



Critical Review Report: 2-MEO-diphenidine 2-MXP

Expert Committee on Drug Dependence
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Executive summary

This critical review has been proposed based on information brought to the attention of the World Health Organization (WHO) that 2-MEO-diphenidine (methoxyphenidine, 2-MXP) is manufactured by several chemical companies and other producers. Case reports demonstrate that the ingestion of this new psychoactive compound can lead to severe intoxication and death. 2-MEO-diphenidine is a controlled substance in Canada, China, Germany, Italy, Sweden and the United Kingdom.

Owing to its very short history of human usage (approximately 7 years), information about the pharmacological properties, metabolism and toxicity of 2-MEO-diphenidine is limited. 2-MEO-diphenidine was first reported in a 1989 patent as a potential treatment for neurotoxic injury. The first reported recreational human use occurred in 2014 when 2-MEO-diphenidine was sold in powder and tablet form on the online research chemical market.

Chemistry: 2-MEO-diphenidine is a dissociative substance of the 1,2-diarylethylamine class, which can produce ketamine-like effects. Three structural isomers (2-, 3- and 4-MXP) are known. These structural isomers can be separated using high-performance liquid chromatography (HPLC) selected-ion monitoring detection or gas chromatography ion trap mass spectrometry. 2-MEO-diphenidine can be synthesized via at least two procedures, within a few days, from standard starting materials, reagents and solvents that can be obtained from various chemical companies.

Pharmacology: 2-MEO-diphenidine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist with an uncompetitive channel-blocking effect. For the three structural MXP isomers, the following rank order of potency for inhibition at the NMDA receptor was found: MK-801 > PCP > 3-MXP > **2-MXP** > ketamine > 4-MXP > memantine, which closely paralleled NMDA receptor binding affinities. Binding affinities for human monoamine transporters (dopamine transporter (DAT), serotonin transporter (SERT) and norepinephrine transporter (NET)) showed highest affinity for DAT > NET > SERT. Importantly, but little discussed in the literature, 2-MEO-diphenidine shows affinity for sigma receptors (σ_1 and σ_2). However, the functional interaction of 2-MEO-diphenidine with the sigma binding sites is not known.

No systematic studies investigating the metabolism of 2-MEO-diphenidine have been published. The main metabolite of 2-MEO-diphenidine detected in blood and urine is hydroxy-2-MXP.

2-MEO-diphenidine is usually taken orally. Threshold doses range between 30 and 50 mg, low doses between 50 and 75 mg, common doses from 75 to 120 mg, and strong doses start at 120 mg. The onset of effects occurs 30 to 60 minutes following oral ingestion. The duration of effects is 6–8 hours with a peak effect after 2 hours. The duration of after-effects, known as a “hangover” or an “afterglow”, ranges from 1 to 3 hours. 2-MEO-diphenidine has a much more rapid onset and shorter duration of effects when vaporized or smoked.

No published safety data are available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of 2-MEO-diphenidine.

Adverse reactions in humans: Information from published case reports, the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory Tox-Portal and various Internet sources shows that 2-MEO-diphenidine can lead to various adverse reactions. These include acute behavioural, emotional, motivational, cognitive and somatosensory and motoric changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, hallucinations and out-of-body experiences can occur. Cognitive alterations at higher doses include

depersonalization, derealization, loss of ego boundaries, and, in some cases, delusions and paranoia. Acute intoxication can lead to emergency department admissions or even death.

In summary, a search of all available information worldwide found that four deaths had been reported and in only two of these cases was 2-MEO-diphenidine determined to be the cause of death. Some descriptions are available of cases of severe intoxication that led to admission to an emergency room and sometimes to admission to a hospital as an inpatient. However, the high proportion of polysubstance use might have played a role in the intoxication and clinical features described in those case reports.

Dependence and abuse potential: One report described symptoms of potential use disorder and withdrawal symptomatology requiring hospitalization. Animal experiments, however, show that 2-MEO-diphenidine does not exhibit pro-dopaminergic stimulant-type effects and, from this neurochemical perspective, there is no indication that this drug has abuse liability. No firm conclusion can be drawn from information retrieved from online forums on the potential for tolerance and cross-tolerance (to other dissociative compounds). In summary, there is limited evidence that 2-MEO-diphenidine has a dependence and abuse potential.

