulated websites selling novel herbal, designer and pharmaceutical psychoactive products. These are advertised online as 'legal' or 'pure' and sold at very low prices. In this respect, the Recreational Drug European Network (ReDNet) aims to pilot various multimedia solutions focused on the prevention of drug abuse, which are based on technical and scientific information. The service is targeted at both professionals and young people. Methods: (a) monitoring the web for emerging novel drugs of abuse; (b) testing these products using the appropriate analytical techniques and (3) disseminating information via technological tools such as interactive websites, SMS alert, social networking (Facebook, Twitter), Multimedia (YouTube), Smartphone applications (iPhone), and seminars for professionals in the virtual learning environments (Second Life). Results: Up to date, 500 health professionals are using the interactive website on regular basis. The ReDNet Facebook page has 250 likes. Seminars for professionals on Second Life have started since January 2011. SMS alerts, phone applications and other innovative services will soon be available for health professionals and young people. Conclusions: The piloting of innovative ICT-based prevention programmes with respect to novel psychoactive drugs is an essential step to tackle their rapid diffusion and promote safer and knowledge-based online environments and healthier life styles.

Nuove Droghe, Nuove Soluzioni: esplorare il potenziale della web-assistance e proposte multimediali nella prevenzione dell'abuso di sostanze

Obiettivi: l'abuso di sostanze nella scorsa decade è cresciuto marcatamente, specialmente con l'emergere di siti web non soggetti ad alcun regolamento che vendono prodotti di origine vegetale, sintetica o farmaceutica. Queste sono pubblicizzate come 'legali' o come ' pure' e vendute ad un prezzo molto basso. A questo proposito, il Recreational Drug European Network (ReDNet) si propone l'obiettivo di implementare varie soluzioni multimediali focalizzate sulla prevenzione dell'abuso di sostanze utilizzando informazioni tecniche e scientifiche. Il target è costituito da professionisti e giovani. Metodi: (a) monitoraggio del web in merito all'emergere di nuove droghe d'abuso; (b) testare questi prodotti con le opportune tecniche di analisi e (c) disseminare le informazioni tramite strumenti telematici, quali

siti web interattivi, SMS di allerta, social networking (Facebook, Twitter), Multimedia (YouTube), applicazioni per gli Smartphone (iPhone), e seminari per professionisti in piattaforme virtuali (Second Life). Risultati: in questo momento 500 professionisti del settore della salute stanno usando il sito web interattivo in modo regolare; la pagina Facebook del ReDNet ha realizzato 250 "Mi piace". A partire da Gennaio 2011 sono iniziati i seminari per professionisti nella piattaforma multimediale di Second Life. SMS informativi, applicazioni per cellulari ed altri servizi innovativi saranno presto disponibili per i professionisti della salute e per i giovani. Conclusioni: testare programmi di prevenzione innovativi basati su strumenti multimediali è un passo essenziale per affrontare la rapida diffusione delle nuove sostanze psicoattive, promuovere un più sicuro e consapevole utilizzo della rete oltre che stili di vita più sani.

Keywords: *Designer drugs, Prevention, ReDNet Project, Multimedia approaches, "Legal highs", Web-assistance*

Parole chiave: *Nuove Droghe, Prevenzione, ReDNet Project, Strumenti multimediali, "Legal highs", Web-assistance.*

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Introduction

During the last decade there has been a sharp change in the social, cultural, legal and political context of drug addiction, which has led to unprecedented new challenges. It has been documented that an increasing number of unregulated websites were dedicated to the dissemination of novel herbal, 'designer' and pharmaceutical psychoactive drugs[1-4]. These drugs are of particular concern as they are advertised as 'legal' and 'pure' making them more attractive to abusers mainly of the teenage group. More specifically they are:

- Not approved for human consumption and might well have unknown pharmacological effects and unpredictable side effects and adverse reactions on users[5,6].
- Legal and thus perceived as 'safe' by users/potential users[7].
- Often sold as something else, like mystical incenses, plant chemicals and bath salts[7,8].
- Unknown to health and other professionals who constantly need to receive updated and accurate information about these new substances. For instance, according to one of our survey 69% of health professionals in the UK are seeing patients who are taking 'legal highs' and 57% judged their knowledge of legal highs 'poor' or 'basic'[9].
- Not mentioned in the scientific literature, generally restricted to studies in animals[5-7].
- Are increasingly accepted as part of a lifestyle rather than being considered as a misuse of drugs[6].
- Are just a 'click away' from our homes and thus potentially available to everyone, especially young people who are amongst the most at risk in taking advantage of information and products available online[7,10].

The situation is even more alarming if it is considered that an estimated 78% of young people aged between 16 to 24 years in the European Union (EU) already use the Internet at least once a week and 60% of parents are worried about their online use[11]. For instance in Italy, about one-third of children ages 2 to 11, three-fourths of adolescents and adult women, and over four-fifths of adult men access the Internet

Fig.1 Leaflet of the ReDNet Project ; volantino del ReDNet Project

on a monthly basis. Children spend an average of 22 hours/month on the computer, with a jump to 87 hours/month for adolescents[12].

In this respect, a variety of Internet-based programs that aims to educate and prevent drug abuse among young people have been attempted. However, the impact of these forms of intervention are relative inconclusive. In general these educational resources appear to be negatively appraised by those who might be considered at risk of becoming users. We suggest here that these forms of intervention are unsatisfactory because they are:

- Fear-based and moralistic.
- Inherently theoretical and didactic.
- These forms are only focused on traditional psychoactive substances such as heroin, cocaine and alcohol.

Recreational Drugs European Network (ReDNet)

The Recreational Drugs European Network (ReDNet; www.rednetproject.eu) is a research project that aims to develop and pilot innovative and effective information communication technologies (ICT) preventive approaches focused on novel psychoactive compounds and combinations (Figure

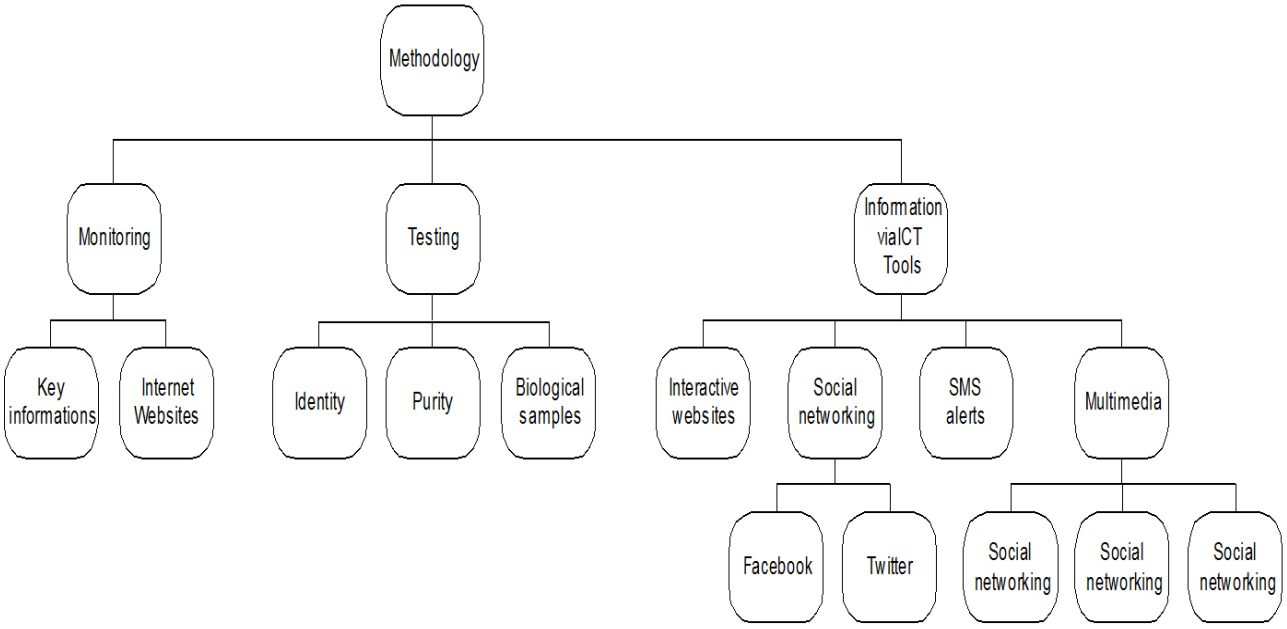

Fig.2 Methodology of the ReDNet Project ; Metodologia del ReDNet Project

1). Piloted ICT tools include the use of interactive websites, SMS alert, social networking (Facebook, Twitter), Multimedia (YouTube), Smartphone applications (iPhone), and seminars for professionals in the virtual learning environments (Second Life)[13-15].

All these tools are developed through the use of technical/scientific information, appropriately adapted and updated, that have been previously indentified and carefully monitored by our research centres. It relies here on the experience of two previously EC-funded research projects (Psychonaut I, II; www.psychoanutproject.eu;[16,17]), which focused on web monitoring and developed a search engine in various languages. Particular attention is also given to health professionals working directly with young people showing problematic behaviours who constantly need to receive updated and accurate information about these new substances.

The project is funded by the European Commission Executive Agency for Health and Consumers in the framework of the Public Health Programme and has a network operative in ten research centres across eight EU countries: the UK, Spain, Germany, Italy, Belgium, Poland, Hungary, Norway.

The main objectives of the ReDNet are:

- To design an innovative and effective ICT-based model to share knowledge and information with health/other professionals and raise awareness of the potential harms associated with new drugs.
- To identify and disseminate key recommendations relevant to the development of the awareness on novel compounds initiatives across the EU.
- To identify any remaining gaps in knowledge and methodological lessons learned.
- To inform future projects in the field of drug prevention using ICT tools.

Methods

The project's methodology is articulated in three main phases (Figure 2):

1. Monitoring.
2. Testing.
3. Informing via ICT tools.

1. *Monitoring*

Monitoring is mainly focused on the observation of the web sources including websites, chat rooms and news groups for any emerging novel synthetic and herbal drugs of abuse. A specific methodology for a qualitative multi-lingual assessment of the material available on the Internet has been previously developed during two previous Psychonaut Projects[16]. Such qualitative searches are now carried out on a regular basis across the research centres. Monitoring is made in two main steps:

1. The first step is to carry out a multilingual (English, German, Norwegian, Spanish, Italian, Dutch, Hungarian, Polish) qualitative assessment of about 200 websites, drug-forums and other online resources (e-newsgroups, chatrooms, mailing lists, e-newsletters, and bulletin boards) using the Google search engine.

2. The second step is to carry out a technical evaluation of all the available information on the novel drugs and trends of abuse emerged during the web monitoring as well as a qualitative and quantitative analysis of the literature found with a particular consideration to the cases of drug abuse in the Accident and Emergency Departments of hospitals. This is essential especially in absence of both 'classical' laws enforcement data and formal peer reviewed medical literature documents.

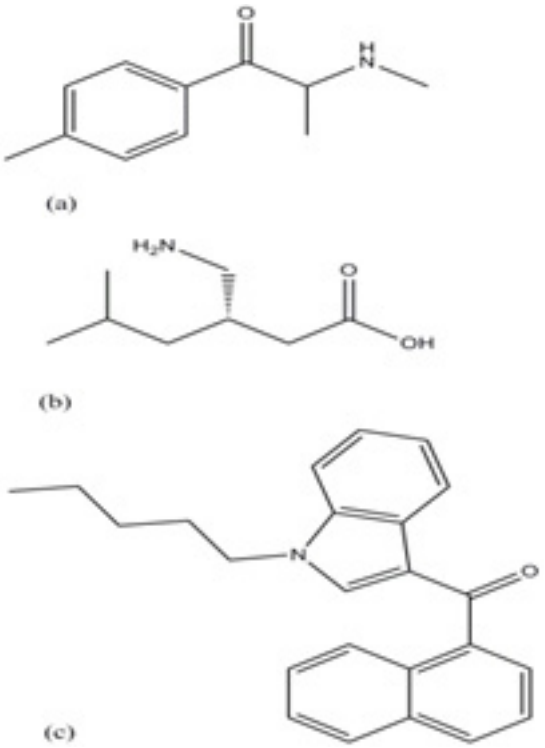

Fig. 3 Chemical structure of (a) Mephedrone (b) Pregabalin (c) JHW-018; Struttura chimica del (a) Mefedrone (b) Pregalin (c) JHW-018.

Mephedrone

The ReDNet/Psychonaut research groups were for instance the first to identify the emerging of mephedrone[13]. Mephedrone is a psychoactive chemical of the cathinone family (Figure 3) with similar activity to amfetamine, cocaine and MDMA. Its use has increased markedly since 2009 especially in the online market since the decrease in availability of ecstasy and cocaine[18].

Pregabalin

In addition, the ReDNet research group was the first to identify the recreational use of Pregabalin (Figure 3) pharmaceutical product, which has not been identified by EMEA as a drug of abuse[19,20]. Pregabalin is a prescription medicine used for the treatment of anxiety, partial epilepsy and neuropathic pain. It is sold under the trade name of Lyrica 75 mg capsules and manufactured by Pfizer. It was sold heavily by illigimate websites at discount prices. It induced benzodiazepine-like effect mixed with euphoria[20].

'Spice drugs'

Another drugs identified by the ReDNet include herbal drugs of abuse such as 'Spice' products, which are often sold online as herbal incense[7]. These are often herbal smoking blends sold as legal substitute to cannabis. Listed ingredients of these products indicated the presence of bioactive herbs or compounds as JWH-018[21,22] (Figure 3).

Bromo-DragonFLY

The research group has also studied the effects of Bromo-DragonFLY, or simply 'B-Fly', a powerful, long lasting (2-3 days), LSD-like, hallucinogenic drug, which has been associated with a number of recent intoxications and fatalities in a number of countries. Although the substance is almost unknown to the scientific literature, discussions on the Internet have been identified since 2003[6].

2. Testing

Testing is made through ordering these drugs from Internet websites and identifying them through the appropriate analytical techniques. In this respect, few questions need to be answered:

- Does the sample contain the drug stated? If yes, at which concentration does it contain?
- If not, what other compound does it contain?
- Are the batches of the same drug consistent?

