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ORIGINAL ARTICLE

Understanding the availability, prevalence of use, desired effects, acute toxicity and dependence potential of the novel opioid MT-45

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Introduction. 1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine (MT-45) is a novel psychoactive substance available over the Internet. MT-45 is an opioid-like compound. This study provides an overview of availability, use and desired and unwanted effects of MT-45 through triangulation of available data sources. *Methods*. Searches of the published scientific literature and 'grey' information sources, using the keywords 'MT 45', 'MT-45' and '1-cyclohexyl-4-(1,2-diphenylethyl)piperazine' were undertaken in June 2014 to identify information on the availability, prevalence of use and desired/unwanted effects of MT-45. In addition an Internet snapshot survey in English was undertaken in May 2014 to determine the availability and cost of MT-45. *Results.* In June 2014 we were unable to identify any studies reporting the prevalence of use of MT-45. The Internet snapshot study identified 17 Internet sites selling MT-45. Information on price was available from 9 sites, with the mean price of MT-45 decreased with increasing purchase amounts from US$57.60 ± 19.37 per gram for a 1-g purchase to US$3.36 ± 1.83 per gram for a 1-kg purchase. We identified one published scientific paper reporting on the acute harms in nine cases of analytically confirmed MT-45 toxicity, one US government report relating to two MT-45-related deaths and 20 user reports on Internet discussion forums relating to the use of MT-45. All these suggest that the desired and unwanted effects of MT-45 are similar to those seen with other opioids, and that the opioid-like unwanted effects may be reversed with the opioid antagonist naloxone. There were user reports of MT-45 being used in heroin withdrawal and of 'withdrawal symptoms' after use, suggesting that long-term use may be associated with dependency as seen with other opioids. *Conclusions.* Combining published scientific literature and 'grey' information sources, we have demonstrated that MT-45 has opioid-like desired and unwanted effects. Whilst the information is limited at the moment, it has the potential to have similar dependence liability to other opioids.

Keywords Recreational drugs; Novel psychoactive substance; Toxicity; MT-45

Introduction

There has been a significant change in the pattern of recreational drugs available and used in the last decade with increasing availability of novel (new) psychoactive substances (NPS) in areas such as Europe, North America and Australasia.[1,2] Whilst many of the NPS are stimulants (e.g. cathinones and phenylethylamines) and synthetic cannabinoids, more recently there has been evidence of availability of a range of different synthetic opioids.[3] In 2012–13 there were reports on the availability of the synthetic opioid 3,4-dichloro-N-[(1-dimethylamino)cyclohexylmethyl]benzamide (AH-7921) in Europe with associated cases of acute intoxication and deaths related to its use.[3] As a result the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) undertook a formal European-level risk assessment of AH-7921 in April 2014, and in September 2014 the European Commission recommended European-wide control of AH-7921 under appropriate control measures in each European country.[4]

1-Cyclohexyl-4-(1,2-diphenylethyl)piperazine (also known as 'MT-45') is a substituted piperazine. It was investigated as an opioid analgesic in the 1970s by the Dainippon Pharmaceutical Company in Japan.[5] Its pharmacological properties have been studied in mice, rats and rabbits *in vitro* and *in vivo*, and these studies suggest that although it has 'opioid like' properties, its mechanisms of action are not fully understood and it is likely to have actions at both opioid and non-opioid receptors.[5–11] There have been no formal studies in humans assessing MT-45 as a potential analgesic or to determine its pharmacology.

MT-45 was first reported as an NPS through the Early Warning System of the European Monitoring Centre for Drugs and Drug Addiction further to detection in Sweden in December 2013.[12] When a new NPS becomes available there is often little information available on the prevalence

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of use or potential for toxicity associated with the NPS. It is therefore necessary to use a process often referred to as data triangulation, to bring together information from a range of sources from both the scientific and 'grey' literature, along with data from Internet snapshot surveys, to understand the patterns of availability and use, desired effects and adverse (unwanted) effects of new NPS.[13–22] The aim of this paper is to bring together the published scientific and 'grey' information sources, through the process of data triangulation, to be able to further understand MT-45 as potential NPS.

