ACMD

Advisory Council on the Misuse of Drugs

ACMD Report – A review of the evidence on the use and harms of Diphenidine and other related substances.

Contents

1. Introduction

1.1 The 43rd meeting of the World Health Organization Expert Committee on Drug Dependence reviewed the 1,2-diarylethylamines, diphenidine and methoxyphenidine (also referred to as methoxphenidine), in October 2020. [Expert Committee on Drug Dependence 2020a; Expert Committee on Drug Dependence 2020b]

1.2 Following this review, the 64th Commission on Narcotic Drugs (CND) meeting in April 2021 voted on the WHO's recommendations to control diphenidine; it was therefore added to the UN Convention on Psychotropic Substances 1971 as a Schedule II material. It was decided that methoxyphenidine would not be added to the UN Convention on Psychotropic Substances 1971 at this time, but would remain under continuing UN surveillance.

1.3 As diphenidine was added to the United Nations Convention on Psychotropic Substances, as amended, in April 2021, the United Kingdom is obliged to review and enact appropriate domestic control of this substance.

1.4 Diphenidine is a 1,2-diarylethylamine and has been reported to have dissociative effects as a derivative of lefetamine, a stimulant controlled as a Class B substance under the UK's Misuse of Drugs Act 1971. Other related variants included methoxyphenidine, fluorolintane, isophenidine and ephenidine.

1.5 This report reviews the evidence of use and harms - diphenidine, methoxyphenidine, fluorolintane, isophenidine and ephenidine and considers whether these compounds merit control under the Misuse of Drugs Act 1971 rather than the Psychoactive Substances Act 2016.

2. Legal and International Controls

2.1 As noted above, diphenidine was added to the UN Convention on Psychotropic Substances 1971 as a Schedule II material in 2021. 2-Methoxydiphenidine at this time is not controlled but remains under continuing UN surveillance.

2.2 In the UK, diphenidine and the related compounds, methoxyphenidine and ephenidine, fluorolintane and isophenidine are not currently controlled under the Misuse of Drugs Act 1971, although, as psychoactive substances, import, supply, possession with the intent to supply and possession in a custodial institution are all offences under the Psychoactive Substances Act 2016.

2.3 Some countries had controlled diphenidine in advance of the United Nations (UN) requirement and some have controlled other 1,2-diarylethylamine derivatives with dissociative effects under their national systems. Examples of national controls at the time of this report are set out in Annex A, showing how some countries have already placed specific controls on other diphenidine-related materials with similar effects, including, ephenidine, isophenidine and 2-methoxydiphenidine and its isomers.

3. Chemistry

3.1 Chemical structures for diphenidine, ephenidine, methoxyphenidine, fluorolintane and isophenidine, along with ketamine for comparison, are shown in Annex B.

3.2 Diphenidine is a 1,2-diarylethylamine (see Annex B), that is, a substance containing an ethylamine (ethanamine) skeleton with an aromatic group attached to each carbon atom. Substances of this type can have stimulant, analgesic and dissociative effects.

3.3 The 1,2-diarylethylamines which have been reported to produce dissociative effects can be regarded as derivatives of lefetamine (*N,N*-dimethyl-1,2-diphenylethanamine), a stimulant controlled as a Class B drug under the UK's Misuse of Drugs Act 1971. In diphenidine (1-(1,2-diphenethyl) piperidine; 1,2-DEP), the amine nitrogen of lefetamine is incorporated into a six-membered piperidine ring; in methoxyphenidine (2-methoxydiphenidine, MXP), a methoxy group is also present at the 2- position of the phenyl ring adjacent to the piperidine ring and in 2-chlorodiphenidine there is a chlorine atom at this position.

3.4 In fluorolintane (1-(1-(2-fluorophenyl)-2-phenylethyl)pyrrolidine, 2F-DPPy), the amine nitrogen of lefetamine is incorporated into a five-membered pyrrolidine ring and there is a fluorine at the 2- position of the phenyl ring adjacent to the pyrrolidine ring. The fluorine-positional isomers of fluorolintane and its un-fluorinated form (1,2-diphenethyl pyrrolidine; 1,2-DEPy) have also been reported to have potential to produce dissociative effects.

3.5 Other examples of lefetamine variants reported to produce dissociative effects include ephenidine (*N*-ethyldiphenidine, EPE or NEDPA), where the two methyl groups of lefetamine are replaced by a single ethyl group and isophenidine (*N*-isopropyldiphenidine, NPDPA) where they are replaced by an isopropyl group.

3.6 Other, more-distantly related, 1,2-diarylethylamines include materials where the lefetamine nitrogen is included in a six-membered piperazine ring, such as MT-45, AD-1211 and diphenpipenol. However, these substances are reported to have opioid-like, rather than dissociative, effects and are not considered in this report. MT-45 was controlled under the Misuse of Drugs Act as a Class A drug in 2015.

3.7 The lefetamine derivatives which are considered here are relatively simple molecules that can be synthesised from readily available and uncontrolled materials, using published synthetic techniques.

4. Misuse

4.1 These drugs are not specifically named as compounds/drugs in the Crime Survey for England and Wales and, therefore, there is no information in regards to the prevalence of use of diphenidine and related substances.

4.2 Information from online user discussion fora on these compounds suggest that route of use is different to the dissociative anaesthetic ketamine which is more typically used by nasal insufflation. User discussions suggest diphenidine and related substances are more typically used by inhalation or smoking. This may be by heating the drug on aluminium foil to vaporise it, combining in herbal smoking mixtures or potentially using electronic delivery devices/e-cigarettes.

4.3 The user discussion fora describe a range of amounts used per dose and in a use session, and that the onset of desired effects tends to occur more rapidly when used by smoking/inhalation compared to other routes of use. The duration of action appears to be “several hours” from user discussion reports, but this depends on the amount used and the duration of use.

4.4 Diphenidine: User data suggests a threshold dose of 30 mg with mild effects occurring at 40 to 65 mg and strong effects at doses of greater than 100 mg; the most commonly used doses are between 65 and 100 mg. Effects occur within 15-30 (faster if smoked/inhaled) minutes of use, the duration of main effects is 4 to 24 hours.

4.5 Methoxyphenidine: User data suggests a threshold dose of 30 mg with mild effects occurring at 50 to 75 mg and strong effects at doses of greater than 120 mg; the most commonly used doses are between 75 and 120 mg. Effects occur within 20 to 60 (faster if smoked/inhaled) minutes of use, the duration of action is 6 to 8 hours.

4.6 Ephenidine: User data suggests a threshold dose of 30 mg with mild effects occurring at 40 to 70 mg and strong effects at doses of greater than 100 mg; the most commonly used doses are between 70 and 100 mg. Effects occur within 10 to 30 (faster if smoked/inhaled) minutes of use, the duration of action is 5 to 7 hours.