The analytical techniques include: spectroscopic, spectrometric, chromatographic and elemental analysis techniques. Products are advertised as high purity drugs; however, other substances or impurities are often encountered in these drugs. Thus, in some cases these drugs analysed contained inorganic impurities, anesthetics (as benzocaine or lidocaine), caffeine or even other pharmaceutical products[23,27]. For identity of drugs, spectroscopic techniques such as nuclear magnetic resonance (NMR) can identify the chemical identities of the drugs. Mass spectrometric techniques can detect the masses of the components in the drug. Purity of the components can be confirmed using chromatographic techniques, which can be efficient even at low concentrations. In addition, elemental analysis can detect elemental impurities in drugs. Most of the references that identified legal high products from the Internet concentrated on the identity of these products[24,26,5]. However, there is still gap in quantifying the concentration of these drugs when they are purchased in tablet or capsule form or when several components exist in a powder form.

Technical folders and reports

From these sources (both monitoring and analysis), a preliminary report and/or technical folder for each drug is generated. Each of these consists of: key points, chemical characteristics of active constituents, appearance, available information on purchase price, modalities of intake, legal status, current use/ medicinal use, information on recreational use/ misuse in the EU (or elsewhere), use in combination with other compounds, pharmacological characteristics, toxicological effects, desired psychoactive effects, physical/ medical untoward effects, psychopathological disturbances associated with its use, clinical advice, related fatalities, Youtube videos, Google Insights, online marketing strategies, bibliography and sitography. These reports are stored in a password protected database, which currently containers information on more than 400 novel substances.

3. Informing via ICT tools

A preliminary survey informed the dissemination of the results derived from both the monitoring and the testing activities via a number of ICT tools[9], which are currently being piloted. These include:

- An interactive website, where health and other professionals (e.g. drugs workers, police, etc) can register and receive full up-to-date access to the technical folders and reports on new compounds. Up to date more than 500 professionals have joined and are using such information on are regular basis, including cases of emergency.
- social networking (Facebook, Twitter). Facebook is used by over 606 million people around the world[28]. This makes it a very important tool to target young people. ReDNet has a Facebook page which helps in the increase of awareness of the drug issues. So far the page has 250 likes. Up to date drug threads, videos and meetings are posted on this page on a regular basis.
- SMS alerts. SMS alerts for health professionals are an important tool, which will be used in the increase of drug awareness. The service will provide instant messages for health and other professionals regarding the up to date novel drugs.

Multimedia

YouTube

Youtube videos are an important tool for publishing online data and presentations. It targets both professional and non-professional people and audience of various age groups. ReDNet have so far a presentation on Linkedin[29]. Yet, more presentations and videos will be published on YouTube. In this respect, various videos focused on 'drug-free lifestyles' are in the progress of being developed by the students at the Film Department at University of Hertfordshire in the UK.

Smartphone applications

Mobile phone applications are replacing laptops as a technological tool. Smartphones offer the advantage of convenience and rapidity in accessing the Internet. They can provide a lot more data in a short time.

Seminars for professionals in the virtual learning environments

Second Life seminars represent a very important tool in increasing drug awareness. It gathers the advantages of both targeting the youth audience who are using technological tools extensively and are not aware of the threat of drugs and researchers who are in different parts of the World but cannot meet occasionally. Thus, collaborative work from various parts of the world can be gathered. On Wednesday the 26th of January 2011 the virtual studio of the ReDNet project in Second Life was launched with participants from various countries. The title of the seminar was: 'Promoting Active Life and Positive Attitude: Tasks, Methods and Proposal for New Drug Legislation'. Figure 4 shows the invitation of the Second Life seminar.

Consultation with the target groups

For the development of target and age appropriate content, consultation groups with young people are involved. The ReDNet research project values the opinion of the young participants, their creativity and their knowledge of new technologies.

Consultation groups with groups of young advisors may become fundamental not only for the promoting innovation in the didactic process, but also for preparing high quality educational resources to be distributed via ICT-tools. In addition such working groups stimulate a mutual positive attitude among students/participants, who learn new ways of expressing themselves and relating to their teachers. In other terms, the discovery of the individual and of the common potential for the benefit of society goes together with the development of the quality of the learning process[30,10].

Consultation groups of health and other professionals working with at-risk groups are also taking place.

Expected outcomes

The expected outcomes of this project will be both immediate and long lasting. It will constitute the first EU-wide ICT-based preventative programme designed for novel psychoactive compounds/combinations targeted at young and vulnerable individuals and professionals working with them. In this sense, it will not only inform and stimulate a much-needed discussion on the rapid and almost unpredictable diffusion of novel compounds, but also contribute to an enhanced scientific understanding of recreational drugs. Furthermore, it is hopeful that the project will be able to offer proper advice to both international agencies and national policy makers.

In addition, the proposed model is a cost-effective prevention and education model that could potentially help to reduce National Health Services costs. In fact, one of the problems of the novel psychoactive drugs is that they are almost completely unknown to the medical community and to the Medline. As a consequence, both the diagnosis and the management of these acute/chronic intoxications are problematic indeed. With a better understanding of these drugs, it is hopeful that the clinical management levels will improve. Furthermore, if the present project will be associated with smaller number of youngsters taking recreational drugs/research chemicals/legal highs, then smaller number of drug related near misses/fatalities will be arguably recorded.

In conclusion, it is believed that the monitoring of the web with respect to drug-related issues as well as the use of ICT tools for the dissemination of information on risky substances and health promotion messages is not only important, but also necessary to tackle the rapid diffusion of these new psychoactive substances and contribute to a safer and knowledge-based online environment in order to improve the quality of public health on a global level.

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References

1. CASA; The National Center on Addiction and Substance Abuse at Columbia University. You've Got Drugs!" V: Prescription Drug Pushers on the Internet, CASA Fifth Annual report, July 2008, available from: http://www.casacolumbia.org/absolutenm/templates/AnnualReports.aspx?articleid=550&zoneid=15 (accessed on: February 5th, 2011).
2. Forman R.F., Marlowe D.B. and McLellan A.T. The Internet a source of drugs of abuse, Curr Psych Rep, 2006, 8 (5), 377-382.
3. Littlejohn C., Baldacchino A., Schifano F. and Deluca P. Internet pharmacies and online prescription drug sales: A cross-sectional study. Drugs Educ Prev and Policy, 2005, 12, 75-80.
4. EMCDDA, EMCDDA report 2010: The state of the drugs problem in Europe. European Monitoring Centre for Drugs and Drug Addiction, 2010.
5. Gibbons S. and Zloh M. An analysis of the legal high mephedrone. Bioorrgan Med Chem Lett, 2010, 20, 4135-4139.
6. Corazza O., Schifano F., Farre et al. Designer Drugs on the Internet: a Phenomenon Out-of-Control? The Emergence of Hallucinogenic Drug Bromo-Dragonfly, Curr Clin Pharm, 2011, May 1; 6 (2); 125-6.
7. Schifano F., Corazza O., Deluca P., Davey Z. et al. Psychoactive drug or mystical incense? Overview of the online available information on Spice products. Inter J of Culture and Mental Health, 2009, 2 (2), 137-144.
8. Schifano F., Albanese A., Fergus S., et al. Psychonaut Web Mapping and ReDNet Research Groups. Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues. Psychopharmacology, 2010, 214 (3), 593-602.
9. Recreational Drugs European Network (ReDNet) Pre-survey results on the health professionals knowledge on legal highs. Unpublished work, 2011.
10. Layard, R., & Dunn, J. A good childhood: Searching for values in a competitive age, 2009. London: Penguin.
11. Eurostat, Youth in Europe: A Statistics portrait, 2007. Available from: http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-78-09-920/EN/KS-78-09-920-EN.PDF. (accessed on 14-03-2011).
12. Bricolo F., Gentile D.A., Smelser R.L., Serpelloni G. Use of the computer and Internet among Italian families: first national study, Cyberpychol Behav, Dec; 2007, 10 (6); 789-97.
13. Schifano F., Corazza O., Corkery J., ReDNet Research project. The web and the legal highs: the role of the Recreational Drugs European Network (ReDNet), SMMGP Newsletter, May 2011.
14. Corazza O., Davey Z., Deluca P., Demetrovics Z., Schifano F., ReDNet Research Group. Le potenzialità della prevenzione digitale in materia di nuove droghe: il ruolo del Recreational Drugs European Network. Dipendenze Patologiche 2010, 2, 43-46.
15. Demetrovics Zs., Mervó B., Corazza O. et al. Az elektronikus prevenció lehetőségei az új (szintetikus) drogok használatának megelőzésében: a Rekreációs Drogok Európai Hálózatának (Recreational Drugs European Network) bemutatása. Addictologia Hungarica, (in press).
16. Schifano F., Deluca P., Baldacchino A. et al. Drugs on the web; the Psychonaut 2002 EU project. Progress in Neuropsy Biol Psychiatry, 2006, 30, 640-646.
17. Mustata C., Torrens M., Pardo R., Perez C., The Psychonaut Web Mapping Group and Farre, M. Spice drugs: Cannabinoids as a new designer drugs [Spanish]. Adicciones, 2009, 21(3), 181-186.
18. Winstock A. R., Mitcheson L. R., Deluca P., Davey Z., Corazza O., Schifano F. Mephedrone, new kid for the chop? Addiction, 2010, 106 (1), 154-161.
19. European Medicines Agency [EMEA] (2006) Scientific Discussion. Available from: http://www.emea.europa.eu/humandocs/PDFs/EPAR/lyrica/Lyrica H-546-II-04-AR.pdf. (accessed on 15-04-2009).
20. Schifano F., D'Offizi S., Piccione M. et al. Is there a recreational misuse potential for pregabalin? Analysis of anecdotal online reports in comparison with related gabapentin and clonazepam data. Psychother and Psychosom, 2011; 80:118-122.
21. Cooper R. Drugs shipped as incense seized at DHL. Wilmington News Journal, 2009, March 2. Available from: http://www.wnewsj.com/main.asp?SectionID=49&SunSectionID=156&ArticleID=173262&TM=1065.236 accessed on 14-03-2011.
22. Auwärter V., Dresen S., Weinmann W., Müller M., Pütz M., Ferreirós N. Spice and other herbal blends: Harmless incense or cannabinoid designer drugs? 2009, JMS Letter, Journal of Mass Spectrometry.
23. Brandt S., Sumnall H.R., Measham F., Cole J. Analyses of second generation legal highs in the UK: Initial findings. Drug Testing and Analysis, 2010, 2, 377-382.
24. Brandt S., Freeman S., Sumnall H. R., Measham F., Cole J. Analysis of NRG 'legal highs' in the UK: identification and formation of novel cathinones. Drug Testing and Analysis, (in press).
25. Concheiro M., De Castro A., Quintela O., Lopez-Rivadulla M. and Cruz A. Determination of MDMA, MDA, MDEA and MBDB in oral fluids using high performance liquid chromatography with native fluorescence detection. Forensic Sci Int, 2005, 150, 221-226.
26. Davies S., Wood D.M., Smith G et al. Purchasing 'legal highs' on the Internet- is there consistency in what you get? QJM, 2010 Jul; 103 (7): 489-93.
27. Neves O. and Neves B. (2011) Report: Adulterants found in mixtures of illegal psychoactive drugs: https://bdigital.ufp.pt/dspace/bitstream/10284/938/3/208-218.pdf (accessed on 09-03-2011).
28. Ryan T. and Xenos S. (2011). Who uses Facebook? An Investigation into the relationship between the Big Five, shyness, narcissism, loneliness and Facebook usage, Computers in Human Behavior, (in press).
29. ReDNet Presentation (2009). Recreational Drugs European Network: an ICT preventation service addressing the use of novel compounds in vulnerable individuals. Available from: http://www.slideshare.net/drugeducationforum/rednet-presentation (accessed on 14-03-2011).
30. Corazza O. (2010) The Young Motivators: the importance of involving young people in policy making. International Festival of Science, UNIWERSYTET SZCZECIŃSKI, Poland, 18-21 September 2010.

Invitation
ReDNet Researh Project - First Second Life Seminar
"Promoting Active Life and Positive Attitude: Tasks, Methods and Proposal for New Drug Legislation".
Prof. Pasquale Policastro and Prof. Janusz Slugock and (University of Szczecin, Poland)
Wed. 26th January 2011 at 15.30 GMT
Where? http://slurl.com/secondlifeUni%20of%20Herts/48/147/26 (in Second Life)

Fig 4. Invitation to the 1st Seminar in Second Life of the ReDNet Project; Invito al primo seminario in Second Life del ReDNet Project

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The new potentialities of digital prevention in the field of the new drugs: the role of the Recreational Drugs European Network

Le nuove potenzialità della prevenzione digitale in materia di nuove droghe: il ruolo del Recreational Drugs European Network

Riassunto

Introduzione: *L'enorme diffusione di una cultura sempre più telematica, sta conducendo, oltre che al diffondersi di nuove idee, valori e comportamenti, all'espandersi di nuove e sempre più sofisticate droghe ricreazionali soprattutto tra i giovani. Questo fenomeno crea una nuova sfida per tutti coloro che operano nel campo delle dipendenze; a tal proposito nasce e si sviluppa il Recreational Drugs European Network (ReDNet).*

Obiettivi: *Il Recreational Drugs European Network (ReDNet), nato da un progetto finanziato dalla Commissione Europea, ha l'obiettivo di costruire e diffondere, inizialmente a livello europeo, un programma ICT che permetta di ampliare, a livello internazionale, il sistema di informazione relativo alle sostanze d'abuso tradizionali ed alle "nuove droghe".*

Metodi: *La metodologia del ReDNet si articola su tre livelli: (1) la ricerca e l'elaborazione del contenuto per cui esperti multidisciplinari renderanno maggiormente accessibili informazioni relative a circa 400 nuove composti/combinazioni psicoattive attraverso un continuo aggiornamento del Psychonaut Web Mapping Project; (2) la diffusione dei messaggi di prevenzione usando ICT nella quale verranno promossi stili di vita sani attraverso una comunicazione che utilizzi il linguaggio e gli strumenti tecnologici dei più giovani; (3) valutazione/ricerca sull'impatto ricevuto da questo nuovo modello di prevenzione.*

Risultati: *Essendo questo un progetto lanciato nell'Aprile del 2010 è ancora prematuro parlare di risultati; tuttavia, nei primi tre mesi di attività del progetto è stato possibile identificare alcune sostanze che costituiscono i nuovi trend attuali e che saranno oggetto di studio e di ricerca da parte del ReDNet Research Group. Si può immaginare quindi, che modelli di prevenzione come quello proposto dal RedNet costituiranno modelli indispensabili di prevenzione per l'abuso di nuove sostanze.*

