ACMD

Advisory Council on the Misuse of Drugs

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Rt. Hon. Mike Penning MP
Minister for Policing, Crime and Criminal Justice,
Home Office
2 Marsham Street
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18th November 2015

Dear Minister,

I am writing to recommend that you lay a temporary class drug order (TCDO) pursuant to section 2A of the Misuse of Drugs Act 1971 on N-methyl-1-(thiophen-2-yl)propan-2-amine, ('methiopropamine' or MPA).

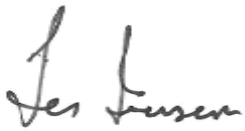
This material is currently being marketed as a New Psychoactive Substance, often in combination with ethylphenidate and there have been a number of deaths associated with this compound. In 2014, 7 cases had been reported where MPA was implicated in death, albeit in combination with a variety of other NPS.

Methiopropamine
N-methyl-1-(thiophen-2-yl)propan-2-amine (MPA) is a stimulant NPS which is similar in structure to methamphetamine but having a thiophene ring rather than a phenyl ring. Iversen et al (2013) reported that MPA was a potent inhibitor of the dopamine and norepinephrine transporters *in vitro*, with no effect on serotonin transporters. This would explain its use as a stimulant drug and demonstrates its pharmacological similarity with the amphetamine class of stimulant drugs. There do not appear to be any *in vivo* studies with this compound to study its amphetamine-like profile.

The attached report contains the ACMD's consideration of the evidence concerning MPA.

In providing this advice I would like to convey my thanks to Police Scotland and the National Programme on Substance Abuse Deaths (NPSAD).

Yours sincerely,



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Minister for Public Health, Scotland
Minister for Health, Social Services & Public Safety, Northern Ireland

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Methiopropamine (MPA): A review of the evidence of use and harm

Background

1. Methiopropamine (MPA) has been visible on the NPS market since 2011; however recent reports suggest an increase in use, particularly by injection, following the Temporary Controlled Drug Order (TCDO) of April 2015 on methylphenidate-based NPS. This proliferation in use and an increasing number of associated deaths and harms related to MPA use has led the Advisory Council on the Misuse of Drugs (ACMD) to consider a TCDO on MPA.

Chemistry and Pharmacology

2. MPA is a thiophene analogue of methamphetamine, originally synthesised in 1942[1]. Its IUPAC name is N-methyl-1-(thiophen-2-yl)propan-2-amine. Other chemical names include methylthienylpropamine and methedrene[2] *(see Annex A, Figure 1).*

3. The hydrochloride salt form of MPA is a crystalline powder at room temperature[1].

4. Iversen et al. (2013) reported MPA to be a potent inhibitor of dopamine and norepinephrine transporters *in vitro*, with no effect on the serotonin transporters[5]. There do not appear to be any *in vivo* studies with this compound to confirm its amphetamine-like profile.

Prevalence of Use

5. MPA was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) following an alert in January 2011 by Finland[6].

6. MPA seizures have since been reported to the EMCDDA[6] by the UK, Spain, Croatia, Germany, Romania, Italy, Lithuania, Denmark, Poland, Belgium, Hungary, Bulgaria, Slovenia, Norway, Czech Republic, Sweden, France and Finland. The World Health Organisation has also noted seizures in North America and Canada[1].

7. Data from the National Crime Agency[7] shows there have been 45 seizures of MPA between April and June 2015.

8. FRANK[8] has received 29 queries in relation to MPA during the period October 2014- September 2015.

9. MPA use has been detected in the UK, in pooled anonymous urine samples collected in street urinals in London since 2012[9]. In a more recent study from

April 2014[10], MPA was detected in pooled anonymous urine samples collected in London, Newcastle and Birmingham.

10. The UK's Forensic Early Warning System's (FEWS) collection plans detected 86 occurrences of MPA in 2013/14 and 65 occurrences in 2014/15, mostly from headshop collection plans (*see Annex B)*[18].

11. An Internet snapshot study performed in June 2013[11] confirmed that MPA was widely available from Internet sites selling NPS. Of 62 sites identified (of which half could be located), 45% of suppliers appeared to originate from the UK. The cost of MPA decreased with increasing purchase amount (£19.49 ± 0.15 per gram for 500 mg to £3.54 ± 0.13 per gram for 1 kilogram).