5. Legitimate Uses

5.1 The ACMD Secretariat contacted Medicines and Healthcare products Regulatory Agency (MHRA) for any information on the legitimate use, clinical trials and/or marking authorisation applications of diphenidine, ephenidine, fluorolintane, isophenidine and methoxyphenidine.

5.2 The MHRA pharmaceutical and clinical trial assessment teams have confirmed that diphenidine, ephenidine and methoxyphenidine are not listed in scientific advice, current marketing authorisation applications and/or in the clinical trials register.

5.3 The MHRA have not responded about whether there are any known legitimate uses, clinical trials and/or marking authorisation applications for fluorolintane or isophenidine

5.4 Diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine are not approved for medical or veterinary use.

5.5 Outside of synthesis for research or analytical purposes, there are no industrial or other uses for diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine.

5.6 There is the potential that diphenidine, methoxyphenidine and other 1,2-diarylethylamines may have clinical relevance in a range of therapeutic areas including management of pain, epilepsy, neurodegenerative disease, alcohol dependence and depression. [Katselou et al 2018; Wallach et al 2018; Expert Committee on Drug Dependence 2020a; Expert Committee on Drug Dependence 2020b]

5.7 In 1989 an EU patent was approved for the potential use of the 1,2-diarylethylamines in the treatment of neurotoxic injury related to anoxia/ischaemia related to stroke, cardiac arrest or perinatal asphyxia. The purported mechanism of potential therapeutic benefit is through NMDA receptor blockade to inhibit excitotoxic actions of glutamate. [European Patent Office 1989]

5.8 As a diarylethylamine, diphenidine has been investigated for neuroprotective effects on neurones in the hippocampus. The NMDA-receptor antagonist effect has been confirmed *in vitro* using rat hippocampal slices and was found to be similar to that of ketamine. Though not of the same chemical class, diphenidine definitely also acts as a pharmacological analogue to the dissociative drug ketamine.

5.9 Ligands targeting the sigma-1 receptor (σ1 receptor) are being tested in clinical trials for treatment of Alzheimer's disease, ischaemic stroke and neuropathic pain. [Soriani et al 2019]. Although diphenidine and methoxyphenidine have σ1 receptor activity [Wallace et al 2016], there is currently no evidence that they have this therapeutic potential.

5.10 Some users of methoxyphenidine have reported an interest in its therapeutic use as an antidepressant. [Van Hout et al 2015]

5.11 Un-competitive NMDA receptor antagonists such as memantine are used clinically to treat dementia and may have a potential use for relapse prevention in people with alcohol dependence. [Holter et al 1996]. Therefore, it remains possible that a therapeutic role for the 1,2-diarylethylamines could be developed for the management of alcohol dependence.

6. Pharmacology

6.1 A detailed discussion of the pharmacology of these compounds is provided in Appendix C and a summary of this detailed information is provided below.

6.2 Diphenidine, methoxyphenidine and ephenidine all act as antagonists of the N-methyl-D-aspartate (NMDA) receptor, a cell protein found throughout the brain that mediates neuronal (brain cell) activation.

6.3 The NMDA receptor has some unique properties which mean it can only lead to neuronal activation under certain conditions. These properties also impact on how efficiently antagonists, such as diphenidine, methoxyphenidine and ephenidine, can inhibit NMDA receptor-mediated neuronal activation.

6.4 The extent to which antagonists can inhibit NMDA receptor function is linked to their physiological effects: potent inhibitors can produce dissociative effects (and at higher doses, anaesthesia, e.g., ketamine), whilst less potent inhibitors are less dissociative (e.g., memantine, which is used to treat cognitive impairments in dementia).

6.5 Diphenidine, methoxyphenidine and ephenidine have a slower onset of action than ketamine but longer duration of effects; this is influenced by both route of use and their pharmacokinetic properties.

6.6 Based on the available data, diphenidine, methoxyphenidine and ephenidine are highly potent inhibitors of NMDA receptor function, making them more similar to ketamine than to memantine.

7. Toxicology

7.1 There are no data currently available relating to the carcinogenic, mutagenic reproductive or teratogenic potential of diphenidine, methoxyphenidine, ephenidine, fluorolintane or isophenidine.

7.2 In the Material Safety Data Sheet (MSDS) there is a single study in mice which estimated the LD50 of diphenidine administered subcutaneously (the dose that would be expected to be lethal (fatal) to 50% of mice injected) to be 325 mg/kg. [Safety Data Sheet: Diphenidine 2022]

7.3 The MSDS for ephenidine reports the lethal dose low (LDLO, the lowest dose when given to an animal that would lead to death) as 585 mg/kg after subcutaneous administration. The LD50 for ephenidine is not provided. [Safety Data Sheet: Ephenidine 2021]

7.4 There are no data for LD50, LDLO or other toxicological information for methoxyphenidine, isophenidine or fluorolintane. [Safety Data Sheet: Methoxphenidine 2022]

7.5 Chronic use of ketamine can be associated kidney, bladder and urinary tract toxicity, particularly haemorrhagic cystitis [Kalsi S et al 2011]. There is currently no evidence to suggest that diphenidine, methoxyphenidine and ephenidine are associated with these kidney, bladder and urinary tract toxicities.

8. Health harms

Acute toxicity

8.1 Below is a summary of the published case reports and/or case series relating to the use of diphenidine and/or methoxyphenidine. In the published case reports/series, where other substances have been detected on analysis of blood and/or urine, it is not always possible to determine the significance of these other compounds to the individual's symptoms and/or clinical findings.

8.2 There have been no published case reports or series describing acute toxicity related to the use of ephenidine, fluorolintane or isophenidine.