Parole chiave: *Nuove sostanze, Prevenzione, Recreational Drugs European Network*

Summary

Introduction: *The explosion of a telematic culture is leading, as well as to the spread of new ideas, values and behaviours, also to the expansion of new sophisticated recreational drugs among young people. This phenomenon creates a new challenge for all those working with addictive disorders; in this regard it was born and developed the Recreational Drugs European Network (ReDNet).*

Aims: *The aims of the Recreational Drugs European Network (ReDNet), born from a project funded by the European Commission, are to build and spread a program that allows ICT to expand, beginning from Europe, the information system on both traditional and "new drugs".*

Methods: *The ReDNet's methodology has three levels: (1) the research and the development of content in which multidisciplinary experts will make more accessible informations about 400 new compounds/combinations of psychoactive substances through a continuous updating of the Web Mapping Psychonaut Project; (2) the diffusion of prevention messages using ICT in which will be promoted healthy lifestyles using the young people's communication and technology tools; (3) the evaluation/research on the impact received by this new model of prevention.*

Results: *This project was launched in April 2010, so it is still premature to talk about results; however in the first three months of project activities, it has been possible to identify some substances that represent the new and current trends and that will be the subject of interest by the ReDNet Research Group. It is possible to hypothesize that the prevention models such as that proposed by RedNet will constitute an important instrument to prevent the abuse of new substances.*

Key words: *New substances, Prevention, Recreational Drugs European Network*

Introduzione

La nuova cultura telematica ha portato all'instaurarsi di nuovi comportamenti, valori e idee, specialmente tra i giovani. Essa può essere considerata un fenomeno affascinante e ricco di potenzialità per il genere umano, ma al tempo stesso anche allarmante. Nel web esistono centinaia di siti e video dedicati alla diffusione di nuove e sempre più sofisticate droghe ricreazionali, come i *legal highs*, di prodotti chimici e farmaceutici, che sono richiesti e venduti anche tramite Internet [1-3]. Questo fenomeno crea una grande sfida per le agenzie sanitarie, i servizi di trattamento, e gli specialisti nel campo delle tossicodipendenze poiché le conoscenze scientifiche sulla farmacologia, tossicologia, effetti psicoattivi e/o abuso di queste sostanze sono molto limitate. Di conseguenza è alquanto difficile, se non impossibile, per i professionisti della salute, operare in modo accurato e valutarne le effettive conseguenze mediche e psichiatriche [4-6]. All'inizio di un nuovo millennio di grande rivelazione tecnologica, l'importanza di trovare risposte sempre più nuove ed adeguate ad un contesto sociale in rapida evoluzione è un fondamentale prerequisito per una prevenzione di successo nel campo delle droghe. Le classiche forme di intervento si limitano spesso alle droghe tradizionali, come l'MDMA, la cocaina, la cannabis, l'eroina, che tuttavia rappresentano solo una minima parte di un mercato molto più vasto. Inoltre, i messaggi di prevenzione promossi sono spesso di natura moralistica e si basano sulla paura; di conseguenza poco efficaci tra gli adolescenti a cui non piace sentirsi dire cosa fare o non fare.

In tale intricato contesto nasce e si sviluppa il Recreational Drugs European Network (ReDNet), il cui obiettivo è quello di rafforzare la conoscenza e la comprensione dei nuovi composti usando strumenti tecnologici.

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ReDNet Research project

Il Recreational Drugs European Network (ReDNet) è un progetto finanziato dalla Commissione Europea con lo scopo di costituire in Europa, e possibilmente a livello più globale, uno dei primi programmi ICT nel campo della prevenzione della salute on-line dedicato alle nuove droghe.

Obiettivi

Il ReDNet ha un network operativo in 9 Paesi europei (Italia, Gran Bretagna, Belgio, Germania, Spagna, Polonia, Ungheria e Norvegia) e si avvale di un sistema di ricerca in 9 lingue al fine di ampliare le fonti d'informazione relative alle sostanze d'abuso a livello internazionale. Basato sui successi riportati dal precedente Psychoanut Web Mapping Project (www.psychonautproject.eu), il ReDNet ha i seguenti obiettivi:

- aumentare la consapevolezza e le potenziali implicazioni cliniche associate all'assunzione di nuove droghe
- contribuire alla conoscenza scientifica in materia di nuove droghe, spesso minima o inesistente
- fornire il primo programma di prevenzione basato su ICT rivolto soprattutto alle nuove generazioni con l'intento di renderle più consapevoli dei rischi connessi all'acquisto e all'uso delle sostanze in vendita su internet e aiutarle a sviluppare quelle qualità che sono necessarie per "prendersi il controllo delle propria vita".

Le attività promosse dal ReDNet si rivolgono sia (a) a giovani con un età compresa tra i 16 e i 24 anni; (b) a medici e altri operatori della salute che non sempre sono a conoscenza degli effetti di queste nuove sostanze.

Metodologia

La metodologia impiegata dal ReDNet è molto semplice e si articola essenzialmente su tre livelli:

(a) Ricerca ed elaborazione del contenuto

Un gruppo di esperti con competenze multidisciplinari analizzerà e quando opportuno, renderà più accessibili le esistenti informazioni tecniche su circa 400 nuovi composti/nuove combinazioni psicoattive, classificabili per loro natura in: (a) erbacee; (b) sintetiche; (c) farmaci d'abuso; (d) miste (ossia una combinazione di sostanze), correntemente custodite in un database ad accesso limitato, ed in continuo aggiornamento, dello Psychoanut Web Mapping Project. Questo avverrà soprattutto per quelle sostanze per le quali sia già stato rilevato un certo grado di diffusione a livello europeo e cui vi è una conoscenza scientifica limitata.

I dati su cui si basano le attività di prevenzione derivano principalmente da attività di monitoraggio di circa 200 siti web, inclusi *forums*, *social networking sites*, *multimedia sites*, etc. e da reports e schede tecniche su oltre 400 sostanze attive che sono strutturate come segue:

- informazioni riguardanti sia il nome comune/formale (binomial; chemical) della sostanza, che lo "*slang/street name*";
- caratteristiche chimiche di base ed informazioni sui possibili precursori chimici della sostanza;
- caratteristiche farmaceutiche ed aspetto (forma, dimensione, colore, peso, logo);
- aspetto commerciale della sostanza e video inerenti la preparazione o l'assunzione del composto in esame;
- informazioni concernenti la storia e l'uso/abuso corrente e medico della sostanza;
- informazioni riguardanti i contesti in cui il prodotto è tipicamente consumato;
- dati circa gli effetti psicoattivi desiderati, quelli negativi (acuti e cronici) e gli eventuali disturbi psicologici o decessi connessi con l'uso/abuso della sostanza;
- informazioni circa gli effetti tossicologici acuti e cronici e dati di tossicologia clinica;
- disponibilità in uno o più Paesi europei;
- fonti della droga, rotte di distribuzione, possibili deviazioni da parte di rifornimenti farmaceutici leciti;
- consapevolezza a livello della popolazione generale.

(b) diffusione dei messaggi di prevenzione utlizzando ICT

Il gruppo di ricerca ReDNet progetterà inoltre nuovi strumenti ICT che verranno impiegati per la prevenzione del consumo di nuove sostanze e la promozione di stili di vita sani, con particolare riferimento a quegli strumenti che rispondono alle caratteristiche di comunicazione veloce e adeguata alle modalità utilizzate dai ragazzi.

Strumenti di prevenzione utilizzati dal ReDNet sono: avvisi via SMS, *social networks* (Facebook, Twitter), programmi multimediali (You Tube), applicazioni per gli smartphones (iPhone), e realtà virtuale (Second Life).

(c) valutazione/ricerca sull'impatto ricevuto da questo nuovo modello di prevenzione

Dati sulla modalità e l'efficacia di questi nuovi modelli di prevenzione verranno raccolti durante tutta la durata del progetto (Aprile 2010 – Aprile 2012). Pubblicazioni scientifiche e manuali per specialisti verranno inoltre prodotti al fine di informare sui potenziali benefici di tali forme di intervento.

Partecipazione dei ragazzi

Un aspetto abbastanza nuovo ed interessante del ReDNet è che i ragazzi saranno coinvolti durante tutte le fasi di implementazione del progetto. La filosofia sottostante a questo loro impegno diretto è quella di far buon uso della loro creatività e altre potenzialità, inclusa la loro conoscenza nel campo delle nuove tecnologie, al fine di sviluppare un'attività di prevenzione di valore e ad alto livello replicabilità anche in altri paesi non ancora associati al progetto.

Grazie a tale approccio aperto e collaborativo, gli strumenti pilotati:

- impegneranno i giovani in attività di alta valenza educativa e formativa, stimolando una riflessione positiva su temi che li riguardano da vicino;
- favoriranno l'espressione degli adolescenti e la loro capacità di influenzare i loro coetanei, attraverso l'assunzione di scelte volte a migliorare la loro salute;
- aumenteranno la quantità e qualità delle informazioni a disposizione dei giovani in materia di nuove droghe.

Risultati

Poiché si tratta di un progetto nuovo, lanciato nell'aprile 2010 e con una durata di due anni, è ancora prematuro parlare di risultati. Tuttavia, le attività di monitoraggio del web nei soli tre mesi di attività del progetto hanno permesso l'identificazione e lo studio iniziale di alcune sostanze che costituiscono i maggiori *trends* attuali e che saranno l'oggetto di studio e di ricerca da parte del ReDNet Research Group.

Mefedrone

Il "Mefedrone" (4-methylmethcathinone), noto anche come "Miaow Miaow", "MMCat" o "Meph", un prodotto chimico stimolante ed empatogeno, come lo Speed, l'MDMA, la cocaina e il metilone. È un composto semi-sintetico, strutturalmente simile al metacatinone e correlato al catinone [7]. Venduto principalmente in forma di polvere bianca e cristallina, che viene ingerita e/o sniffata, on-line si trova anche nella veste fasulla di fertilizzante per piante o sale da bagno, entrambi non per uso umano. Viene assunto come droga ricreazionale perché induce euforia, socievolezza, intensificazione della stimolazione sensoriale ed eccitazione sessuale; con un tranquillo *come-down* rispetto, ad esempio, all'MDMA, e assenza di hangover nel giorno successivo. Tra gli effetti collaterali principali riportati dai consumatori vi sono la tachicardia, l'aumento della pressione sanguinea, difficoltà respiratorie, disidratazione, dermatiti, tremori e convulsioni, aumento dell'aggressività, ansia, paranoia, disforia e allucinazioni. Secondo quanto riferito dagli utenti on-line, inoltre, il mefedrone sembra indurre dipendenza e una forte compulsione ad assumerne una seconda dose, forse dovuta alla modesta durata degli effetti psicoattivi. Questo porta frequentemente ad ingerirne grosse quantità in una sola volta [8, 9].

NRG-1

NRG-1 è una nuova *legal high*, comparsa nel mercato inglese nel mese di maggio 2010 come sostituto del mefedrone. Conosciuta anche come "Energy-1", "E-wizz" e "0-2482", probabilmente proveniente dalle fabbriche cinesi, è un composto chimico venduto on-line e negli *smart shops* come fertilizzante per piante e purificatore di stagni. È un derivato del naphyrone (naphthylpyrovalerone), che produce effetti stimolanti ed eccitanti ed è disponibile sotto forma di polvere e di cristalli di polvere. Viene assunta sniffandola e/o ingerendola soprattutto nei party e nei rave, anche se diversi consumatori ne fanno un uso domestico, da soli o con pochi amici. Dalle indagini effettuate sui commenti degli stessi *users*, è emerso che sono sufficienti dosi relativamente minime per sviluppare gli effetti stimolanti e che, nonostante questo, è frequente il manifestarsi di numerosi effetti collaterali di carattere fisico (insonnia, tachicardia, pressione sanguinea elevata, sudorazione eccessiva e tremore agli arti) e psicopatologico (paranoia, ansia, disforia e depressione dell'umore). Nelle ultime settimane sono comparse sul mercato NRG-2 ed NRG-3. Queste vengono considerate evoluzioni dell'NRG-1 ma, in realtà, posseggono una struttura chimica totalmente differente e di cui ancora si conosce poco [10].

Whack

Whack è un prodotto vegetale acquistabile negli *smart shops* irlandesi. Le analisi sulla sostanza hanno evidenziato la presenza di fluorotropacocaina (un derivato del tropano), che agisce come stimolante ed anestetico locale. È recentemente diventata un'emergenza a seguito dei 40 casi di ricovero per intossicazione acuta avvenuti in soli dieci giorni in Irlanda. Tutti i soggetti che ne hanno fatto uso, hanno mostrato un aumento della frequenza cardiaca, respiratoria e della pressione arteriosa. Si sono evidenziati anche alti livelli di ansia e, in alcuni casi, gravi episodi psicotici, ritenuti difficilmente trattabili [11].

N-Joy

N-Joy è una sostanza comparsa prevalentemente sul mercato italiano e sembra essere il "naturale successore" delle Spice Drugs, in quanto analisi di laboratorio hanno rivelato anche in essa la presenza dei cannabinoidi sintetici JWH-018 e JWH-073. È possibile acquistarla negli *smart shops* o in Internet, dove è venduta come profumo/deodorante per ambienti, il cui uso umano è sconsigliato. Nonostante le informazioni riguardo ad essa non siano molte, sono già stati documentati dai *media* casi di ricovero ospedaliero a seguito dell'assunzione, con effetti collaterali quali alterazioni dello stato di coscienza, attacchi di panico, tachicardia e parestesie [12].

