

ACMD

Advisory Council on the Misuse of Drugs

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Sarah Newton MP
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16 June 2017

Dear Minister,

Re: Further advice on Methiopropamine

In November 2015, the ACMD recommended that the Novel Psychoactive Substance, methiopropamine (MPA), be placed under a Temporary Class Drug Order.

MPA is a synthetic drug of abuse which is similar in structure to amphetamine and often marketed as a 'legal alternative' to cocaine, often in concoction with other stimulant drugs. The ACMD's advice concerned an apparent increase in the harms associated with the use of MPA, particularly related to its potential intravenous injection.

In September of last year, my predecessor Professor Les Iversen wrote to the then minister for Preventing Abuse, Exploitation and Crime, requesting that the TCDO be re-laid for a further year (to expire 26 November 2017) to allow the Council time to gather and consider more evidence to make a substantiated recommendation in relation to its permanent control under the Misuse of Drugs Act 1971.

I am now pleased to enclose the ACMD's further advice on methiopropamine 'MPA'.

The ACMD recommends that methiopropamine (MPA) is placed in Class B of the Misuse of Drugs Act 1971 (as amended) and Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended), as the ACMD found no legitimate medicinal use of this substance.

Yours sincerely

A handwritten signature in black ink, appearing to read 'Owen Bowden-Jones', written in a cursive style.

Dr Owen Bowden-Jones
Chair of ACMD

ACMD

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

Further advice – June 2017

Background

1. In November 2015, the ACMD recommended Methiopropamine (MPA) be subject to a Temporary Class Drug Order (TCDO). This advice concerned the possible displacement to MPA from ethylphenidate following the TCDO on methylphenidate-related NPS in March 2015. This proliferation in use and an increased number of associated deaths and harms, as well as its potential intravenous use, led the ACMD to advise urgent control.
2. In September 2016, the ACMD heard reports that the prevalence and problematic use related to MPA had abated. This led the ACMD to advise that the TCDO be re-laid for a further year, as an appropriate and effective level of control, whilst the council gathered more evidence to consider recommending full control under the Misuse of Drugs Act 1971.

Chemistry and Pharmacology

3. MPA (*see Appendix, Figure 1*) is a thiophene analogue of methamphetamine, originally synthesised in 1942¹. Its IUPAC name is N-methyl-1-(thiophen-2-yl)propan-2-amine. Other chemical names include methylthienylpropamine, N, α -dimethyl-2-thiopheneethanamine and methedrene².
4. The hydrochloride salt form of MPA is a crystalline powder at room temperature¹.
5. Iversen et al. (2013) reported MPA to be a potent inhibitor of dopamine and norepinephrine transporters *in vitro*, with no effect on the serotonin transporters⁵. There do not appear to be any *in vivo* studies with this compound to confirm its amphetamine-like profile.
6. 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 administration⁴. 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.

Prevalence of Use

7. MPA was first reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) following an alert in January 2011 by Finland⁶.
8. MPA seizures have since been reported to the EMCDDA⁶ 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 Organization has also noted seizures in North America¹.