12. The National Poisons Information Service (NPIS)[20] reported 450 accesses to the TOXBASE entry for MPA: 236 during 2014 and 214 during 2015 (between 1st January and 26th October 2015).

13. The NPIS have also reported telephone enquiry data (1st January 2011 to 27th October 2015). Over this period, there were 94 cases (65 males, 19 females, 10 not recorded) discussed with NPIS where there had been reported exposure to MPA or a product previously shown to contain MPA as a major ingredient. Of these, 7 involved MPA alone, 41 a single MPA-containing product and 46 reported use of other substances in addition. The median age of exposed cases was 31 years (range 17-64 years).

14. MPA is reportedly taken orally, by inhalation, snorting, administering rectally, and by injecting, with the dosage ranging between 5-60 mg depending on the route of administration[4]. The onset of effects vary depending on the route of administration and generally last between 2-4 hours but can persist for up to 24 hours.

15. In Scotland, MPA injecting has reportedly replaced ethylphenidate injecting as the drug of choice following the TCDO on methylphenidate-based NPS, with reports of associated mental health issues, hospital admissions and public space needle discards[12].

16. MPA is manufactured clandestinely with distribution and trafficking facilitated mainly via the Internet[1].

17. MPA has been seen under the following brand names (not exhaustive): Ivory Dove Ultra, China White, Walter White, Quick Silver Ultra[3], Bullet, Mind Melt, Pink Panthers, Poke, Rush, Snow White[4].

Polysubstance Use

18. MPA has been seen in branded packages in combination with ethylphenidate, 5-MeO-DALT, N-methyl-2AI as well as adulterants such as lidocaine, benzocaine and caffeine[3].

19. 'Synthacaine' (a synthetic substance that purportedly mimics the effect of cocaine) has been found to contain MPA amongst varying other substances[3, 14].

20. Other branded combinations include: Charley Sheen (MPA and 2-AI), Go Gain (MPA and ethylphenidate).

21. The brand name and the corresponding contents can vary, with the same branding being used for different drugs/combinations[14].

Acute Harm

22. Users report similar effects to other stimulants such as MDMA, amphetamine and cocaine: stimulation, alertness and an increase of energy and focus; with adverse effects reported by users including tachycardia, anxiety, panic attacks, sweating, headaches, nausea, difficulty breathing, vomiting, difficulty urinating and sexual dysfunction[1].

23. The United Kingdom first issued alerts in 2012[6] when the national Focal Point reported three cases involving deaths associated with this substance. The first alert (January 2012) concerned two cases; the first involved a 'legal high' product known as 'Blow' that was suspected to have been snorted. Chemical analysis of the powder and post-mortem results both confirmed the presence of MPA, methylenedioxyaminoindane (MDAI), lidocaine, and caffeine, with MPA found in greater concentrations; in the second case, both MPA and methoxetamine were detected. The information from this case suggested that a 'legal high' product called 'China White' had been snorted by the deceased. The second alert (September 2012) related to a case where MPA was detected in post-mortem blood along with oxycodone, temazepam, venlafaxine and its metabolite O-desmethylvenlafaxine. The deceased was found collapsed with no other significant post-mortem findings.

24. The National Programme of Substance Abuse Deaths[16] (NPSAD) reported 30 cases where MPA was found in post mortem toxicology, between 2012 and 2015. In 22 of these, MPA was implicated in the cause of death *(see Annex A, Table 1)*.

25. The EU-MADNESS Project[19] reports that there had been no deaths involving MPA registered in Northern Ireland by the end of June 2015, but during the same period in Scotland, 8 deaths were registered where the substance was recorded in the cause of death, and 7 cases where it was found in post mortem toxicology *(see Annex A, Table 2).*

26. There is one published case[15] of analytically confirmed acute MPA toxicity in a patient who presented with mild stimulant toxicity: a 27-year-old woman presented to the Emergency Department (ED) 21 hours after oral ingestion of 'Hawaiian baby woodrose seeds' and nasal insufflation of 50 mg of 'Quicksilver' powder. On arrival in the ED she had nausea and dizziness and reported having had difficulty sleeping, intermittent palpitations and chest tightness. On examination she was agitated with dilated pupils but had a normal heart rate, blood pressure and temperature. She received a 5 mg dose of oral diazepam and intravenous fluid replacement. Her symptoms settled and she was discharged with no sequelae 16 hours after ED presentation. Toxicological screening detected MPA at a concentration of 400 ng/mL and two MPA metabolites (N-desmethyl- and hydroxy N-desmethyl-MPA), and ergonovine (concentration <10 ng/mL) a compound present in members of the Hawaiian baby woodrose family. A number of other substances were also detected: morphine 100 ng/mL; and metabolites of the synthetic cannabinoids JWH-018 and JWH-019 (concentrations <5 ng/mL). As other drugs were present in the body, it was not possible to determine the exact role of MPA in this case, however MPA was found in the greatest concentration and in the opinion of the treating clinicians, was likely to be responsible for the effects seen.