8.3 A 33-year-old man presented to a French Emergency Department (ED) with severe agitation, hyperthermia (elevated body temperature), tachycardia (elevated heart rate), mydriasis (dilated pupils) and sedation (Glasgow Coma Score (GCS) 10). He had possibly used yellow pills, which a relative reported to be methoxyphenidine. He subsequently developed worsening hyperthermia with acute liver injury and rhabdomyolysis with associated acute kidney injury. Blood taken shorty after presentation was positive for his usual medication and alpha-methyltryptamine (AMT). Urine collected 16 hours after presentation was positive for his usual medication, as well as alpha-methyltryptamine and methoxyphenidine. It is likely that the clinical presentation was due to the AMT rather than the reported methoxyphenidine used [Chrétien et al 2018]

8.4 A 53-year-old male was found on the street in Switzerland in a somnolent (drowsy) and confused state, with transient echolalia (repeating noises and sounds that he had heard) and unable to communicate. He had with him a packet labelled 'methoxyphenidine', the contents of which were subsequently analysed and confirmed to be methoxyphenidine. On arrival in the ED, he had a reduced level of consciousness (GCS 10), was hypertensive (elevated blood pressure) (220/125 mmHg) and tachycardic (112 bpm) and he had nystagmus (abnormal eye movements). He developed mild rhabdomyolysis without evidence of acute kidney injury. Qualitative analysis of blood and urine was positive for methoxyphenidine. [Hofer et al 2014]

8.5 A 35-year-old man was found somnolent on the street in Hong Kong, China with retrograde amnesia of 13–15 hours. On arrival in the ED, he had slurred speech and hypertension (179/95 mmHg). He developed significant rhabdomyolysis with associated acute kidney injury. Analysis of the urine collected on presentation detected methoxyphenidine and its metabolites (hydroxy-2-methoxydiphenidine, dihydroxy-2-methoxydiphenidine and hydroxyl-O-demethyl-2-methoxydiphenidine); also detected were methylphenidate metabolite (exact metabolite not specified by the authors), tramadol and lorazepam. [Lam et al 2016]

8.6 A 30-year-old man in Italy was found confused, agitated and unable to communicate, with a small plastic bag labelled "Diphenidine 1 g" later confirmed to contain diphenidine. In the ED he was agitated, disorientated, had a reduced level of consciousness (GCS 9); he was tachycardic (160

bpm), pyrexial (38.0°C), had muscular rigidity and miotic pupils. He developed liver dysfunction and significant rhabdomyolysis without acute kidney injury. Subsequent analysis detected diphenidine in plasma (308 ng/ml), urine (631 ng/ml) and hair (4400 pg/ng hair). A range of benzodiazepines and metabolites (diazepam, nordiazepam, temazepam, diclazepam, lormetazepam, delorazepam, lorazepam, midazolam) as well as haloperidol and methylphenidate were detected in blood plasma and urine. [Gerace et al 2017]

8.7 A 25-year-old man was brought to an Italian ED after an episode of syncope following a head trauma. He had excitatory behaviour, psychomotor agitation, confusion, dysarthria, aphasia, mild hypertension (150/100 mmHg) and a slight tachycardia (85 bpm). Subsequent analysis of blood detected methoxyphenidine (247 ng/ml); also detected was flubromazepam (411 ng/ml). [Valli et al 2017]

8.8 A 33-year-old male driver crashed into a railway-crossing gate and damaged a wall while reversing a vehicle in Germany. When the police attended his apartment, which had been damaged significantly, he was confused, agitated and self-reported amnesia for events over the preceding 2 days. Analysis of a blood sample subsequently taken identified methoxyphenidine (57 ng/ml); also detected were amphetamine (111 ng/ml), MDMA (28 ng/ml) and MDA (3 ng/ml). [Stachel et al 2016]

8.9 Of the 750 cases of suspected NPS intoxication between January and December 2014 enrolled in the STRIDA project in Sweden, 14 (1.9%) tested positive for diphenidine and 3 (0.4%) tested positive for methoxyphenidine. Of the 14 diphenidine cases, 11 were males aged 20 to 39 years and 3 were female aged 27 to 33 years. In only one case was diphenidine detected on its own. The serum concentrations detected were 2 to 262 ng/ml and the urine concentration was 0.5 to 1158 ng/mmol creatinine. Of the 3 methoxyphenidine cases, 2 were male (aged 25 and 33 years) and 1 was female aged 48 years. Methoxyphenidine was detected in the serum of two cases (187 and 409 ng/ml); it was detected in urine from all three cases (0.3 to 343 ng/mmol creatinine). Commonly reported adverse symptoms were hypertension (systolic blood pressure >140 mmHg (76%), tachycardia (heart rate >100/min (47%), anxiety (65%) and agitation (47%), and less frequently (≤35%) with nystagmus, dilated pupils and muscle rigidity. 65% of cases had an altered mental status, which the authors defined as including altered level of consciousness (graded by the GCS or RLS), hallucinations, confusion, disorientation and dissociation. All cases were discharged from hospital and the time in hospital treatment ranged between 1 and 3 (mean: 1.6, median: 2.0) days. [Helander et al 2015]

8.10 The European Drug Emergencies Network Plus (Euro-DEN Plus) project has had a total of 62,613 cases reported to its registry from October 2013 to December 2021.
There has been a single report in 2015 from Munich, Germany of a 35-year-old man with acute toxicity related to the use of diphenidine along with cannabis, 4-Chloromethcathinone (4CMC) and 1-(Benzofuran-5-yl)-N-

methylpropan-2-amine) (5MAPB). The individual developed drowsiness (GCS 14) and a headache. They self-discharged from the ED after 29 hours. [Wood et al 2022] There have also been five reports of acute toxicity involving the use of methoxyphenidine, three from London, UK (1 case in 2013, 2015 and 2016) and two reports from Msida, Malta (both 2019). All five were male and were aged between 20 and 36 years old (mean ± SD age was 27.6 ± 6.5 years). The reported clinical features were agitation/aggression (2 patients), hallucinations (2), anxiety (1) and seizures (1). Four were discharged from the ED (3 medically and 1 self-discharged) and one was admitted to hospital. The overall median (IQR) length of stay was 3 hrs 14 mins (2 hrs 7 mins to 3 hrs 34 mins). [Wood et al 2022]

8.11 There have been no reports of presentations involving ephenidine, fluorolintane or isophenidine within the Euro-DEN Plus project.

Fatal Cases

8.12 A detailed review was undertaken in late August 2022 by members of the ACMD NPS Committee and the ACMD Secretariat in preparation of this ACMD report. The review included information from a systematic literature review of published scientific papers and other information in the public domain; anonymised data provided by the National Records of Scotland, the National Programme on Substance Abuse Deaths, and EU-MADNESS project; and information from the Office for National Statistics and the Northern Ireland Statistics and Research Agency.

8.13 This review did not identify any deaths where fluorolintane, isophenidine or ephenidine had been detected, reported to have been used prior to death and/or were determined to have been involved in the death.

8.14 The review identified 48 deaths worldwide involving diphenidine and/or methoxyphenidine. The majority (40) of these deaths occurred in Europe, including the United Kingdom (37 deaths), France (1 death), Germany (1 death) and Hungary (1 death). Only one of these deaths were reported after 2016, a UK death involving diphenidine in 2019. Detailed review of the deaths reported within the United Kingdom is provided in the UK prevalence section of this report.

