Australian Government
Department of Health

Application to Reschedule

N, α -DIMETHYL- 3,4 (METHYLENEDIOXY)PHENYLETHYLAME (MDMA) from Schedule 9 to Schedule 8 of the Poisons Standard

15 July 2020

Mind Medicine Australia Limited

Level 1/ 10 Dorcas St
South Melbourne VIC 3006

Contents

CONFIDENTIALITY

The Application contains no information claimed to be commercial-in - confidence.

APPLICANT'S DETAILS

1. **Applicant's Name;** Mind Medicine Australia Limited
2. **Applicant's Address;** Level 1, 10 Dorcas Street, South Melbourne, Victoria 3205
3. **Business Name;** Mind Medicine Australia
4. **Date of Submission;** 15 July 2020
5. **Contact Person;** Mr. Peter Hunt AM
6. **Email Address of Contact Person;** peter@mindmedicineaustralia.org
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8. **Phone Number of Contact Person;** 0419 271 483
9. **Fax Number of Contact Person;** Not Applicable

DECLARATION

I, Peter John Hunt, Chair of Mind Medicine Australia Limited:

- declare that the information provided in this application is true and current.
- undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.

Signature:

Name: Peter Hunt AM
Position: Chair of Mind Medicine Australia Limited
Date: 15 July 2020

PART 1 - SUMMARY OF THE APPLICATION

A. PROPOSED RESCHEDULING OF THE POISONS STANDARD

Mind Medicine Australia Limited requests a rescheduling of N,a-Dimethyl-3,4 (methylenedioxy) Phenylethylamine (MDMA) from Schedule 9 to Schedule 8 of the Poisons Standard.

B. SUGGESTED SCHEDULING OR OTHER WORDING

MDMA for use in the treatment of medical conditions:

(a) In preparation for oral use under the authorisation of a treating psychiatrist or addiction specialist physician in a medically controlled environment
(b) Manufactured in accordance with the Narcotic Drugs Act 1967; and/or
(c) Imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
(d) In therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989

C. DISTINCTION BETWEEN MEDICINAL MDMA & THE STREET-DRUG ECSTASY

In assessing this application an important distinction needs to be made between medicinal MDMA and the street-drug Ecstasy for the following reasons;

- Ecstasy may only contain a minimal amount of MDMA, if any at all.
- Ecstasy may contain other ingredients unknown, thus being dangerous.
- Dosage of Ecstasy cannot be regulated.
- Ecstasy use is uncontrolled.
- Ecstasy users do not undergo any testing to ensure that they are fit to consume.

Medicinal MDMA, administered in a medically - controlled clinical setting, is pharmaceutical grade, dosage is known, patients are properly screened, the use of the medicine is regulated and the medicine is administered only by trained health professionals.

Understanding the distinction between the two types of drugs is fundamental. This application reports the benefits, toxicity and harm associated with medicinal MDMA. Recreational Ecstasy is discussed but differentiated by name in the case of recreational non-clinical use.

D. SUBSTANCE SUMMARY

1. Chemistry

(source https://pubchem.ncbi.nlm.nih.gov/compound/1615)

Chemical Formula: $C_{11}H_{15}NO_2$

CAS Number: 42542-10-9

IUPAC Name: 1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine

Molar Mass: 193.24g/mol

Melting Point: 147-153°C

2. Chemical structure

(source https://pubchem.ncbi.nlm.nih.gov/compound/1615)

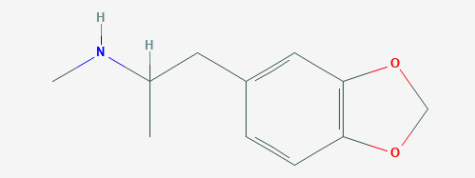


Image 1. Molecular structure of MDMA

3. Description of Substance

MDMA is a ring-substituted phenethylamine first synthesised by the Merck pharmaceutical company in 1912 (Cooper, 2018). MDMA is described as an 'entactogen' for its ability to produce anxiolytic and prosocial effects. MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA (Shulgin, 1986). The MDMA which has been used in all clinical trials to date is racemic, containing roughly equal amounts of each enantiomer (MAPS, 2019). There is currently limited evidence of differential effects of either enantiomer in humans. The racemic anhydrous hydrochloride salt of MDMA is readily water soluble with a pKa of 9.9. MDMA is stable at room temperature.

4. Pharmacology

i. Dose range

Therapeutic doses in current Phase 3 studies are standardised to 80mg for the first therapeutic session with an optional supplemental half dose during the therapeutic session (MAPS, 2018). Clinicians may choose to increase the dose to 120 mg in subsequent sessions based on their observation of the patients therapeutic and physical response. This is to account for individual differences in sensitivity to MDMA. There is a lower weight limit of 48kg for patients following this dosage protocol.

Table 1. MDMA Phase 3 Dosing Protocol for One Patient's Full Treatment (MAPS, 2018)

Medicinal Session	Initial Dose	Supplemental Dose*	Min – Max Cumulative Dose
1	80mg	40mg	80mg to 120 mg
2	80 or 120* mg	40 mg or 60 mg	80 mg to 180 mg
3	80 or 120* mg	40 mg or 60 mg	80 mg to 180 mg
Total Cumulative Dose:			240 mg to 480 mg

* if initial dose well tolerated and with clinician judgement

ii. Metabolism

MDMA is broken down in the liver, principally by the cytochrome P450; CYP2D6 enzyme, though others contribute (de la Torre, et al, 2004). MDMA reaches peak concentrations in plasma 2.4 hours after administration (Hysek & Simmler et al., 2014). The elimination half-life for MDMA is 8 hours. The key therapeutic effects of MDMA last 4-6 hours (Thal & Lommen, 2018).

Table 2. Peak Blood Flow Concentrations of MDMA by dose

Dose	Peak Blood Flow Concentrations
50mg	0.106 mg/L
75mg	0.131 mg/L
125mg	0.236 mg/L

iii. Pharmacology

MDMA stimulates release of pre-synaptic serotonin, norepinephrine, and dopamine in multiple brain regions (Amoroso, 2015). MDMA, like selective serotonin reuptake inhibitors (SSRI), binds with the pre-synaptic serotonin transporter, SERT, as well as the noradrenaline transporter, NET, and the dopamine transporter, DAT. This binding blocks the reuptake of these catecholamine neurotransmitters in presynaptic neurons, increasing the concentration in the synapse leading to increased downstream catecholamine signalling. MDMA's ability to increase serotonin is believed to be a major contributor to its therapeutic efficacy. It is interesting to note, that MDMA does not display as strong an affinity for DAT as methamphetamine (Han, 2016).

At high doses, well above the therapeutic range, MDMA has been observed to inhibit monoamine oxidase A (MAO-A) in vitro (Pilgrim, 2012). This may account for medical emergencies involving Ecstasy and MAO inhibitors in epidemiological settings. MDMA also binds with a range of post-synaptic serotonin receptors, including 5-$HT_{2A,}$ 5-HT_{1A} and 5-$HT_{2B,}$ as well as dopamine receptor D_2 (Amoroso, 2015). Catecholamine activation by MDMA also produces downstream effects, including the release of neurohormones such as oxytocin, prolactin and vasopressin (Dumont, 2009; Hysek & Schmid, 2014). Oxytocin, prolactin and vasopressin are implicated in attachment and bonding processes and may contribute to the prosocial effects of MDMA.

5. Therapeutic Effects in Human Studies

Under the influence of MDMA, patients can more readily experience and process their emergent psychological material in a state of psychological ease and safety (Amoroso, 2015). In a controlled setting, MDMA supports patients in reprocessing traumatic and painful memories, making MDMA efficacious for treating PTSD and addictions associated with trauma (Feduccia & Mithoefer, 2018). MDMA in this context facilitates:

- Feelings of closeness and affiliation
- Increased awareness of emotions
- Greater compassion and understanding of interpersonal relationships
- A sense of well-being
- Sensory intensification
- Changes to the encoding of emotional memory
- Reduction of fear response

6. Commonly Reported Spontaneous Adverse Events in Human Studies

In a study of 166 psychologically healthy participants given MDMA, the most frequent complaints were low appetite, dry mouth, difficulty concentrating, sweating, and bruxism (Vizeli and Leichti, 2017). It is noted that there are some mild potential side-effects observed 24 hours post dose, headache being the most common. For a full analysis of adverse effects reported in the trial, see Table 3 below.

Table 3. Acute and subacute adverse effects of MDMA total n = 166 (Vizeli and Leichti, 2017)

Acute and subacute adverse effects of MDMA (total N = 166)						
	Placebo			MDMA		
		acute	subacute		acute	subacute
	0h	up to 6h	24h	0h	up to 6h	24h
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Lack of appetite	2 (1)	3 (2)	1 (1)	4 (2)	98 (59)***	52 (31)***
Dry mouth	1 (1)	3 (2)	3 (2)	1 (1)	91 (55)***	37 (23)***
Difficulty concentrating	6 (4)	10 (6)	4 (2)	5 (3)	76 (46)***	35 (22)***
Cold feet	8 (5)	7 (4)	2 (1)	10 (6)	69 (42)***	10 (6)*
Sweating	2 (1)	0 (0)	0 (0)	0 (0)	68 (41)***	7 (4)*
Bruxism[a]	2 (2)	1 (1)	1 (1)	3 (2)	54 (40)***	19 (14)***
Restless legs	1 (1)	2 (1)	2 (1)	2 (1)	62 (37)***	12 (7)*
Dizziness	2 (1)	2 (1)	3 (2)	5 (3)	57 (34)***	12 (7)*
Hot flushs	1 (1)	0 (0)	0 (0)	1 (1)	52 (31)***	12 (7)***
Headache	9 (5)	27 (16)	25 (15)	8 (5)	42 (25)	55 (33)***
Heart palpitation	1 (1)	2 (1)	1 (1)	1 (1)	40 (24)***	11 (7)**
Lack of energy	9 (5)	23 (14)	5 (3)	8 (5)	38 (23)*	49 (30)***
Nausea	3 (2)	2 (1)	1 (1)	2 (1)	19 (11)***	9 (6)*
Anxiety	0 (0)	0 (0)	0 (0)	2 (1)	9 (6)**	3 (2)

N: number of subjects; [a]N = 134; *P < 0.05, **P < 0.01, ***P < 0.001 compared with placebo (Fisher's exact test)

In MAPS sponsored Phase 2 trials spontaneously reported reactions were observed upon drug administration but were generally transient and decreased as MDMA was metabolised and did not significantly detract from the therapeutic process (MAPS, 2019). Only nausea (6.9%), tight jaw (5.2%), dizziness (3.4%) and fatigue (3.4%) and irritability (1.7%) were described as severely limiting normal daily functioning. Most reactions reduced over the 24 hours after administration with some mild reactions resolving within several days to one week after dosing. During the 7-day period after dosing, the most common reactions were lack of appetite, jaw tension, restlessness, muscle weakness, dry mouth, thirst, impaired balance, and sensitivity to cold. For a full overview of spontaneously reported reactions in MAPS sponsored Phase 2 trials please see the MAPS Investigator Brochure page 101 for further detail.

7. Toxicity

For a comprehensive review of toxicity data please also see the Multidisciplinary Association for Psychedelic Studies (MAPS) Investigators Brochure section 4.4 Toxicity in Animals and Epidemiological settings (MAPS, 2019). This document is attached and contains a complete summary of available data. The following sections will summarise key findings. Please also see sections 2.1[F] B for a detailed exploration of the potential limitations of early toxicology research.

[i] Human Studies

The lethal dose in humans is LD_{50} ($human_{PO}$) = 10-20mg/kg (Jerome 2007, p. 7). This equates to between 700-1400mg for a 70kg person. The greatest dose used in clinical studies is between 1 and 2 mg/kg or 80mg to 120mg at one time (MAPS, 2018). Cases of human toxicity or fatality have occurred in uncontrolled settings where Ecstasy is being used and involve

MDMA blood levels ranging from 0.5 mg/L to 10mg/L at hospitalisation or the post-mortem (Kalant, 2001). This is up to 8 times the therapeutic dose of MDMA at T_{MAX} (see Table 2 on page 7 to compare therapeutic dose blood levels of MDMA). It is important to note the involvement of other drugs in many of these Ecstasy cases.