Conclusioni

Il ruolo guida assunto dal web, il quale a differenza di pubblicazioni scientifiche che non riescono a "stare al passo" con i radicali cambiamenti che interessano il mercato delle nuove sostanze, permette ad una nuova popolazione di utenti di rimanere costantemente aggiornata, di conoscere i prezzi dei nuovi composti, di individuare le migliori combinazioni, di limitare gli effetti collaterali e di acquistare una vasta serie di nuove sostanze [7,13]. Innumerevoli sono i commenti, le informazioni più o meno accurate, le esperienze e i consigli, che quotidianamente vengono messi sul web e condivisi on-line con altri utenti, al fine esplorare la modalità migliore per trarre piacere dall'esperienza, limitandone gli effetti collaterali. Questo fenomeno ha portato alla nascita di una popolazione sempre più esperta nelle diverse sostanze, consentendo anche ai consumatori inesperti di divenire in breve tempo profondi conoscitori dell'ampia gamma di composti psicoattivi esistenti e di tutti gli effetti ad essi correlati. Nella maggior parte dei casi, si tratta di sostanze legali e quindi percepite come non pericolose soprattutto da parte dei giovani consumatori. Forse, l'aspetto più sconcertante di questo fenomeno e' la carenza di informazioni scientifiche su questi composti, che rende impossibile, per i professionisti della salute, operare in modo accurato e valutarne le effettive conseguenze mediche e psichiatriche. In tale contesto di rapido mutamento, sembra evidente che le nostre competenze multidisciplinari nel campo delle dipendenze, la collaborazione internazionale, e lo sviluppo di modelli di prevenzione innovativi basati sugli ICT, come quello proposto dal ReDNet, siano strumenti indispensabili per contribuire in maniera sempre più avanzata a

risolvere quel grave e persistente problema sociale che è l'abuso di nuove sostanze.

Bibliografia

1. Boyer, E.W., Shannon, M., Hibberd, P.L.: Web sites with misinformation about illicit drugs *N Engl J Med*. 2001; 345, 469-471.
2. Forman, R.F., Marlowe, D.B., McLellan, A.T.: The Internet a source of drugs of abuse. *Current Psychiatry Reports*. 2006; 8 (5), 377-82.
3. CASA, The National Center on Addiction and Substance Abuse at Columbia University: *You've Got Drugs! V: prescription drug pushers on the Internet*. 2008; CASA, fifth report, July.
4. Corazza, O., Schifano, F., Deluca, P., Davey, Z. on behalf of the Psychonaut Web Mapping Group: *Cultura telematica, trascedenza corporea e nuove droghe: come gli internauti diventano psiconauti*. In La Barbera, D. (ed) *Proceedings of III Convegno Internazionale della Società Italiana di Psicotecnologie e Clinica dei nuovi Media*, Palermo, Italy, 23-25 Nov 2009 (in press)
5. Schifano, F., Deluca, P., Baldacchino, A., Peltoniemi, T., Scherbaum, N., Torrens, et al.: Drugs on the web; the Psychonaut 2002 EU project. *Progress in Neuro-psychopharmacology and Biological Psychiatry*. 2006; 30: 640-646.
6. Schifano, F., Corazza, O., Deluca, P., Davey, Z. and the Psychonaut Web Mapping Group: Psychoactive drug or mystical incense? Overview of the online available information on Spice products. *International Journal of Culture and Mental Health*. 2009; 2(2), 137-144.
7. Newcombe, R.: *Mephedrone: The Use of Mephedrone (M-cat, Meow) in Middlescrough*. (2009); Manchester UK: Lifeline Publications
8. Psyhonaut Web Mapping project: *Mephedrone report*. (2009); Available from www.psychonautproject.eu
9. ReDNet Research Project (2010a): *Mefedrone report* (in italiano). In press.
10. ReDNet Research Project (2010b): *NRG-1 report* (in preparation).
11. ReDNet Research Project (2010c): *Whack report* (in preparation).
12. ReDNet Research Project (2010d): *N-joy report* (in preparation).
13. Deluca, P., Schifano, F., Davey, Z., & Corazza, O.: Legal highs and new recreational drugs: the Psychonaut Web Mapping project. (2009); *SCANbites*, 6(4), 4-5.

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Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine

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On the basis of the material available both in the scientific literature and on the web, this paper aims to provide a pharmacological, chemical and behavioural overview of the novel compound methoxetamine. This is a dissociative drug related to ketamine, with a much longer duration of action and intensity of effects. A critical discussion of the availability of information on the web of methoxetamine as a new recreational trend is here provided. Those methodological limitations, which are intrinsically associated with the analysis of online, non-peer reviewed, material, are here discussed as well. It is concluded that the online availability of information on novel psychoactive drugs, such as methoxethanine, may constitute a pressing public health challenge. Better international collaboration levels and novel forms of intervention are necessary to tackle this fast-growing phenomenon. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—methoxetamine; ketamine; designer drugs; Internet monitoring; research chemicals

INTRODUCTION

The recent emergence of new synthetic drugs, combined with the ability of the Internet to disseminate information quickly, has raised a number of concerns in the fields of drug policy, substance use research, forensic toxicology, pharmacology and public health (Schifano *et al*., 2006; Corazza *et al*., 2010). During 2010, 41 psychoactive substances were officially notified for the first time in the European Union, up from 24 the previous year (EMCDDA 2010). In this article, the authors present the results of a study on the novel chemical compound methoxetamine (MXE; Figure 1), which has recently emerged, according to the Recreational Drugs European Network (ReDNet; www.rednetproject.eu; Corazza *et al*., 2010) observations, as a new drug of abuse.

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At present, there is a lack of information on MXE in the scientific literature, and no clinical or animal studies have been conducted. However, so far as it can be ascertained, the toxicological and side effects of MXE might resemble those of ketamine (Enarson *et al*., 1999; Jansen 2001; Dillon *et al*., 2003; Morgan *et al*., 2011; Wood *et al*., 2011). MXE is a dissociative anaesthetic classified in the arylcyclohexylamine class but not formally profiled. The term 'dissociative' suggests that the sensory loss and analgesia as well as amnesia are not accompanied by any actual loss of consciousness (Bonta 2004; Corazza 2010; Corazza and Schifano, 2010). Due also to its chemical similarities to ketamine (Figures 1 and 2), it is thought to be both a glutamate *N*-methyl-D-aspartate receptor antagonist and a dopamine reuptake inhibitor (Jansen 1989; Jansen 2001; Bonta 2004; Purechemicals 2010; Methoxetamine 2011; PureChemicals 2011; Viceland 2011). Both 1-[1-(3-methoxyphenyl)cyclohexyl]-piperidine (methoxyphencyclidine; 3-MeO-PCP) and

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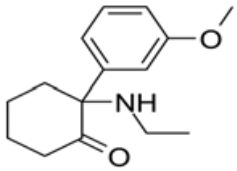

Figure 1. 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine)

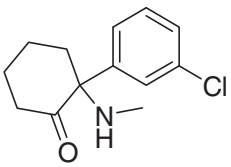

Figure 2. 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (ketamine)

N-ethyl-1-phenylcyclohexylamine (eticyclidine) are analogues of MXE. In particular, the 3-methoxy group of 3-MeO-PCP, also a dissociative anaesthetic, is considered to be responsible for the euphoric effects experienced by 3-MeO-PCP users, although it does not present with any significant affinity for the μ-opioid receptor (Viceland 2011). MXE has been marketed (Methoxetamine 2011) and described (Erowid, 2010; 2011; Viceland 2011) as having much more powerful and longer lasting effects than ketamine because of its *N*-ethyl group. Although the group modification, from 2-chloro to 3-methoxy, seems to give MXE lower levels of analgesic and anaesthetic properties than ketamine, it may be responsible for a half-life that is longer than that of ketamine (Drugs-Forum 2011).

MATERIALS AND METHODS

The literature on MXE was searched in three databases: PsycINFO, PubMed and Medscape. Keywords used to carry out the database searches included he following: '2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone', 'Methoxetamine', 'MXE', 'MXE-Powder', 'METH-O' and 'Special K'. Considering the limitation of peer-reviewed data, results were integrated with a multilingual qualitative assessment of a range of websites, drug fora and other online resources (i.e.: e-newsgroups, chat-rooms, mailing lists, e-newsletters and bulletin boards). This was carried out using the Google search engine in eight languages from a number of collaborating countries (the UK, Norway, Belgium, Germany, Hungary, Poland, Italy and Spain; see www.rednetproject.eu). The online assessment was carried out over the period of six months (January–June 2011) and involved the close monitoring of 203 websites. Of these, 108 were considered to be relevant for the present exercise and as such were monitored on a regular basis, that is, daily ($n = 21$), weekly ($n = 32$) or monthly ($n = 53$), depending on their relevance. The remaining 95 websites were considered not to bear any interest for this study and thus were no longer monitored. Once the MXE availability of information was identified on these websites, further specific searches were carried out for narratives focusing on the following issues: (i) the nature of its effects on users, including adverse reactions; (ii) motivations behind its recreational use and possible trends of misuse, with particular attention to polydrug misuse/idiosyncratic combinations; (iii) any other relevant information in the original language of the narratives. Data collected were stored in a password-protected online database of the ReDNet (www.rednetproject.eu). For the purpose of reporting the results in this paper, any data collected from online fora, such as usernames and complete URLs for specific threads that were considered personal identifiable, were anonymized. The study was cleared for ethical approval by the School of Pharmacy Ethics Committee, Hatfield, UK (15 December 2010; PHAEC/10-42).

RESULTS

Information on methoxetamine online availability and consumption

Online shops advertise and sell MXE as a legal alternative to ketamine (Methoxetamine 2011; PureChemicals 2011; YouTube 2011). Indeed, MXE can be acquired legally without a veterinary licence (e.g. Methoxetamine 2011), which is the minimum requirement for the purchase of ketamine in the UK as well as in other European Union countries and in the USA. MXE is sold as a bright white powder in different brand names, such as MXE powder and Special K, a colloquial term also used for ketamine. Products are labelled 'not for human consumption', an online marketing strategy that might be interpreted by some as an incentive to use it as a recreational drug (Corazza *et al*., 2011). A few videos advertising the drug were here identified on YouTube (YouTube 2011a; YouTube 2011b).

According to most online reports, MXE's primary route of administration is either intranasal or sublingual, whereas intramuscular administration seems to be less common (Drugs-Forum 2011). Very few cases of intravenous administration have also been mentioned over the Internet, including an unconfirmed fatality following an 80- to 100-mg intravenous MXE injection combined with 400 mg of 5,6-Methylenedioxy-2-aminoindane (Drugs-Forum 2011; LegalHighsGuide 2011; Viceland 2011).

The desired effects and dosages of MXE differ in relation to the modalities of intake. The 'typical' dose

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reported by users is 20–100 mg for oral administration and 10–50 mg for intramuscular injection. However, users suggest to increase the dosages gradually and not to exceed 50 mg on the first occasion when taken orally (Bluelight 2010). After insufflation, the perceived effects can be delayed for 30 to 90 min (Erowid 2010). This delay has often led recreational users to ingest another dose of the substance (Erowid 2011), thinking that the first dose was inadequate. The duration of action has been described as being in the range of 5–7 h (Bluelight 2010; Erowid, 2010; 2011). When the MXE is injected intramuscularly, the first effects appear within 5 min (Drugs-Forum 2011; Erowid 2011) and may last for about 1 h. The average price for 1 g of MXE is approximately £26 (€29; $41), whereas a single dose is sold for around £3–6 (BulkResearchChemicals 2011; PureChems 2011).

Desired effects and adverse reactions

According to MXE users, its effects are similar to those of ketamine, although much longer lasting (5–7 h; Bluelight 2010; Erowid 2011) and with a longer delay in the onset of its effects (up to 90 min).

Being a dissociative anaesthetic, MXE can produce sensory deprivation, derealization and dissociation from the physical body (Bluelight 2010). These are common features of the so-called 'near-death experiences', which have also been reported after ketamine use (Corazza 2010; Coull *et al*., 2011; Moore *et al*., 2011; Morgan *et al*., 2011; Wood *et al*., 2011).

The desired effects may vary according to the dosage and the modality of intake, these include euphoria, empathy, 'cosiness', pleasant intensification of sensory experiences especially whilst listening to music, mild-to-strong sense of dissociation from the physical body, distortion of the sense of reality, vivid hallucinations, introspection and brief antidepressant effects (Bluelight 2010; Erowid 2010; Psychonaut 2010; Purechemicals 2010; Bluelight 2011; Drugs-Forum 2011; Erowid 2011; Hipforums 2011). Some users' comments on their MXE experience included 'music sounds great', 'trapped inside a glass chopping board', 'not for social situation', 'feeling like another inanimate object' and '. . .just seems so absurdly surreal and it makes no sense, but I'm quite happy just to stare at the TV screen, feeling all snugly and warm'. Somebody described MXE as a 'big Christmas cardigan', whose intake was providing both 'spinning sensations' and 'naturalistic hallucinations in waves', overall referring to the 'M-Hole', as opposed to the ketamine 'K-hole' (Erowid 2011). The term is typically referring to a subjective state of dissociation from the body, which may mimic the out-of-body experiences or near-death experiences (Corazza and Schifano, 2010; Schifano *et al*., 2008) and is often accompanied by feelings of intense derealization, depersonalization and disorientation, as well as vivid hallucinations. Most reports indeed, however, conclude that MXE may be different from ketamine, even if they share some similarities, both because of MXE's 'longer come up', which might lead to a high risk of re-dose, and its longer lasting effects. In summary, MXE seems to work as a short-acting mood enhancer with powerful (visual) hallucinogenic and dissociative properties. However, dizziness and other unpleasant aspects, such as confusion, time distortion, aphasia, synaesthesia and psychomotor agitation (Bluelight, 2010; 2011), are described as well.

Withdrawal symptoms include low mood and/or depressive thoughts (Bluelight 2010; Psychonaut 2010; Hipforums 2011). A user reported decreased levels of cognitive impairment for many hours as well as 2 days of insomnia after the intranasal consumption of 100 mg (Bluelight 2010). A further anecdotal report mentioned a suicidal attempt after the consumption of unconfirmed MXE dosages (Viceland 2011).

Methoxetamine is allegedly used in combination with a variety of other drugs to enhance or prolong the duration of action of its effects. This includes LSD, 4-chloro-2,5-dimethoxyphenethylamine, alpha-methyltryptamine and 5,6-Methylenedioxy-2-aminoindane (Bluelight 2010; Erowid 2011; Hipforums 2011). However, users on web fora advise not to consume it with alcohol, tetrahydrocannabinol, selective serotonin reuptake inhibitors or monoamine oxidase inhibitors.

It was not possible to understand from here if those untoward medical effects that are typically reported with ketamine (such as painful bladder, ureter obstruction, papillary necrosis and hepatic dysfunction; Enarson *et al*., 1999; Jansen 2001; Dillon *et al*., 2003; Wood *et al*., 2011) may be associated with MXE ingestion as well (Erowid 2011). It may not be possible at present to fully conclude about the untoward medical effects of MXE, both because of the lack of appropriate peer-reviewed MXE-related literature and the paucity of web users' reports. In terms of psychopathological disturbances associated with its use, it seems appropriate to conclude that they may be similar to those reported for ketamine (Fletcher and Honey, 2006).