Potential therapeutic applications: In 1989, a patent was granted on 1,2-diarylethylamines for controlling brain damage that occurs during periods of anoxia or ischaemia, by selectively reducing the hyperexcitatory effects of glutamate, which binds primarily to NMDA receptors. 2-MEO-diphenidine may have a role in controlling brain damage during periods of anoxia or ischaemia and may have clinical relevance in a range of therapeutic areas including pain, neurodegenerative disease, depression and alcohol dependence. On online forums, people who use 2-MEO-diphenidine reported an interest in its therapeutic use as an antidepressant.

Magnitude of public health problems: A few people have required hospitalization for heavy 2-MEO-diphenidine intoxication. In most of those cases, underlying psychiatric disorders and use of other drugs may have contributed to clinical complications. An estimation of public health problems is provided by the STRIDA project from Sweden, which showed that only 0.4% of the high-risk population (e.g. psychonauts from the drug scene) tested positive for 2-MEO-diphenidine. More importantly, in the past 2 years no relevant publication or case report has appeared in the scientific literature and discussions of its use online have ceased. In conclusion, in recent years no intoxications, fatalities or user experiences have been reported, which is indicative of a decreasing interest of the worldwide drug scene in 2-MEO-diphenidine.

1. Substance identification

A. International Nonproprietary Name (INN)

NA

B. Chemical Abstract Service (CAS) Registry Number

CAS Number: 8-46-127529

C. Other chemical names

- MXP
- 2-MXP
- methoxyphenidine
- methoxydiphenidine
- 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine
- piperidine, 1-(1-(2-methoxyphenyl)-2-phenylethyl)-, (+/-)-
- 1-(2-methoxyphenyl)-2-phenyl-1-(piperidine-1-yl)ethane

D. Trade names

None

E. Street names

None

F. Physical appearance

Powder, tablets

G. WHO review history

2-MEO-diphenidine has not previously been pre-reviewed or critically reviewed by the WHO Expert Committee on Drug Dependence.

2. Chemistry

A. Chemical name

IUPAC name: 1-[1-(2-methoxyphenyl)-2-phenylethyl]piperidine

CA Index name: None

B. Chemical structure

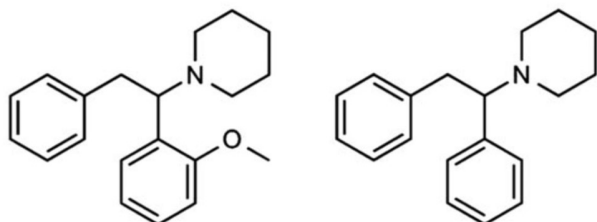
Free base:

Molecular formula: C₂₀H₂₅NO

Molecular weight: 295.426 g/mol

Fig. 1

Structure of 2-MEO-diphenidine (left) and, for comparison, diphenidine (right)



C. *Stereoisomers*

2-MEO-diphenidine is chiral, which makes the development of chiral separation methods necessary. Weiß et al. (1) tried several methods to separate the enantiomers, but up to now no information about the separation of stereoisomers of 2-MEO-diphenidine has become available. However, three structural isomers (2-, 3- and 4-MXP) are known to exist. These structural isomers can be separated using high-performance liquid chromatography (HPLC) selected-ion monitoring detection or gas chromatography ion trap mass spectrometry as shown in Fig. 2 (2).

D. *Methods and ease of illicit manufacturing*

The three structural MXP isomers (2-, 3- and 4-MXP) can be synthesized by two procedures. Procedure 1 is based on a three-component approach published by Le Gall et al. (3). This one-step procedure can be used to synthesize the desired isomers. Procedure 2 is based on the Grignard reagent, which is added to the Weinreb amide to give the corresponding ketone intermediate (4). Conversion to the primary amine followed by reaction with 1,5-dibromopentane yields the three MXP isomers (see McLaughlin et al. for a full description (2)).

With these two procedures, 2-MEO-diphenidine can be synthesized, within a few days, from standard starting materials, reagents and HPLC-grade solvents that can be obtained from various chemical companies.