[ii] Animal Studies

MDMA increases the concentration of serotonin in the brain which at higher doses may cause chemical damage to cells (Kalant, 2001). Studies of rodent brains exposed to high doses of MDMA have shown decreased numbers of serotonin containing cells, reduced overall serotonin content and degeneration to serotonergic axon terminals.

In rodent and primate studies, single and multiple doses of between 5-300mg/kg have been used to investigate MDMA's toxicity (MAPS, 2019 pg 32). Major systems implicated in contributing to MDMA toxicity in animal studies include; cardiotoxicity, hepatotoxicity, neurotoxicity, hyperthermia and hyponatremia. The majority of all animal studies rely on frequent repeated doses. Studies investigating toxicity involve a regular dosing interval of two to four times per day, others use daily doses for 5 to 7 days. This dosing pattern makes it difficult to translate the relevance of high dose, multi-day dosing regimens to intermittent, irregular dosing patterns in humans. , These studies suggest that high and or chronic doses of MDMA may cause various forms of toxicity (Kalant, 2001).

[iii] Human Studies – Poly Drug Users

There have been numerous studies of cognitive effects of long-term poly drug users who use ecstasy (MAPS, 2019 pg 31) Changes have been observed in SERT receptor density, memory, impulse control and executive function when compared to non-drug users (Muller et al, 2019; Mercer et al 2017). A recent meta-analysis suggests that drug use per occasion may indicate duration and magnitude of changes and that the changes may be reversible with abstinence (Muller, 2019).. The challenge of these studies is three-fold (Krebs & Johnasen, 2012):

1. It is impossible to separate effects of various illicit drugs to determine effects of ecstasy alone since very few people use only ecstasy.
2. It is impossible to know the quality and possible contaminants of the drugs used by the participants.
3. These studies are cross-sectional and therefore are not making longitudinal comparisons in the same people; they may more accurately be describing premorbid attributes and detecting cognitive differences in a risk-taking subgroup of the population.

There has been one post-mortem study of the brain of an acute and chronic ecstasy user (Kish, 2000). The individual used ecstasy 4-5 nights every week at doses above the therapeutic range between the ages of 23-26 every week until his unrelated death at age 26. He also used cocaine and heroin. It was found that there was a 50-80% reduction in serotonin in the striatum when compared to controls.

[iv] Human Studies – Ecstasy Only Users

1. None of the therapeutic clinical studies that employed rigorous experimental controls have found long-term neurocognitive deficits or toxicology associated with MDMA in their participants (MAPS, 2019).
2. A Harvard study compared the cognitive functioning of 52 moderate to heavy Ecstasy *only* drug users to 59 non-drug users (Halpern, 2011). This group was comprised largely from the Mormon and some other religious communities. The discovery of this user population provided a unique opportunity to investigate the cognitive effects of regular Ecstasy use in individuals with limited exposure to other drugs. Moderate use was defined as 17-50 lifetime experiences of ecstasy and heavy use was defined as 50+ experiences. Exposures to other drugs were limited to 10. Few differences between Ecstasy and non-Ecstasy users were found in a range of measures including verbal and visuospatial memory, verbal fluency, attention, processing speed, manipulative dexterity, and executive function. Most differences were not significant and were attributed to chance. The only consistent finding was that heavy users showed greater impulsivity, which the authors suggest may be causally related to their heavy consumption rather than caused by ecstasy itself. These findings emphasise the need for caution when attributing cognitive changes to ecstasy use.
3. A study investigating chronic Ecstasy use, in those who use Ecstasy more than other drugs, showed decreased declarative memory function in the primarily Ecstasy drug user group with additional cognitive changes in the poly-drug group (Wunderli, 2017).
4. A meta-analysis investigating cognitive changes in Ecstasy users suggest that changes are related to drug doses and frequency and that changes diminish with abstinence (Muller, 2019).

[v] Human Studies – in clinical trials

Thermoregulatory Effects

Across Phase 2 trials, body temperature elevations above 1°C from pre-drug readings occurred in 44-50% of participants (MAPS, 2019). The proportion of participants for whom this was recorded was: 20% for the placebo group, 44% for the active blinded group and 50% for the open label group. The maximum temperature recorded was 38.7°C; all values returned to normal after treatment.

Cardiovascular (CV) Effects

As a sympathomimetic, MDMA can cause increases in Blood Pressure (BP) and Heart Rate (HR). No participants required medical intervention in MAPS sponsored studies (MAPS, 2019). Most individuals do not experience rises in BP and HR beyond that seen during moderate exercise. Greater elevations were observed in people with specific COMT and SERT genotypes but these were not severe enough to warrant contraindication. In a study of MDMA in 166 psychologically healthy individuals, transient severe hypertension (systolic blood pressure > 180 mmHg) was observed in 5% of participants on a 125mg dose of MDMA (Vizeli and Liechti et al, 2017). The duration of these Adverse Events (AE) was not long enough to require medical intervention. Individuals with cardiovascular disease that is poorly controlled by medication are contraindicated in current studies (MAPS, 2018).

Table 4. Summary of observed toxic effects of MDMA in animals, clinical research and in epidemiological settings

Pathology	Mechanism	Clinical use*	Epidemiological settings
Cardiotoxicity	Sympathomimetic elevation of blood pressure and heart rate (Frith, 1987)	Changes in trials safe for those without CV disease	Some toxicity observed in those with 900+ exposures to MDMA (and other drugs) (Droogmans, 2007). Other studies did not find any toxic effects with fewer exposures. (Lester et al. 2000). Individuals with CV or pulmonary disease are more at risk of SAE and morbidity.
Hyponatremia	MDMA may reduce plasma sodium causing electrolyte imbalances (Forsling, 2001). At chronic levels, with water consumption, this can result in brain swelling, heart failure and death.	Not observed in clinical settings. Patients provided with electrolyte water.	Major contributor to harm and morbidity. Occurs most commonly in environments of high physical activity or heat with poly-drug use. Leads to overconsumption of water (Baggott et al. 2016) particularly in individuals with certain variations of COMT and CYP2D6 genotypes.
Neurotoxicity	High doses (5-300 mg/kg) causes neurotoxicity to serotonergic and possibly dopaminergic axon terminals. (Colado, 1999; Mercer, 2017)	Not observed in clinical settings.	Mild cognitive effects observed in poly-drug users (including memory, impulsivity and executive functions (Muller, 2019, Lyvers, 2006)) (). Reduction of serotonin in the post-mortem brain of a chronic user (Kish, 2000) No significant evidence of cognitive changes for moderate MDMA-only users (Halpern, 2011). Chronic primarily MDMA poly-drug users show decreased declarative memory performance (Wundereli, 2017).
Hepatotoxicity	A dose of 20mg/kg in rats was capable of causing cell death in the liver. High body temperature is implicated (Cerretani, 2011).	No clinically relevant cases of liver toxicity in trials.	16-19% of case reports of SAE in Ecstasy (poly-drug) users report some liver complications (Carvalho et al, 2010).
Hyperthermia/ Hyperpyrexia (>40°C)	Raised body and cerebral temperature combined with vasoconstriction (Colado, 1999).	Temperature remains in normal bounds in clinical settings	Major contributor to harm and morbidity (Dafters, 1995). Occurs most commonly in environments of high physical activity or heat with poly-drug use. Women more vulnerable than men.

* Refers to data collated from The Multidisciplinary Association for Psychedelic Studies Phase 2 trials investigating MDMA (n= 72) (MAPS, 19).

8. Range of use

MDMA shows strong potential as a therapeutic adjunct in the treatment of PTSD (Mithoefer et al, 2019), with Phase 3 trials now in progress.

The following conditions are currently being investigated in clinical studies (see Part 3 for a list of completed and current studies):

- PTSD
- Anxiety and emotional processing in adults with Autism
- Anxiety disorders, and
- Addictions.

E. OVERVIEW

PTSD (post-traumatic stress disorder) is notoriously hard to treat, with current antidepressant pharmacotherapy achieving relief from symptoms in only about 20%-30% of sufferers (Stein et al. 2009). While 44% of patients experience some clinical improvement in their PTSD symptoms from trauma focused psychotherapies, 60-72% still retain the PTSD diagnosis, with 35% still experiencing debilitating symptoms (Bradley, 2005; Lee et al. 2016; Steenkamp et al; 2015). A significant impediment to the treatment of PTSD is the high drop-out rate ranging from 30-50% across clinical trials, significantly higher than for other mental health disorders (Schottenbauer et al., 2008). Therapeutic efficacy is limited by a PTSD patient's 'narrow therapeutic window', caused by the anxious arousal associated with traumatic memory (Thal & Lommen 2018). This means psychotherapy can be confronting for patients and can lead to traumatisation and/or dissociation symptoms.

There is strong evidence for the safety and efficacy of MDMA-assisted psychotherapy for the treatment of PTSD (Bahji et al, 2020). Indeed, many mental health experts are now paying close attention to this re-emerging field, in the belief that MDMA-assisted psychotherapy may offer treatment-resistant patients a breakthrough option in the treatment of mental health conditions such as PTSD, addiction, end-of-life anxiety and social anxiety in autistic adults (Sessa et al., 2019). MDMA places the patient in a "zone of optimal arousal", enhancing access to emotions, increasing a perceptible sense of ease, and expanding a patient's therapeutic window (Mithoefer, 2011).

Through a series of worldwide trials, The Multidisciplinary Association for Psychedelic Studies (MAPS) has finalised Phase 2 trials for the use of MDMA-assisted psychotherapy in the treatment of PTSD (Mithoefer et al. 2019). Participants underwent two or three 90-minute preparatory psychotherapy sessions which were followed by two to three supervised MDMA (or placebo) sessions. The data across six Phase 2 trials was published in *Psychopharmacology*, showing that MDMA has a 54.2% remission rate for treatment-resistant PTSD sufferers, compared to 23% in the placebo group. Across these Phase 2 studies the dropout rate was only 7.6%, which illustrates its tolerability and strong patient adherence. The six trials included in this study were conducted between 2004–2017 with a total of 103 participants. In the follow ups of two of these studies it was also found that following treatment with MDMA, patients continued to improve. This was observed in subsequent follow ups a year later which showed a 63-68% rate of remission at this time point (Otálora, 2018; Mithoefer, 2018).

MDMA-assisted therapy has been granted 'Breakthrough Therapy' status by the US Food and Drug Administration (FDA), expediting its transition to prescription medicines subject to positive outcomes from current Phase 3 trials (MAPS PR, 2017). This designation highlights the FDA's anticipation that MDMA-assisted therapies may offer substantial advantage over current treatments. An interim report on the MAPS Phase 3 trial revealed a 90% or greater chance that the completed trial will show significant results (MAPS PR3, 2020). Release of the final data is expected as soon as 2021. If the final results confirm the interim results MDMA may become available as a registered medicine in the United States for the treatment of PTSD as early as 2022. MDMA has recently been approved for advanced access "Compassionate Use" in Israel for patients who have not improved with current treatment modalities (MAPS

PR2, 2020). Likewise, MDMA has received approval for use under a similar program (Expanded Access) in the USA (MAPS PR1, 2020), Switzerland and, more recently, Australia (under Special Access Scheme-B).

PART 2 - BODY OF THE APPLICATION

A. BACKGROUND – CURRENT SCHEDULING

The SUSMP currently lists MDMA as a Schedule 9 drug.

B. HISTORICAL CONTEXT

1. Discovery and Early Therapeutic use of MDMA

MDMA was originally synthesised in 1912 by Merck as a drug intermediate for medication to stop bleeding (Amoroso, 2015). Dow Chemist, Alexander Shulgin refined the synthesis of MDMA in 1976. In the first clinical study of MDMA, researchers found that the drug produced "an easily controlled altered state of consciousness with emotional and sensual overtones" (Shulgin and Nichols, 1978). It is estimated that between 1976 and 1986, over 150 therapists used MDMA-assisted psychotherapy to treat over 4,000 patients with remarkable results (Rosenbaum & Doblin, 1991). MDMA was used in the treatment of PTSD, depression, phobias, addiction, couples therapy, as well as for pain and psychiatric morbidity in end-stage cancer patients. In 1988 the Swiss Medical Society for Psycholytic Therapy reviewed individual and group psychotherapy with MDMA in over 100 patients (Sessa et al. 2019). Over 90% of patients described improvements at the 19-month follow-up.

