Australian Government
Department of Health

Application to Amend the Poisons Standard by Retaining

N,α-DIMETHYL-3,4-(METHYLENEDIOXY) PHENYLETHYLAMINE (MDMA)

In Scheduling 9 But also having a Schedule 8 Entry for Restrictive Medical Use with Appendix D and Appendix F Controls

3rd March 2022

Mind Medicine Australia Limited

Level 1/ 10 Dorcas St
South Melbourne VIC 3006

MIND MEDICINE AUSTRALIA

The Secretariat
Medicines Rescheduling Unit
Therapeutic Goods Administration
Canberra, ACT.

2 March 2022

Dear Sir/Madam

Application to Amend the Poisons Standard by Retaining MDMA in Schedule 9 But Also Having a Schedule 8 Entry for Restrictive Medical Use

We are attaching our second application for the rescheduling of MDMA as a Schedule 8 controlled medicine when used as part of psychotherapy in medically controlled environments. Our first application was lodged in July 2020.

The urgency for reapplying is that ongoing trials of MDMA assisted psychotherapy (and importantly the release of published results for a Phase 3 trial) continue to show that this treatment can be used safely and achieve high remission and response rates for patients with treatment resistant post-traumatic stress disorder (PTSD) when used in a controlled environment. This is in the context of worsening mental health conditions in Australia and mental illness levels that were already some of the highest in the World even before the current Covid-19 pandemic and the extensive lockdowns that we have all experienced.

Important, MDMA assisted psychotherapy therapy in the Phase 3 trial was equally effective for participants with comorbidities often associated with treatment resistance. **This is particularly relevant to our ADF Veteran and First Responder communities where comorbidities and suicide rates are far higher than those suffering from PTSD in the general population.**

As you will be aware, treatment resistant conditions can lead to immense suffering and, unfortunately for some people, they can lead to suicide

In preparing this new application we have specifically sought to address:

(i) The findings and concerns of the Delegate acting for the Secretary of the Department of Health in its Final Decision to Not Amend the Current Poisons Standard for Psilocybin and MDMA dated 15 December 2021.

(ii) The views of the Independent Expert Panel in its report to the TGA on the therapeutic value, risks, and benefits of MDMA and psilocybin for the treatment of mental, behavioural or development disorders published in November 2021.

(iii) The views of the Royal Australian and New Zealand College of Psychiatrists in letters to the TGA responding to our first rescheduling application.

(iv) The views of the Australian Medical Association in its letter to the TGA responding to our first rescheduling application.

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Australia

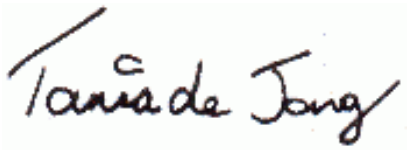
As a result, we have made this application for rescheduling significantly more restrictive than our first application dated 15 July 2020 and added additional information from recent trials to support this application.

Rising rates of mental illness around Australia are a major focus of both Federal and State Governments and there is a desperate need for new treatment innovation in the mental health sector so that we can see many more people going into remission.

We are available to meet with the Therapeutic Goods Administration, the Advisory Committee on Medicines Scheduling and the nominated Delegate of the Secretary of the Department of Health at your convenience to discuss all aspects of our Application.

We also have access to an extraordinary Advisory Panel of leading psychiatrists, psychologists, pharmacologists, psychotherapists and researchers in this field (see https://mindmedicineaustralia.org/advisory-board/) and we will make sure that the appropriate experts are available for that meeting.

Yours faithfully,



Peter Hunt AM
Co-Founder, Chairman
Mind Medicine Australia

Tania de Jong AM
Co-Founder, Executive Director
Mind Medicine Australia

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DETAILS OF THE APPLICATION

Confidentiality

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

Medicine Details

1. **Name of Medicine Requiring Scheduling;** on a restrictive basis *N*,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE(MDMA)
2. **Active Ingredient;** MDMA
3. **Dosage Form;** Capsule
4. **Container Type;** Plastic polypropylene bottle
5. **Indications of Medicine;** Treatment resistant mental illness when used as part of psychotherapy
6. **Current Poisons Scheduling;** Schedule 9
7. **Proposed Poisons Scheduling;** Schedule 9 with a restrictive entry in Schedule 8

Applicant's Details

1. **Applicant's Name;** Mind Medicine Australia Limited
2. **Applicant's Business Address;** Level 1, 10 Dorcas Street, South Melbourne, Victoria 3205
3. **Applicant's Business Name;** Mind Medicine Australia
4. **Date of Submission**; 3 March 2022
5. **Contact Person;** Mr. Peter Hunt AM
6. **Email Address of Contact Person;** peter@mindmedicineaustralia.org
7. **Postal Address of Contact Person**; Same as item 2 above
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
3rd March 2022

Acknowledgments

Vitor Chiruta for scientific input, Robert D. Renshaw for his assistance as a disability scribe, Paulina K. Zemla for proof-reading, Julia Neubauer for formatting and graphic design, Anthony Licciardi for data collection and reference checking, Ilan Hayman for the collation of the final submission.

Part 1 - SUMMARY OF THE APPLICATION

1. PROPOSED RESCHEDULING TO THE POISONS STANDARD

Mind Medicine Australia requests a limited rescheduling of MDMA as detailed below.