8.15 There were 8 deaths identified that occurred outside of Europe; 4 deaths reported from Japan and 4 from the USA.

Abuse, dependency and withdrawal

8.16 There have been no animal studies or human reports of dependency and/or withdrawal related to diphenidine, fluorolintane or ephenidine.

8.17 There have been no animal studies relating to methoxyphenidine dependency and/or withdrawal. A 21-year-old male with a history of using methoxyphenidine for a period of "a few weeks to a month" was hospitalised with agitation and anxiety having suddenly stopped methoxyphenidine use. After 7 days in hospital, he developed methoxyphenidine withdrawal symptoms with abdominal pain, vomiting, and low-grade fever (38°C). The

management of this withdrawal was not clearly reported in the case report. Using a Drug Dependence Severity Scale based on DSM-IV items developed by the authors, he had a high score across all the six different domains of the scale. [Champeau et al 2017]

9. Social harms

9.1 There is no information on the social harms that may be caused by diphenidine, ephenidine, methoxyphenidine, fluorolintane or isophenidine misuse, but any potential social harms are likely to be similar to those seen with other arylcyclohexylamine dissociatives such as ketamine, methoxetamine and PCP derivatives.

10. UK Prevalence

Welsh Emerging Drugs and Identification of Novel Substances (WEDINOS) project

10.1 Funded by Public Health Wales, WEDINOS provides laboratory testing of drug samples volunteered by the community. These are received anonymously by post from either individuals or participating organisations (e.g. substance misuse services, housing and hostels, youth clubs and young people's services, education, night clubs and bars, mental health community teams, Local Authorities, Ambulance Services and the Police). Anonymised test results are publicly available online.

10.2 The publicly available 'sample results' section on the WEDINOS website was searched for samples that had been analysed where diphenidine, ephenidine, methoxyphenidine (searched using the term methoxphenidine), isophenidine or fluorolintane were identified.

10.3 There have been no samples analysed by WEDINOS where isophenidine or fluorolintane have been detected.

10.4 The samples analysed where diphenidine, ephenidine or methoxyphenidine have been detected are summarised in the table below by year of detection, along with the total number of samples in each year.

Year	Samples Analysed	Diphenidine	Methoxyphenidine	Ephenidine
2013-2104	1,869	1	2	-
2014-2015	1,350	5	11	-
2015-2016	1,333	3	11	5
2016-2017	1,345	-	2	4
2017-2018	6,851	-	-	-
2018-2019	9,031	-	-	-
2019-2020	13,329	-	4	-
2020-2021	16,904	-	-	-
2021-2022	23,249	-	-	-

10.5 Two of the 2020 samples where methoxyphenidine was detected were green plant material; one had nothing else detected and one had MDMB-4en-PINACA detected. The other two samples were a brown crystalline substance

which also contained MDMA and a white powder which did not contain any other substance.

FEWS

10.6 The ACMD Secretariat contacted Forensic Early Warning System (FEWS) for any information on the detection of diphenidine, ephenidine, fluorolintane, isophenidine and methoxyphenidine (MXP, 2-MeO-diphenidine).

10.7 FEWS confirmed in November 2022 that methoxyphenidine had been detected in two samples they had analysed as summarised below:

- Sample collected from Langley postal hub in the 20/21 financial year.
- Sample of paper collected from Highdown Prison in Surrey in the 20/21 financial year. The sample contained a mixture of other compounds including cocaine, caffeine, 3,4-methylenedioxymethamphetamine (MDMA) and ketamine.

10.8 FEWS have not detected diphenidine, ephenidine, fluorolintane or isophenidine in any samples analysed.

National Poisons Information Service (NPIS)

10.9 The NPIS is commissioned by the UK Health Protection Agency to provide poisons information and clinical advice to UK health professionals managing patients who may have been exposed to potentially toxic substances, including drugs of misuse. For most cases information is provided via an internet database (TOXBASE); this received almost 3 million substance enquires in the year 2021-22 via its online and TOXBASE app platforms. When TOXBASE cannot be accessed or for more complex cases a 24/7 telephone enquiry line is available with consultant support, and this received almost 40,000 health professional enquiries during the 2021-22 reporting year. Numbers of accesses to TOXBASE and NPIS telephone enquiries reflect (but do not measure directly) the frequency of contacts between health professionals and patients presenting following suspected exposures.

10.10 Online and app TOXBASE accesses for diphenidine and methoxyphenidine are summarised in the Table below. No data are available for ephenidine, isophenidine or fluorolintane as no information about these compounds is currently available on TOXBASE.

	2017-2018	2018-2019	2019-2020	2020-2021	2021-2022
Diphenidine					
TOXBASE online	27	37	15	15	11
TOXBASE app	33	10	19	24	14
Methoxyphenidine					
TOXBASE online	30	35	11	13	10
TOXBASE app	8	11	8	6	3

10.11 There have previously been telephone calls to the NPIS related to diphenidine and methoxyphenidine in 2017-18 (Diphenidine -2;

methoxyphenidine -1) and 2018-19 (Diphenidine - 1; methoxyphenidine - 1) but no calls for either compound since then. There have been no calls to the NPIS related to ephenidine, fluorolintane or isophenidine.

Identification Of Novel psychoactive substances (IONA) study

10.12 The IONA study, now funded by the Office for Health Improvements and Disparities, has been collecting demographic and clinical information and analysing blood and/or urine samples from consenting adults presenting to participating EDs in England, Wales and Scotland with toxicity following suspected drug misuse. The study was launched in March 2015 and by November 2022 samples from almost 1700 patients had been collected.

10.13 Over this period there have been two detections of diphenidine (2016 and 2018), four detections of methoxyphenidine (2016 – 3; 2017 – 1) and no detections of ephenidine, fluorolintane or isophenidine.

10.14 Diphenidine was detected in samples from 2 young men (aged 24 and 30), one presenting in London and one in Edinburgh. One experienced pyrexia (40.1 degrees) with sweating, rapid heart rate and anxiety and was treated with active cooling measures and cyproheptadine. He recovered and was discharged from hospital after 44h. Multiple other substances were also detected in his samples (MDMB-CHMICA, 4-chloromethcathinone, methamphetamine, methadone and its metabolite). Clinical features reported in the second patient were agitation, confusion, paranoia, depression, and suicidal ideation. These resolved rapidly and he was discharged from the Emergency Department after 4h. Again, multiple other substances were also detected in his samples (MDMA, flubromazepam, citalopram, fentanyl, cocaine). In both cases these other substances detected are likely to have contributed to the clinical features observed.