27. Hospital admissions for MPA have been reported in the US and in Europe, with clinical features including anxiety, paranoia and vomiting[1].

28. One fatal case was reported in Sweden[1], where the concentration of MPA was 1.4 μg/g in femoral blood. Twenty-one non-fatal cases were also reported in Sweden in 2013.

Chronic Harm

29. As MPA has reportedly only been in use since 2011, there are no data available on any chronic harms.

International Data

30. MPA is controlled in Denmark, Estonia, Germany, Hungary, Portugal, Slovenia, Sweden, Turkey, Republic of Belarus and China[6]. MPA is controlled in the US state of Florida and could be considered under the Analog Act 1986, as an analogue of methamphetamine, a Schedule II substance in the US Controlled Substance Act.

Legitimate Use

31. The Medicines and Healthcare products Regulatory Agency (MHRA) has not found any evidence of any past or present legitimate medicinal use for MPA[17].

Recommendation

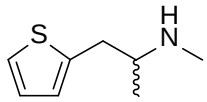
32. The ACMD has reviewed the evidence and, pursuant to Section 2B(6) of the Misuse of Drugs Act 1971, it considers that, in the case of the N-methyl-1-(thiophen-2-yl)propan-2-amine ('methiopropamine' or MPA), it is a drug that is being, or is likely to be, misused, and that misuse is having, or is capable of having, harmful effects. The ACMD therefore recommends that N-methyl-1-(thiophen-2-yl)propan-2-amine (MPA) be subject to a Temporary Class Drug Order (TCDO).

33. The control of the compound should extend to include any stereoisomeric forms, any salts of such compounds and any preparation or product containing such compounds.

34. The Council has found no evidence that N-methyl-1-(thiophen-2-yl)propan-2-amine (MPA) has a recognised medicinal use and therefore advise that it is treated as a Schedule 1 drug in applying the provisions of the Misuse of Drugs Regulations (as amended).

Annex A

***Figure 1**: Structure of Compound recommended for control under a TCDO*



N-methyl-1-(thiophen-2-yl)propan-2-amine (MPA)

***Table 1**: MPA entry on deaths involving Novel Psychoactive Substances and resurging substances reported to the NPSAD*

Found in post mortem toxicology				**Implicated in cause of death**			
2012	*2013*	*2014*	*2015*	*2012*	*2013*	*2014*	*2015*
6	8	13	3	4	5	12	1

***Table 2**: MPA mentions in deaths in Scotland collated by the EU-MADNESS Project until end June 2015. None reported in Northern Ireland.*

Found in post mortem toxicology			**Implicated in cause of death**		
2013	*2014*	*Q1 & Q2 2015*	*2013*	*2014*	*Q1 & Q2 2015*
1	4	2	2	5	1

Annex B – Number of Occurrences of MPA in FEWS collection plans (2011-2015)

2011 Collection Plan

Collection Plan	Number of Occurrences
Web survey	1
Headshop	0
Festival (combined)	1
Police custody	2
Fast parcel	6

2012-13 Collection Plan

Collection Plan	Number of Occurrences
Web survey	34
Headshop	9
Festival	1
Fast Parcel	11
pooled urine	3

2013-14 collection plan

Collection Plan	Number of Occurrences
Web survey	22
Headshop	62
Festivals	2

2014-15 collection plan

Collection Plan	Number of Occurrences
Headshop	59
Festivals	4
Prisons	1
Police seizures	1

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19. EU-MADNESS Project, University of Hertfordshire and St George's University of London (November 2015), *Northern Ireland and Scotland (Registered until end of June 2015).*

20. The National Poisons Information Service (NPIS) (October 2015), *TOXBASE entry for MPA.*