E. *Chemical properties*

Melting point 171.5 °C

Boiling point not known

Solubility ~3 mg/mL in phosphate-buffered saline (pH 7.2), ~30 mg/mL in ethanol and dimethyl sulfoxide, ~50 mg/mL in dimethylformamide (5)

F. *Identification and analysis*

Standard analyses are conducted using gas chromatography (GC) and HPLC coupled to various forms of mass spectrometry (MS) (e.g. matrix assisted inlet ionization).

Nuclear magnetic resonance spectroscopy, infrared spectroscopy and thin layer chromatography have also been used (2).

In forensic drug analysis, separation of the three MXP structural isomers (see Fig. 2) is necessary to clarify the identity of the drug that led to intoxication. This can be done using HPLC selected-ion monitoring detection or gas chromatography ion trap MS; however, the discrimination of structural isomers using these methods is both cost- and labour-intensive. Therefore, a rapid and highly sensitive isocratic LC–MS friendly method (i.e. retention time within 4 minutes) was developed. This methodology is highly suitable for the rapid, specific and sensitive detection of structural MXP isomers in bulk forensic samples (6). However, a separation method for the stereoisomers of 2-MEO-diphenidine is still lacking.

3. Ease of convertibility into controlled substances

2-MEO-diphenidine is not readily converted into other internationally controlled substances.

4. General pharmacology

A. *Routes of administration and dosage*

2-MEO-diphenidine is usually taken orally. User forums report that threshold doses range between 30 and 50 mg, lower doses are between 50 and 75 mg, common doses are between 75 and 120 mg and strong doses start at 120 mg (7).

The onset of effects occurs 30–60 minutes following oral ingestion. The timing is dependent on several factors including dose, potential tolerance and cross-tolerance to other dissociatives, and route of administration. The duration of effects is 6–8 hours with a peak effect after 2 hours. The after-effects last from 1 to 3 hours. The after-effects are also known as a “hangover” or an “afterglow” (7, 8).

Some users described long-lasting and cumulative psychoactive effects with repeated dosing and have speculated that this might have been due to a long half-life (9) or, alternatively, that active metabolites might accumulate under these conditions.

Almost 30 user experiences with 2-MEO-diphenidine are available on Erowid (10). All of them were reported between 2014 and 2018. This suggests that interest in this drug has declined since 2018. One report describes non-fatal toxicity following consumption of 300 mg of 2-MEO-diphenidine, which was managed in an emergency department. This occurred despite the user’s tolerance to ketamine.

2-MEO-diphenidine has a much more rapid onset and shorter duration of effects when vaporized or smoked. Some user reports indicate that vaporization requires as little as 20% of a standard oral dose to produce the same effect (8).

B. *Pharmacokinetics*

Wallach & Brandt (9) have summarized what is known about the pharmacokinetics of 2-MEO-diphenidine. No systematic studies on the metabolism of 2-MEO-

diphenidine have been published. The main metabolite detected in blood and urine is hydroxy-2-MXP. Other metabolites are present at much lower concentrations (trace concentrations) including *O*-demethyl-MXP and hydroxyl-*O*-demethyl-2-MXP (9).

Hydroxy-MXP, dihydroxy-MXP and hydroxyl-demethyl-MXP metabolites (position of hydroxylation undetermined) were also detected in the urine of a 35-year-old man who was hospitalized as a result of 2-MEO-diphenidine intoxication (11).

Three hydroxylation products *O*-demethyl-MXP and three glucuronidated hydroxylation products (positions of modifications not specified) were detected in a urine sample collected in a case of acute intoxication (12).

C. *Pharmacodynamics*

Effects in vitro

2-MEO-diphenidine is an *N*-methyl-D-aspartate (NMDA) receptor antagonist (13–16). Electrophysiological studies suggest that 2-MEO-diphenidine provides receptor antagonism via an uncompetitive channel-blocking effect (16). Thus, this substance blocks NMDA receptor-mediated field excitatory postsynaptic potentials (fEPSPs) in rat hippocampal slices in a manner consistent with a channel blocker such as MK-801 – which is the gold standard for uncompetitive NMDA receptor blockade. For the three structural MXP isomers, the following rank order of potency for inhibition was found: MK-801 > PCP > 3-MXP > 2-MXP > ketamine > 4-MXP > memantine, which closely paralleled NMDA receptor binding affinities (16).

