ACMD

Advisory Council on the Misuse of Drugs

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Minister of State for Crime Prevention and Antisocial Behaviour Reduction,
Home Office
2. Marsham Street
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23rd March 2012

Dear Minister,

I am writing in response to your formal request for the Advisory Council on the Misuse of Drugs (ACMD) to provide advice on the drug methoxetamine, pursuant to section 2A of the Misuse of Drugs Act 1971 (a temporary class drug order). I have pleasure in providing the ACMD's consideration of the evidence concerning this drug.

In providing this advice I would like to convey my thanks to the Home Office for its provision of information obtained via the Drugs Early Warning System (DEWS) and the Forensic Early Warning System (FEWS).

Background
In September 2010 internet dealers began to advertise a new product, methoxetamine, a close chemical analogue of ketamine. It was said to mimic the psychoactive effects of ketamine but represented a legal alternative. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) first detected this compound in the UK in September 2010, and has now received reports of its presence in many European countries. Its presence in police seizures has now been reported in samples from many different regions. There has been a rise in visits to the FRANK help site, and to the National Poisons Information Service (TOXBASE) in the past 6 months and also an increased, although small total number, of presentations of users with acute methoxetamine toxicity to hospital Emergency Departments. No deaths have presently been positively linked to methoxetamine use.

Chemical composition and Pharmacology
The chemical structure of methoxetamine bears a close resemblance to that of both ketamine and phencyclidine (PCP) which are controlled drugs under the Misuse of

Drugs Act 1971 and which produce well-documented and serious adverse effects following both acute and chronic usage. This chemical similarity makes it probable that methoxetamine will have a similar pharmacological mode of action to ketamine and PCP. Preclinical studies are planned to confirm this. Case reports so far available suggest that the pattern of adverse effects reported following acute use is similar to that seen with ketamine. Results from the current and planned preclinical studies will become available over the next few months as will more clinical results from both acute and chronic users.

Prevalence of use

The ACMD has received evidence of methoxetamine use in England, Scotland, and Wales. However, it is unclear to what extent methoxetamine has dispersed amongst the general population and whether geographic variations in use exist.

There is very little information on prevalence of use of methoxetamine in the UK, mirroring the lack of international epidemiology. It is therefore not possible to estimate prevalence in the UK. The ACMD is aware of the following evidence:

- An unpublished survey of London nightclub attendees in July 2011 (Wood DM *et al*., in preparation) found use (6.4% lifetime use). However, a survey by Measham *et al*., in Lancashire nightclubs in March 2012 did not find any reports of methoxetamine (Measham, personal communication to ACMD).
- An online self selecting survey of self-reported substance use conducted November 2011 (Global Drug Survey) found, of the 7,700 respondents in the UK:
  - 4.2% reported using methoxetamine in the last year (6% of clubbers and 4% of non clubbers)
  - 2.4% reported using methoxetamine in the last month (3% of clubbers and 1% of non clubbers)
  - self reported methoxetamine use amongst this group was higher than the use of a range of other drugs including: DMT; synthetic cannabis; Benzofury; DMAI; crack; GBL; BZP; heroin etc.
- There are a small number of documented cases of Emergency Department presentations where methoxetamine has been used (e.g. Wood et al., 2011[1]).
- A high level survey of the clinical leads network of the Royal College of General Practitioners Substance Misuse and Associated Health has shown no reported issues with methoxetamine coming through the medical services of community drug teams or shared care[2] (Personal communication by Dr L Harris).
- A London Club Drug Clinic (opened September 2011) has 150 clients, of which 5 report methoxetamine use as part of a repertoire of poly drug and alcohol use (Personal communication to ACMD by Dr O Bowden-Jones).
- Other treatment services across the country have reported awareness, and use of, methoxetamine amongst clients (Personal communications to ACMD from treatment providers).
- Discussions on online forums suggest use and some present detailed self-reports of methoxetamine use experiences (Corazza *et al*., 2012[3])

[1] Wood D.M., Panayi P., Davies S. *et al*, (2011) Analysis of recreational drug samples obtained from patients presenting to a busy inner-city emergency department: a pilot study adding to knowledge on local recreational drug use. *Emerg. Med. J.* 28, 11-13.

[2] This provides an indicator only of reported prevalence through the medical intervention elements of local drug treatment system

[3] Corazza O., Schifano F., *et al*, (2012) Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine, *Hum. Psychopharmacol Clin Exp,* 27(2), 145–149.

- Reports in the popular media also indirectly suggest use (e.g. Mixmag, January 2012).
- Between 1 June 2011 and 17 February 2012 FRANK/Know The Score telephone helpline received approximately 17 calls relating to methoxetamine. The *Methoxetamine* information page on the FRANK website notes that there is a lack of evidence available on the acute and potential long term effects of methoxetamine but draws parallels with ketamine. FRANK offers general advice that based upon its NMDA pharmacology methoxetamine, like ketamine, should not be co-consumed with alcohol.

There is currently no evidence available on user typology and so it is not possible to predict which groups are most likely to use methoxetamine. Surveys have been conducted which have indicated pockets of use amongst gay male `clubbers' and young adult `clubbers' and music festival attendees, however, there have not been wider surveys that would suggest an 'at risk' demographic.