Methods

The following searches were undertaken in June 2014 to identify information on the prevalence of use, desired effects associated with using MT-45 and its adverse effects:

Published scientific literature

PubMed and MEDLINE were searched using the Keywords: 'MT 45', 'MT-45' and '1-cyclohexyl-4-(1,2-diphenylethyl)piperazine'. In addition, abstracts of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) and North American Congress of Clinical Toxicology (NACCT) meetings from 2010 to 2014 were searched using the same keywords.

Grey information sources

Using the same keywords, the Internet search engine Google and online drug discussion forums Erowid, Bluelight.org, Drugs Forum, Shroomery.org and Ukchemicalresearch.org were searched in May 2014.

Relevant information on the prevalence and pattern of use, desired effects and/or adverse effects were extracted from identified published papers, meeting abstracts and grey information sources. Extracted information was then collated to extract relevant themes.

MT-45 internet snapshot study

To supplement the above information searches an Internet snapshot survey was undertaken in English in June 2014, using the EMCDDA methodology for the availability and pricing of MT-45.[21,22] The internet search engines google.co.uk and google.com were both searched using the term 'buy MT-45'. Using the EMCDDA methodology, the first 100 sites identified were fully reviewed to understand their content and then sampling continued until 20 successive unrelated sites were identified. Data were extracted by the authors from each unique identified website, where this was available without registration, on (i) country of origin; (ii) purchase amounts available and (iii) cost for those amounts. To allow comparison across different purchase quantities and countries, the cost of different purchase amounts of MT-45 were converted into cost per gram, and the currency was standardised to US dollars using the European Commission Financial Programming and Budget online conversion tool (http://ec.europa.eu/budget/contracts_grants/info_contracts/inforeuro/inforeuro_en.cfm).

Results

Scientific and grey literature searches

We identified 20 user reports on Internet discussion forums relating to the use of MT-45, one published scientific paper reporting on the acute harms following MT-45 use, one US government report relating to two MT-45-related deaths and the EMCDDA-Europol joint report on MT-45.[23–28]

MT-45 prevalence and patterns of use

In June 2014, we were unable to identify any population or sub-population studies that have reported on the prevalence of use of MT-45. The most commonly reported route of use of MT-45 in the user reports is oral ingestion (13 user reports); nasal insufflation (4 reports), inhalation (2 reports) and rectal insertion (1 report) were less common.[23–25] One oral ingestion report related to 'parachuting' (wrapping in toilet paper prior to ingestion) of MT-45; this is similar to 'bombing' as seen with mephedrone.[23,29] Of the nine cases of acute toxicity in Sweden, routes of use were reported in six patients: oral ingestion (2 cases); nasal insufflation (1 case); combined nasal insufflation and intravenous injection (1 case); combined oral ingestion and rectal insertion (1 case); and oral ingestion or intravenous injection (1 case).[26]

Using information compiled from Internet discussion forums, oral doses of MT-45 ranged from 20 to 500 mg, although the majority of users reported limiting the dose to less than 100 mg.[23–26] Nasal insufflation doses ranged from 1 to 50 mg; users reported using smaller doses initially either to 'test the scent' or as an 'allergy dose'.[23–25] The one report of rectal use of MT-45 was by insertion of '80 mg of MT-45 salt as the solution'.[23] Limited information was available from three cases of acute toxicity, although the dose amounts (60–100 mg) in these cases were similar to those reported by users in the Internet discussion forums.[23–26]

Four reports on the Internet discussion forums related to co-use of MT-45 with other recreational drugs, alcohol or NPS.[23–25] These included cannabis (3 reports), intramuscular ketamine (1 report), and methoxetamine and alcohol (1 report). Only one user stated the reason for co-using MT-45 with cannabis: the MT-45 was taken to 'accentuate the high from cannabis as it did not have sufficient effect on its own'. In the cases of acute toxicity, five (55.6%) reported use of MT-45 only.[26] Of those who reported using MT-45 with one or more other substance, these included MT-45 used in combination with (i) alcohol; (ii) oxycodone; (iii) 'benzofurans', flubromazepam, pyrazolam and alpha-pyrrolidinopentiophenone; and (iv) methiopropamine and phencyclidine (PCP).