Two studies reported the inhibitory constant (K_i) value at the NMDA receptor for 2-MEO-diphenidine: 36 nM (16) and 170 nM (14), respectively. The discrepancy in binding affinities between these two studies may be explained by the different radioligands and tissue preparations used for NMDA receptor binding. Whereas, Wallach et al. (16) used [^3H]MK-801 in rat forebrain, in the study in the initial patent description [^3H]TCP in whole rat brain was used (14).

Binding affinities for human monoamine transporters (dopamine transporter (DAT), serotonin transporter (SERT) and norepinephrine transporter (NET)) were also determined. 2-MEO-diphenidine showed the highest affinity for DAT ($K_i = 2915$ nM (16) and $K_i = 4800$ (17)), followed by NET ($K_i = 6900$ nM) and negligible affinity for SERT ($K_i = 20$ μM) (17). The low affinity for SERT relative to NET and DAT was also reflected by very low reuptake inhibition. Thus, the range for the half maximal inhibitory constant (IC_{50}) – which is more reflective of the functional strength of the ligand – was between 10 and 741 μM depending on the study (9). The low affinity/activity for SERT is seen for all structural MXP isomers (9).

Although it has been little discussed in the literature, 2-MEO-diphenidine shows affinity for sigma receptors (σ_1 $K_i = 124$ nM and σ_2 receptor $K_i = 508$ nM (16)). The functional interaction of 2-MEO-diphenidine with the sigma binding sites is not well understood, but it is noteworthy that the σ_1 receptor is a membrane protein

expressed throughout the human body. It acts like an inter-organelle signalling regulator and fine tunes electrical activity and calcium homeostasis.

Effects in vivo

Similar to classical NMDA receptor antagonists such as MK-801, a high dose of 2-MEO-diphenidine (20 mg/kg, subcutaneously) significantly disrupted prepulse inhibition (PPI) of the startle reflex in rats (9). PPI of the startle reflex is an established measure of sensorimotor gating and NMDA receptors in the hippocampus play a critical role in the regulation of PPI. PPI disruption caused by NMDA receptor antagonists may reflect alterations in information processing that contribute to their dissociative effects (19). However, 2-MEO-diphenidine was less potent in these PPI experiments than ketamine (20), which was unexpected given its higher NMDA receptor affinity (16).

5. Toxicology

No published safety data are available concerning the toxicity, reproductive impact and carcinogenic/mutagenic potential of 2-MEO-diphenidine.

6. Adverse reactions in humans

Information from published case reports, the UNODC EWA Tox-Portal and various Internet sources shows that 2-MEO-diphenidine can cause acute behavioural, emotional, motivational, cognitive and somatosensory, and motoric changes, as well as cardiovascular effects including hypertension and tachycardia. At higher doses, acute intoxication can lead to emergency department admissions or even to death. Experiences reported by almost 30 users between 2014 and 2018 were retrieved from Erowid (10). In addition, the information obtained by Van Hout & Hearne (21) who searched the Internet using specific keywords: “methoxphenidine”, “MXP” and combinations with “experience”, “report”, “forum” and “trip” was consulted.

Drug user experiences show that the effects of 2-MEO-diphenidine vary greatly from person to person and according to the dose taken. After oral administration, the effects occur after approximately 30–80 minutes and following nasal administration, after approximately 10–30 minutes. The effect is also heavily dependent on the set and setting, which is a common drug phenomenon. At higher doses (from 70 mg orally) hallucinations and out-of-body experiences can occur. A typical out-of-body experience was described by a user who reported ingesting an extremely high dose of 500 mg of 2-MEO-diphenidine (10).

“I could visually see in front of me, but I could no longer feel any of my body. I was no longer in my room, but a collection of static images were ahead of me. The images would shift continually – consisting of a multitude of grainy, static colours. I could hear a very loud audible buzzing coming from all around me. I could still think. And I was stuck in what seemed to be a never ending loop. I was trying to convince myself that I hadn't died. I'd find a way out of this box I'd found myself in, that my body would start working again if I kept trying to move it. After what genuinely felt as though many years had

passed I started to accept my fate. I accepted that this was death, that my life in the previous world was over and that this was it forever more – slowly, I became content with my surroundings and my presence in whatever world I had found myself in. Suddenly, I was jolted from the static images and I felt as though my body were reconnecting. My vision started to pull upwards – I could see the ceiling in my room again and then I became one with my physical body gain” (10).