In 1984, in response to rising population use and police seizures of the drug ecstasy, the Drug Enforcement Administration in the United States announced the intention to ban MDMA (Sessa et al, 2019). Research into the therapeutic use of MDMA as a therapeutic agent was ceased in 1985 when MDMA was scheduled under the Controlled Substances Act (CSA).

Subsequent research focused on the potential harms of MDMA. A number of studies indicated that MDMA had neurotoxic effects in animals and in human recreational users (Amoroso, 2015). However, these studies studied doses significantly higher than therapeutic doses and their designs were at times flawed. For example, it was found that MDMA produced severe neurotoxicity and sometimes death in non-human primates. However, several years later, it was found that the investigators had accidentally used methamphetamine rather than MDMA (Ricaurte et al. 2002). Please see sections 2.1[F]B. for a detailed exploration of the limitations of early toxicology research.

2. Research Resurgence

In the early 2000s restrictions on MDMA research loosened. The FDA approved experiments for MDMA-assisted psychotherapy. In 2001, the first RCT looking at the efficacy of MDMA-assisted psychotherapy for treatment-refractory PTSD commenced. It found that after 12 sessions of psychotherapy, including two MDMA-assisted sessions, 83% of participants no longer met DSM-IV criteria for PTSD (Mithoefer, 2010). These effects were maintained at a 3.5-year follow-up, with only 10% of participants relapsing in that time. In 2017, the FDA referred to MDMA-assisted psychotherapy for PTSD as a 'breakthrough therapy', formally endorsing the use of the drug in clinical trials (see also Part 1D).

C. BASIC CHEMISTRY FACTS

1. Chemistry

(source https://pubchem.ncbi.nlm.nih.gov/compound/1615)

Chemical Formula: $C_{11}H_{15}NO_2$

CAS Number: 42542-10-9

IUPAC Name: 1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine

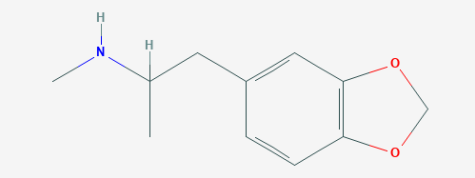
Molar Mass: 193.24g/mol

Melting Point: 147-153°C

2. Chemical structure

(source https://pubchem.ncbi.nlm.nih.gov/compound/1615)

Image 1. Molecular structure of MDMA



3. Description of Substance

MDMA is a ring-substituted phenethylamine first synthesised by the Merck pharmaceutical company in 1912 (Cooper, 2018). MDMA is described as an 'entactogen' for its ability to produce anxiolytic and prosocial effects. MDMA is a chiral molecule, possessing two enantiomers, S(+)-MDMA and R(-)-MDMA (Shulgin, 1986). The MDMA which has been used in all clinical trials to date is racemic, containing roughly equal amounts of each enantiomer (MAPS, 2019). There is currently limited evidence of differential effects of either enantiomer in humans. The racemic anhydrous hydrochloride salt of MDMA is readily water soluble with a pKa of 9.9. MDMA is stable at room temperature.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 - PROPOSAL TO CHANGE PART 4 OF THE POISONS STANDARD

PART 2.1 [A]: RISKS AND BENEFITS ASSOCIATED WITH THE USE OF MDMA

A. WHAT ARE THE BENEFITS?

1. Positive Psychological Effects

Outcomes for psychotherapy rely on a strong therapeutic alliance between patient and therapist which can be challenging for many patients with PTSD (Schottenbauer et al., 2008). PTSD patients are described as having a narrow therapeutic window, meaning psychotherapy can trigger patients outside the zone of optimal arousal and into overwhelm, leading to dissociation or re-traumatisation (Mithoefer, 2011).

MDMA releases the social bonding neurohormones of oxytocin, prolactin and vasopressin as well as serotonin (Hysek & Schmid et al, 2014). Oxytocin, prolactin and vasopressin have been described as a key modulators of trust and bonding. MDMA is known to produces a warm, emotionally grounded feeling with a sense of self-acceptance, and a reduction of fear and defensiveness (Amoroso, 2015). This increase in emotional safety underlies MDMA's ability to ease the patient's experience of challenging emotional memories and enhance the therapeutic alliance. It is important to note that MDMA is not pharmacotherapy alone but an adjunct for the therapeutic process. Please see section 2.1[F]C for a detailed outline of the MDMA-assisted therapy protocol.

2. Reduction of Fear Response and Memory Reconsolidation

PTSD patients show increased sensitivity, or attentional bias, to threat related stimuli. This bias correlates to overactivity in the amygdala and decreased activity in the anterior cingulate cortex during a conditioned fear response (Bremner et al, 2005). MDMA has been shown to create the opposite brain state, decreasing activity in the amygdala and increasing activity in the anterior cingulate cortex during recollection of negative memories (Carhart-Harris, 2014). MDMA's neuropsychological state appears to support the reconsolidation of emotional memory with a diminished fear response as well as the experience of a felt sense of safety (Feduccia & Mithofer, 2018).

A leading trauma therapy approach, Exposure Therapy, relies on slowly enabling a patient to extinguish their fear response to allow processing of traumatic memory (Thal & Lommen, 2018). MDMA may accelerate this process by diminishing the fear response, enhancing the ease by which a patient can tolerate and reprocess traumatic memory (Doss, 2018). MDMA-assisted therapy was compared to exposure therapy in a 2016 meta-analysis (Amoroso & Workman, 2016). The analysis found MDMA-assisted therapy had a larger effect size (Hedges'

g=1.17 vs. g=1.08, respectively) and that the dropout rate was significantly lower for MDMA-assisted therapy. It is interesting to note that this analysis was done prior to release of several larger more positive Phase 2 trial data (Mithoefer, 2018; Otálora, 2018)

3. Promising Results from Phase 2 Clinical Trials and from Phase 3 Interim Analysis

Of those diagnosed with PTSD, 20-30% respond to pharmacotherapy (Stein, 2009). SSRI's are considered a second line treatment (WHO, 2013). Current psychotherapy treatments provide 44% of those entering treatment to experience some clinical relief from PTSD but remission rates are lower (Bradley, 2005). The need for more effective PTSD treatments that address the unique neuropsychological state of trauma is essential.

In Phase 2 trials investigating MDMA for the treatment of PTSD, MDMA showed a 54.2% remission rate for treatment-resistant PTSD sufferers (with an average of 17.9 years of PTSD), compared to 23% in the placebo group (Mithoefer, 2019). Phase 3 trials are now in progress. An interim report generated by a third-party data monitoring committee (DMC), in agreement with the FDA, analysed data from the first 60 of 100 participants in current Phase 3 trials (MAPS PR 3, 2020). The DMC found "…a 90% or greater probability that the trial will detect statistically significant results when all participants have been treated, and that the trial will not require additional participants beyond the first 100".

4. Low Risk of Dependence

Following a therapeutic protocol, the administration of MDMA will be limited to in clinic treatments, with minimal risk of dependence. Medicinal MDMA does not produce dependence as defined in the contemporary versions of the *Diagnostic and Statistical Manual of Mental Disorders* or the *International Statistical Classification of Diseases* (Kalant, 2001). Therapeutic treatment with MDMA has not be shown to increase illicit drug use, see Part 2.1[E]C1 also (MAPS, 2019)

5. Historic Therapeutic Use Without Issue

Early therapeutic use of MDMA was without complication (Passie, 2018). In more recent trials, adverse effects (AEs) have been rare and there have been no life threatening or serious adverse effects (SAEs). In MAPS sponsored Phase 2 studies one individual was hospitalised due to increased frequency of ventricular extrasystoles during an open-label 125mg MDMA treatment (MAPS, 2019 pg 168). The individual was observed in a hospital setting and all readings returned to normal ranges.

B. WHAT ARE THE HAZARDS?

1. Medical Condition Contraindications

For the following please see also Table 4 page 13 and Part 1[C]7 for further details.

[i]. Cardiovascular and Cerebrovascular Risks

Current clinical trials exclude individuals with uncontrolled blood pressure (MAPS, 2018). In a therapeutic setting cardiovascular health will be assessed prior to use and a physician is to be on premises at all times.

[ii].Thermoregulatory Risks

Although body temperatures remain stable in clinical settings, in uncontrolled settings there is a greater risk of hyperthermia (Drafter, 1995). A physician is recommended to assess patients for thermoregulatory risk.

[iii] Osmoregulatory Risks

MDMA administered in controlled settings is not expected to pose osmoregulatory risks as patients are relaxed and are provided with electrolyte water. However, in uncontrolled settings, particularly in hot environments accompanied by physical exertion, MDMA may produce electrolyte imbalances which can be dangerous in vulnerable individuals (Baggott et al, 2016). It is recommended to assess patients for osmoregulatory risk and to have electrolyte supplements available on premises.

2. Pharmaceutical Contraindications

[i] Monoamine oxidase inhibitors (MAOIs). Their combination with MDMA predisposes individuals to serotonin syndrome and has been the cause of some fatalities (Pilgrim, 2012).

[ii] Caution must be used if MDMA is co-administered with drugs that are also metabolised by CYP2D6 due to the possibility of increased concentrations of MDMA caused by enzyme saturation. This is more likely to be a problem with high doses (Vizeli and Leitchi, 2017).

[iii] Tramadol which acts as a serotonin norepinephrine reuptake inhibitor and is metabolised by CYP2D6 enzymes is known to increase the risk of serotonin syndrome (Hassamal et al, 2018).

[iv] In clinical trials all psychiatric medications are stopped to ensure MDMA's effectiveness. A two-week washout period is followed prior to treatment. This is because many psychiatric medications may reduce MDMA's efficacy (MAPS, 2019)

3. Increased Health Risks with High Doses

Adverse effects increase with higher non-therapeutic doses (Vollenweider, 1999). It is therefore recommended that prescription of MDMA follow the dosing protocol outlined in Table 1 page 7.

4. Increased risk in uncontrolled non-clinical settings

Morbidity and mortality have only occurred in uncontrolled, non-clinical settings (Sessa, 2019). This application is for the prescription of MDMA for in clinic settings only.

5. Acute spontaneous reactions in clinical trials

MDMA can elicit a range of acute spontaneous reactions rated mild to moderate, the majority of which resolve with 24 hours and the remainder within a week (Part 1[C]6). The most common are nausea, jaw clenching, muscle aches, numbness, dizziness, headache, sweating, and decreased appetite (Thal & Lommen, 2018). These reactions are not considered to be significant hazards.

C. HOW WIDESPREAD ARE THE HAZZARDS?

1. All significant hazards are primarily in uncontrolled settings

The hazards are significantly more likely in any person who administers MDMA (in the form of Ecstasy) in an uncontrolled setting (i.e. non-medical environment, recreational). ***However, with the rescheduling of MDMA to Schedule 8, the Schedule 8 MDMA use will be limited to strictly controlled medical environments***.

2. Harms to users and others in epidemiological settings

Analysis of harms caused by a range of psychotropic substances ranked Ecstasy as among the least harmful to the user and least harmful to others in epidemiological settings (Nutt et al. 2010). Current Schedule 8 drugs; buprenorphine, methadone, cannabis, ketamine, amphetamine; Schedule 4 drugs; anabolic steroids, benzodiazepines; and unscheduled drugs; tobacco and alcohol; all ranked as causing more harm to the user and more harm to others when compared to Ecstasy. This research was recently repeated in Australia at St Vincent's Hospital Melbourne (Nutt, D and Castle, D et. al. 2019), see Table 5 below.

3. Prevalence of Ecstasy Use in Australia

The 2016 National Drug Strategy Household Survey report showed that about 11.2% of Australians over the age of 14 have used ecstasy in their lifetimes (AIHW, 2017). During 2016, ecstasy use in people over 14 was 2.2% which was a decrease from 2007 (3.5%), 2010 (3.0%) and 2013 (2.5%). The most common frequency of use was once or twice per year (51.5%).