DISCUSSION AND CONCLUSION

To the best of our knowledge, this is the first paper providing both an overview of the current state of

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knowledge of MXE and a critical analysis of the information that is available online relating to its psychoactive effects, adverse reactions and use in combination with other drugs (Table 1).

It seems that the reasons behind MXE's increase in popularity include both its powerful psychoactive, ketamine-like, effects and affordability. Indeed, it was found here that MXE may at times be promoted with special offers as well. The online popularity of MXE may have increased as a result of technical facilities such as 'alerts' about novel psychoactive products via text messages and/or instant messaging and 'e-mail this product to a friend' (Schifano *et al*., 2009). Young/vulnerable individuals might be encouraged by a range of widely available online comments/messages/videos relating to the MXE intake experiences. This may be an issue of concern, if one considers that an estimated 61% of young European people aged between 15 and 24 years typically quote the Internet as a potential source of information on illicit drugs (Eurobarometer 2008). Furthermore, it appeared that only a minority of drug-selling websites were allegedly limiting access to the relevant links to underage individuals. The current legal status of MXE may arguably facilitate the increasing levels of popularity of the drug and might affect as well the users' perception of risks associated with its consumption. The idea that legality can equate with safety still remains well grounded amongst some recreational users (Schifano *et al*., 2006; Schifano *et al*., 2009; Corazza *et al*., 2010; Davies *et al*., 2010; Ramsey *et al*., 2010). Most of the novel psychoactive compounds available online, such as MXE, share a number of characteristics that may constitute a public health challenge (Corazza *et al*., 2011), including the following: (i) they are not approved for human consumption; (ii) their intake is possibly associated with a number of unknown side effects/adverse reactions); (iii) very few related pharmacological/toxicological data are available in the peer-reviewed, scientific, literature, with the limited knowledge being mostly restricted to pre-clinical studies; (iv) they are rapidly appearing in always more sophisticated forms and remain unregulated for a long period; (e) they are most often synthesized in underground laboratories simply modifying the molecular structure of remaining controlled drugs, hence raising further concerns in terms of the presence of contaminating agents; and (f) they are largely available online and thus 'just a click' away from our homes and potentially available to everyone.

A possible limitation of this study could be given by the fact that only publicly available websites, fora and similar sources were monitored. Conversely, to improve the coverage of the study not only the web pages but also more private ways of communication (including newsgroups, chatrooms, mailing lists, e-newsletters, and bulletin boards) were here considered. A further limitation may be given by the fact that the present findings do rely mostly on what is reported by users. In particular, we did not have any possibility here to ascertain if the substance the online alleged drug users were taking was indeed MXE.

One could conclude that a constant level of web-monitoring activities with respect to drug-related issues is necessary to better understand the level of the diffusion of novel psychoactive substances, such as MXE. In this context, the ReDNet (www.rednetproject.eu; Corazza *et al*., 2010) project aims to pilot one of the initial prevention programmes based on information communications technology targeted at both young people (aged 16–24 years) and health professionals looking for information about novel psychoactive compounds. Finally, it is here suggested

Table 1. Methoxetamine: key points

Chemical name	2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone
Class	Arylcyclohexylamine
Mechanism of action	Supposedly similar to ketamineglutamate *N*-Methyl-D-Aspartate receptor antagonismdopamine reuptake inhibition
Synonyms—colloquial names	MXE; MXE-Powder; METH-O; Special K
Type	Dissociative anaesthetic, synthetic designer drug
Legal status	Not illegal in Europe or in the USA
Dosage	20 to 100 mg (oral administration), 10 to 50 mg (intramuscular injection)
Duration of action	5 to 7 h (longer than ketamine)high risk of re-dose due to a delay in the onset of its effects
Price	1 g = £26 (€29; $41)
Desired effects	Sensory deprivation, derealization, dissociation, euphoria, empathy, pleasant intensification of sensory experiences (M-Hole), short-acting mood enhancement and (visual) hallucinations
Untoward effects	Confusion, psychomotor agitation, time distortion, aphasia, synaesthesia, depressive thoughts, insomnia and cognitive impairment
Used in combination with	LSD, 2CC, aMT and MDAI
Psychopathological disturbances	Unknown; there might be similarities with those reported with ketamine

MXE, methoxetamine; 2CC, 4-chloro-2,5-dimethoxyphenethylamine; aMT, alpha-methyltryptamine; MDAI, 5,6-Methylenedioxy-2-aminoindane.

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that better international collaboration levels may be needed to tackle the novel and fast growing phenomenon of novel psychoactive drugs availability from the web.

CONFLICT OF INTEREST

No conflicts of interest are declared here that may have influenced the interpretation of the present data. Please, however, note the following: FS is a full member of the Advisory Council on the Misuse of Drugs/ACMD in the UK; NS is a member of the German Advisory Council and both MF and MT are members of the Spanish Advisory Council; and JC is a member of the ACMD New Psychoactive Drugs working group in the UK.

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REFERENCES

Bluelight. 2010; 2011. Bluelight forum, Retrieved June 1, 2011, from http://www.bluelight.ru

Bonta IL. 2004. Schizophrenia, dissociative anaesthesia and near-death experience; three events meeting at the NMDA receptor. *Med Hypotheses* **62**(1): 23–28.

BulkResearchChemicals. 2011. Bulk research chemicals—methoxetamine price. Retrieved June 1, 2011 from http://bulkresearchchemicals.com.

Corazza O. 2010. Exploring space consciousness other dissociative experiences: a Japanese perspective. *JCS* **17**: 173–190.

Corazza O, Schifano F. 2010. Near-death states reported in a sample of 50 misusers. *Subst Use Misuse* **45**(6): 916–924.

Corazza O, Davey Z, Deluca P, *et al*. 2010. Le nuove potenzialità della prevenzione digitale in materia di nuove droghe: il ruolo del Recreational Drugs European Network. *Dip Pat* **2**: 43–46.

Corazza O, Schifano F, Farre M, *et al*. 2011. Designer drugs on the Internet: a phenomenon out-of-control? The emergence of hallucinogenic drug Bromo-Dragonfly. *Curr Clin Pharmacol* **6**(2): 125–129.

Coull J, Morgan H, Cambridge V, *et al*. 2011. Ketamine perturbs perception of the flow of time in healthy volunteers. *Psychopharmacology*: 1–14.

Davies S, Wood DM, Smith G, *et al*. 2010. Purchasing 'legal highs' on the Internet—is there consistency in what you get? *QJM* **103**(7): 489–493.

Dillon P, Copeland J, Jansen K. 2003. Patterns of use and harms associated with non-medical ketamine use. *Drug Alcohol Depend* **69**(1): 23–28.

Drugs-Forum. 2011. Drug forum, Retrieved June 1 2011, from http://www.drugs-forum.com .

EMCDDA. 2010. EMCDDA report 2010: the state of the drugs problem in Europe, European Monitoring Centre for Drugs and Drug Addiction.

Enarson M, Hays H, Woodroffe MA. 1999. Clinical experience with oral ketamine. *J Pain Symptom Manage* **17**(5): 384–386.

Erowid. 2010; 2011. Erowid, Retrieved June 1, 2011, from http://www.erowid.org

Eurobarometer. 2008. Young people and drugs: analytical report. E. Commission.

Fletcher P, Honey GD. 2006. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. *Trends Cogn Sc* **10**(4): 167–174.

Hipforums. 2011. Hip forums, Retrieved June 1, 2011, from http://www.hipforums.com

Jansen KLR. 1989. Near-death experiences and the NMDA receptor. *BMJ* **298**:1708.

Jansen KLR. 2001. *Ketamine: Dreams and Realities*. Sarasota:MAPS.

LegalHighsGuide. 2011. Legal highs guide Retrieved June 1, 2011 from http://www.legalhighsguide.com

Methoxetamine. 2011. Methoxetamine, Retrieved June 1 2011, from http://www.methoxetamine.co.uk

Moore J, Turner DC, Corlett PR, *et al*. 2011. Ketamine administration in healthy volunteers reproduces aberrant agency experiences associated with schizophrenia. *Cogn Neuropsych* **16**(4): 364–381.

Morgan HL, Turner D, Corlett PR, *et al*. 2011. Exploring the impact of ketamine on the experience of illusory body ownership. *Biol Psychiatry* **69**(1): 35–41.

Psychonaut. 2010. Psychonaut forum, Retrieved June 1, 2011, from http://www.psychonaut.com.

Purechemicals. 2010. Purechemicals: methoxetamine, Retrieved June 1, 2011, from http://www.purechemicals.co.uk.

PureChemicals. 2011. Research chemicals: methoxetamine, Retrieved June 1 2011, from http://www.purechemicals.net.

PureChems. 2011. Pure chemicals—methoxetamine price, Retrieved June 1 2011, from http://www.purechems.net.

Ramsey J, Dargan PI, Smyllie M, *et al*. 2010. Buying 'legal' recreational drugs does not mean that you are not breaking the law. *QJM* **103**(10): 777–783.

Schifano F, Deluca, P, Baldacchino A, *et al*. 2006. Drugs on the web; the Psychonaut 2002 EU project. *Prog Neuropsychopharmacol Biol Psychiatry* **30**(4): 640–646.

Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. 2008. Trapped in the 'K-hole'; overview of deaths associated with ketamine misuse in the UK (1993–2006). *J Clin Psychopharmacol* **28**: 114–116.

Schifano F, Corazza O, Deluca P, *et al*. 2009. Psychoactive drug or mystical incense? Overview of the online available information on spice products. *Int J Cult Mental Health* **2**(137–44).

Viceland. 2011. Interview whit a ketamine chemist. Viceland, Retrieved June 1 2011, from http://www.viceland.com/int/v18n2/htdocs/interview-with-ketamine-chemist-704.php

Wood D, Cottrell A, Baker SC, *et al*. 2011. Recreational ketamine: from pleasure to pain. *BJU Intern* **107**(12): 1881–1884.

YouTube.com. 2011a. Methoxetamine, research chemical. Retrieved July 1, 2011 from http://www.youtube.com/watch?v=_gIalok602E&NR=1.

YouTube.com. 2011b. Pop star talks about methoxetamine (research chemicals). Retrieved July 1, 2011 http://www.youtube.com/watch?v=XBlMUnzcf-4.

Forum

Un'introduzione al nuovo fenomeno delle nuove sostanze d'abuso e alla loro diffusione tramite Internet

Shapiro, H., Corazza, O., Simonato, P., and Schifano, F. on behalf of the ReDNet Research Project

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Gentile Direttore,

Nel corso del ultimi cinque anni si è riscontrata una rapida crescita di sostanze pubblicizzate, distribuite e vendute mediante Internet, le cui proporzioni sono state tali da indurre l'International Narcotic Control Board (INCB) a dichiarare che la produzione e la disseminazione di 'designer drugs' rappresenta un problema 'fuori controllo' (2011). L'INCB ha bandito 51 nuove sostanze in Giappone, mentre l'European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) segnala regolarmente la scoperta di nuovi composti psicoattivi. Che cosa sta succedendo?

Gli operatori sanitari e gli altri professionisti del settore conoscono molto bene le droghe illegali, quali l'eroina, la cocaina, la cannabis, le amfetamine e l' "ecstasy" (MDMA). Tuttavia, a partire dagli anni '80, i chimici underground, impegnati con la produzione clandestina di droghe sintetiche come l'amfetamina o l'LSD, iniziarono a sperimentare con l'idea di poter alterare le formule chimiche delle note droghe illegali, così da poter creare nuove sostanze non ancora regolamentate.

È proprio qui che nasce il termine "designer drugs", in quanto si tratta di composti "progettati" per essere legali.

L'Internet ricopre un ruolo fondamentale in questo processo, per le seguenti ragioni:

1. Molte delle nuove sostanze sono state inizialmente sintetizzate da compagnie farmaceutiche con legittime finalità mediche, ma mai rilasciate nel mercato. Nonostante questo, tali prodotti sono stati brevettati e i brevetti sono consultabili online, a disposizione di chi sa cosa e dove cercare.
2. Coloro che sono interessati, contattano via email dei potenziali produttori, localizzati prevalentemente in Cina e in Estremo Oriente, ordinando ciò che desiderano.
3. Internet quindi offre una opportunità ideale per la vendita su scala globale.
4. I consumatori di queste sostanze possono facilmente scambiarsi informazioni nei forum online dedicati, ed in genere Internet permette l'accesso ad un imponente numero di informazioni su questi composti, compresi video

An introduction to the new phenomenon of Internet-based drugs

Dear Director,

The last five years has seen a rapid growth in the internet-driven manufacture, supply and sale of drugs to the point where in their 2011 report the UN International Narcotic Control Board (INCB) declared that designer drug production and distribution was 'out of control'. The INCB stated that 51 new drugs had been controlled in Japan while the European drugs agency (EMCDDA) regularly announces the discovery of new drugs. So what is going on?

Health and other professionals are well aware of the illegal drugs that have been available for many years, such as heroin, cocaine, cannabis, amphetamine and ecstasy (MDMA). Since the 1980s, the underground chemists who produced synthetic drugs like amphetamine and LSD in laboratories began to experiment with the idea that you could alter the chemical formulas of illegal drugs, so that the new drug created would fall out side the law. This is where we get the term 'designer' drugs – designed to be legal.

The Internet is important in this development for the following reasons:

1. *Many of the new drugs were originally developed by pharmaceutical companies for legitimate medical purposes, but never made it to market. Even so, these drugs were patented and the patents are online to be searched by those who know where to look and what they are looking for.*
2. *These researchers will then email potential manufacturers, mainly in China and the Far East to order what they want.*
3. *The Internet provides an ideal opportunity for selling to a global market*
4. *Users of these drugs can easily exchange information In Internet forums and generally the Internet provides access to a substantial amount of information about these new drugs, including videos on You Tube.*
5. *Users can contact the seller directly, and/or receive regular alerts on new products via email or SMS and easily forward these to friends.*

Designer drugs have become increasingly popular mainly for the following

su You Tube.
5. I consumatori possono contattare i venditori direttamente, e/o ricevere avvisi regolari su nuovi prodotti mediante servizi email o SMS, che possono facilmente essere inoltrati ad amici.