MT-45 internet snapshot

We identified 17 sites selling MT-45 in powder form using the Internet snapshot methodology; 16 were common to both the 'google.co.uk' and 'google.com' searches, and one was identified by the 'google.com' search only. The country of origin was reported on the Internet site as follows: China – 8; Canada – 2; Germany – 1; India – 1 and Sweden – 1; it was not possible to identify the country of

origin for 4 Internet sites. Nine Internet sites had no information directly available on cost and this was only available to registered users and/or on request. Of the eight Internet sites where information was available on cost, six were selling in dollars (assumed to be US dollars, although not explicitly stated), one in Euros and one in Swedish Krona. MT-45 was for sale in amounts ranging from 500 mg to 5 kg. The mean price of MT-45 decreased with increasing purchase amounts from US$ 57.60 ± 19.37 per gram for a 1-g purchase to US$ 3.36 ± 1.83 per gram for a 1-kg purchase (Fig. 1).

Desired and unwanted effects

There have been no formal human studies investigating the pharmacodynamics and/or the desired/adverse effects related to the use of MT-45.

From the user reports, the onset of desired effects following nasal insufflation occurred within 15 min, with a duration of action of 150–180 min.[23–25] With oral ingestion, onset of desired effects occurred between 25 and 400 min, with a duration of action of 300–630 min.[23–25] Some users reported a 'threshold' oral dose of 25–30 mg for the desired effects.[23–25] Interestingly, there appeared to be no relationship between oral dose used and time to onset of desired effects (Fig. 2).

The most common desired effects by users on the Internet discussion forums include getting a 'high', feeling sedated, euphoria, feeling of 'warmth', feeling 'trippy', having a sense of well-being, 'quietness of mind', feeling 'drunk', disorientated or 'zoned out' and 'being relaxed'.[23–25] Specific user comments relating to the desired effects included 'getting a mellow buzz but one that lacked the opiate euphoria'; 'feeling a strange mixture of simultaneous peace and irritation'; and 'mostly felt like a dissociative but was pretty mild'.[23–25] Users reported that they took MT-45 as it was perceived to have 80% of the activity of morphine.[23] Some users reported that a specific desired property of MT-45 was its long half-life and the duration of desired effects which often last up to 12 h.[23,24]

Similar to other NPS, there were specific unwanted effects associated with the route of use, with 'nasal burn' and 'nasal drip' reported after nasal insufflation and a 'bitter taste' after oral ingestion.[23] Information from the Internet discussion forums suggest that other unwanted effects include itchiness, dizziness, nausea, vomiting, insomnia, respiratory depression, inco-ordination, muscle twitches, anxiety, sweating and disorientation.[23–25] Users also reported 'withdrawal symptoms' after use, including restlessness, dehydration and 'feeling hungover', which they described as 'similar to the low after taking MDMA'.[23–25] As noted above in relation to the long duration of desired effects, the reported duration of unwanted effects was up to 12 h.[23] In addition, there were concerns raised in the discussion forums about the strong urge to re-dose when coming down from the MT-45 high, with an associated increase in the risk of overdose.[25]

Interestingly, many users thought on balance that MT-45 was not a desirable recreational drug and therefore would not buy it again.[23–25] This was because of a combination of lack of euphoric effect, numerous unwanted effects and the apparent high cost of MT-45.[23]

Published cases of acute toxicity

The STRIDA project, a collaborative project between the Karolinska University Laboratory, the Karolinska Institutet and the Swedish Poisons Information Centre reported that they had had 'several' cases of acute toxicity related to the use of MT-45 between November 2013 and February 2014, of which nine had analytical confirmation of MT-45 use.[26] Toxicological screening, done up to 3 days