In addition to out-of-body experiences, depersonalization, delusions, paranoia and amnesia have been described (22, 23). Importantly, polysubstance use might have played a role in most of the intoxication cases and in the clinical features described by users.

Worldwide, four deaths have been reported. In two of these cases 2-MEO-diphenidine was determined to be the cause of death, in one case death was due to a fall and in the other case it was due to drowning in a bathtub (24–26). These four deaths are described below in more detail, in addition to several severe cases of intoxication.

Fatalities

The report of the first three fatal cases was published by Elliott et al. (24). Although it is not clear from the publication, the cases were presumably reported from the United Kingdom. The first case report describes a 34-year-old male who was found dead at home. The autopsy revealed an enlarged heart and hypertensive heart disease. 2-MEO-diphenidine was found to be present at a concentration of 24.0 mg/L in postmortem femoral blood and was also detected in the urine. Drug toxicity was probably the cause of death (25). The second case was a 34-year-old male who was found dead at home. He had a medical history of epilepsy, attention deficit hyperactivity disorder and social anxiety. He had been prescribed levetiracetam, dexamphetamine and diazepam. A sachet labelled “methoxphenidine 2 g” was found in his pocket. Autopsy results did not reveal any somatic abnormalities. 2-MEO-diphenidine was found to be present at a concentration of 2.0 mg/L in postmortem femoral blood and was also detected in urine. Prescription drugs (diazepam and quinine) were found at therapeutic concentrations and no ethanol was detected. The cause of death was most likely 2-MEO-diphenidine toxicity. In the third case, a 38-year-old male with a medical history of schizophrenia was found dead on a road having jumped or fallen from a road bridge. 2-MEO-diphenidine was found to be present at a concentration of 1.36 mg/L in postmortem femoral blood and was also detected in urine. The prescription antipsychotic drug risperidone was present at a therapeutic concentration and no ethanol was detected. The cause of death was fatal injuries sustained from the fall (24). The fourth death involved a 21-year-old male who had drowned in a bathtub. 2-MEO-diphenidine was found to be present at a concentration of 0.19 mg/L in postmortem femoral blood. However, substantial amounts of other drugs were also detected. These included lorazepam (5.7 ng/mL), delorazepam (54 ng/mL), amphetamine (64 ng/mL) and 4-fluoroamphetamine

(2.1 ng/mL). Blood alcohol concentration was determined to be 0.93% (26). The cause of death was related to multi-intoxication and finally drowning.

Intoxication

A 33-year-old man who had taken 2-MEO-diphenidine crashed into a railway-crossing gate (27) and was admitted to hospital. He presented with amnesia, out-of-body experiences and bizarre behaviour. The concentration of 2-MEO-diphenidine in his serum was 57 ng/mL. Amphetamine and MDMA were also present in concentrations of 111 and 28 ng/mL, respectively.

Another case of intoxication involved a 53-year-old male who was found on the street in a somnolent and confusional state, with transient echolalia and inability to communicate (12). On arrival at the emergency room he lost consciousness, and developed opisthotonus and nystagmus. He also had hypertension and tachycardia. Intravenous lorazepam was administered to treat his hypertension and tachycardia, resulting in a decrease in his blood pressure and heart rate within 30 minutes. Concomitantly, nystagmus and miosis resolved. He then regained consciousness but was confused and disoriented. He received further lorazepam treatment and by the next morning he was asymptomatic except for amnesia regarding the event. 2-MEO-diphenidine was identified qualitatively in plasma and urine, together with trace amounts of benzoylecgonine, amlodipine, buprenorphine, norfentanyl, hydrochlorothiazide, metformin and lidocaine. The man had a history of diabetes mellitus and multiple substance abuse, which contributed to this heavy intoxication.

In a similar case, a 35-year-old man with a history of hypothyroidism, Wolff-Parkinson-White syndrome, adjustment disorder and alcohol dependence was found somnolent in the street (11). He exhibited retrograde amnesia, hypertension and slurred speech. Severe rhabdomyolysis and acute kidney injury were also noted. 2-MEO-diphenidine was identified qualitatively in urine. A methylphenidate metabolite, tramadol and lorazepam were also detected.