9. The National Crime Agency⁷ reports 105 seizures of MPA submitted for forensic analysis in 2015- 2016, comprising 1.48 kilograms of powder and 1468 tablets.
10. MPA use has been detected in the UK, in pooled anonymous urine samples collected in street urinals in London since 2012⁹. In a study from April 2014¹⁰, MPA was also detected in pooled anonymous urine samples collected in London, Newcastle and Birmingham. MPA was also detected recently in a pooled urine sample at 2016 Creamfields festival²².
11. The UK's Forensic Early Warning System's (FEWS) headshop collection plans reported 51 occurrences of MPA in 2015/2016, 17 of which were post-implementation of the TCDO²³ (*see Appendix, Table 3* for data from previous years).
12. Prior to control, MPA had been widely available from Internet sites selling NPS¹¹. 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).
13. The National Poisons Information Service (NPIS)²⁰ reported a total of 677 accesses to the TOXBASE entry for MPA between May 2012 and March 2017 (these peaked in the lead up to the TCDO).
14. There were also 101 telephone enquiries relating to MPA (1st January 2011 to 31st March 2017). Of these, 51 involved exposure to MPA alone and the remaining 50 reported use of other substances in addition. The most common reported products involved were Gogaine, Pink Panther, Purple Bomb and Pikey Dust, which had been identified as containing MPA (WEDINOS data).
15. The clinical effects reported by NPIS include predominantly tachycardia, chest tightness, anxiety and nausea, which is consistent with an amphetamine-type substance.
16. MPA is manufactured clandestinely with distribution and trafficking facilitated mainly via the Internet¹. Border Force seizure data reported a number of intercepted packages at Coventry International Postal Hub containing MPA between 2013-2015, ranging from 4 grams to 2 kilogram quantities²⁴.
17. MPA has been also seen under the following brand names (not exhaustive): Ivory Dove Ultra, China White, Walter White, Quick Silver Ultra³, Bullet, Mind Melt, Poke, Rush, Snow White⁴.

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 caffeine³.
19. ‘Synthacaine’ a substance designed to mimic the effects of cocaine and often termed ‘legal cocaine’ has been found to contain MPA amongst varying other substances. This has reportedly been sold on both the surface web and the dark web for prices 3-4 times lower than cocaine²⁶.
20. A patient admitted to a psychiatry ward reported acute anxiety crisis accompanied by a sense of imminent danger following consumption of ‘Synthacaine’. The patient reported intense fatigue and visual hallucinations as well as self harming related to body dysmorphia. MPA was identified as being present in this ‘Synthacaine’ sample as well as N-methyl-2-amino-indane, 2-amino-indane and lidocaine²⁵.
21. Other branded combinations include: Charley Sheen (MPA and 2-AI), Go Gain (MPA and ethylphenidate).
22. The brand name and the corresponding contents can vary, with the same branding being used for different drugs/combinations¹⁴.

Acute Harm

23. 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 dysfunction¹.
24. The United Kingdom first issued alerts in 2012⁶ 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.

25. The National Programme of Substance Abuse Deaths¹⁶ (NPSAD) reported 46 cases where MPA was found in post mortem toxicology, between 2012 and April 2017. In all of these occurrences, MPA was found in combination with other substances, mainly NPS.
26. MPA was implicated in the cause of death for 33 cases. MPA was found in combination with other substances in most instances. In the cases with only MPA implicated, the blood levels of MPA ranged from 0.74 micrograms per millilitre to 4.6 micrograms per millilitre (*see Appendix, Table 1*).
27. The EU-MADNESS Project¹⁹ reported that there had been no deaths involving MPA registered in Northern Ireland by the end of December 2015, but during the same period in Scotland, 10 deaths were registered where the substance was recorded in the cause of death, and a further 8 cases where it was found in post mortem toxicology (*see Appendix, Table 2*). Provisional data for 2016 death registrations in Scotland do not indicate the presence of MPA as being either implicated in the cause of death or being found in PM toxicology. Similarly, provisional data for Northern Ireland do not indicate the presence of MPA as being implicated in the cause of death.
28. Hospital admissions for MPA have been reported in the US and in Europe, with clinical features including anxiety, paranoia and vomiting¹.
29. There is a published case¹⁵ 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.

30. Another report²⁶ detailed the case of a 30 year old man who was admitted to a hospital emergency department having ingested 'Synthacaine'. The patient displayed symptoms of paranoid delusion, auditory and visual hallucinations and incoherent speech. Toxicological screening detected only the presence of MPA which was quantified. 13 hours after presentation to the emergency department, the plasma concentration of MPA was found to be 14 ng/mL.
31. One fatal case was reported in Sweden¹, 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

32. As MPA has reportedly only been in use since 2011, there are no data available on any chronic harm. However, the Scottish Drugs Forum²⁶ suggested that the extended use of MPA similar to other stimulant drugs are likely to result in symptoms including tiredness, weight loss and an increased risk of mental health issues such as paranoia, mood swings and low mood.