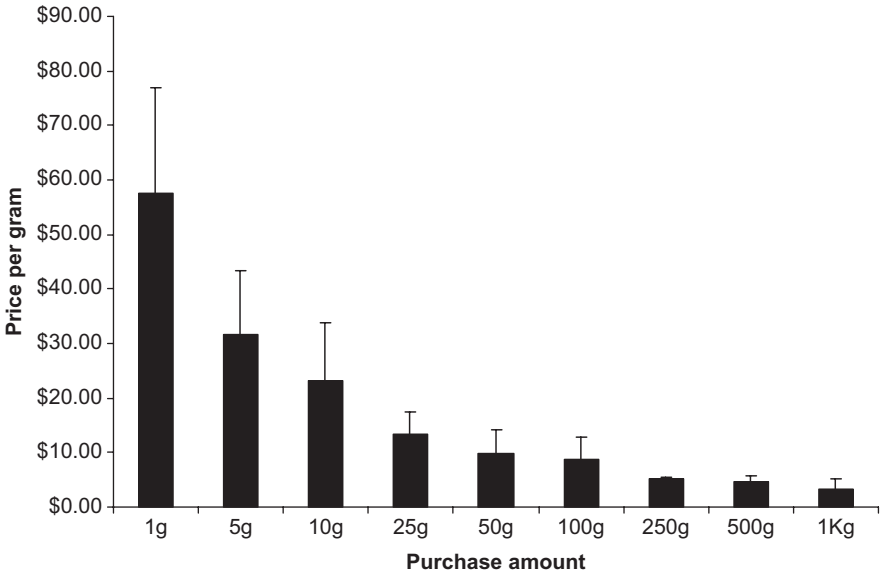

Fig. 1. Mean ± standard deviation price per gram (standardised to US$) for different purchase amounts of MT-45 from an Internet snapshot survey in June 2014.

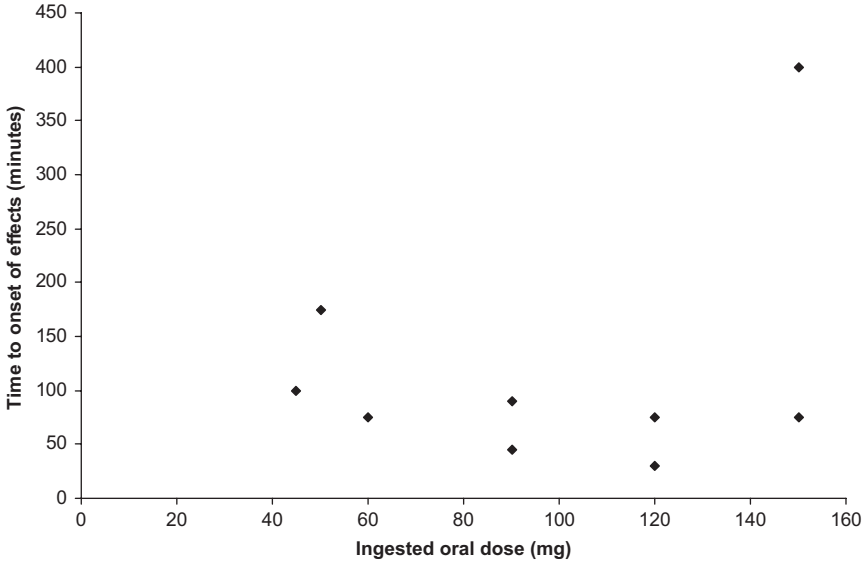

Fig. 2. Time to onset of symptoms following oral use of MT-45 as self-reported by users.

after admission to hospital, demonstrated blood and urine MT-45 concentrations of 6–157 ng/mL and 0–221 ng/mmol of creatinine respectively. Urine toxicological screening was positive for MT-45 only in four cases; other drugs detected in combination with MT-45 were (i) cannabis, dextromethorphan and methiopropamine; (ii) cannabis and pyrazolam; (iii) 3-methoxy-PCP; (iv) cannabis and flubromazepam; and (v) 3-methylmethcathinone and pyrazolam. The majority of clinical features on presentation to hospital were like that of opioid [reduced level of consciousness or coma (7 cases), reduced respiratory effort, oxygen saturation or cyanosis (7 cases) and miosis (3 cases)]. Single or repeated boluses of naloxone were administered to seven patients (total doses: 0.1–2.0 mg, with four (57%) of patients reported to have 'responded well'; only one patient was intubated for failing to respond to naloxone treatment, although he was only administered a total of 0.4 mg). The other reported clinical features included neurological disturbances (paraesthesia or weakness) (3 cases) and hearing impairment or loss (3 cases); limited information is available on the degree and/or duration of hearing loss, but in one of these three patients it 'persisted also after 2 weeks'.