10.15 Methoxyphenidine was detected in samples from 4 participants (2 males, 2 females) aged 18-45 years. Other substances were also detected in 2 patients (MDMA and cocaine in one each and benzodiazepines in both). In the two without other drugs detected tachycardia and hypertension were reported in both patients and confusion requiring sedation was recorded in one. Clinical features reported overall (4 patients) included pyrexia (2 patients), reduced level of consciousness (2), tachycardia (2), hypertension (2), seizures, dystonia, chest pain, agitation, hallucinations, paranoia and minor creatine kinase increase (1 patient each). All 4 patients recovered and were discharged after 2-60 hours.

European Drug Emergencies Network Plus (Euro-DEN Plus) Project: UK Centres

10.16 The European Drug Emergencies Network (Euro-DEN) was established in 2013 with European Union funding. After the first year of data collection, it was expanded as the Euro-DEN Plus project, with ongoing support from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). The project collects data on presentations with acute drug toxicity related to the use of recreational drugs, novel psychoactive substances and recreationally used prescription and over the counter medicines to sentinel emergency

departments/toxicology units across Europe. Between October 2013 and December 2021 there were 14,113 presentations to the sentinel UK EDs in the Euro-DEN Plus project.

10.17 There have been no UK reported cases of acute toxicity related to diphenidine, ephenidine, isophenidine or fluorolintane to the Euro-DEN Plus Network.

10.18 There have been three cases (all male aged 20 to 36 years) of acute toxicity related to methoxyphenidine reported by the UK centres in the Euro-DEN Plus network – 1 in each of 2013, 2015 and 2016. All three cases were from the London centres. No other drugs were reported to have been used in these cases. Demographics and clinical features reported were: i) 36-year-old male with hallucinations, seizures and anxiety/agitation; ii) 22-year-old male with drowsiness (GCS 14) and tachycardia; and iii) 20-year-old male with hypertension and tachycardia. All were medically discharged from the ED with overall lengths of stay between 1 hour 59 minutes and 3 hours 34 minutes. [Wood et al 2022]

UK Deaths

10.19 The 1,2-diarylethylamine class of drugs and the individual drugs diphenidine and methoxyphenidine are not specified in the Office of National Statistics (ONS) annual reports for England and Wales. The ONS reported to the ACMD that by 2nd November 2022 there had been 21 deaths involving diphenidine or methoxyphenidine (all occurred between 2014 and 2017); twelve deaths did not mention the use of any other drug and/or alcohol and there were no deaths where both diphenidine and methoxyphenidine were mentioned. The deaths reported by the ONS are summarised below.

	Year of death registration			
	2014	2015	2016	2017
Any Mention				
Diphenidine	1	2	0	0
Methoxyphenidine	2	5	9	2
Mentioned without other drugs/alcohol				
Diphenidine	0	1	0	0
Methoxyphenidine	1	2	5	2

10.20 As noted previously in this report, a detailed review was undertaken in late August 2022 by members of the ACMD NPS Committee and the ACMD Secretariat in preparation of this ACMD report. The review included information from a systematic literature review of published scientific papers and other information in the public domain; anonymised data provided by the National Records of Scotland, the National Programme on Substance Abuse Deaths, and EU-MADNESS project; and information from the ONS and the Northern Ireland Statistics and Research Agency.

10.21 This review did not identify any deaths in the United Kingdom where fluorolintane, isophenidine or ephenidine had been detected, reported to have been used prior to death and/or were determined to have been involved in the death.

10.22 There was a total of 48 deaths worldwide identified involving diphenidine and/or methoxyphenidine by this review; of these 37 occurred in the United Kingdom. Of these 37 deaths, 27 occurred in England, 7 in Scotland and 3 in Wales. There were no deaths identified in Northern Ireland.

10.23 The summary of deaths involving diphenidine and/or methoxyphenidine for the United Kingdom as a whole and by separate countries is shown below.

Region	Compound	Year of Death				
		2014	2015	2016		2019
UK	Diphenidine	2	1	1		1
	Methoxyphenidine	11	12	8		-
	Diphenidine and methoxyphenidine	1	-	-		-
	Total	***14***	***13***	***9***		***1***
England	Diphenidine	1	1	1		-
	Methoxyphenidine	8	11	5		-
	Diphenidine and methoxyphenidine	-	-	-		-
	Total	***9***	***12***	***6***		***-***
Scotland	Diphenidine	-	-	-		1
	Methoxyphenidine	2	-	3		-
	Diphenidine and methoxyphenidine	1	-	-		-
	Total	***3***	***-***	***3***		***1***
Wales	Diphenidine	1	-	-		-
	Methoxyphenidine	1	1	-		-
	Diphenidine and methoxyphenidine	-	-	-		-
	Total	***2***	***1***	***-***		***-***

10.24 More detailed demographic information was available for analysis for 35 of these identified deaths:

- The majority (32, 91.4%) were males
- The overall mean (range) age was 37.2 (19-65) years old; the mean age differed between countries: Wales 34.7 years; England 36.3 years; Scotland 41.4 years
- Ethnicity was available for 19 deaths, of which 18 were white and 1 was black.
- Employment status was available for 24, and 13 were currently employed at the time of the death

10.25 Previous/current drug use status was known in 25, and 18 (72%) had a history of drug use

10.26 The majority (65.7%) of deaths had one or more other drug and/or alcohol detected or implicated in the death. The most common substances detected were morphine (11 deaths), codeine (7 deaths), alcohol (6 deaths) and methiopropamine (6 deaths).

10.27 The place of death was known in 24 deaths, and 20 died at home, in university accommodation or in another private residential property, 3 died in hospital and 1 died on the street.

10.28 The underlying cause of death was i) acute drug toxicity: 33 deaths; ii) cardiac causes: 2 deaths; iii) trauma: 1 death; iv) unascertained: 1 death. Of the 33 deaths due to acute drug toxicity, 14 were due to diphenidine or methoxyphenidine alone, 15 due to diphenidine or methoxyphenidine in combination with other drugs/alcohol and 4 were due to other drugs (where diphenidine or methoxyphenidine were noted to have been used but were not listed as the underlying cause of the death).

11. Conclusions

11.1 Diphenidine is a 1,2-diarylethylamine and has been reported to have dissociative effects as a derivative of lefetamine, a stimulant controlled as a Class B substance under the UK's Misuse of Drugs Act 1971. Other related variants included methoxyphenidine (also referred to as methoxphenidine), fluorolintane, isophenidine and ephenidine.

11.2 In October 2020, the 43rd meeting of the World Health Organization Expert Committee on Drug Dependence reviewed the 1,2-diarylethylamines diphenidine and methoxyphenidine (also referred to as methoxphenidine). Based on the recommendations of these reviews, the 64th Commission on Narcotic Drugs (CND) meeting in April 2021 voted to add Diphenidine to the UN Convention on Psychotropic Substances 1971 as a Schedule II material. The CND meeting decided that methoxyphenidine would not be added to the UN Convention on Psychotropic Substances 1971 at this time, but would remain under continuing UN surveillance. The other related substances, fluorolintane, ephenidine and isophenidine have not as yet been reviewed by the WHO.