Le "designer drugs" sono diventate rapidamente popolari per le seguenti ragioni:

1. I loro effetti psicoattivi sono molto simili a quelli delle sostanze illecite più note.
2. Molte di queste sostanze sono legali o rimangono tali finché non vengono regolamentate.
3. Le "designer drugs" possono essere acquistate in modo anonimo, senza i rischi connessi all'acquisto da spacciatori di strada.
4. Soprattutto nel Regno Unito, la purezza di cocaina e amfetamine è molto bassa, e queste nuove sostanze possono dare effetti molto più intensi.
5. Vengono spesso pubblicizzati e venduti su internet come "qualcosa d'altro" (sali da bagno, fertilizzanti, profumi, incensi, disinfettanti per stagni, etc.) e pertanto meno identificabili come droghe d'abuso.

Nuove proposte legislative sono essenziali per affrontare le sfide poste da questo nuovo fenomeno a livello internazionale. Ogni Paese possiede un proprio sistema legislativo, pertanto una sostanza "designer drug" potrà essere messa al bando in un Paese, ma risultare ancora legale in altri. Attualmente, il maggior problema per i legislatori nazionali è quello di stare al passo o, meglio ancora, quello di anticipare i chimici che progettano nuove droghe nell'intento di aggirare le norme vigenti. Questo ovviamente è estremamente difficile, ma ciò nonostante alcuni Paesi hanno introdotto delle leggi sperimentali più ampie che sono in grado di controllare anche sostanze completamente nuove e altre di genere affine. Questo è accaduto ad esempio nel Regno Unito dove è stata introdotta l'idea di una "messa al bando" temporanea. In questo caso, un composto che si sospetti possa essere pericoloso è temporaneamente reso illegale in attesa di approfondimenti scientifici. Tuttavia, la sfida per soluzioni legislative più omogenee a livello internazionale rimane ancora aperta.
In risposta a tale fenomeno, uno degli obiettivi del progetto europeo ReDNet, finanziato dall' Unione Europea (Health Programme, contratto numero: A/800102; 2006 348), e' quello di fornire informazioni multidisciplinari sempre più accurate ed aggiornate in tema di queste nuove sostanze. Per ulteriori informazioni invitiamo a consultare il nostro sito www.rednetproject.eu.

reasons:

1. *They offer very similar effects to well known illegal drugs.*
2. *Many of them are legal or remain legal for some while until they are controlled.*
3. *Drugs can be purchased anonymously and without the dangers of buying drugs from street dealers.*
4. *Particularly in the UK, the purity of drugs like cocaine and amphetamine is very low and these new drugs can often be stronger in their effects.*
5. *Are often advertised online as 'something else' (bath salts, fertilizers, perfumes, incenses, pound cleaners, etc) and thus less noticeable as drugs.*

Novel legal responses are necessary to tackle this new phenomenon at the international level. Each country will have its own laws, so while a designer drug might be banned in one country, it could be legal in others. At present, the main problem for lawmakers is to try and stay ahead of the chemists who are devising new drugs to be outside the law. This is of course is very difficult, but nevertheless some countries have introduced new more generic legislations, which tries to capture new drugs, and all subsequent drugs, in the same 'family'. This has happened in the UK, where the idea of temporary bans has also been introduced. In this case, a drug which looks as if it might be dangerous is temporarily banned while a scientific investigation is carried out. However, the challenge to find new and more harmonized legislative solutions at the international level still remains open.
In response to this phenomenon, one of the aims of the Europe-wide ReDNet Research Project, funded by the European Union (Health Programme, grant number: A/800102; 2006 348), is to provide up to date and accurate multidisciplinary information about these new drugs. For more information please visit our website www.rednetproject.eu

The Recreational Drugs' European Network:

piloting technology-based prevention services addressing the use of novel psychoactive drugs in vulnerable individuals

A project co-funded by the European Union
in the framework of the Public Health Programme

www.rednetproject.eu

Background

The recent emergence of new designer drugs, combined with the ability of the Internet to disseminate information quickly and act as an online marketplace, have raised concerns across drug and health policy and research. Both the number of largely unregulated substances, and the rapidity with which they appear and evolve has led to challenges for government, professionals and (potential) users alike. However, here is still a distinct paucity of information available.

About the project

The Recreational Drugs European Network (ReDNet) project is a multi-site research study with the aim of improving the level of information available to young people (16-24) and professionals on the effects of these new recreational drugs and the potential health risks associated with their use. It also aims to explore the potential of a number of innovative information communication technologies (e.g. texting, social networking sites, Second Life and other multimedia platforms) in the timely dissemination of accurate and non-judgmental, evidence-based, information in line with the needs of each target group

The project aims to:

- Develop accurate information on new recreational drugs
- Develop and pilot a variety of innovative and effective ICTs to disseminate this information
- To access the feasibility of different ICTs and the relevance of the information being disseminated to the target groups
- To inform future technology-based research in health education, prevention and harm reduction

ReDNet Project

Project Partners

ReDNet Research Centre, School of Pharmacy, University of Hertfordshire, Hatfield, UK

National Addiction Centre, Institute of Psychiatry, King's College London, London, UK

Institute of Psychiatry and Neurology, Warsaw, Poland

Bergen Clinics Foundation, Bergen, Norway

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National Institute for Drug Prevention, Institute for Social Policy and Labour, Budapest, Hungary

DrugScope, London, UK

The ReDNet project international conference on novel psychoactive drugs will take place on **12-13 March 2012 in Budapest, Hungary**.
Would like you to attend or present a paper? Visit our website **www.rednetproject.eu** or email **info@rednetproject.eu** for more information.

Join the ReDNet project mailing list for regular updates about our activities, including virtual seminars in Second Life:
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Psychopharmacology
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REVIEW

Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues

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Abstract
Background Recently, those substances deriving from the active ingredient of the Khat plant, cathinone, have been rising in popularity. Indeed, 4-methylmethcathinone (mephedrone; 'meow meow' and others) has been seen by some as a cheaper alternative to other classified recreational drugs.
Aims We aimed here at providing a state-of-the-art review on mephedrone history and prevalence of misuse, chemistry,

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pharmacology, legal status, product market appearance, clinical/management and related fatalities.
Methods Because of the limited evidence, some of the information here presented has been obtained from user reports/drug user-orientated web sites. The most common routes for mephedrone recreational use include insufflation and oral ingestion. It elicits stimulant and empathogenic effects similar to amphetamine, methylamphetamine, cocaine and MDMA. Due to its sympathomimetic actions, mephedrone may be associated with a number of both physical and psychopathological side effects. Recent preliminary analysis of recent UK data carried out in 48 related cases have provided positive results for the presence of mephedrone at postmortem.
Discussion and Conclusions Within the UK, diffusion of mephedrone may have been associated with an unprecedented combination of a particularly aggressive online marketing policy and a decreasing availability/purity of both ecstasy and cocaine. Mephedrone has been recently classified in both the UK and in a number of other countries as a measure to control its availability. Following this, a few other research psychoactives have recently entered the online market as yet unregulated substances that may substitute for mephedrone. Only international collaborative efforts may be able to tackle the phenomenon of the regular offer of novel psychoactive drugs.

Keywords Mephedrone · Meow meow · Cathinones · Drug misuse · Drug-related deaths · Psychoactive drugs

Introduction

Mephedrone (4-methylmethcathinone; 'plant food', 'meow meow', 'miaow', 'drone', 'meph', 'bubbles', 'spice E', 'charge', 'M-Cat', 'rush', 'Ronzio', 'Fiskrens' and 'MMC hammer') is the most popular of the cathinone derivatives, which also include butylone; methylone and remaining compounds (ACMD 2010; Morris 2010). It has been readily available for purchase both online and in head shops and its circulation has been promoted by aggressive web-based marketing (Deluca et al. 2009; Mephedrone2you 2010; National Treatment Agency 2010).

Mephedrone is a psychoactive research chemical that elicits stimulant and empathogenic effects similar to amphetamines, methylamphetamine, cocaine and MDMA (Winstock et al. 2010a). It has drawn wider attention from the media since it has been allegedly linked to a number of fatalities. As we write, only few formal papers and experimental/clinical data have been published (Dargan et al. 2010; Winstock et al. 2010a, b). Some of the information contained in this review has been obtained from user reports and drug user-orientated web sites, again highlighting the lack of peer-reviewed resources. Given the limited information available, we aimed here at providing a state-of-the-art review on mephedrone chemical, pharmacological and clinical issues.

History and prevalence of misuse

In 1929, Saem de Burnaga Sanchez first described the synthesis of mephedrone (Saem de Burnaga Sanchez 1929). However, khat-extracted cathinones which first appeared in Israel in early 2000s, locally named as 'Hagigat' (Urquhart 2004), were eventually outlawed following a large number of hospitalisations caused by its exposure (Bentur et al. 2008). As a result of the ban, chemists began altering the chemical structure of cathinone to synthesize related unscheduled compounds. The first online reference to mephedrone reportedly occurred in May 2003 (Power 2009), but both its availability for online purchase (Camilleri et al. 2010; Roussel et al. 2009) and related popularity (Deluca et al. 2009) started in 2007. Data collected by the European Monitoring Centre for Drugs and Drug Addiction show that over the first quarter of 2010, there have been detections in some 20 EU Member States, with most of them reporting small- to medium-sized seizures (Europol-EMCDDA 2010).

Although not well known in the USA, 4-methylmethcathinone appears to be particularly popular in the UK (Brandt et al. 2010a; Mephedrone2you 2010). During the second quarter of 2009, the 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 only very 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. Main settings of use might be nightclubs, parties and people's home (Newcombe 2009). A research project led by the National Addiction Centre in London with 2,295 readers of the dance magazine 'Mixmag' disclosed that 41.7% of surveyed people had ever tried 4-methylmethcathinone and 33.2% had used during the last month, making it the sixth most popular drug among clubbers, after tobacco, alcohol, cannabis, ecstasy and cocaine. Cathinone derivative methylone was mentioned as well in the survey (Winstock et al. 2010b). Dargan et al. (2010) assessed both the prevalence and frequency of use of mephedrone. Data were collected using a questionnaire survey in schools, colleges and universities in the Tayside area of Scotland in February 2010. Some 1,006 individuals completed the survey and 205 (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 sourced mephedrone from street-level dealers and 10.7% from the Internet. Although both the Mixmag and Scottish schools surveys are limited by the nature of sampling technique and target populations, the heightened interest in mephedrone (National Treatment Agency 2010) might be readily testified by the rise in the number of both telephone inquiries and visits to both the TOXBASE and FRANK web sites (ACMD 2010).

Mephedrone appearance on the UK market may have been associated with an unprecedented decreasing purity of both MDMA and cocaine (Hand and Rishiraj 2009; Fleming 2010; Measham et al. 2010; National Treatment Agency 2010). Similar observations have been recently reported from the Netherlands (Brunt et al. 2010). As a consequence, drug users may have switched to mephedrone, being allegedly cheaper and more powerful than the currently available 'traditional' stimulants (Deluca et al. 2009). Moreover, recent changes in the attitudes of drug users, as well information sharing and marketing through the Internet, are likely to have played a significant role. The ready availability of mephedrone may well have boosted its diffusion, and prior to its ban, many surveyed people thought 4-methylmethcathinone not to be harmful because of its appealing legal status (Daly 2010; Ramsey et al. 2010). This combination of circumstances has been massively capitalized on by suppliers who may conceivably have made huge profits by promoting the drug through an aggressive e-commerce advertising policy and by arranging a widespread delivery system (Power 2010; Freepressindex 2010; Mephedrone2you 2010). Paradoxically, online newspaper articles about mephedrone contained banners pointing towards drug vendors, and some editorialists have indicated mephedrone as an example of the future of drug dealing (Power 2009). One could also wonder about the possible role the media has played in promoting mephedrone use (Davey et al. 2010). From this point of view, Measham et al. (2010) have referred to the conceptualization of mephedrone in the media as a 'moral panic', and as such, this may have obscured the potential for accurate and valuable safety information to be transmitted and received on a large scale.

Immediately after the mephedrone ban, novel compounds have already appeared on the horizon, with molecules such as naphyrone (also known as naphthylpyrovalerone, 'energy 1' or 'NRG-1') and MDAi (5,6-methylendioxy-2-aminoindane) representing two of the emerging research chemicals set to replace mephedrone as alternative psychoactives. In fact, they are marketed and advertised with modalities similar to those referring to mephedrone up to a few months ago (Townsend 2010). Interestingly, some of these products have been shown to contain mephedrone and/or methylenedioxypyrovalerone (MDPV; Brandt et al. 2010b).

Chemical characteristics

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 *Catha edulis* (Khat; 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. Different acronyms include 1-(4-methylphenyl)-2-methylaminopropan-1-one, 2-methylamino-1-p-tolylpropan-1-one, 4-methylmethcathinone, 4-MMC and MMCAT. The molecular formula and mass are $C_{11}H_{15}NO$ and 177.242 g/mol, respectively (Chemspider 2010; Kalix 1992; Pubchem 2010). The structure of mephedrone is shown in Fig. 1 where it 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 (Fig. 1), and hence analogues of amphetamines (Chemspider 2010). Since they are mainly synthetic in origin, beta-keto amphetamines are also known as 'bk designer drugs'. Each of the phenethylamine compounds has a parallel cathinone analogue. For example, methcathinone is the cathinone anologue of methylamphetamine (ACMD 2010).

Like other cathinone derivatives, mephedrone possesses a single chiral centre thereby existing in two enantiomeric forms, (*S*)- and (*R*)-mephedrone (Europol-EMCDDA 2010; Gibbons and Zloh 2010). For cathinone, the *S*(−) form is more potent than the *R*(−) enantiomer, and this may be similar for mephedrone. The synthesis of (*S*)-4-methylcathinone, an (*S*)-mephedrone precursor, has been carried out via Friedel–Crafts acylation, as shown in Fig. 2 (Osorio-Olivares et al. 2003). Further methylation of the amino group would yield (*S*)-mephedrone.

It is relatively easy to produce mephedrone in non-professional laboratories (Fig. 3) via bromination of 4-methylpropiophenone followed by reaction with methylamine or by oxidation of 4-methylephedrine (Archer 2009; Europol-EMCDDA 2010). Both reactions would result in a mixture of *R*- and *S*-mephedrone. However, a stereoselective synthesis in the latter is possible using a single enantiomeric form (Lee et al. 2007) of 4-methylephedrine (Europol-EMCDDA 2010).