Social Harm

33. In Scotland, MPA injecting had reportedly replaced ethylphenidate injecting as the drug of choice following the TCDO on methylphenidate-based NPS. There were reports of associated mental health issues, hospital admissions and public space needle discards¹².
34. Updates from Police Scotland report that the instances of NPS injecting appears to have abated following the TCDO's on methylphenidate-related NPS and MPA in 2015.

International Data

35. MPA is controlled in Denmark, Estonia, Germany, Hungary, Poland, Portugal, Slovenia, Sweden, Turkey, Republic of Belarus and China⁶. MPA is controlled explicitly in some US states and could be considered under the Analog Act 1986, as an analogue of methamphetamine, a Schedule II substance in the US Controlled Substance Act.

36. At its 7th meeting, on 16 March 2017, the Commission on Narcotic Drugs decided to include MPA in Schedule II of the 1971 Convention²¹. This inclusion will require all signatories to the Convention to place appropriate controls on MPA.

Legitimate Use

37. The ACMD has consulted with our stakeholders in Annex 2 to determine whether there are legitimate uses of these substances. Based on the feedback from the consultation, the ACMD is not aware of any confirmed legitimate medicinal, industrial or commercial uses of MPA¹⁷.

Recommendation

38. 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 controlled as a Class B substance under the Misuse of Drugs Act 1971 (as amended).
39. 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.
40. The ACMD 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 also controlled as a Schedule 1 substance under the Misuse of Drugs Regulations 2001 (as amended).

Annex 1: Tables and figures

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

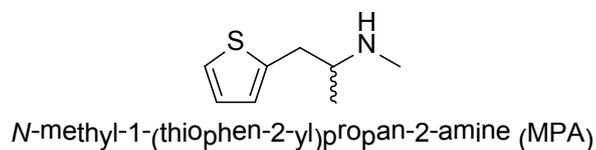


Table 1: MPA entry on deaths involving Novel Psychoactive Substances and resurging substances reported to the NPSAD

Found in post mortem toxicology					Implicated in cause of death				
2012	2013	2014	2015	2016	2012	2013	2014	2015	2016
4	8	16	13	5	3	5	15	6	4

(The data presented here are based on official notifications received by NPSAD up to 13th April 2017, submitted voluntarily by Coroners in England, Wales, Northern Ireland, the Isle of Man and the Channel Islands. Due to the procedures undertaken during an inquest, there is often a significant delay between the death occurring and the inquest being concluded, and as such we anticipate receiving more cases for 2016 and to a lesser extent 2015 and earlier years. No reports for MPA have been received for deaths prior to 2012. Data are submitted voluntarily by Coroners and as such there may be variable and incomplete geographic coverage, in particular for Wales where we no longer have majority coverage.)

Table 2: MPA mentions in deaths in Scotland collated by the EU-MADNESS Project until end December 2016. None reported in Northern Ireland.

Also found in post mortem toxicology				Implicated in cause of death			
2013	2014	2015	2016	2013	2014	2015	2016
1	4	3	0	2	5	3	0

(The data presented here do not duplicate those collated by NPSAD.)

Table 3: Number of occurrences of MPA in FEWS collection plans (2014-2015)¹⁸

2013-14 collection plan		2014-15 collection plan	
Collection Plan	Number of Occurrences	Collection Plan	Number of Occurrences
Web survey	22	Headshop	59
Headshop	62	Festivals	4
Festivals	2	Prisons	1
		Police seizures	1

Annex 2: Bodies contacted by the ACMD to check for legitimate uses (during consultation period 28 February – 15 March 2017)

- Medical Research Council (MRC)
- Department of Health
- Public Health England (PHE)
- Pistoia Alliance
- Office for Life Science (OLS)
- Department for Business, Energy and Industrial Strategy (BEIS)
- Medicines and Healthcare products Regulatory Agency (MHRA)
- The Academy of Medical Sciences (AMS)
- Association of the British Pharmaceutical Industry (ABPI)
- Health Research Authority (HRA)
- The Royal Society
- British Pharmacological Society (BPS)

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