11.3 Although there was an EU patent approved in 1989 for the potential use of 1,2-diarylethylamines in the treatment of neurotoxic injury, outside of synthesis for research or analytical purposes, there are no approved medicinal, veterinary or industrial use for diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine.

11.4 Diphenidine and related compounds all act as relatively potent antagonists of the NMDA receptor, a cell protein found throughout the brain that mediates neuronal (brain cell) activation. Based on the available pharmacological data, diphenidine and related compounds are highly potent inhibitors of NMDA receptor function, making them more similar to ketamine than memantine. There is no evidence to suggest that diphenidine, methoxyphenidine and ephenidine cause the bladder-related issues which can occur with chronic ketamine use.

11.5 There are no population or sub-population data on the prevalence of use of diphenidine, methoxyphenidine, ephenidine, fluorolintane and isophenidine and there are no published cases or detections in acute toxicity cases of ephenidine, fluorolintane or isophenidine. The use of diphenidine and methoxyphenidine appears to be low based on the small number of cases of acute toxicity (published case reports/series: diphenidine 15 cases, and methoxyphenidine 9 cases; Euro-DEN Plus cases: 1 diphenidine and 5 methoxyphenidine; IONA analytical detections: diphenidine 2; methoxyphenidine 4) and deaths (48 worldwide, of which 37 have been in the UK: diphenidine 5 deaths, methoxyphenidine 31 deaths, combined diphenidine/methoxyphenidine 1 death). Additionally, the reports and deaths are historical with none occurring in the UK or elsewhere since 2019.

11.6 The information from the case reports/series, Euro-DEN Plus cases and the IONA detection cases have shown that the clinical features seen were of

acute stimulant (e.g. hypertension and tachycardia) and neuropsychiatric (hallucinations, sedation/drowsiness, confusion, paranoia and anxiety/agitation) toxicity. These features are similar to drugs such as ketamine. It should be noted that in the majority of self-reported use or analytically detected cases there were other substances detected that could have explained some or all of the reported clinical features seen.

11.7 As diphenidine has been controlled under the UN Convention on Psychotropic Substances 1971 as a Schedule II material, it has to be controlled under the UK's Misuse of Drugs Act 1971. There is evidence that diphenidine, methoxyphenidine and ephenidine have similarities to ketamine from pharmacological studies and/or cases of acute toxicity and, therefore, the control of these substances should be similar to that for ketamine. There is limited or no evidence for the related substances fluorolintane and isophenidine to recommend that they be controlled at this time. They should remain subject to the controls of the Psychoactive Substances Act 2016 and under active monitoring by the Advisory Council of the Misuse of Drugs (ACMD). If any evidence of their use and related harm subsequently becomes available, further consideration at that time for control under the Misuse of Drugs Act 1971 would be appropriate.

12. Recommendations

1. The following compounds *(listed under point 2 underneath)* should be added to Class B of the Misuse of Drugs Act 1971, consistent with the classification of ketamine and other controlled dissociatives such as methoxetamine and PCP-related materials.

2. As these materials have no medical use it is recommended that they should be placed in Schedule 1 of the Misuse of Drugs Regulations 2001 (as amended) and added to schedule 1 of the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015, Northern Ireland 2001, to which section 7(4) of the Misuse of Drugs Act 1971 applies.

    - **Diphenidine**
    - **Ephenidine**
    - **Methoxyphenidine (also known as methoxphenidine)**

Lead: Home Office

Measure of outcome: The inclusion of the listed compounds in Class B of the Misuse of Drugs Act 1971 and Schedule 1 of the Misuse of Drugs Regulations 2001 and the Misuse of Drugs (Designation) (England, Wales and Scotland) Order 2015, Northern Ireland 2001.

Annex A: Summary of International control at the time of the report

Canada
Schedule 1 of Canada's Controlled Drugs and Substances Act (CSA) includes "...MT-45…derivatives…and analogues…" and the substances specifically named in the CSA text as being within the scope of this control include diphenidine, methoxyphenidine, ephenidine and isophenidine.

China
China placed 2-methoxydiphenidine under national control with effect from September 2015.

Denmark
Denmark has controlled diphenidine, ephenidine and all three positional isomers of methoxyphenidine (2-, 3- and 4-methoxy).

France
In the French list of "Substances classées comme stupéfiants", diphenidine, ephenidine and methoxyphenidine are all listed as Annex IV materials.

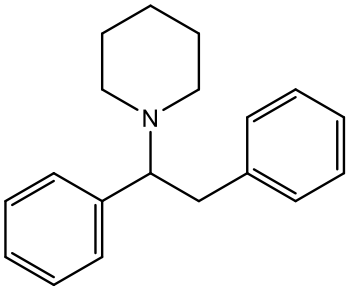
Germany
Diphenidine is specifically listed within Appendix II of Germany's Narcotics Trafficking Act (BtMG). In addition, the New Psychoactive Substances Act (NpSG) includes a very broad generic control on "Compounds derived from 2-phenethylamine" incorporating an extensive range of structural modifications, subject to an overall maximum molecular weight of 500 mass units. The scope of this generic includes all the lefetamine derivatives considered here.

Italy
2-Methoxyphenidine was controlled in Italy in August 2016 and ephenidine became controlled in Italy in October 2021.

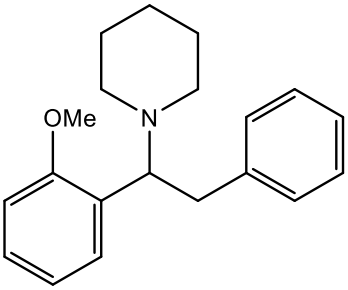
Japan
Japan's list of Designated Substances (i.e. controlled NPS) includes both ephenidine and 2-methoxyphenidine. Diphenidine is listed as a narcotic.

Sweden
Swedish drug controls include diphenidine, 2-methoxydiphenidine, ephenidine and isophenidine, the last two having been brought under control in 2015.