Pharmacology

Some cathinone derivatives are currently under active research as a promising class of monoamine uptake inhibitors (Meltzer et al. 2006). However, only little is known about the

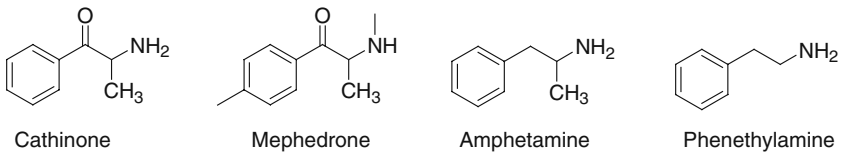


Fig. 1 Mephedrone and related structures

pharmacology of 4-methylmethcathinone. Given cathinone derivatives affiliation to beta-ketoamphetamines, mephedrone is expected to act as a central nervous system stimulant by promoting the release of monoamine neurotransmitters and likely inhibiting their reuptake (Kalix 1990; Feyissa and Kelly 2008). Indeed, 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, therefore being characterized by a predominant action on plasma membrane catecholamine transporters (Cozzi et al. 1999). Both amphetamines and cathinones bind to noradrenalin, dopamine and serotonin transporters (Nagai et al. 2007), each of them differing from each other by its relative binding potency. In particular, the presence of the ring substituent on the phenethylamine core modifies the pharmacological properties by giving the compound some MDMA-like effects, whereas amphetamines and cathinone derivatives without ring substituents exert mostly stimulant 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. Intake of both mephedrone and other beta-keto amphetamines can be detected with appropriate urine testing technology (Meyer et al. 2010; Zaitsu et al. 2009).

Legal status

At the time of writing, mephedrone is not under a consistent international control. In fact, misuse of mephedrone has spread very quickly in a relatively short period of time, notably arising in popularity among drug users (see Electronic supplementary material (ESM) Table 1). In the UK, where mephedrone has been greatly drawing both mass media and government attention, the Advisory Council on the Misuse of Drugs has published a report on the cathinone derivatives, recommending their inclusion in the Misuse of Drugs Act 1971 under class B. As a result, mephedrone was made a controlled drug (class B) on the 16th April 2010 (ACMD 2010). It may be of interest that control in some countries (e.g. Finland) has been by use of legislation other than the Misuse of Drugs Act or equivalent measures (see ESM Table 1).

Although in a way similar to many other recreational drugs 4-methylmethcathinone has been specifically synthesized to avoid existing drug misuse laws (BBC News 2009; Deluca et al. 2009; Financiarul online 2010), many synthetic 'legal highs' may not be legal. In fact, active ingredients in legal highs purchased from Internet-based suppliers do not remain consistent over time, hence increasing the risk of individuals purchasing a 'legal high' that contains a controlled drug (Ramsey et al. 2010). Furthermore, even if they have no history of previous use as drugs, specific psychoactive substances may still be liable to control under the Medicines Act. However, labelling is likely to be the key to better understand the phenomenon. In fact, a number of recreational psychoactive drugs available for online purchase, including mephedrone, are claimed to be 'plant feeders', 'bath salts' and 'not for human consumption' (Mephedrone2you 2010), and prosecution as such may be difficult (Winstock and Ramsey 2010). Many online suppliers' sites implicitly, however, suggest its use as a drug, referring to the rave and party culture in the web site graphic design and/or providing the customers with ambiguous reviews written by self-styled gardeners (Mephedrone.com 2010). It is of concern that despite the banning of mephedrone, little may indeed prevent suppliers from using the same marketing approach for novel and shortly forthcoming compounds (Brandt et al. 2010a).

Finally, it is worth noting that in March 2010, the EMCDDA and Europol submitted a joint report on mephedrone (Europol-EMCDDA 2010) to the Council of the EU, the European Commission and the European Medicines Agency (EMA), presenting the case for the forthcoming formal risk assessment of the drug.

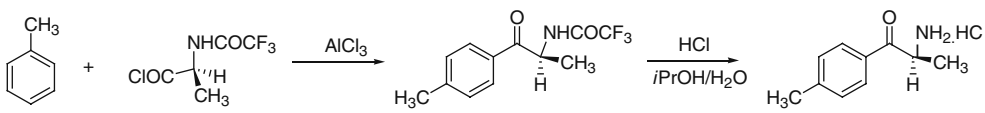
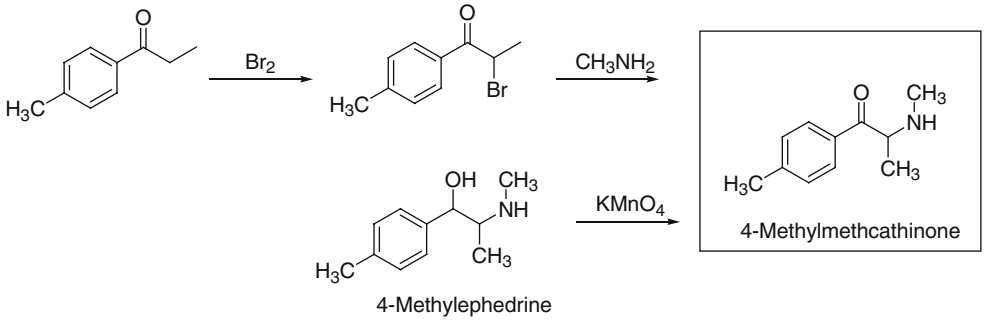


Fig. 2 Stereoselective synthesis of (*S*)-4-methylcathinone

Fig. 3 Synthesis of mephedrone



Market and commercial appearance

Mephedrone occurs as a white, sometimes off-white or slightly yellowish, powder or fine crystals. Less frequently, it is marketed as capsules or tablets of various colours, shape and thickness, with or without a logo. 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 cocaine (Deluca et al. 2009; ABC News 2008). Furthermore, it may be found to be mixed with some adulterants, such as caffeine, paracetamol and even cocaine, amphetamine and ketamine (Camilleri et al. 2010).

Routes of administration, dosage, use in combination with other drugs

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 (dissolved in an enema or within gelatine capsules) as well or injected intravenously. Insufflation is likely to be the most common modality. When snorted, mephedrone elicits its effects within a few minutes, with the peak being reached in <30 min followed by a rapid comedown. According to online users' advice, mephedrone dosage for snorting may range between 25 and 75 mg, with the lower threshold being at 5–15 mg and with a level in excess of 90 mg to be 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. 2010a, b).

Other typical methods of intake include oral administration, through ingestion of capsules or tablets; swallowing mephedrone powder wrapped up in cigarette paper (bombing); or mixed with water. On average, the most common oral dosages are higher than the snorting ones (Sumnall and Wooding 2009), being in the range between 150 and 250 mg. Time of onset may be of 45 min–2 h and may vary in association with the amount of food contained in the stomach. Because of this, users suggest to take mephedrone on an empty stomach. With oral administration, psychoactive effects may last longer (up to 2–4 h); side effects might be milder and the urge to re-dose less pressing. Some consumers exploit both insufflation and oral ingestion in combination to achieve both faster onset and long-lasting effects (Deluca et al. 2009). With respect to oral ingestion, users report that rectal administration is characterized by faster onset of the effects and requires lower doses, e.g. 100 mg on average (Deluca et al. 2009).

Although not typically advised, because this may increase the drug 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). This method of intake appears to be fairly well known in Romania where mephedrone may be combined with heroin (Europol-EMCDDA 2010). Because of the capability of the drug to induce tolerance upon repeated doses, 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). 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 (Drugsforum 2010). Although withdrawal symptoms are not typically reported, users often describe strong cravings for the drug (Newcombe 2009). In a survey carried out in Scotland in February 2010, roughly one out of six users' surveyed reported 'addiction or dependence' symptoms associated with their mephedrone use (Dargan et al. 2010).

Although one could argue about the limited generalizability of most studies here quoted and of the advice provided from online fora, according to web users mephedrone may be taken in combination with a number of stimulants, sedatives and psychedelics (Deluca et al. 2009). These may include: cocaine, amphetamine, modafinil, butylone, MDPV, methylone, metamfepramone, alcohol,

GBL/GHB, benzodiazepines, kratom (mytraginin), heroin, cannabis, ketamine (with this combination being known as 'challenge'), MDMA, BZP, TFMPP, DMAA and sildenafil. One could conclude that the above combinations are likely to increase mephedrone toxicity effects and harm potential.

Desired and untoward mephedrone effects

Mephedrone effects have been variously compared by users to those of cocaine, amphetamine and MDMA. Self-reported subjective effects may include (Winstock et al. 2010b; Deluca et al. 2009):

- Intense stimulation and alertness, euphoria
- Empathy/feelings of closeness, sociability and talkativeness
- Intensification of sensory experiences
- Moderate sexual arousal
- Perceptual distortions (reported with higher dosages only)

According to Dargan et al. (2010), some 56% of those who had used mephedrone may complain of at least one unwanted effect associated with its use; these may include (ACMD 2010; Deluca et al. 2009; James et al. 2010; Wood et al. 2009, 2010b):

- *Gastrointestinal system:* Loss of appetite, dry mouth, nausea, vomiting and stomach discomfort;
- *Central nervous system/neurological*: Tremors, tense jaws, trismus, bruxism, mild muscle clenching, stiff neck/shoulders, headache (very common), dizziness/lightheadedness, tinnitus, seizures, nystagmus, pupil dilation, blurred vision, numbness of tactile sensitivity (reported at higher dosages);
- *Central nervous system/psychiatric*: Anxiety, agitation, confusion, dysphoria, irritability, aggression; depression, lack of motivation, anhedonia; time distortions, long-lasting hallucinations, paranoid delusions, short-term psychosis, short-term mania; insomnia and nightmares; impaired short-term memory, poor concentration, mental fatigue. Psychopathological consequences are more frequently reported if the drug is taken at higher dosages/in prolonged sessions (Deluca et al. 2009; Winstock et al. 2010b) and/or if the misuser presents with an underlying psychobiological vulnerability (Odenwald et al. 2005, 2009);
- *Cardiovascular system*: Tachycardia, elevated blood pressure, respiratory difficulties, chest pain and elevated blood pressure, peripheral vasoconstriction. Possibly due to vasoconstriction, users have anecdotally described cold/blue fingers;
- *Renal/urinary excretory system*: Difficulties in urination, possible nephrotoxicity, anorgasmia;
- *Miscellaneous*: Changes in body temperature regulation, with hot flushes and sweating (so-called mephedrone sweat, characterized by a strong body odour); painful nasal drip, nose and throat bleeds with burns and ulcerations (following insufflation); immunological toxicity (vasculitis, infections and ulcerations).

Most of the above untoward effects seem to be similar to those already documented for amphetamine, methamphetamine 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).

Treatment and management

Acute management of adverse events

The only available information relating to treatment of mephedrone acute behavioural toxicity derives from observations carried out in an Emergency Department in central London. In most cases, mephedrone-related agitation was treated with benzodiazepines. All 15 patients were discharged after appropriate observation with no sequelae (Wood et al. 2009, 2010a, b). Since no guidelines have yet been specifically provided, treatment is to be considered empirical. One could argue that the treatment for the more life-threatening conditions might be broadly similar to that of amphetamine poisoning. Those individuals presenting with less severe symptoms should be assessed and managed as for any other users of psychoactive drugs and 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. 2010a).

Longer term therapeutic psychological and harm reduction approaches

Harm reduction advice has been provided by prodrug web sites, including using the drug not exceeding 500 mg per session and dosing orally rather than

insufflating (Newcombe 2009). Since too little is known about mephedrone potential neurotoxicity or long-term consequences of its use, only common sense advice about the use of any psychoactive stimulant has been provided (Winstock et al. 2010a). This may include: 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. Both a brief motivational intervention and appropriately adapted psychosocial intervention have been suggested to treat mephedrone addiction (Winstock et al. 2010a).

Mephedrone-related deaths

During the last few months, British media and newspapers have been reporting about fatalities allegedly related to mephedrone consumption almost on a weekly basis, but only a proportion of them have already been 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 (Gustaffsson and Escher 2009). Previously, a Danish teenager found in possession of mephedrone died in May 2008, although toxicology reports were inconclusive (Campbell 2009). Published data regarding the first mephedrone-related death in the USA involved the combined use of mephedrone and heroin (Dickson et al. 2010).

Data collected by the National Programme on Substance Abuse Deaths (Ghodse et al. 2010) suggest that by the beginning of October 2010, there have been 45 suspected deaths related to mephedrone in England, 12 in Scotland, 1 in Wales, 1 in Northern Ireland and 1 in Guernsey. Preliminary analysis carried out in 48 out of these 60 cases has provided positive results for the presence of mephedrone at postmortem. Remaining cases are, to date, awaiting further investigation. It is important to emphasize that a number of fatalities reported to the np-SAD implicated mephedrone consumption in combination with other substances/other recreational drugs, such as alcohol, cannabis, cocaine, amphetamine, methadone, methylone and 4-MTA.

Conclusions

This paper may represent a comprehensive and critical review of the currently available information on the novel psychoactive drug 4-methylmethcathinone. Data have been collected from the very few published articles in scientific peer-reviewed journals, from official bodies' reports and from the users' grey literature/prodrug web sites. It is worth emphasizing the importance of the latter since mephedrone was indeed first identified by the Psychonaut Web Mapping project (Deluca et al. 2009) whilst examining new trends in drug use by actively monitoring drug user-orientated web sites.

Although pharmacodynamics data are currently uncertain and further data from peer-reviewed studies are needed, effects of 4-methylmethcathinone are reported to be broadly similar to those of MDMA/ecstasy and cocaine. In fact, mephedrone may feature mainly stimulant-like effects, such as mood enhancement and alertness, but possesses as well both empathogenic and hallucinogenic properties at higher dosages. Only a few related case reports have been published so far, and there is a distinctive lack of information about the acute and chronic toxicity of 4-methylmethcathinone. In the UK, mephedrone has been tentatively associated with a number of deaths. However, most of them may have been reported by the popular press with some levels of inaccuracy, and this is likely to have generated confusion in the general public (Davey et al. 2010). Preliminary data from the np-SAD here commented emphasize the need of continuing to monitor mephedrone. In fact, because of the recent appearance of the drug into the market and the lack of mephedrone knowledge on the coroners' side, one could still think that the number of related fatalities has been underreported. It is worth noting that after ban legislation came into effect, postmortem samples taken in June 2010 in the UK have still tested positive for mephedrone (Ghodse et al. 2010; Davies et al. 2010).