In another case, the clinical features present after ingestion of 2-MEO-diphenidine mimicked ischaemic neurological symptomatology (28). A 25-year-old male presented at the emergency room after an episode of syncope with secondary head trauma. He was treated with midazolam and propofol and discharged from hospital two days later. 2-MEO-diphenidine and flubromazepam concentrations in his blood were 247 ng/mL and 411 ng/mL, respectively. Thus, intoxication with 2-MEO-diphenidine may result in atypical neurological symptoms, such as severe focal neurological signs.

Finally, a person with a history of polysubstance use developed a serotonin syndrome after using 2-MEO-diphenidine (29). A 33-year-old man with autism, who used methadone, loxapine and lorazepam, was admitted to an emergency room after being found in a state of agitation. The patient presented with profuse sedation, hyperthermia, tachycardia and mydriasis. Hyperthermia worsened within minutes and his body temperature rose to 42 °C. Supportive care included mechanical ventilation with sedation, endovascular targeted temperature management, large hydration, haemodialysis and blood transfusions. The patient

was discharged after 16 days having made a good recovery. Qualitative blood analysis revealed 2-MEO-diphenidine and the tryptamine-based hallucinogen α -methyltryptamine (AMT) (29). Given that it blocks serotonin reuptake, it is likely that AMT also contributed to the observed serotonin syndrome.

7. Dependence potential

A. *Animal studies*

No information on animal studies was available.

B. *Human studies*

In 2017, Champeau et al. (30) reported the first case in which 2-MEO-diphenidine was linked with a potential use disorder and with withdrawal symptomatology requiring hospitalization. A 21-year-old man with bipolar disorder was admitted to the emergency room with agitation and aggression. The patient reported chronic consumption of 2-MEO-diphenidine for 1 month, with doses up to 150 mg. Cessation of 2-MEO-diphenidine led to pronounced craving with anxiety. He also developed physical withdrawal symptoms including abdominal pain, vomiting and low-grade fever (38 °C), which lasted several days.

8. Abuse potential

A. *Animal studies*

Sahai et al. (31) analysed the mechanism of binding and functional relevance between rat DAT and structural MXP isomers using in silico and in vitro approaches. In addition to docking simulations, molecular dynamics simulations in rat DAT complexes (rDAT-2-MXP, rDAT-3-MXP and rDAT-4-MXP) were conducted in biophysically relevant membrane environments. When 2-MXP (or 3- and 4-MXP) was bound to DAT, it led to an inward facing conformation of DAT. Although this is a conformation seen by the classical dopamine releaser amphetamine, 2-MXP does not appear to be a DAT inhibitor nor does it demonstrate reverse transport. These in silico data are coherent with the in vitro data provided by Sahai et al. (31). Thus, 2-MEO-diphenidine had no significant effect on either RTI-121 binding (specific radioligand for the DAT), or evoked dopamine efflux in the nucleus accumbens measured by in vitro voltammetry. When considered together, these experiments do not indicate that 2-MEO-diphenidine has pro-dopaminergic stimulant-type effects and, from this neurochemical perspective, there is no indication that this drug has abuse liability.

B. *Human studies*

The case report by Champeau et al. (30) used a Drug Dependence Severity Scale developed by the Addictovigilance Center of Nantes, France (which contains mainly Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)-derived items). Using this scale, the patient had a high score, endorsing all six domains able to be assessed. These included tolerance, withdrawal and dose escalation as well as

behavioural aspects of dependence. This suggested that dependence on 2-MEO-diphenidine can develop.

No firm conclusion can be drawn about tolerance and cross-tolerance (to other dissociative compounds) from the information available.

9. Therapeutic applications and extent of therapeutic use and epidemiology of medical use

In 1989, a patent was granted on 1,2-diarylethylamines for controlling brain damage occurring during periods of anoxia or ischaemia by selectively reducing the hyperexcitatory effects of glutamate (which binds primarily to NMDA receptors) (32). This patent includes procedures for preparing 2-MEO-diphenidine. Since then 2-MEO-diphenidine has not been developed for use as a pharmaceutical, but reappeared in 2013 as a new psychoactive substance.

2-MEO-diphenidine may have a role in controlling brain damage occurring during periods of anoxia or ischaemia, and may have clinical relevance in therapeutic areas including treatment of pain, neurodegenerative disease, depression and alcohol dependence (9). Some users of 2-MEO-diphenidine reported an interest in its therapeutic use as an antidepressant (21). Non-competitive NMDA receptor antagonists such as memantine may have a potential use in relapse prevention in people with alcohol dependence (33). This suggests that 2-MEO-diphenidine may also interfere with chronic alcohol effects.