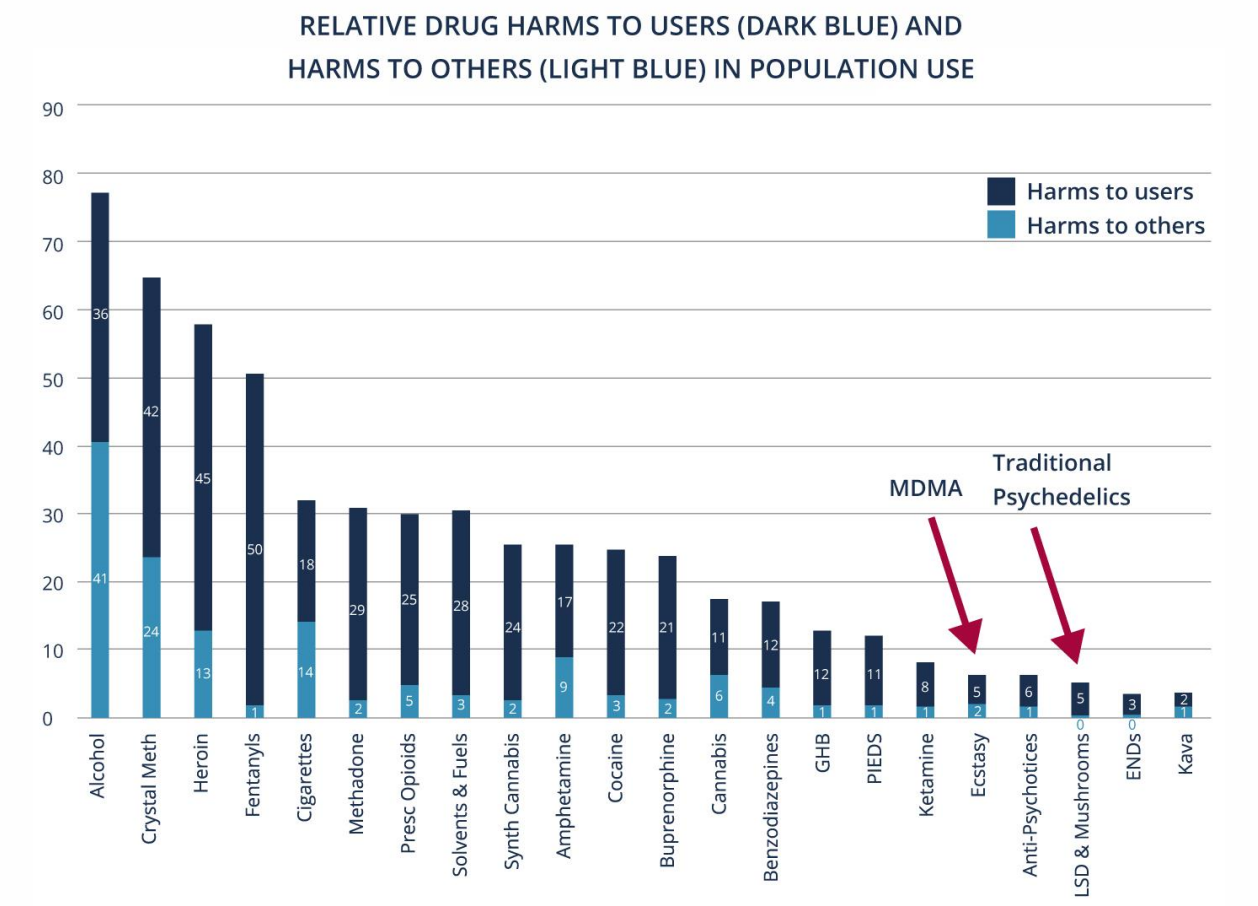


Table 5. The Australian Drug Harms Ratings Study examined the psychological, medical and social harms of substances in population use adjusted for number of users.

D. IN WHAT CIRCUMSTANCES CAN HAZZARDS ARISE?

Hazards are far more likely to arise in uncontrolled, non-clinical settings where the MDMA is in the form of or part of the street-drug ecstasy. Use in these settings exacerbates MDMA's risk profile. They include taking ecstasy in the following circumstances:

- In combination with other drugs: 48% of ecstasy related deaths occurred from multiple drug toxicity (Roxburgh & Lappin, 2020)

- In hot and poorly ventilated environments during high levels of physical activity such as night clubs though only 7% of recreational ecstasy-related toxicity occurred at music festivals or dance parties (Roxburgh & Lappin, 2020)

E. ECSTASY IMPLICATED DEATHS IN AUSTRALIA

The following is a summary of all deaths where ecstasy was found in the individual's system at the time of autopsy.

All deaths	Total *n* = 392 % (*n*)	Female *n* = 74 % (*n*)	Male *n* = 318 % (*n*)
Drug toxicity	62 (244)	76 (56)	59 (188)
Multiple drug toxicity	48 (189)	43 (32)	49 (157)
MDMA toxicity only	14 (55)	33 (24)	10 (31)
Other cause	38 (148)	24 (18)	41 (130)
Traumatic accident	29 (115)	19 (14)	32 (101)
Violent suicide	6 (23)	3 (<5)	7 (21)
Disease	3 (10)	3 (<5)	3 (8)

Table 6. Cause and Intent of Ecstasy-related deaths in Australia between 2000-2018 (Roxburgh & Lappin, 2020)

In Australia between the years 2000 to 2018, 56% of recreational ecstasy-related toxicity occurred in private locations whereas 44% occurred in public places (Roxburgh & Lappin 2020). The most common public places were streets/roadways, followed by outdoor places (parks, beaches, countryside).

F. WHO IS AT RISK?

i. Individuals with medical conditions listed in part 2.1[A]B1 and individuals who do not cease use of drugs listed in 2.1[A]B2

ii. Individuals who take MDMA in uncontrolled settings in combination with other drugs (Roxburgh & Lappin, 2020). 86% of recreational users reported consuming alcohol at the same time as ecstasy (AIHW, 2017)

iii. In cases of ecstasy toxicity alone, deaths among women are more likely to be attributed to drug toxicity (Roxburgh & Lappin, 2020).

G. IN WHAT CIRCUMSTANCES CAN HAZZARDS ARISE?

i. In controlled settings there have been no major adverse events and minor side effects related to MDMA resolve within a few days (MAPS, 2019).

ii. For a comprehensive review of morbidity and mortality of MDMA use internationally, please see MAPS Investigators Brochure pg. 43.

PART 2.1 [B]: PURPOSE AND EXTENT FOR WHICH THE SUBSTANCE IS TO BE USED

A. Post-Traumatic Stress Disorder (PTSD)

The US Food and Drug Administration (FDA) has granted MDMA-assisted therapy Breakthrough Therapy status for PTSD (MAPS, 2017). PTSD is a major health issue worldwide. It is a debilitating anxiety disorder involving the re-experiencing of a trauma, a hyper-aroused nervous system and avoidance symptoms. PTSD has been described as a complex neuro-psychosocial condition, often characterised by a number of symptoms including:

1. hypervigilance, anxiety, and sleep disturbance.
2. Intrusive memories, nightmares, or flashbacks.
3. Avoidance symptoms, including emotional numbing and withdrawal (Sherin, 2011).

Over the past decade, MAPS completed six Phase 1 and Phase 2 trials testing MDMA-assisted psychotherapy for the treatment of PTSD. 107 participants underwent a treatment program that included preparatory and follow-up psychotherapy sessions, along with two or three supervised MDMA or blinded placebo sessions (MAPS, 2019). The primary outcome measure used was the Clinician Administered PTSD Scale (CAPS-IV), the gold standard for PTSD assessment. CAPS-IV scores were reduced by over 50% after the treatment protocol and by 60% at the 12-month follow-up.

Table 7. Changes to CAPS-IV scores in Phase 1 and 2 Studies of MDMA-assisted therapy for PTSD (MAPS, 2019)

Dose	Baseline Mean (SD)	Primary Endpoint Mean (SD)	End of Stage 1 Mean (SD)
0-40 mg Blinded	81.3 (15.89) N=31	69.7 (21.98) N=31	---
75-125 mg Blinded	85.8 (19.3) N=74	47.4 (30.56) N=72	40.8 (26.22) N=51
Open-label 125 mg	98.5 (27.58) N=2	56.5 (37.48) N=2	---
Dose Stage 2	**Secondary Endpoint Mean (SD)**	**End of Stage 2 Mean (SD)**	**12-month Follow-up Mean (SD)**
Open-label 100-125 mg	37.9 (20.58) N=30	34.6 (23.48) N=27	---
All Participants	---	---	34.5 (24.23) N=90

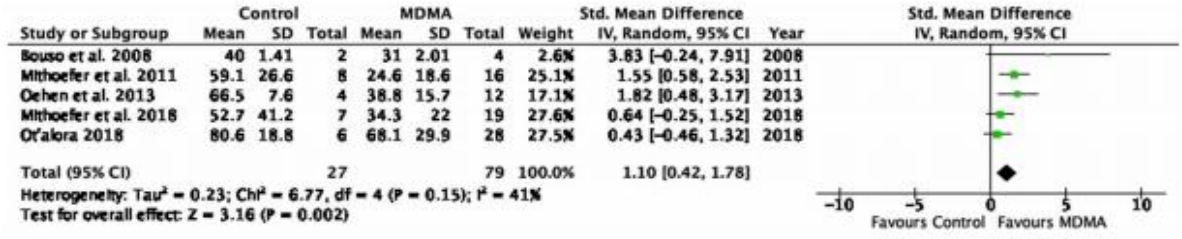
The Phase 2 data across 6 trials showed that overall, 54% of participants in the MDMA group no longer met diagnostic criteria for PTSD, compared with 23% in the placebo group (Mithoefer, 2019). The patients had experienced PTSD for an average of 17.9 years. It was also found that patients treated with MDMA-assisted therapy continued to improve over subsequent follow-ups (Otálora, 2018; Mithoefer, 2018). The effect size found by Cohen's d scale was d= 0.8 which is considered to be a large effect. There was a 71.4% chance that a

person picked at random from the MDMA-assisted therapy group would have a more favourable outcome than someone in the control group. Due to the large effect size, the FDA approved the final Phase 3 trials to commence despite a smaller sample size than normal in the MAPS-sponsored Phase 2 studies. These results are especially significant given the severe and previously treatment-resistant nature of the PTSD for most of the participants.

Table 8. Summary of MAPS Phase 2 and Phase 3 trials for MDMA-assisted therapy treating PTSD

Indication	Details	Dose	Sponsor	Results
Treatment resistant PTSD	n = 72 Phase 2 2-3 MDMA sessions	75-125mg	MAPS	54.2% remission rate (Mithoefer, 2019)
	n =200-300 Phase 3 2-3 MDMA sessions	80- 125 mg with additional optional half dose	MAPS	In progress: 90% chance of significant results (MAPS, 2020)

Table 9. Forest plot of Standardised Mean Differences (SMD) of Pre-vs-Follow-Up Effect of MDMA (versus control) on PTSD symptom scores in Phase 1 and 2 trials using random-effects meta-analysis (Bahji et al, 2020)



MDMA-assisted therapy has been granted 'Breakthrough Therapy' status by the US Food and Drug Administration (FDA), expediting its transition to prescription medicines subject to positive outcomes from current Phase 3 trials (MAPS PR, 2017). This designation highlights the FDA's anticipation that MDMA-assisted therapies may offer substantial advantage over current treatments. An interim report on the MAPS Phase 3 trial revealed a 90% or greater chance that the completed trial will show significant results (MAPS PR3, 2020). Release of the final data is expected as soon as 2021. If the final results confirm the interim results MDMA may become available as a registered medicine in the United States for the treatment of PTSD as early as 2022.

B. Expanded Access Schemes

The FDA has approved an "Expanded Access" or "Compassionate Use" scheme using MDMA for PTSD in patients who have limited treatment options (MAPS PR1, 2020). Israel launched a Compassionate Use program for MDMA-assisted therapy for PTSD in 2019 (MAPS PR2, 2020). The use of MDMA in treatment is as directed by the open-source MAPS's Manual of MDMA-Assisted Psychotherapy (Mithoefer, 2015). Switzerland also has a compassionate use program for MDMA with individual authorizations by the Federal Office of Public Health (Sessa et al, 2019). Recently, the Australian Therapeutic Goods Administration (TGA) approved the first application for the use of MDMA-assisted therapy for the treatment of a patient with treatment resistant PTSD under the Special Access Scheme-B.

C. Other Promising Indications Currently Being Trialed Internationally

Table 10. Summary of other promising avenues for MDMA-assisted therapy

Treatment Indication	Research Institution
Anxiety and depression in *people* with a cancer diagnosis	University of Otago
Couples therapy *when* one member *is* diagnosed with PTSD	MAPS
Alcohol addiction with childhood trauma	Imperial College London
Social anxiety and emotional processing in adults with Autism	University of Chicago and Los Angeles Biomedical research Institute

For further information see the Supporting Data Summary in Part 3.