A large quantity of personal advice and suggestions with respect to mephedrone dosage, best ways of experimenting with its effects and avoiding untoward reactions was here largely available in the web sites we sampled. The technical knowledge on new products entering the market, hardly obtained through reference books and scientific journals, is often held in closed groups of users who exchange online information with each other without any contact with the scientific world (Littlejohn et al. 2005; Schifano et al. 2006; Schmidt et al. 2010). Much of the material quoted here referring to web-based sources was, however, not evidence-based and, for this reason, has proved to be difficult indeed to critically evaluate. In particular, we did not have any possibility to confirm if the substance the misusers were referring to was indeed mephedrone. We did not survey here the actual *use* of the online information by interested web surfers, but only the availability and the content of data on mephedrone.

Future studies should better assess both the acute and chronic toxicity of mephedrone and related cathinone derivatives. With a better understanding of these drugs' clinical pharmacology, it is hopeful that related clinical

management levels will improve. Furthermore, the characteristics of those consumers who take advantage of the online available information on mephedrone and similar compounds should be better assessed and, as a result, the stereotypical image of the 'drug misuser' may need to change (Littlejohn et al. 2005). Finally, the potential of innovative ICT prevention programmes for novel psychoactive compounds, such as the EC-funded 2010-2012 ReDNet research project (www.rednetproject.eu; Corazza et al. 2010) remains to be tested.

Mephedrone has been recently classified in both the UK and in a number of other countries as a measure to control its diffusion. One could argue that the designer drug market appears to be constantly one step ahead of the authorities. Although it is beyond the scope of this paper to comment on the effectiveness of these control measures, it is a matter of fact that a few psychoactive compounds (e.g. NRG-1, NRG-2, MDAi, MDPV, etc.) have recently entered the online market as substitutes for mephedrone. It is our opinion that only international collaborative efforts may be able to tackle the phenomenon of the regular offer of novel psychoactive drugs.

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Conflict of interest No conflicts of interest are declared here which may have influenced the interpretation of present data.

References

Advisory Council on the Misuse of Drugs/ACMD (2010) Advisory Council on the Misuse of Drugs on Consideration of the Cathinones. http://www.homeoffice.gov.uk/publications/drugs/acmd1/acmd-cathinodes-report-2010, accessed 18 August 2010

Archer RP (2009) Fluoromethcathinone, a new substance of abuse. Forensic Sci Int 185:10–20

Bentur Y, Bloom-Krasik A, Raikhlin-Eisenkraft B (2008) Illicit cathinone ("Hagigat") poisoning. Clin Toxicol Phila 46:206–210

Brandt SD, Sumnall HR, Measham F, Cole J (2010a) Analyses of second-generation 'legal highs' in the UK: initial findings. Drug Test Anal 2:377–382

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

Brunt TM, Poortman A, Niesink RJ, van den Brink W (2010) Instability of the ecstasy market and a new kid on the block: mephedrone. J Psychopharmacol (Sep 8, in press)

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

Campbell D (2009) Online sales of legal alternatives to class A drugs raise safety fears. http://www.guardian.co.uk/society/2009/mar/12/online-legal-drugs-stimulants, accessed 19 August 2010

Chemicalbook (2010) http://www.chemicalbook.com, accessed 21 March 2010

Chemspider (2010) http://www.chemspider.com, accessed 21 March 2010

Corazza O, Davey Z, Deluca P, Demetrovics Z, Drummond C, Enea A, Moskalewicz J, Di Melchiorre G, Di Furia L, Farre' M, Flesland L, Scherbaum N, Siemann H, Skutle A, Torrens M, Pasinetti M, Pezzolesi C, Shapiro H, Sferrazza E, van der Kreeft P, Schifano F (2010) Le potenzialità della prevenzione digitale in materia di nuove droghe: il ruolo del Recreational Drugs European Network-ReDNet [Potential of digital prevention relating to novel drugs' misuse: the role of the Recreational Drugs European Network-ReDNet] Dipend Patol (in press)

Cozzi NV, Sievert MK, Shulgin AT, Jacobill P, Ruoho AE (1999) Inhibition of plasma membrane monoamine transporters by beta-ketoamphetamines. Eur J Pharmacol 381:63–69

Daly M (2010) Teenage kicks. http://www.drugscope.org.uk/Resources/Drugscope/Documents/PDF/Good%20Practice/DruglinkJanFeb10.pdf, accessed 19 August 2010

Dargan PI, Albert S, Wood DM (2010) Mephedrone use and associated adverse effects in school and college/university students before the UK legislation change. QJM 103:875–879

Davey Z, Corazza O, Schifano F, Deluca P, Psychonaut Web Mapping Group (2010) Mass-information: mephedrone, myths, and the new generation of legal highs. Drugs Alcohol Today 10:24–28

Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, Holt DW, Dargan PI (2010) Purchasing 'legal highs' on the Internet—is there consistency in what you get? QJM 103:489–493

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

Dickson AJ, Vorce SP, Levine B, Past MR (2010) Multiple-drug toxicity caused by the coadministration of 4-methylmethcathinone (mephedrone) and heroin. J Anal Toxicol 34:162–168

Drugsforum (2010) http://www.drugs-forum.com, accessed 17 April 2010

Europol–EMCDDA joint report on a new psychoactive substance: 4-methylmethcathinone (mephedrone). http://www.emcdda.europa.eu/attachements.cfm/att_102496_EN_Europol-EMCDDA_Joint_Report_Mephedrone.pdf, accessed 16 August 2010

Feyissa AM, Kelly JP (2008) A review of the neuropharmacological properties of khat. Progr Neuro Psychopharmacol Biol Psychiatry 32:1147–1166

Financiarul online (2010): *Salvia divinorum*, psilocybe mushrooms are among hallucinogenic herbs banned by gov't. http://www.financiarul.ro/?s=Salvia+divinorum%2C+psilocybe+mushrooms+are+among+hallucinogenic+herbs+banned+by+gov%E2%80%99t+, accessed 18 August 2010

Fleming N (2010) Miaow-miaow on trial: truth or trumped-up charges? http://www.newscientist.com/article/dn18712-miaowmiaow-on-trial-truth-or-trumpedup-charges.html, accessed 19 August 2010

Freepressindex (2010) Get mephedrone very easily. Posted on March 16, 2010. http://www.freepressindex.com/news-get-mephedrone-very-easily-17851.html, accessed 19 August 2010

Ghodse AH, Corkery J, Oyefeso A, Schifano F, Ahmed K, Naidoo V (2010) Drug related deaths in the UK. Annual Report 2010. International Centre for Drug Policy, St George's, University of London, UK

Gibbons S, Zloh M (2010) An analysis of the 'legal high' mephedrone. Bioorg Med Chem Lett 20:4135–4139

Gustaffsson D, Escher C (2009) Mefedron. Internetdrog som tycks ha kommit för att stanna [Mephedrone—Internet drug that seems to have come to stay]. Lakartidningen 106:2769–2771

Gygi MP, Gibb JW, Hanson GR (1996) Methcathinone: an initial study of its effects on monoaminergic systems. J Pharmacol Exp Ther 276:1066–1072

Hand T, Rishiraj A (2009) Seizures of drugs in England and Wales 2008/09. Home Office Statistical Bulletin 16/09. Home Office, London

James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, Thomas SH; on behalf of the National Poisons Information Service (2010) Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J (Aug 25, in press)

Kalix P (1990) Pharmacological properties of the stimulant khat. Pharmacol Ther 48:397–416

Kalix P (1992) Cathinone, a natural amphetamine. Pharmacol Toxicol 70:77–86

Lee WS, Chan MF, Tam WM, Hung MY (2007) The application of capillary electrophoresis for enantiomeric separation of *N*,*N*-dimethylamphetamine and its related analogs: intelligence study on N,N-dimethylamphetamine samples in crystalline and tablet forms. Forensic Sci Int 165:71–77

Littlejohn C, Baldacchino A, Schifano F, Deluca P (2005) Internet pharmacies and online prescription drug sales: a cross-sectional study. Drugs Ed Prev Policy 12:75–80

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

Meltzer PC, Butler D, Deschamps JR, Madras BK (2006) (4-Methylphenyl)-2-pyrrolidin-1-yl-pentan-1-one (Pyrovalerone) analogues: a promising class of monoamine uptake inhibitors. J Med Chem 49:1420–1432

Mephedrone.com (2010) http://www.mephedrone.com, accessed 15 March 2010 and 20 August 2010)

Mephedrone2you (2010) http://www.mephedrone2u.com/, accessed 20 August 2010

Meyer MR, Wilhelm J, Peters FT, Maurer HH (2010) Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography–mass spectrometry. Anal Bioanal Chem 397:1225–1233

Morris K (2010) UK places generic ban on mephedrone drug family. Lancet 9723:1333–1334

Nagai F, Nonaka R, Kamimura KSH (2007) The effects of non-medically used drugs on monoamine neurotransmission in rat brain. Eur J Pharmacol 559:132–137

National Treatment Agency (2010) Drug treatment in 2009–2010. www.nta.nhs.uk, accessed 8 October 2010

Newcombe R (2009) Mephedrone: the use of mephedrone (M-cat, meow) in Middlesbrough. Lifeline Pubblications, Manchester

ABC News (2008) Police warn of potentially fatal 'fake ecstasy'. http://www.abc.net.au/news/stories/2008/06/17/2277735.htm, accessed 19 August 2010

BBC News (2009) Call for ban on 'legal high' drug. http://news.bbc.co.uk/1/hi/health/8023451.stm, accessed 19 August 2010

Odenwald M, Neuner F, Schauer M, Elbert T, Catani C, Lingenfelder B, Hinkel H, Häfner H, Rockstroh B (2005) Khat use as risk factor for psychotic disorders: a cross-sectional and case–control study in Somalia. BMC Med 12:3–5

Odenwald M, Hinkel H, Schauer E, Schauer M, Elbert T, Neuner F, Rockstroh B (2009) Use of khat and posttraumatic stress disorder as risk factors for psychotic symptoms: a study of Somali combatants. Soc Sci Med 69:1040–1048

Osorio-Olivares M, Caroli Rezende S, Sepulveda-Boza BK, Cassels RF et al (2003) A two-step method for the preparation of homochiral cathinones. Tetrahedron Asymm 14:1473–1477

Power M (2009) Mephedrone: the future of drug dealing. http://www.drugscope.org.uk/Resources/Drugscope/Documents/PDF/Good%20Practice/Druglink_March_09_mephedrone.pdf, accessed 19 August 2010

Power M (2010) How mephedrone shook the drug trade. http://www.drugscope.org.uk/Resources/Drugscope/Documents/PDF/Good%20Practice/DruglinkJanFeb10.pdf, accessed 19 August 2010

Pubchem (2010). http://pubchem.ncbi.nlm.nih.gov, accessed 21 March 2010

Ramsey J, Dargan PI, Smyllie S, Davies S, Button J, Holt DW, Wood DM (2010) Buying 'legal' recreational drugs does not mean that you are not breaking the law. QJM 103:777–783

Roussel O, Perrin M, Herard P, Chevance M, Arpino P (2009) La 4-méthyléphédrone sera-t-elle une "Ecstasy" du XXIème siècle? Ann Toxicol Anal 21:169–177

Saem de Burnaga Sanchez J (1929) Sur un homologue de l'ephedrine. Bull Soc Chim Fr 45:284–286

Schifano F (1996) Cocaine misuse and dependence. Curr Opin Psychiatry 9:225–230

Schifano F, Deluca P, Baldacchino A, Peltoniemi T, Scherbaum N, Torrens M, Farre' M, Flores I, Rossi M, Eastwood D, Guionnet C, Rawaf S, Agosti L, Di Furia L, Brigada R, Majava A, Siemann H, Leoni M, Tomasin A, Rovetto F, Ghodse AH, Psychonaut 2002 Research Group (2006) Drugs on the web: the Psychonaut 2002 EU project. Progr Neuropsychopharmacol Biol Psychiatry 30:640–646

Schifano F, Corkery J, Naidoo V, Oyefeso A, Ghodse AH (2010) Comparison between amphetamine/methylamphetamine and ecstasy (MDMA, MDEA, MDA, 4-MTA) mortality data in the UK (1997–2007). Neuropsychobiology 61:122–130

Schmidt MM, Sharma A, Schifano F, Feinmann C (2010) Legal highs on the net: evaluation of UK based websites, products and product information. Forensic Sci Int (Jul 20, in press)

Sumnall H, Wooding O (2009) Mephedrone: an update on current knowledge. Centre for Public Health, Liverpool John Moores University. http://www.drugsandalcohol.ie/12762/, accessed 19 August 2010

Townsend M (2010) New drug set to replace banned mephedrone as a 'legal high'. http://www.guardian.co.uk/society/2010/apr/18/drug-replace-ban-mephedrone, accessed 19 August 2010

Urquhart C. (2004): Drugs and dance as Israelis blot out intifada. http://www.guardian.co.uk/world/2004/sep/04/israel, accessed 18 August 2010

Winstock AR, Ramsey JD (2010) Legal highs and the challenges for policy makers. Addiction 105:1685–1687

Winstock AR, Marsden J, Mitcheson L (2010a) What should be done about mephedrone? BMJ 340:c1605

Winstock A, Mitcheson L, Deluca P, Davey Z, Corazza O, Schifano F (2010b) Mephedrone; new kid for the chop. Addiction (August 23rd, in press)

Wood DM, Davies S, Puchnarewicz M, Button J, Archer R et al (2009) Recreational Use of 4-methylmethcathinone (4-MMC)

presenting with sympathomimetic toxicity and confirmed by toxicological screening. Clin Toxicol 47:7331

Wood DM, Davies S, Puchnarewicz M, Button J, Archer R, Ovaska H, Ramsey J, Lee T, Holt DW, Dargan PI (2010a) Recreational use of mephedrone (4-methylmethcathinone, 4-MMC) with associated sympathomimetic toxicity. J Med Toxicol 6:327–330

Wood DM, Greene SL, Dargan PI (2010b) Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. Emerg Med J. doi:10.1136/emj.2010.092288

Zaitsu K, Katagi M, Kamata HT, Kamata T, Shima N, Miki A, Tsuchihashi H, Mori Y (2009) Determination of the metabolites of the new designer drugs bk-MBDB and bk-MDEA in human urine. Forensic Sci Int 188:131–139