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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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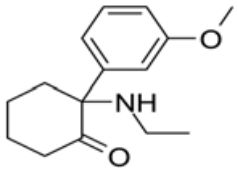


Figure 1. 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone (methoxetamine)

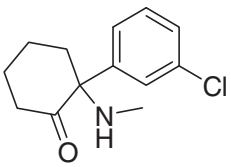


Figure 2. 2-(2-chlorophenyl)-2-(methylamino)cyclohexanone (ketamine)

*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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