Deaths related to MT-45 use

At the time of the published literature searches, there had been no deaths published in the scientific literature attributed directly to the use of MT-45 or where it has been detected in post-mortem samples. We were able to identify two deaths in the United States reported by the US Department of Homeland Security through its Immigration and Customs Enforcement's Homeland Security Investigations.[27] They reported that a man and a woman in Hamburg, New York were found dead in August 2013 and that subsequent autopsies confirmed that they 'died of acute intoxication from MT-45, an opioid analgesic drug, and ethanol'. There was no other information provided, and therefore it is not possible to determine the significance of either the MT-45 or ethanol detected at post-mortem, and their contribution to the deaths.

In addition, Sweden has reported to the European Monitoring Centre for Drugs and Drug Addiction 21 deaths in males aged 19 to 43 deaths between November 2013 and April 2014 where MT-45 has been detected in post-mortem toxicological analysis.[28] The post-mortem concentrations of MT-45 ranged from 0.006 to 1.9 microgram/gram of femoral blood. In 17 cases at least one other 'psychoactive substance' was detected, including recreational drugs (e.g. cannabis and amphetamine), novel psychoactive substances (e.g. 2-aminoindane, ethylphenidate, methiopropamine and 4,5 or 6-(2-aminopropyl)-2,3-dihydrobenzofuran [ADPB]) and/or prescription medicines (e.g. codeine, tramadol, diazepam, quetiapine, sertraline, gabapentin, alprazolam, morphine, mirtazapine and fentanyl). In 6 of the deaths a novel benzodiazepine not currently licenced for use in the European Union was detected; flubromazepam was detected in 5 deaths and pyrazolam was detected in 3 deaths. Nineteen of the deaths had a cause of death determined by the time of the publication of the EMCDDA-Europol Joint report: MT-45 was determined to be the cause of death in eight; the others were determined to be mixed intoxication (8 deaths), pneumonia and intoxication (2 deaths) and injury (1 death). Of note, of the eight deaths where MT-45 was determined to be the cause of death, in three an opioid and/or a benzodiazepine were detected: (i) oxycodone and flubromazepam; (ii) codeine (with gabapentin, methiopropamine and 2-aminoindane) and (iii) diazepam and alprazolam (with gabapentin, venlafaxine, alimemazine, carbamazepine and levopromazine).

Discussion

MT-45 was first detected and reported through the EMCDDA Early Warning System from Sweden in December 2013. Currently there is no information on the prevalence of use of MT-45; however, it appears to be available for purchase from a similar number of Internet-based suppliers to other NPS such as methiopropamine, alpha-

methyltryptamine (AMT), diphenylprolinol (D2PM) and desoxypipradrol (2-DPMP) at the time of their emergence as NPS.[15,30,31]

In our Internet snapshot survey we were able to identify 16 Internet sites reporting to sell MT-45 from Europe, Canada, India and China; this compares to 12 Internet sites from the same geographical regions identified by the EMCDDA in their joint report (date Internet snapshot survey undertaken was not reported).[28] The amounts for sale were comparable between the two Internet snapshot surveys: 500 mg to 5 Kg in our survey and 1 g to 5 Kg in the EMCDDA Internet snapshot survey. Similar to the previous Internet snapshot studies reporting the availability and cost of AMT, D2PM, 2-DPMP and 4,4'-dimethylaminorex (4,4'-DMAR), bulk purchase of MT-45 in quantities more likely to be 'dealer amounts' rather than 'user amounts' was associated with a substantial reduction in the price per gram.[15,30–32] The country of origin of Internet suppliers for MT-45 was most commonly China; this differs from that seen with methiopropamine where China was the location for only one supplier and 4,4'-DMAR where China did not appear to be the location of any of the Internet suppliers identified.[31,32] Interestingly no suppliers appeared to be in the UK, compared with methiopropamine in June 2014 where 28 of 32 the Internet sites for which location was available were UK-based.[31] The price of MT-45 from Internet suppliers is comparable to that for other recent NPS, for example approximately US$29 per gram for a 500-mg purchase of methiopropamine and approximately €36 per gram for an 1-g purchase of 4,4'-DMAR.[31,32] Since reported user amounts of these NPS (5–300 mg for methiopropamine and 10–200 mg for 4,4'-DMAR) are comparable to those for MT-45 (20–500 mg in this study), it would suggest that the overall price of MT-45 is comparable to other NPS.