PART 2.1 [C]: TOXICITY AND SAFETY OF MDMA

A. United Nations Convention Scheduling

MDMA is included in Schedule I of the United Nations Convention on Psychotropic Substances 1971; https://www.unodc.org/pdf/convention_1971_en.pdf.

B. MDMA Dependency at Its Established Therapeutic Dose

MDMA does not produce dependency at its established therapeutic dose (Part 2.1[A]A.4).

C. Does MDMA Have An Established Therapeutic Use But Carry Substantial Risk Of Misuse, Abuse Or Illicit Use?

MDMA does have established therapeutic use (Part 2[B]).

MDMA carries limited potential risk for misuse, abuse or illicit use in clinical settings (Part 1A6, Part 2.1[A]A4&5, Part 2.1[A]H and Part 2.1[E]C1). Ecstasy has potential for misuse, abuse and illicit use in recreational settings (Part 2.1[A]C and Part 2.1[E]).

D. Toxicity

See Section 7 of Part 1 on pages 9 – 13.

PART 2.1 [D]: DOSAGE, FORMULATION, PACKAGING AND PRESENTATION OF MDMA

Note: MDMA at medical grade GMP standard is currently not manufactured in Australia. Until this changes, medical grade GMP MDMA will need to be imported into Australia (with appropriate government approvals) for medical use and clinical trials. Assuming MDMA becomes a Schedule 8 medicine it will also need to be securely stored at a compounding pharmacy that has Schedule 8 holding facilities until transferred to the prescribing medical practitioner.

A. Dosage

Table 1 MAPS Phase 3 Dosing Protocol for Full Treatment of One Patient (MAPS, 2018)

Medicinal Session	Initial Dose	Supplemental Dose*	Min – Max Cumulative Dose
1	80mg	40mg	80mg to 120 mg
2	80 or 120* mg	40 mg or 60 mg	80 mg to 180 mg
3	80 or 120* mg	40 mg or 60 mg	80 mg to 180 mg
Total Cumulative Dose:			240 mg to 480 mg

* if initial dose well tolerated and with clinician judgement.

Please note this dosing protocol is based on a lower weight limit of 48kg

B. Formulation

Capsule sizes of 40 and 60 mg to be available through a compounding pharmacy.

C. Labelling

1. Label requirements

- The container, intermediate packaging (if any) and primary pack in which the medicine is packed must each bear a label or labels that comply with the requirements of this Part 2.1[D]
- The registration number, which must be in a text size of not less than 1.0 millimetre in height as required by subparagraph 15(1)(c)(i) of the Regulations; and
  Be in a colour or colours contrasting strongly with the background, except for:
  - The expiry date and expiry date prefix; and
  - The batch number and batch number prefix when that information is embossed or debossed and not printed; and
  - Be in metric units of measurement

2. Information required on label

- The name of the medicine; and
- The name of the dosage form; and
- The quantity of the medicine; and

- The batch number of the medicine preceded by the batch number prefix; and
- The expiry date of the medicine, preceded by the expiry date prefix; and
- The storage conditions applicable to the medicine; and
- The name and contact details of the sponsor or distributor of the medicine; and
- Relevant warning statements (see below)

D. Statements of caution on packaging

- CONTROLLED DRUG
    - Written on the first line or lines of the main label; and
- POSSESSION WITHOUT AUTHORITY ILLEGAL
    - Written in a separate line or lines immediately below the signal words required by "CONTROLLED DRUG"
- KEEP OUT OF REACH OF CHILDREN
    - Written on a separate line or lines where the cautionary statement "POSSESSION WITHOUT AUTHORITY ILLEGAL", on the line immediately below that statement.

E. Statements of quantity, proportion and strength

- In the manner prescribed by orders made under subsection 10(3) of the *Commonwealth Therapeutic Goods Act 1989*.
- A certificate of GMP can be supplied by the manufacturer.

F. Packaging

The pack size per patient is a full course of MDMA-assisted therapy (up to 480mg) with individual capsules to be dispensed by the prescribing doctor in each session. The pack will have appropriate child resistant locks and the above warnings and be held in a secure safe. The pack will NEVER be given to the patient – only individual capsules as authorised by the supervising medical practitioner.

MDMA (x)mg Caps (1): Take capsule only in the presence of your psychiatrist/specialist addiction physician/therapist. For in-clinic use only. Do not take this medicine at home. Do not drive a motor vehicle or consume alcohol within 48 hours of taking this capsule.

G. Presentation

To be given to a patient by a treating psychiatrist or specialist addiction physician in a clinical setting after they have read and signed a patient informed consent form specifically for MDMA-assisted therapy.

H. Pharmacy Procedure

The intermediary importation pack will be held at a compounding pharmacy under Schedule 8 regulations with a reporting register of mg use. Each primary pack will be compounded and provided to psychiatrists and physicians only under authorised Schedule 8 prescription.

PART 2.1 [E]: POTENTIAL FOR MISUSE/ABUSE OF MDMA

A. BACKGROUND

Please note that cases below all refer to the recreational use of Ecstasy which may or may not contain MDMA. We are proposing a rescheduling to Schedule 8 on the basis that use of the medicine will only be able to be authorised by psychiatrists and specialist addiction physicians in medically controlled environments under strict supervision. The medicine will never be available to the patient to take home.

B. OVERDOSE

Please see Table 6 for a full breakdown of Ecstasy implicated deaths in Australia.

- Between the years 2000 and 2018 there were a total of 55 deaths due to Ecstasy-only toxicity but this related to recreational /non-medical use (Roxburgh & Lappin 2020, p. 4).
- Between the years 2000 and 2018 there were a total of 148 deaths reported from indirect Ecstasy-related misuse (Roxburgh & Lappin 2020, p. 4). 115 deaths were due to accidental trauma, 23 deaths were due to suicide, and 10 deaths were due to disease.
- Between the years 2000 and 2018 there were a total of 189 deaths due to multiple drug toxicity involving Ecstasy (Roxburgh & Lappin 2020, p. 4). 67% involved Ecstasy and prescription drugs (opioids, antidepressants, antipsychotics, benzodiazepines) and 43% involved Ecstasy and alcohol.

C. MISUSE AND ABUSE

1. Would Using MDMA Therapeutically Lead to Illicit Use?

Across a number of MAPS sponsored MDMA studies, subsequent Ecstasy use was measured in participants (MAPS, 19 pg 157). Of those surveyed, 8 of 92 participants reported use of MDMA after the trial was completed for attempted therapeutic or recreational reasons. 6 of the 8 reported using MDMA in this context prior to the trial commencing. The average number of times the 8 participants used MDMA was once in a 12-month period. This data suggests that therapeutic use of MDMA does not substantially increase illicit use or abuse.

2. The Abuse Model vs The Salutogenic Model

There is precedence for the determination that recreational risk data may have limited value in estimating risks for medical treatments of the same drug. A prime example is the prescription of amphetamines, a common ADHD medication. Research into epidemiological setting show potential neurotoxic effects of amphetamine while research within the medical paradigm does not (Advokat, 2007). Research on Ecstasy appears to be largely inapplicable to establish the potential for misuse, abuse, or toxicity 0f MDMA in clinical settings.

3. Dependence in Epidemiological Settings

Although there is limited data on Ecstasy dependence in Australia, in 2016, the proportion of Australian recreational Ecstasy users who reported difficulty limiting their Ecstasy use was very low, only 1.7% percent of users (AIHW, 2016).

4. Ecstasy deaths vs prescription and licit drugs

Although Ecstasy may have potential for abuse, misuse, and overdose in a recreational setting Ecstasy is far less misused or abused than many other prescription drugs. The prevalence of misuse for prescription painkillers in 2016 was 3.6% of Australians, increasing from 2.3% in 2013. This is comparable to Ecstasy in a recreational setting, with prevalence of 2.2% in 2016 and 2.5% in 2013 (AIHW, 2017).

The information below is from the Australian Bureau of Statistics (ABS 2018, p. 6). The ABS has only published drug-related deaths from three years (1999, 2007, 2018). As ecstasy-related deaths were published across 18 years, the below comparison extrapolates the percentage of 18 years vs 3 years.

- Deaths involving Ecstasy totalled 392 across 18 years. This is an average of ≈ 21.8 per year
- Deaths attributable to Ecstasy alone totalled 55. This is an average of ≈ 3 per year
- Prescription opioids total on average ≈ 506.7 deaths per year
- Benzodiazepines total on average ≈ 506.7 deaths per year
- Antidepressants total on average ≈ 190.7 deaths per year
- Antipsychotics and neuroleptics total on average ≈ 96.7 deaths per year
- Paracetamol totals on average ≈ 120.7 deaths per year
- Alcohol totals on average ≈ 202 deaths per year

Table 11. Drug related deaths in comparison to MDMA

Drug Type	Average Deaths More Than Ecstasy
Prescription Opioids	23.2x
Benzodiazepines	23.2x
Antidepressants	8.7x
Antipsychotics and Neuroleptics	4.4x
Paracetamol	5.5x
Alcohol	9.3x

A major difference with this application is that unlike prescription painkillers, MDMA will only ever be used in a medically controlled environment and will never be given to the patient to take home.

PART 2.1 [F]: OTHER CONSIDERATIONS

A. WHY MDMA SHOULD BE IN SCHEDULE 8

Poisons Standard February 2020

Schedule 8 - **Controlled Drug** – Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

Schedule 9 - **Prohibited Substance** – Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities.

Schedule 9 contains substances that should be available only for teaching, training, medical or scientific research including clinical trials conducted with the approval of Commonwealth and/or State and Territory health authorities. Although appearing as a Schedule in this Standard, the method by which it is implemented in the States and Territories may vary.

This application has supplied evidence that MDMA shows strong therapeutic benefit for individuals suffering from PTSD whose condition has not improved after standard forms of treatment. Given the therapeutic benefits and high remission rates shown in clinical trials, alongside the FDA's designation of Breakthrough Therapy status and use in several international "Expanded Access Schemes", including Australia's own SAS-B scheme, it is apparent that MDMA used in a medically controlled environment does not fit within the requirements of a Schedule 9 Substance and more closely reflects the requirements of Schedule 8.

The current Schedule 9 classification of MDMA places hurdles on research (cost, stigma and ease of access) and on its use in a medically controlled environment as part of evidence-based treatment. Reclassifying MDMA as a Schedule 8 substance will reduce cost and improve ease of access for researchers and specialist medical practitioners for treatment of individuals seeking relief for treatment resistant conditions via the Special Access Scheme.

MDMA treatment is only to be used in clinical settings according to the guidelines of a Schedule 8 controlled substance in the Poisons Standards Act 2020 and in accordance with strict safety protocols for supplying MDMA-assisted therapy through health care providers in a medically controlled environment.

As the evidence shows (see Part 2.1[E]), MDMA in a controlled clinical setting has shown limited abuse, misuse, or overdose potential internationally. With the breakthrough therapeutic potential discussed in Part 2.1[B], we submit that MDMA should be rescheduled to Schedule 8.

B. MDMA MAY BE MUCH SAFER THAN EARLY STUDIES SUGGEST

1. Researchers have written extensively on the neurocognitive effects produced by Ecstasy, which include: deficits in retrospective memory, higher cognition, reduced serotonin transporter levels in the cerebral cortex, disturbed sleep architecture, and other behavioural and psychiatric problems (Lyvers, 2006; Droogmans et al, 2007).

2. However, the majority of the studies exploring the above effects in humans have many methodological flaws (Krebs & Johansen, 2012):
    - Most employ non-randomised and retrospective methodologies, which have inherent biases.
    - Most studies do not control for MDMA-only, poly-drug use, drug dose and purity, as well as pre-existing or underlying mental disorders.
    - Most studies have a selection bias when recruiting participants because heavy drug users from the rave culture are typically invited to participate in these studies.
        - Schilt et al. (2008) conducted a study measuring the cognitive deficits caused by Ecstasy use in participants who had an average lifetime exposure of 15-2000 tablets.
        - It may be argued that in research like this, it is impossible to separate consequences of having a reckless personality type from the long-term neurocognitive effects of a drug.
        - Only 20-30% of Ecstasy users consume more than 25 doses in their lifetime (De Win, 2005)
    - Some studies have failed to link MDMA-serotonin metabolism to behavioural or long-lasting psychological changes from MDMA use.
        - Other factors, such as impulsivity or poly-drug use, contribute to the neurocognitive deficits found among Ecstasy users in studies that do not control for poly-drug use.
    - Retrospective studies with participants who are not poly-drug users have been unable to find neurocognitive deficits in Ecstasy users (Halpern, 2011).