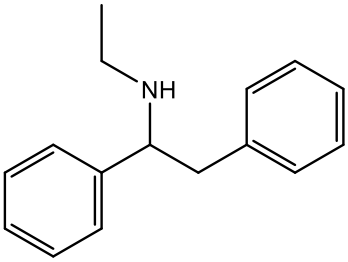
Annex B: Chemical Structures of Diphenidine, Methoxphenidine, Ephenidine, Isophenidine and Fluorolintane, with Ketamine for comparison



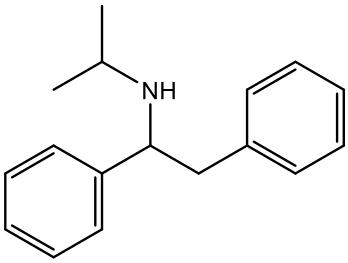
Diphenidine



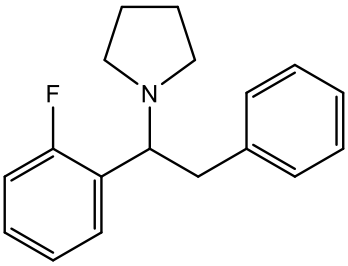
Methoxphenidine



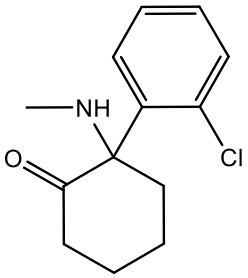
Ephenidine



Isophenidine



Fluorolintane



ketamine

Annex C: Additional detailed pharmacological information

1. The primary target for diphenidine and related drugs in the central nervous system is the NMDA receptor, a ligand-gated ion channel. When activated, it leads to an increase in the excitability of the neurone. The NMDA receptor is widely distributed throughout the brain and the effects of drugs vary depending on the specific properties of the drug and the dose.

2. Drugs used clinically which block the NMDA receptor include ketamine and memantine. Both drugs act at the same location on the receptor and block the channel and thus prevent the normal passage of ions. However, within this group of drugs, the effects vary considerably due to a characteristic known as channel block and ion trapping. Channel block is one of the characteristic features of the NMDA receptor. Under physiological conditions there is a strong voltage-dependent block by Mg^{2+} ions. The effects of the NMDA antagonists used clinically differs because of these channel blocking properties and this is important because it influences their dissociative effects. Ketamine has a relatively high (~86%) trapping capability but lower than phencyclidine (phenylcyclohexyl piperidine or PCP) (>98% trapping) and MK-801 (Dizocilpine) (100% trapping). Both memantine and amantadine have low ion trapping properties. Based on the available data, from both user reports of their dissociative effects and pharmacological studies, diphenidine, ephenidine and methoxyphenidine are more similar to ketamine than memantine.

3. Some data are available on diphenidine, methoxyphenidine and ephenidine receptor affinity and selectivity, although full receptor binding profiles have not been published. Less information is available for isophenidine or fluorolintane, but they are also reported to be NMDA receptor antagonists and dissociative anaesthetics. [Berger et al 2009; Wallach et al 2019] Overall, they exhibit broadly similar effects to other NMDA receptor antagonists such as ketamine and phencyclidine and are less like drugs such as memantine.

4. Diphenidine, methoxphenidine and ephenidine have been studied in preclinical animal models and in brain slices where they exhibit similar effects to each other and to the NMDA antagonists ketamine and PCP. The main findings are inhibition of the NMDA-mediated excitatory neurotransmission consistent with channel block. [Kang et al 2017]. Studies in animal models include the pre-pulse inhibition assay which quantifies sensory motor gating and may predict psycho-activity. In this assay diphenidine, methoxphenidine and ephenidine induce similar disruptions to pre-pulse inhibition as seen with ketamine and PCP although the potency was lower than predicted by their affinity at the NMDA receptor suggesting possible pharmacokinetic differences.

5. The receptor binding affinities for diphenidine, methoxyphenidine and ephenidine at the NMDA receptor, norepinephrine transport (NET),

dopamine transporter (DAT) and serotonin transport (SERT) are published in Wallach et al 2018 and the key findings summarised below.

6. All three compounds exhibit moderate to high affinity and selectivity for the PCP binding site in the NMDA receptor, where they function as un-competitive antagonists and channel blockers.
   - Uncompetitive antagonists are characterised by their ability to bind to the receptor when the pore is open, at an alternative site to that used by the agonist, therefore being left trapped inside the channel following its closure
   - Diphenidine has the highest affinity with a Ki of 18-39 nM
   - Diphenidine has two enantiomers with the S-enantiomer exhibiting 40 times greater potency at NMDA receptors when quantified in brain slices.
   - Methoxyphenidine has high affinity with a Ki of 36-170 nM
   - Ephenidine has moderate affinity with a Ki of 66-257 nM
   - For reference, in a comparative assay, ketamine had an affinity of 324nM
   - The inhibition of NMDA-mediated excitatory neurotransmission in brain slices had a rank order of potency of MK-801 > PCP > DPP / 3-MXP / 2-MXP > ketamine > 4-MXP / memantine. [Wallach et al. 2016]
   - Ephenidine was not included in this study but based on its affinity in the rat brain slice electrophysiology, it would be expected to be more potent than ketamine but less potent than 2-MXP.

7. Summary of dopamine transporter activity (Ki values)
   - Diphenidine has a higher affinity for the dopamine transporter (230-317nM) than methoxyphenidine (3000nM) but similar to ephenidine (379nM). It is unlikely to be mediating effects for commonly used doses but may have effects at higher doses.
   - Methoxyphenidine has been shown to have lower affinity for the dopamine transporter than diphenidine or ephenidine (although users suggest they experience effects they would link to inhibition of dopamine and noradrenaline re-uptake).

8. Summary of 5HT (serotonin) receptor activity (Ki values)
   - Diphenidine, methoxphenidine and ephenidine have very low affinity for the serotonin transporter and serotonin receptors including 5-HT1A, 2A and 2C (>10,000nM)

9. Summary of other receptor activity (Ki values)
   - Diphenidine has moderate affinity for sigma-1 (Ki 290 nM) and sigma-2 receptors (Ki 193 nM) and low affinities for the alpha-adrenergic receptor subtypes (α1A, α2A, α2B, and α2C), histamine receptors, muscarinic receptor subtypes, and the kappa opioid receptor (KOR) although with some differences between studies (Wallach et al. 2016; Luethi et al. 2018).
   - Affinities for sigma-1 (Ki ¼ 124 nM) and sigma-2 (Ki ¼ 508 nM) were also seen for methoxyphenidine and low μM affinities for the α-adrenergic receptor subtypes (α2A), histamine receptors, muscarinic receptor subtypes, and KOR. [Wallach et al. 2016; Luethi et al. 2018]

- Ephenidine has modest affinity for sigma-1 and sigma-2 receptors (Ki 629 and 722 nM, respectively) and noradrenaline transporter (841nM). [Kang et al. 2017]
- The N-dealkylation metabolite, DPA, has been reported to have modest affinity for NMDAR (Ki 690 nM) and, therefore, could contribute to the pharmacological effects of ephenidine. [Thurkauf et al. 1989]
- Both diphenidine and methoxyphenidine lacked significant affinity (greater than 15 μM) at rat and mouse trace amine-associated receptor one (TAAR-1) in transfected HEK293 cells. [Simmler et al. 2016]

10. Based on their pharmacology these compounds will likely lead to tolerance with prolonged and repeated use. This will depend on half-life and frequency of use in terms of extent of tolerance which develops and subsequent withdrawal effects on termination of use. Anecdotal evidence, based on user experience, would suggest 3-7 days for reduction by half and up to 2 weeks to return to baseline levels. They will likely generate cross-tolerance with other NMDA-receptor antagonists and dissociatives e.g. ketamine.