The therapeutic potential of 2-MEO-diphenidine may be provided by NMDA receptor blockade and by its interaction with the σ_1 receptor. Ligands targeting the σ_1 receptor are being studied in clinical trials for the treatment of Alzheimer's disease, ischaemic stroke and neuropathic pain (18). Although this has not been tested experimentally, it is possible that the σ_1 receptor activity of 2-MEO-diphenidine may contribute to its therapeutic potential.

10. Listing on the WHO Model List of Essential Medicines

2-MEO-diphenidine is not listed on the WHO Model List of Essential Medicines (20th List) or the WHO Model List of Essential Medicines for Children (6th List).

11. Marketing authorizations (as a medicinal product)

2-MEO-diphenidine has never been marketed as a medicinal product.

12. Industrial Use

2-MEO-diphenidine has no industrial use.

13. Nonmedical use, abuse and dependence

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14. Nature and magnitude of public health problems related to misuse, abuse and dependence

As described in section 6, a small number of people with 2-MEO-diphenidine intoxication have required hospitalization. In most of those cases, underlying psychiatric disorders and use of other drugs may have contributed to the clinical picture. 2-MEO-diphenidine might have short- to long-term effects on memory function. For example, one user reported that after using the substance over several days he experienced serious cognitive impairment (10).

An indication of the scale of the public health problem related to 2-MEO-diphenidine is provided by the STRIDA project from Sweden. The study covered a 12-month period from January to December 2014 during which 750 cases of suspected drug intoxication originating from emergency rooms were enrolled. Only three of the patients enrolled tested positive for 2-MEO-diphenidine (with concentrations ranging from 187 to 409 ng/mL in serum) (33).

In the UNODC EWA Tox-Portal, one case of intoxication requiring hospital admission was reported from Germany. The concentration of 2-MeO-diphenidine in the urine was 440 ng/mL. The sample also contained methylone (120 ng/mL) and a very high concentration of desoxypipradrol.

In the past two years no studies or case reports that describe 2-MEO-diphenidine use have been published in the scientific literature. Similarly, there have been no recent discussions on online forums. The lack of reports of intoxication, fatalities or user experiences suggest a decreasing interest of the worldwide drug scene in 2-MEO-diphenidine.

15. Licit production, consumption and international trade

Not applicable.

16. Illicit manufacture and traffic and related information

Not applicable.

17. Current international controls and their impact

2-MEO-diphenidine is not controlled under the 1961, 1971 or 1988 United Nations Conventions.

18. Current and past national controls

Legal status of 2-MEO-diphenidine (retrieved from references 7, 8, 10):

Brazil: 2-MEO-diphenidine has recently been included in Brazil's controlled substances lists because of its potential to cause harm to public health.

Canada: 2-MEO-diphenidine has been a schedule I controlled substance since March 2016.

China: As of October 2015, 2-MEO-diphenidine is a controlled substance in China.

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Germany: 2-MEO-diphenidine is a controlled substance. Production and sale is illegal. Possession is not penalized if intended for self-consumption.

Italy: 2-MEO-diphenidine is a prohibited substance in Italy.

Sweden: 2-MEO-diphenidine is a prohibited substance in Sweden.

United Kingdom: Since May 2016, it has been illegal to produce, supply or import 2-MEO-diphenidine.

19. Other medical and scientific matters relevant for a recommendation on the scheduling of the substance

No data.

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Annex 1. Report on WHO Questionnaires for Review of Psychoactive Substances for the 43rd ECDD: evaluation of 2-MEO-DIPHENIDINE

Data were obtained from 105 Member States (19 African Region, 13 Eastern Mediterranean Region, 40 European Region, 16 Region of the Americas, seven South-East Asia Region and 10 Western Pacific Region) for the WHO Questionnaires for the Review of Psychoactive Substances. The total number of countries opting out of participation in the questionnaire is 13 (three African Region, two Eastern Mediterranean Region, two European Region, three Region of the Americas, one South-East Asia Region and two Western Pacific Region), leaving 92 active countries. Of these, 32 countries had information on the substance (Table 1).