3. Although MDMA has been widely studied, there is still debate on its level of neurotoxicity at higher doses and its implicated dangers. However, the FDA has deemed it safe enough for clinical research to be conducted in the treatment of PTSD and for its use in Expanded Access Schemes. Importantly, none of the clinical trials employing rigorous experimental controls have found long-term neurocognitive deficits in their participants (MAPS, 2019).

C. MDMA-ASSISTED PSYCHOTHERAPY PROTOCOL

MDMA-assisted therapy involves 'talk-therapy' alongside the ingestion of medicinal MDMA (Mithoefer, 2015). Importantly, the psychotherapy elements of this approach are essential for both effectiveness and safety. Medicinal MDMA is not a complete therapy, but rather acts as a catalyst or accelerator for the therapeutic process. MDMA increases feelings of safety and enhances the bond between the therapist and patient. Researchers and clinicians often describe four distinct therapy phases: screening and medication wash-out, preparation, the medicinal experience and integration.

- **Screening and medication wash-out:** This phase allows the treating physician to screen for any contraindications and provides a two week period during which the patient must cease any co-current contraindicated medicines (See Part 2.1[A]B2)
- **Preparation** sessions before medicine-assisted therapy to support development of a therapeutic bond and provide patient education
- **Acute medicinal experience** 6-8 hour therapy session while patient is in a receptive, open and loving state.
- **Integration** is a process by which therapists support patients to process and implement insights from their experiences. Patients are encouraged to pursue other opportunities such as journaling and meditation to further integrate the experience into their lives.

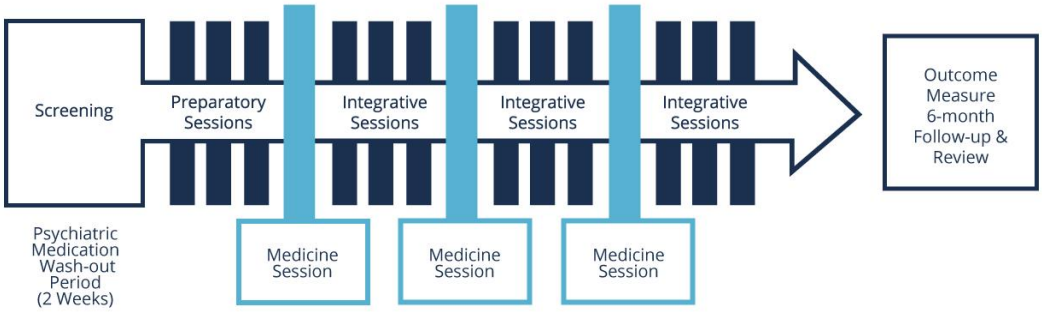


Image 2. MDMA-assisted therapy protocol

In the Phase 3 clinical trials, a flexible dosing regimen was chosen to mimic proposed clinical practice and better adapt to risk benefit considerations (MAPS, 2018). This refers to an initial dose followed by an optional supplemental dose equal to half the initial dose at 1.5 to 2.5 hours later. The patient can accept or decline the supplemental dose, or the treatment team may withhold if contraindicated as discussed with the patient. Medicinal sessions are conducted once every three to four weeks. These sessions span 6-8 hours. To support the patients therapeutic process, 2-3 integration sessions occur in the month after each medicinal session.

For 7 days after a medicinal session, the therapy team checks in with the patient through brief phone calls. The estimated total duration of treatment is 16 – 20 weeks.

MDMA-assisted psychotherapy occurs within a clinical, aesthetic and private space. The medicinal sessions generally last 6-8 hours, with two trained specialist therapists working together.

During some of the experience, patients are invited to listen to music played through headphones and are encouraged to wear an eye mask. The patient is made aware of all safety measures and equipment that are in place to ensure their safety, in the unlikely event of a medical complication.

The patients BP and HR are monitored at regular intervals with set limits for risk bounds for both reading and duration in place. Patients are supplied with electrolyte infused water to minimise risk of low plasma sodium.

While the therapy can be challenging and bring up difficult experiences, these may be crucial to the therapeutic process and occur in a well-supported environment and neuropsychological state induced by the MDMA (Sessa, 2019).

PART 2.2 CRITERIA TO CHANGE THE POISONS STANDARD

The application has given medical and scientific justification, reasoning, and critical objective discussion for all the legislative requirements set out by the *Therapeutic Goods Act 1989*, subsection 52E. The following is a brief discussion of the evidence presented in this application:

1. In exercising a power under subsection 52D(2), the Secretary must take the following matters into account (where relevant):

i. **the risks and benefits of the use of a substance**;

- Phase 2 and interim Phase 3 results assessing MDMA-assisted therapy for PTSD suggest that MDMA may be a unique therapeutic aide creating a bridge between pharmacotherapy and psychotherapy. Current evidence suggests that the combined prosocial, anxiolytic, and neurological effects of MDMA provide a novel and effective therapy for PTSD (Part 1D, Part 2.1[A]A, Part 2.1[B] and Part 2.1[F].
- MDMA has low toxicity at therapeutic doses, and MDMA's low risk of dependence outweigh the associated risks (Part 2.1[A]) which can be fully mitigated with medical use only in a controlled setting.

ii. the purposes for which a substance is to be used and the extent of use of a substance;

- MDMA-assisted psychotherapy for PTSD and addictions associated with trauma in a controlled medical setting (Part 2.1[B]).

iii. the toxicity of a substance;

- MDMA is contraindicated in those with uncontrolled blood pressure or significant cardiac diseases. In healthy individuals, MDMA does not demonstrate toxicity when administered at a therapeutic dose (Part 1[C]7). Part 2.1[A]B and Part 2.1[C]).
- MDMA can elicit a range of spontaneous reactions rated mild to moderate the majority of which resolve within 24 hours and the remainder within a week (Part 1[C]6)

iv. the dosage, formulation, labelling, packaging and presentation of a substance;

See Part 2.1[D].

v. the potential for abuse of a substance;

See Part 2.1[E].

CONCLUSION

The application meets all the criteria specified in the *Therapeutic Goods Act 1989*, subsection 52E. There is the demonstrated efficacy of MDMA for PTSD and potentially for substance dependence in cases where the dependence originates in trauma. MDMA also demonstrates low toxicity and low abuse potential when administered in a medically controlled setting. It is therefore detrimental for Australians suffering from treatment-resistant PTSD and addictions associated with trauma not to have medically supervised access to this breakthrough medicine. Increasing access would not only represent a large saving to the Australian economy by reducing service use and increasing productivity once people suffering from such mental illnesses achieve remission but would importantly improve the quality of life of Australians suffering from these debilitating illnesses.

We acknowledge and support the premise that the use of MDMA should only be authorised by psychiatrists and specialist addiction physicians and only be used under strict medical supervision in a medically controlled environment. We believe that it is reasonable to reschedule MDMA from being a Schedule 9 drug to being a Schedule 8 drug when used according to the conditions described above.

PART 3 - SUPPORTING DATA

A. Supporting Data Summary

The tables on the following pages contain the following data:

1. Patterns of overseas use of MDMA completed clinical trials

2. Patterns of overseas use of MDMA incomplete clinical trials

B. Supporting Data Details – Expert Comment

Appendix A contains a letter of support for the proposed rescheduling of MDMA in accordance with this application from 42 psychiatrist, psychologists, specialist physicians, pharmacologists, researchers and other relevant health experts from both Australia and overseas.

Appendix A also contains separate Expert letters of support from:

1. Professor Arthur Christopoulos, the Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University and a Professor of Analytical Pharmacology.

2. Dr Robin Carhart-Harris *, who heads the Centre for Psychedelic Research at Imperial College, London and is one of the leading researchers in the World into the medical application of psychedelic medicines.

3. Drug Science (www.drugscience.org.uk), the leading independent scientific body on drugs in the UK. The Chair of Drug Science, Professor David Nutt+, is head of Neuropsychopharmacology and the Deputy Head of the Centre for Psychedelic Research at Imperial College, London. Professor Nutt is one of the World's foremost authorities on the medical use of psychedelic substances. The Drug Science Letter of support is signed by its Chief Executive, Mr David Babcock and 25 members of its Science Advisory Committee.

* Dr Robin Carhart-Harris is a member of the Advisory Panel of Mind Medicine Australia. This is an honorary position with no financial or other benefit attached.

\+ Professor David Nutt is an Ambassador of Mind Medicine Australia. This is an honorary position with no financial or other benefit attached

C. Copies of Papers Referenced

Copies of all papers referenced in this application can be found in **Appendix B (separate attachment)** at the following link:

https://www.dropbox.com/s/oeo3ameg0i1q9a5/Mind%20Medicine%20Australia%20MDMA%20Rescheduling%20S9%20to%20S8%2013%20July%202020_Appendix%20B_v1.0.pdf?dl=0

We have also posted via Express Mail a USB stick to you containing all the papers in **Appendix B.**

SUPPORTING DATA SUMMARY

Table 12. Patterns of overseas use of MDMA completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
PTSD	Significant Improvement	100-125 mg	Offices of Dr. Ingrid Pacey MBBS FRCP[C], Canada	Phase 2 Clinical Trial Randomized, Double-blind, Controlled of MDMA-assisted Psychotherapy in 12 Subjects With PTSD	ClinicalTrials.gov Identifier: NCT01958593 Mithoefer et al. 2019
	Significant Improvement	12.5-125 mg	Beer Yaakov Hospital, Israel	Phase 2 Clinical Trial Randomized, Double-blind, Active-placebo Controlled Study of MDMA-assisted Psychotherapy in People With Chronic PTSD	ClinicalTrials.gov Identifier: NCT01689740 Mithoefer et al. 2019
	Significant Improvement	62.5-125 mg	Multidisciplinary Association for Psychedelic Studies Offices of Michael Mithoefer MD, SC, US	Phase 2 Clinical Trial MP-1: A Test of MDMA-Assisted Psychotherapy in People With Posttraumatic Stress Disorder	ClinicalTrials.gov Identifier: NCT00090064 Mithoefer et al. 2010 Mithoefer et al. 2013

Table 12. Patterns of overseas use of MDMA completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
PTSD	Significant Improvement	80-180mg	Multidisciplinary Association for Psychedelic Studies New School Research LLC, CA, US San Francisco Insight and Integration Center, CA, US University of California San Francisco, CA, US Aguazul-Blue Water Inc., CO, US Wholeness Center, CO University of Connecticut, CT, US Ray Worthy Psychiatry LLC, LA, US Trauma Research Foundation, MA, US New York University, NY, US Affective Care, NY, US Zen Therapeutic Solutions, LLC, SC, NY University of Wisconsin at Madison, WI, US	Phase 2 Clinical Trial Open Label Multi-Site Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD	2017, ClinicalTrials.gov Identifier: NCT03282123

Table 12. Patterns of overseas use of MDMA completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
PTSD	Unreleased	62.5-125 mg	Multidisciplinary Association for Psychedelic Studies Offices of Michael Mithoefer, SC, US	Phase 2 Clinical Trial Additional MDMA-assisted Psychotherapy for People Who Relapsed After MDMA-assisted Psychotherapy Trial	2011, ClinicalTrials.gov Identifier: NCT01458327
	Significant Improvement	25-125 mg	Multidisciplinary Association for Psychedelic Studies Swiss Medical Association for Psycholytic Therapy	Phase 2 Clinical Trial MP-2: Study MDMA-assisted Psychotherapy in People With Posttraumatic Stress Disorder	ClinicalTrials.gov Identifier: NCT00090064 Oehen et al 2013
	Significant Improvement	40-125 mg	Multidisciplinary Association for Psychedelic Studies	Phase 2 Clinical Trial MP-12: Dose-Response Study of MDMA-assisted Psychotherapy in People With PTSD	ClinicalTrials.gov Identifier: NCT01793610 Ot'alora, 2018
	Significant Improvement	30-125 mg	Multidisciplinary Association for Psychedelic Studies Offices of Michael Mithoefer MD, SC, US	Phase 2 Clinical Trial MP-8: Comparing Three Doses of MDMA Along With Psychotherapy in Veterans With Posttraumatic Stress Disorder	ClinicalTrials.gov Identifier: NCT01211405 Mithoefer et al, 2018