11. Diphenidine has been found to evoke dopamine efflux in the nucleus accumbens in animal studies, but to a lesser extent than seen with cocaine (approximately 10-fold less potent and with lower peak effect). These studies show diphenidine exhibits pro-dopaminergic stimulant type effects at higher doses. [Sahai et al 2018]

Annex D: Chair and Members of ACMD Diphenidine and other related substances working group

Chair of Working Group		
Dr David Wood	ACMD Member	Consultant Physician and Clinical Toxicologist at Guy's and St Thomas' and Reader in Clinical Toxicology at King's College London
Members of Working Group		
Dr Caroline Copeland	ACMD Co-opted member	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery	ACMD Co-opted member	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Professor Emma Robinson	ACMD Co-opted member	Professor of Psychopharmacology, University of Bristol
Dr Richard Stevenson	ACMD Member	Emergency Medicine Consultant, Glasgow Royal Infirmary
Professor Simon Thomas	ACMD Member	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University
Mr Ric Treble	ACMD Co-opted member	Retired Laboratory of the Government Chemist (LGC) expert

Annex E: ACMD NPS Committee membership, at time of publication

Dr Kostas Agath	ACMD Member	Consultant psychiatrist (addictions), Change Grow Live Southwark
Mr Paul Bunt	ACMD Co-opted member	Director of Casterton Event Solutions Ltd, Former Drug Strategy Manager for Avon and Somerset Constabulary
Dr Anne Campbell	ACMD Member	Reader in substance use and mental health and co-director of the Drug and Alcohol Research Network at Queens University Belfast
Mr Peter Cain	ACMD Co-opted member	Drugs Scientific Advisor, Eurofins Forensic Services
Dr Caroline Copeland	ACMD Co-opted member	Lecturer in Pharmaceutical Medicine at King's College London, and the Director of the National Programme on Substance Abuse Deaths
Mr John Corkery	ACMD Co-opted member	Senior Lecturer in Pharmacy Practice at University of Hertfordshire; mortality and epidemiological lead for EU-MADNESS project
Mr Lawrence Gibbons	ACMD Member	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Hilary Hamnett	ACMD Member	Associate Professor in Forensic Science, University of Lincoln
Professor Graeme Henderson	ACMD Member	Professor of Pharmacology at the University of Bristol
Professor Stephen Husbands	ACMD Co-opted member	Professor of Medicinal Chemistry, University of Bath
Professor Roger Knaggs	ACMD Member	Associate Professor in clinical pharmacy practice at the University of Nottingham
Professor Fiona Measham	ACMD Co-opted member	Professor and chair in criminology, University of Liverpool; co-founder and co-director, the Loop
Mr Harry Shapiro	ACMD Member	Director – DrugWise
Dr Richard Stevenson	ACMD Member	Emergency Medicine Consultant, Glasgow Royal Infirmary
Dr Ann Sullivan	ACMD Member	Consultant physician in HIV and sexual health
Professor Simon Thomas	ACMD Member	NPS Committee Chair, Emeritus Professor of Clinical Pharmacology and Therapeutics, Newcastle University

Mr Ric Treble	ACMD Co-opted member	Retired Laboratory of the Government Chemist (LGC) expert
Dr Derek Tracy	ACMD Member	Medical director of West London NHS Trust
Dr Mike White	ACMD Co-opted member	Former Forensic Intelligence Adviser
Dr David Wood	ACMD Member	Consultant Physician and Clinical Toxicologist at Guy's and St Thomas' and Reader in Clinical Toxicology at King's College London

Annex F: ACMD membership at the time of publication

Dr Kostas Agath	Consultant psychiatrist (addictions), Change Grow Live Southwark
Professor Judith Aldridge	Professor of criminology at the University of Manchester
Professor Owen Bowden-Jones	Chair of Advisory Council on the Misuse of Drugs, Consultant psychiatrist, Central North-West London NHS Foundation Trust
Dr Anne Campbell	Reader in substance use and mental health and co-director of the Drug and Alcohol Research Network at Queens University Belfast
Dr Emily Finch	Clinical director of the Addictions Clinical Academic Group and a consultant psychiatrist for South London and Maudsley NHS Trust
Mr Mohammed Fessal	Chief pharmacist, Change Grow Live
Professor Sarah Galvani	Professor of social research and substance use at Manchester Metropolitan University
Mr Lawrence Gibbons	Head of drug threat – National Crime Agency Intelligence Directorate – Commodities
Dr Carole Hunter	Lead pharmacist at the alcohol and drug recovery services at NHS Greater Glasgow and Clyde
Dr Hilary Hamnett	Associate Professor in forensic science, University of Lincoln
Professor Graeme Henderson	Professor of pharmacology at the University of Bristol
Professor Roger Knaggs	Associate professor in clinical pharmacy practice at the University of Nottingham

Professor Tim Millar	Professor of substance use at the University of Manchester
Mr Rob Phipps	Former head of Health Development Policy Branch, Department of Health, Social Services and Public Safety, Northern Ireland
Dr Ann Sullivan	Consultant physician in HIV and sexual health
Mr Harry Shapiro	Director – DrugWise
Dr Paul Stokes	Senior clinical lecturer in mood disorders, King's College, London
Dr Richard Stevenson	Emergency medicine consultant, Glasgow Royal Infirmary
Professor David Taylor	Professor of psychopharmacology, King's College, London
Professor Simon Thomas	Emeritus professor of clinical pharmacology and therapeutics, Newcastle University
Dr Derek Tracy	Medical director of West London NHS Trust
Dr David Wood	Consultant Physician and Clinical Toxicologist at Guy's and St Thomas' and Reader in Clinical Toxicology at King's College London
Ms Rosalie Weetman	Public health lead (alcohol, drugs and tobacco), Derbyshire County Council - (currently on secondment to Office for Health Improvement and Disparities, as programme manager, Drug and Alcohol Improvement Support Team)

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