Poly substance use
Anecdotal evidence obtained from drug user forums suggests that some users combine methoxetamine with other compounds such as the tryptamine and phenethylamine derivatives (Corazza *et al*., 2012), although the veracity of this information is uncertain. The London Club Drug Clinic users were all poly substance users, who had all previously used ketamine and reported that they had switched to methoxetamine either because they thought it did not damage the bladder or because they reported a shortage in ketamine availability.

Methoxetamine seizures
Methoxetamine has been seized by a number of UK police forces (evidence submitted to ACMD), although there are currently no data available on the total number of seizures. Although not specifically targeted, methoxetamine has been seized from several high street retailers, and police intelligence logs databases include a number of further mentions of the drug.

Availability
In July 2011, the EMCDDA suggested that around one fifth (of a total of 631) of the total retailers offering all types of Novel Psychoactive Substances (NPS) within the EU were probably based in the UK - noting that it is often difficult to accurately determine the actual country of operation of online retailers. In the same period, across all countries, the EMCDDA identified 58 online retailers offering methoxetamine to EU customers (an increase from 14 in January of the same year). However, the methoxetamine data was not broken down by the likely country of sale, so it is not possible to say how many UK based online retailers are offering methoxetamine. The country of origin for the methoxetamine sold online is not known.

Acute harms
There have been at least nine cases of analytically confirmed acute methoxetamine toxicity presenting to hospitals in the UK in the last 6 months (Wood *et al*., 2011; Dargan personal communication to ACMD). These include cases from Northern Ireland, London and York. In addition there is anecdotal information on presentations to hospitals in other areas of the UK including Scotland, the Midlands and the South West.

There have been 40 telephone enquiries to the UK National Poisons Information Service (NPIS) concerning cases of acute methoxetamine toxicity; the first of these was

in October 2010. No further detail is currently available on the clinical pattern of toxicity seen in these cases. In addition there were 183 accesses to the monograph for methoxetamine on TOXBASE, the online poisons information database for the NPIS from 31st May 2011 to 23rd February 2012. Data from NPIS needs to be interpreted with caution as poisons information service usage can only give surrogate information on presentations to hospital with toxicity. However these data suggests increasing presentations to hospitals related to use of methoxetamine, particularly since November 2011 with 3-6 calls to the poisons service per month and 36-56 TOXBASE accesses per month since November 2011.

In the analytically confirmed cases the patients presented with some features similar to those seen with acute ketamine toxicity including hallucinations, catatonia and dissociative effects. However in addition to this there appears to be significant additional toxicity; these effects include agitation, cardiovascular effects including tachycardia (a fast heart rate) and hypertension (a high blood pressure) and cerebellar features. Cerebellar features such as ataxia (unsteadiness on the feet), are rarely seen with other recreational drugs and are not seen with acute ketamine toxicity.

There have been no confirmed deaths related to methoxetamine in the UK. Early information suggests that methoxetamine *may* have been used in four individuals in the time leading up to their death. However, detailed toxicology testing and coroners investigations into these deaths are pending and so it is not possible at this stage to determine what role, if any, methoxetamine played in these deaths.

Chronic harms
Regular use of ketamine is associated with a range of chronic problems including chronic bladder and other lower urinary tract pathology. The chronic harms of methoxetamine are, as yet, unknown: the chronic harms of ketamine only became recently apparent after many years of its use. Despite this, there are scientifically unsubstantiated marketing claims that methoxetamine is “bladder friendly”.

International Data
There have been no confirmed deaths related to methoxetamine reported in Europe or elsewhere in the world. There has been one published case of acute methoxetamine toxicity from Switzerland (Hofer *et al*., 2011[4]) and one from the USA (Ward et al., 2011[5]). In addition there are anecdotal reports of acute methoxetamine toxicity presentations to hospitals in other countries in Europe including in Belgium.

Legitimate use and marketing authorisation
The Department of Business Innovation and Skills has made enquiries, on behalf of the Home Office, and has been unable to identify any legitimate industrial or medicinal use of methoxetamine.

The Medicines Healthcare Products Regulatory Agency has made enquiries on behalf of the Home Office and confirms that there are no marketing authorisations for medicines containing methoxetamine.

Recommendations

[4] Hofer K. E., Grager B., *et al*, (2012) Ketamine-like effects after recreational use of methoxetamine, *Ann Emerg Med* [Epud ahead of print]

[5] Ward J. (2011), Methoxetamine: a novel ketamine analog and growing health-care concern, *Clinical Toxicology*, 49, 874-875.

Pursuant to Section 2B(6) of the Misuse of Drugs Act 1971, it is the view of the ACMD from the evidence collected and presented in this report that, in the case of methoxetamine 2-(ethylamino)-2-(3-methoxyphenyl)cyclohexanone, the substance is a drug that is being misused and that the misuse is having harmful effects. The ACMD therefore advise that methoxetamine be subject to a temporary class drug order.

The Council have found no evidence that methoxetamine has a recognised medicinal use and therefore advise that methoxetamine be treated as a Schedule 1 drug in applying the provisions of the Misuse of Drugs Regulations (as amended).

The control of methoxetamine should also extend to include all esters, ethers and salts, including all steroisomeric forms, and also preparations or products.

The ACMD would recommend that the Department of Health make appropriate provisions for public health information, including reviewing the information on FRANK in light of this report with regard to methoxetamine.

Yours sincerely,

Professor Les Iversen

Cc:
Minister for Public Health