Table 12. Patterns of overseas use of MDMA completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
PTSD	Mechanism Study	30-125 mg	Multidisciplinary Association for Psychedelic Studies Offices of Michael Mithoefer, SC, US	Phase 2 Clinical Trial Exploring Mechanisms of Action in MDMA-assisted Psychotherapy for PTSD	2014, ClinicalTrials.gov Identifier: NCT02102802
Couples with one member with PTSD	Case study: Significant improvement	75-100 mg	Multidisciplinary Association for Psychedelic Studies Offices of Michael Mithoefer MD, SC, US	Phase 1 & 2 Clinical Trial MDMA-assisted and Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads With One Member With Chronic PTSD	ClinicalTrials.gov Identifier: NCT02876172
Couples with one member with PTSD	Publication forthcoming	75-100 mg	Multidisciplinary Association for Psychedelic Studies	Phase 2 Clinical Trial MDMA-assisted and Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads With One Member With Chronic PTSD	2019, ClinicalTrials.gov Identifier: NCT02876172

Table 12. Patterns of overseas use of MDMA completed clinical trials

Outcome	Impact	Dose	Institute	Comments	Reference
Anxiety	Publication forthcoming	62.5-125 mg	Multidisciplinary Association for Psychedelic Studies Offices of Philip Wolfson MD, CA, US	Phase 2 Clinical Trial MDMA-assisted Psychotherapy for Anxiety Associated With a Life-threatening Illness	2015, ClinicalTrials.gov Identifier: NCT02427568
Autism Spectrum Disorder	Significant Improvement	75-125 mg	Los Angeles Biomedical Research Institute, CA, US	Phase 2 Clinical Trial MAA-1: MDMA-assisted Therapy for Social Anxiety in Autistic Adults	ClinicalTrials.gov Identifier: NCT02008396 Danforth et al. 2018
Social Cognition	Significant: Increased empathy No effect: Moral judgement	40-75 mg	University Hospital Basel, Switzerland	Early Phase 1 Clinical Trial Effects of MDMA and Methylphenidate on Social Cognition	ClinicalTrials.gov Identifier: NCT01616407 Schmid et al. 2014

Table 13 - Patterns of overseas use of MDMA incomplete clinical trials

Outcome	Institute	Comments	Reference
PTSD	National Institute of Mental Health (NHIM), Czechia Maastricht University, Netherlands Sykehuset Østfold Hf, Norway Fundação de Anna de Sommer Champalimaud, Portugal University Hospital of Wales, United Kingdom	Phase 2 Clinical Trial Open Label Multi-Site Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD With Optional fMRI Sub-Study	**2019**, ClinicalTrials.gov Identifier: NCT04030169
	Multidisciplinary Association for Psychedelic Studies (MAPS)	Phase 3 Clinical Trial A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1)	**2018**, ClinicalTrials.gov Identifier: NCT03537014
	Emory University, GA, US	**Phase 1 Clinical Trial** Evaluation of MDMA on Startle Response	**2017**, ClinicalTrials.gov Identifier: NCT03181763
	VA Loma Linda Healthcare System, CA, US	**Phase 2 Clinical Trial** MDMA-Assisted Psychotherapy in Veterans With Combat-Related, Refractory PTSD (VALLMDMA_001)	**2020**, ClinicalTrials.gov Identifier: NCT04264026

Table 13 - Patterns of overseas use of MDMA incomplete clinical trials

Outcome	Institute	Comments	Reference
PTSD	Providence Health Center, Canada Dr. Simon Amar, Inc., Canada Assaf Harofeh Research Fund, Israel Sheba Fund for Health Services and Research, Israel New School Research LLT, CA, US San Francisco Insight and Integration Center, CA, US University of California San Francisco, CA, US Aguazul-Blue Water Inc., CO, US Wholeness Center, CO, US Ray Worthy Psychiatry LLC, LA, US Trauma Research Foundation, MA, US New York University, NY, US New York Private Practice, NY, US Zen Therapeutic Solutions LLC, SC, US University of Wisconsin at Madison, WI, US	**Phase 3 Clinical Trial** A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP2)	**2019**, ClinicalTrials.gov Identifier: NCT04077437
	Yale University	**Phase 1 Clinical Trial** The Effects of MDMA in PTSD.	**2018**, ClinicalTrials.gov Identifier: NCT03752918
	University Hospital, Basel, Switzerland	**Early Phase 1 Clinical Trial** Effect of Methylenedioxymethamphetamine (MDMA) (Serotonin Release) on Fear Extinction (MFE)	**2018**, ClinicalTrials.gov Identifier: NCT03527316

Table 13 - Patterns of overseas use of MDMA incomplete clinical trials

Outcome	Institute	Comments	Reference
Autism Spectrum Disorder	University of Chicago	**Early Phase 1 Clinical Trial** Effects of Drugs on Responses to Brain and Emotional Processes (MAT)	**2019**, ClinicalTrials.gov Identifier: NCT04053036
Alcohol Addiction	Imperial College London	**Phase 2 Clinical Trial** The Safety, Tolerability and Role of MDMA-Assisted Psychotherapy for the treatment of detoxified patients with Alcohol Use Disorder.	**2019**, ClinicalTrials.gov Identifier: NCT04158778
Anxiety	Multidisciplinary Association for Psychedelic Studies	**Phase 2 Clinical Trial** MDMA-assisted Psychotherapy for Anxiety Associated With a Life-threatening Illness	**2019**, ClinicalTrials.gov Identifier: NCT02427568
PTSD	British Columbia Centre on Substance Abuse, Canada Dr. Simon Amar LLC, Canada	**Phase 2 Clinical Trial** Study of Safety and Effects of MDMA-assisted Psychotherapy for Treatment of PTSD	**2018**, ClinicalTrials.gov Identifier: NCT03485287

PART 4 - BIBLIOGRAPHY

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Application to Reschedule

N, α -DIMETHYL- 3,4 (METHYLENEDIOXY)PHENYLETHYLAME (MDMA) from Schedule 9 to Schedule 8 of the Poisons Standard

APPENDIX A - Experts' Letters of Support

For Rescheduling of MDMA from Schedule 9 of the Poisons Standard to Schedule 8

15 July 2020

Mind Medicine Australia Limited

Level 1/ 10 Dorcas St
South Melbourne VIC 3006

MIND MEDICINE
AUSTRALIA

15 July 2020

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration
Canberra
Australia

Application to Amend the Poisons Standard by Rescheduling MDMA

Mind Medicine Australia Limited is applying to the Therapeutic Goods Administration to amend the Poisons Standard by rescheduling MDMA (the long form in Schedule 9 of the poisons Standard is given as "N, a - Dimethyl - 3,4 (Methylenedioxy) Phenylethylamine) from Schedule 9 (Prohibited Substance) to Schedule 8 (Controlled Drug).

The experts listed below have read the application prepared by Mind Medicine Australia and have authorised Mind Medicine Australia to advise the Therapeutic Goods Administration that they support the proposed rescheduling.

Title	First Name	Surname	Position
Dr	Tanveer	Ahmed +	Australian Psychiatrist and Author based in NSW.
Dr	Christopher	Bench	Australian Psychiatrist in private practice in Newcastle, NSW.
Dr	Jillian	Broadbear	Adjunct Clinical Associate Professor, Monash University; Senior Research Fellow, Spectrum - Statewide Service for Personality Disorder, Eastern Health.
Prof	Ashley	Bush +	NHMRC Senior Principal Research Fellow, Director of the Melbourne Dementia Research Centre.
Dr	Robin	Carhart-Harris (UK)* +	Head of the Centre for Psychedelic Research - Imperial College London. Leading published researcher in psychedelic assisted therapies. Holds a PhD in Psychopharmacology.
Dr	Ted	Cassidy +	Australian psychiatrist. Chief Medical Officer and Co-Founder of TMS Australia, Australia's largest provider of outpatient Depression and PTSD treatment using transcranial magnetic stimulation technology.
Dr	Juthica	Chaudhary	Australian Psychiatrist in private practice in South Australia.
Dr	Lukas	Cheney	Australian consultant psychiatrist in Victoria.

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Prof	Arthur	Christopoulos *	Dean, Faculty of Pharmacy and Pharmaceutical Sciences and Head of the Analytical and Structural Neuropharmacology Laboratory, Monash Institute of Pharmaceutical Sciences at Monash University. World leading molecular pharmacologist.
Dr	Mark	Cross +	Psychiatrist, Senior Conjoint Lecturer at the Universities of NSW and Western Sydney, and SANE Board Director.
A/Prof	Mark	Daglish	BSc MBChB MD FRANZCP Associate Professor in Addiction Psychiatry, University of Queensland.
Dr	Rick	Doblin (USA) #	BSc, Ph.D Founder and Executive Director of the Multidisciplinary Association for Psychedelic Studies (MAPS), USA. MAPS are sponsoring the current Phase 3 global multi-site trials and secured Breakthrough Therapy Designation for MDMA from the FDA.
Dr	James	Fadiman (USA) +	American Psychologist, Author and Researcher. Co-founder, Institute of Transpersonal Psychology, which later became Sofia University.
	Amanda	Fielding (UK) +	Founder and Executive Director of The Beckley Foundation in the UK, which has been a major funder of research into psychedelic assisted therapies.
Prof	Paul	Fitzgerald +	Professor of Psychiatry at Monash University and Director of the Epworth Centre for Innovation in Mental Health.
Prof	David	Forbes +	Director of Phoenix Australia - Centre for Posttraumatic Mental Health and Professor in the Dept of Psychiatry, Melbourne University.
Dr	Nick	Ford	Australian Psychiatrist in private practice in South Australia, specializing in PTSD.
Dr	Robert	Gordon	Australian Psychiatrist in private practice in Sydney, NSW.
Dr	Al	Griskaitis	Australian Psychiatrist in private practice in Wollongong, NSW.
Dr	Walter	Hipgrave	Psychiatry Registrar at Alfred Hospital, VIC
Dr	Karen	Hitchcock +	Specialist Physician (acute and general medicine) based in Melbourne and Author.
Prof	Malcolm	Hopwood +	Ramsay Health Care Professor of Psychiatry, University of Melbourne, specialising in clinical aspects of mood and anxiety disorders, psychopharmacology and psychiatric aspects of acquired brain injury and epilepsy. Past President of RANZCP.

Dr	Pieter	Hurter	Psychiatrist at Eastern Health, Melbourne.
Dr	Linda	Kader +	Psychiatrist and Senior Lecturer at the Department of Psychiatry, University of Melbourne.
	Michael	Kornhauser +	Australian Pharmaceutical and Clinical Trial Research Specialist.
Dr	Eli	Kotler +	Psychiatrist and Director of Medicine at Malvern Private Hospital, Melbourne, specialising in addictions.
Dr	Anish	Modak	Psychiatry Registrar, Adult Mental Health Unit Canberra Hospital, ACT Health.
Prof	Rob	Moodie AM +	Professor of Public Health – University of Melbourne and Advisor to World Health Organisation (WHO).
A/Prof	David	Nichols (USA) +	Adjunct Professor of Chemical Biology and Medicinal Chemistry - University of North Carolina, Chapel Hill. Published over 300 scientific articles. Major focus on psychedelic chemistry.
Prof	David	Nutt (UK) **#**	BA, MB BChir, MRCP, MA, DM, MRC Psych, FRCPsych, FMedSci, FRCP, FSB Head of Neuropsychopharmacology at Imperial College London, one of the world's foremost psychedelic research laboratories, publishing landmark research on psychedelic therapies and neuroimaging studies of the psychedelic state.
Dr	Nikola	Ognyenovits +	Australian Addiction Medicine Specialist Physician, QLD.
Dr	Prash	Puspanathan +	Previously a Medical Doctor at the Alfred Hospital where he most recently held the position of Neuropsychiatry Fellow.
A/Prof	Sathya	Rao	Executive Clinical Director of Spectrum, Personality Disorder Service for Victoria, Australia. He is also the Deputy President of Australian Borderline Personality Disorder Foundation, Adjunct Associate Clinical Professor at Monash University and a a Consultant Psychiatrist at Delmont Private Hospital.
Dr	James	Rucker (UK) +	Consultant Psychiatrist & Senior Clinical Lecturer at Kings College London where he leads the Clinical Trials Group which is currently undertaking clinical trials using psilocybin in healthy volunteers and patients with resistant depression.
Dr	Anne	Schlag (UK) *	Head of Research at Drug Science, UK and Honorary Fellow at Imperial College London.
Dr	Ben	Sessa (UK) #	MBBS, B.SC, MRC PSYCH Psychiatrist and researcher at Bristol and Imperial College London

			University, He is currently conducting the world's first clinical study using MDMA to treat alcohol addiction.
Dr	Steven	Stankevicius	Australian Consultant Psychiatrist and Accredited TMS Clinician at Toowong Private Hospital, QLD.
Dr	Jorg	Strobel	Senior Consultant Psychiatrist / Clinical Lead Mental Health Informatics Research Unit, SA Health and Flinders University.
Prof	John	Tiller **+**	MD, MBCHB, BSC, DPM, FRACP, FRANZCP, GAICD Professor Emeritus Psychiatry, University of Melbourne and Albert Road Clinic. Past President of RANZCP. His primary research interests have been in the assessment and treatment of depressive and bipolar disorders, anxiety disorders including PTSD and psychoses.
Dr	Emile	Touma	Senior Addiction Psychiatrist and Addiction Medicine Specialist, Senior Lecturer, School of Clinical Medicine University of Queensland.
Dr	John	Webber +	Australian Psychiatrist in private practice in Melbourne.
Dr	Alex	Wodak AM +	Physician with expertise in addiction. Previously Director of the Alcohol and Drug Service at St Vincent's Hospital in Sydney.