There have been several *in vitro* and *in vivo* studies in mice, rats and rabbits investigating the pharmacology of MT-45.[5–11] The analgesic properties of MT-45 have been demonstrated to be comparable to morphine following both subcutaneous and oral administration in mice, rat and guinea pig *in vivo* models.[5–11] There are some data from *in vitro* and *in vivo* studies that demonstrate that MT-45 has actions at not only μ opioid receptor, but also at δ and κ opioid receptors and at non-opioid receptors (sigma-1 and sigma-2 receptors).[8,10,11] Overall these studies suggest that in addition to having opioid-like activity, MT-45 has additional pharmacological activity. The data from Internet discussion forums suggest that both the desired and unwanted (or adverse) effects of MT-45 are similar to that seen with opioids. In addition, the pattern of reported clinical features seen in the cases of acute toxicity related to MT-45 use were predominately opioid-like, and a proportion of these responded to use of the opioid antagonist naloxone.[26] Finally, there are some data from the previous animal studies suggesting that MT-45 may have a dependence potential and that MT-45 may be a substitute for morphine in morphine-dependent animals.[6,8] There are reports on the Internet discussion forums of 'withdrawal symptoms' following use of MT-45.[23] Additionally, one user reported that he took MT-45 to treat his heroin withdrawal symptoms as it was easily available and its legality was a 'grey area', supporting the limited animal data that MT-45 may be able to substitute other opioids.[23]

It is noteworthy that in the cases of acute toxicity, benzodiazepines not licenced for use in the European Union (pyrazolam and flubromazepam) were detected on urine toxicological screening, suggesting that these users had also been using novel benzodiazepines. Similar to the published cases of acute toxicity from Sweden, the same novel benzodiazepines were detected in six deaths reported from Sweden to the EMCDDA (flubromazepam in five deaths and pyrazolam in three deaths).[28] In addition, a range of other sedatives including opioids (e.g. codeine, fentanyl, morphine, oxycodone and tramadol), benzodiazepines (alprazolam, diazepam and diclazepam) and/or ethanol were detected.[28] The use of MT-45, an opioid-like compound, with novel benzodiazepines and/or other sedatives (users also reported combining use with alcohol and oxycodone), may increase the risk of acute toxicity and/or death, particularly a reduced level of consciousness and associated respiratory depression, and complicate the management of this neurological compromise. There is also an important public health message here to users of NPS, such as MT-45, about the potential risk of inadvertent toxicity related to polydrug use by combining with other drugs and/or alcohol.

Using published scientific and 'grey literature' sources, along with Internet snapshot methodology, is a relatively new technique to understand the pattern of availability and use and the acute harms of an individual NPS. There are a number of limitations to this. The limitations of the Internet snapshot methodology are more clearly understood, in that the actual products identified are not purchased to know whether they do in fact contain the NPS of interest.[31,32] With the searches of the published scientific and 'grey literature' sources, no standardised searching methodology has currently been described. For example, it is possible that data on prevalence of use or acute toxicity may be presented at a range of different scientific, medical or social science meetings, so it is possible that relevant data may not be found if the scientific meeting abstract reviews are not comprehensive enough. Additionally, for most of these types of studies, the searches are undertaken in English only; it is possible that relevant data may be published in other languages. Future work needs to consider how these types of studies can be standardised to allow greater comparison of results between individual NPS studied.

Conclusions

Over the last few years, bringing together data from different sources each with their own limitations, through a process known as data triangulation, has been used to enable a better understanding of an NPS, whilst minimising the limitations from each of the individual sources.[4,13–15,33] Using these techniques, we have demonstrated that MT-45 has opioid-like desired and unwanted effects. Whilst the information is limited at the moment, it has the potential to have similar dependence liabilities as other opioids. This will be useful not only to law enforcement and legislative authorities considering whether MT-45 should be controlled, but also to clinical/medical toxicologists managing patients using MT-45 to enable them to provide appropriate targeted advice

and information about the potential for dependence associated with its long-term use.

Declaration of interest

PID is a member of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Scientific Committee and the UK Advisory Council on the Misuse of Drugs; DMW is an expert advisor to the EMCDDA and a co-opted member of the UK Advisory Council on the Misuse of Drugs.

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