Table 1. Numbers of countries providing information on 2-MEO-DIPHENIDINE

Region	Number of countries without information	Number of countries with information on substance
Africa Region	15	1
Eastern Mediterranean Region	7	4
European Region	21	17
Region of the Americas	10	3
South-East Asia Region	4	2
Western Pacific Region	3	5
Total 92	60	32

LEGITIMATE USE

No countries reported approved human medical products or veterinary products containing 2-MEO-DIPHENIDINE.

One country (Region of the Americas) reported 2-MEO-DIPHENIDINE being currently used in medical or scientific research (excluding use as an analytical reference standard), specifically in cell line studies (binding/functional assays) and animal studies.

No countries reported 2-MEO-DIPHENIDINE being used in industrial or other non-medical or non-scientific use.

No countries reported approved therapeutic indications for 2-MEO-DIPHENIDINE.

EPIDEMIOLOGY OF NON-MEDICAL/NON-SCIENTIFIC USE – USE FOR PSYCHOACTIVE PURPOSES OR RECREATIONAL DRUG USE

Eleven countries reported that 2-MEO-DIPHENIDINE is being misused or abused for its psychoactive properties/recreational use.

The most common known route of administration reported was oral (Table 2).

Table 2. Common routes of administration

Route of administration	Number of countries
Oral	6
Injection	1
Inhalation	0
Sniffing	2
Smoking	0
Don't know	19

The most common known formulation of 2-MEO-DIPHENIDINE reported was powder (Table 3).

Table 3. Common formulations reported by countries

Formulation	Number of countries
Powder	9
Tablets	5
Liquid for oral use	0
Solution for injection	0
Don't know	15

To the above, countries added:

- “liquid (route of administration unknown)”
- “capsule”
- “in plant materials together with other substances”.

Nine countries reported the health impact due to 2-MEO-DIPHENIDINE’s non-medical consumption as “serious” or “substantial” (Table 4).

Table 4. Level of negative health impact

Serious	Substantial	Negligible	Don't know
4	5	10	12

One country (European Region) commented, “... there may be unknown cases of negative health impacts because ... there is no reporting obligation by hospitals, poison centers, etc.”.

Three countries (three European Region) reported emergency room admissions related to the non-medical use of 2-MEO-DIPHENIDINE.

Concerning adverse effects, one country (European Region) commented, “High heart rate, pluckiness, warmed up, confused”.

No countries reported users of 2-MEO-DIPHENIDINE presenting for drug dependence treatment.

Regarding mortality, only two countries (one European Region, one Region of the Americas) reported deaths involving 2-MEO-DIPHENIDINE:

- three fatal cases where other substances were also involved (2015)
- one fatal case where other substances were also involved (2018).

STATUS OF NATIONAL CONTROL AND POTENTIAL IMPACT OF INTERNATIONAL CONTROL

Fourteen countries responded that 2-MEO-DIPHENIDINE is currently controlled under national legislation to regulate its availability.

Table 5 shows the main reported activities involving 2-MEO-DIPHENIDINE.

Table 5. Reported illicit activities involving 2-MEO-DIPHENIDINE

Activities	Number of countries
Smuggling from other countries	4
Manufacture of substance by chemical synthesis	0
Manufacture of substance by extraction from other products	0
Production of consumer products containing the substance	0
Trafficking	2
Diversion from legal supply chain	0
Internet sales – seller or website located in country	1
Internet sales – from abroad to buyers in country	1
Internet sales – other, or location of sellers and website unknown	3
Direct sales to people who use the substance	1
Don't know	17

To the above, countries added:

- “trafficking through postal services”
- “probably drug dealing”.

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Seven countries (four European Region, one Region of the Americas, one Western Pacific Region, one South-East Asia Region) reported seizures.

Table 6. Reported seizures of 2-MEO-DIPHENIDINE

Year	Seizures
2020	0
2019	2
2018	40
Total	42

Twenty-five countries have the forensic laboratory capacity to analyse 2-MEO-DIPHENIDINE.

One country (European Region) commented, "Forensic laboratories have the capacity to analyse 2-MEO-DIPHENIDINE if reference material is available".

Another country (Western Pacific Region) remarked, "In our opinion 2-MEO-DIPHENIDINE is not capable of inducing a psychoactive effect".