*** Signatory to separate letter addressed to the Medicines Scheduling Secretariat at the Therapeutic Goods Administration endorsing the rescheduling application.**
 # Ambassador of Mind Medicine Australia. Note that this is an honorary position with no financial or other benefit attached.
+ Member of the Mind Medicine Australia Advisory Panel. Note that this is an honorary position with no financial or other benefit attached.

Yours sincerely

Peter Hunt AM
Chairman
Mind Medicine Australia Limited

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MONASH University
Pharmacy and Pharmaceutical Sciences

June 28th, 2020

Dear Sir/Madam

I have been asked by Mr Peter Hunt, the Chairman of Mind Medicine Australia, to comment on their application for psilocybin and MDMA to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

My Background

I am the Professor of Analytical Pharmacology and the Dean of the Faculty of Pharmacy & Pharmaceutical Sciences, Monash University, which is currently ranked as No. 2 in the world (after Oxford) in Pharmacy and Pharmacology (QS World Rankings 2020). Prior to my appointment as Dean, I was a Senior Principal Research Fellow of the National Health and Medical Research Council of Australia. I am a world leader in novel modes of drug discovery, with a particular focus on neuropharmacology, neuropsychiatric diseases and protein targets for psychoactive medicines, including those modulated by mood-altering compounds such as psilocybin and MDMA. I have published over 320 peer reviewed articles, delivered over 180 invited presentations, served on the Editorial Board of 8 international journals and consult for numerous pharmaceutical companies. I have been the recipient of the highest Pharmacology awards from the Australian, American, British and International Pharmacological Societies, as well as having received the GSK Award for Research Excellence and a Doctor of Laws from the University of Athens. In 2018, I was elected a Fellow of the Australian Academy of Health and Medical Sciences. Since 2014-present, Clarivate Analytics have named me a Highly Cited Researcher in Pharmacology and Toxicology, which places me in the top 1% of all cited scientists worldwide in my field.

Safety and Efficacy of Psilocybin and MDMA in a Medically Controlled Environment

There is now a substantive body of highly compelling scientific evidence to support the fact that both psilocybin and MDMA offer superior efficacy to existing psychotherapies in treating major mental health conditions, including depression, PTSD, substance abuse disorders and anxiety, to name a few. In addition, and given the short dosing regimens associated with clinical application of the substances, there is minimal likelihood of any safety concerns or addiction liabilities. It is also worth highlighting that the US Food and Drug Administration have granted MDMA-assisted therapies for PTSD “breakthrough therapy” status, paving the way for availability of this form of therapy as a prescribed medicine pending further clinical trial results. Given that virtually all currently marketed medicines to treat psychiatric illnesses are based on science that is over 50 years old, it is imperative that we explore newer, more efficacious and safer alternatives for treating mental illness; medicinal psilocybin and medicinal MDMA represent such alternatives.

Proposed Change of Scheduling

Based on my professional experience and a review of the international data I believe that psilocybin and MDMA should be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard. There is simply no reasonable scientific rationale for the current scheduling of either substance as Schedule 9; in a clinical environment, they

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present minimal risks of harm, adverse events or addictive liability compared to the majority of other psychoactive medicines currently listed as either Schedule 8 or even Schedule 4. I therefore support the applications for rescheduling being made by Mind Medicine Australia Limited.

Declaration

In stating my views in this letter, I have made an objective and impartial assessment of Mind Medicine Australia's Rescheduling Application in the light of current scientific knowledge.

Sincerely,

Arthur Christopoulos, B.Pharm., Ph.D.
Professor of Analytical Pharmacology
Dean
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University

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Centre for Psychedelic Research
Burlington Danes Building, Du Cane Rd
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W12 0NN
Dr. Robin Carhart-Harris
r.carhart-harris@imperial.ac.uk

June 13th, 2020

Dear Sir/ Madam,

I head the Centre for Psychedelic Research at Imperial College London. The world's first Centre dedicated to scientific and medical research with psychedelic compounds, founded in April 2019. Here in the UK, the Conservative Drug Policy Reform group is presently making a case to the UK Govt. to reschedule psilocybin from its present position as a Schedule 1, Class A drug. This campaign is backed by signatures from the leading scientists in this field.

There is no scientific basis for the present scheduling. Psilocybin has consistently been ranked in the lowest bracket harm among drugs of potential abuse according to a number of independent scientific assessments (1) and increasing evidence has shown its considerable potential as a therapeutic adjunct to treat a broad range of serious mental health conditions (2).

Regarding my expertise on this topic, I have the highest annual citation rate in the field (see below), was ranked in the Times top 31 medical scientists (REF) and have over 85 original publications in the field, having pioneered neuroimaging studies with both psilocybin and MDMA and impactful clinical trials of psilocybin for depression that were the main inspiration for the FDA's decisions to designate psilocybin a 'breakthrough therapy'.

Peter Hunt has forwarded to me the applications by Mind Medicine Australia (MMA) to reschedule psilocybin and MDMA in Australia and I have reviewed the rescheduling applications. The argument to reschedule psilocybin is compelling. As this is the compound with which I have the most scientific expertise, I am happiest to lend my support to its rescheduling. Psilocybin has a remarkably good therapeutic index, negligible toxicity and addiction potential and an extremely promising medical potential. Given my expertise on this topic, I strongly support the campaign to reschedule psilocybin from Schedule 9 to 8 in Australia. I support the same rescheduling for MDMA therapy, as the evidence for its efficacy as a tool to facilitate trauma-focused psychotherapy, is compelling.

Declaration
I am on the Advisory Panel of MMA. This is purely an honorary position and I receive no payments (either directly or indirectly) for undertaking this role.

In stating my views in this letter I have made an objective and impartial assessment of MMA's Rescheduling Applications in the light of current scientific knowledge.

Sincerely,

Dr Robin Carhart-Harris, BSc, MA, PhD
Head of Centre for Psychedelic Research
https://www.imperial.ac.uk/psychedelic-research-centre
Dept. Brain Sciences
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References

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Rank	First Author	Title	Year	Journal	Annual Citation Rate	Total Number of Citations	Country	Classic psychedelic(s) Studied	Study Type	Outcome of Interest (where applicable)
1	RL Carhart-Harris	Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study	2016	The Lancet Psychiatry	111.3	334	UK	Psilocybin	Experimental case-series	Treatment-resistant depression
2	RL Carhart-Harris	Neural correlates of the LSD experience revealed by multimodal neuroimaging	2016	PNAS	98.7	296	UK	LSD	Experimental case-series	Neuroimaging (PET) and neurophysiology
3	RR Griffiths	Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial	2016	Journal of Psychopharmacology	96.3	289	USA	Psilocybin	Randomized, double-blind, placebo-like crossover trial	Cancer-related depression and anxiety
4	S Ross	Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial	2016	Journal of Psychopharmacology	87.7	263	USA	Psilocybin	Randomized, double-blind, placebo-controlled, crossover trial	Cancer-related depression and anxiety
5	RL Carhart-Harris	Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin	2012	PNAS	74.7	523	UK	Psilocybin	Placebo-controlled, open crossover study	Neuroimaging (fMRI)
6	Nicols DE	Hallucinogens	2004	Pharmacology & Therapeutics	72.6	1089	USA	LSD, psilocybin, DMT, mescaline	Review	Historical perspective, toxicity, pharmacology, and therapeutic applications
7	RL Carhart-Harris	The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs	2014	Frontiers in Human Neuroscience	71.4	357	UK	Psilocybin, LSD, and DMT	Review	Neuroimaging and neurophysiology
8	RL Carhart-Harris	Psilocybin with psychological support for treatment-resistant depression: six-month follow-up	2018	Psychopharmacology	71.0	71	UK	Psilocybin	Experimental case-series	Treatment-resistant depression

London, June 18th 2020

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration
Canberra
Australia

Dear Sir/Madam,

we have been asked by Mr Peter Hunt, the Chairman of Mind Medicine Australia, to comment on their application for MDMA to be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard.

Drug Science

Drug Science is the leading independent scientific body on drugs in the UK. We work to provide clear, evidence-based information without political or commercial interference.
Drug Science was formed by a committee of scientists with a passionate belief that the pursuit of knowledge should remain free of all political and commercial interest. Our expert scientists comprise a wide range of disciplines: https://drugscience.org.uk

Prof David Nutt, Chair of Drug Science, is deputy Head of the Centre for Psychedelic Research at Imperial College London (https://www.imperial.ac.uk/psychedelic-research-centre/). He has extensive experience and scientific understanding of MDMA being used in a clinical setting, having been leading- amongst other areas- MDMA trials for the treatment of alcoholism.

Safety and Efficacy of MDMA in a Medically Controlled Environment

There is an increasing amount of scientific evidence for the safety and efficacy of MDMA-assisted psychotherapy for the treatment of PTSD and other mental health conditions. It is hoped that MDMA-assisted psychotherapy can offer treatment-resistant patients a breakthrough option in the treatment of conditions such as PTSD, addiction, end-of-life anxiety and social anxiety in autistic adults.

In 2017, the US Food and Drug Administration (FDA) granted MDMA-assisted psychotherapy for PTSD a 'breakthrough therapy' status, formally endorsing the use of the drug in clinical trials. This designation highlights the FDA's anticipation that MDMA-assisted therapies may offer substantial advantages over current treatments. If the developing data- expected to be released within the next year- confirm the treatments to be effective, MDMA for the treatment of PTSD may become available as prescribable medicine as in the United States as early as 2021.

Proposed Change of Scheduling

Based on our professional experience and a review of the international data we believe that MDMA should be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard. We therefore support the application for rescheduling being made by Mind Medicine Australia Limited.

Declaration

Prof David Nutt is an Ambassador of Mind Medicine Australia Limited. This is purely an honorary position and David Nutt receives no payments (either directly or indirectly) for undertaking this role.

In stating our views in this letter, we have made an objective and impartial assessment of Mind Medicine Australia's Rescheduling Application in the light of current scientific knowledge.

We would be happy to respond to any questions that you may have.

Yours Faithfully,

David Badcock (CEO Drug Science)

Drug Science Scientific Committee signatories

Prof David Nutt- Founder and Chair of Drug Science, Imperial College London
Dr Dima Abdulrahim
Dr Steve Bazire
Dr Simon Brandt
Prof Brigitta Brander
Prof Val Curran
Prof Colin Drummond
Niamh Eastwood
Prof Barry Everitt
Dr Roz Gittins
Prof Patrick Hargreaves
Prof Graeme Henderson
Prof Michael Lynsky
Dr John Marsden
Prof Fiona Measham
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Prof Jo Neill
Prof Larry Phillips
Dr John Ramsey
Steve Rolles
Prof Ilina Singh
Prof Alex Stevens
Dr Polly Taylor
Dr Steven Willot
Prof Adam Winstock