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA)

Schedule 9

Schedule 8

Appendix D, Item 3

Appendix D, Item 5

Appendix F, Part 1, Item 36

SCHEDULE 9 – Proposed Amended Entry

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA) **except** when separately specified in Schedule 8.

SCHEDULE 8 – Proposed New Entry

N,α-DIMETHYL-3,4-(METHYLENEDIOXY)PHENYLETHYLAMINE (MDMA) for use in the treatment of treatment resistant mental illness when:

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and
d) where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967 and/ or;
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
f) in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

Relevant controls to be derived from Appendix D and Appendix F of the Poisons Standard as follows:

Appendix D – Additional Controls on Possession or Supply of Poisons Included in Schedule 4 or 8	
Item 3	Poisons available only from or on the prescription or order of a medical practitioner authorised or approved by the Secretary of the Commonwealth Department of Health and Ageing under section 19 of the *Therapeutic Goods Act 1989*
Item 5	Poisons for which possession without authority is illegal (e.g. possession other than in accordance with a legal prescription)

Appendix F – Warning Statements and General Safety Directions for Poisons	
Item 36	For use under medical supervision only.

2. SUBSTANCE SUMMARY

2.1 CHEMISTRY

(1) Chemical Properties

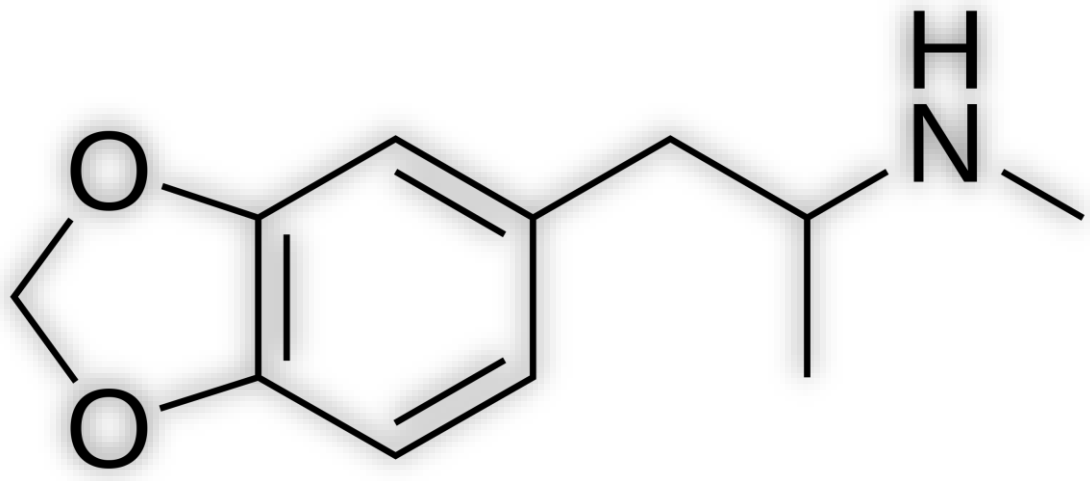
The Chemical properties of MDMA are set out in Table 1 below.

Table 1. Chemical properties of MDMA.

Property	Value
Chemical Formula	C11H15NO2
CAS Number	42542-10-9
IUPAC Name	1-(1,3-benzodioxol-5-yl)-N-methylpropan-2-amine
Molar Mass	193.24 g/mol
Boiling Point	147-153°C

(2) Chemical Structure

Figure 1. Chemical structure of MDMA.



(3) Description of Substance

MDMA is a ring-substituted phenylethylamine first synthesised by the Merck pharmaceutical company in 1912.[3] MDMA is described not only as a psychedelic, but 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.[4] The MDMA which has been used in all clinical trials to date is racemic, containing roughly equal amounts of each enantiomer.[5] 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) Toxicity

The lethal oral dose in humans is LD_{50} or 10-20 mg/kg.[6] This equates to between 700-1400 mg for a 70 kg person. The greatest dose used in clinical studies is between 1-2 mg/kg or 80-120 mg at one time.[7] Cases of human toxicity or fatality have occurred in uncontrolled settings where the recreational drug Ecstasy (which is often adulterated with other substances) is being used and involve MDMA blood levels ranging from 0.5-10 mg/L at hospitalisation or the post-mortem.[8] This is up to eight times the therapeutic dose of MDMA. It is important to note the involvement of other drugs in many of these Ecstasy cases.

Table 2. Acute toxicity of MDMA in mammals.

Species	ROA	LD_{50}
Human	PO [4]	10-20 $mg.kg^{-1}$
Monkey	IV [9]	22 $mg.kg^{-1}$
Mouse	IV [9]	97 $mg.kg^{-1}$
Mice	IV [10]	20 $mg.kg^{-1}$ (aggregate)
Rat	IV [11]	49 $mg.kg^{-1}$
Dog	IV [11]	14-18 $mg.kg^{-1}$

MDMA increases the concentration of serotonin in the brain which at doses which are far higher than therapeutic doses may cause chemical damage to cells.[8] 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 5-300 mg/kg have been used to investigate MDMA's toxicity.[5] Major systems implicated in contributing to MDMA toxicity in animal studies include; cardiotoxicity, hepatotoxicity, neurotoxicity, hyperthermia and hyponatremia. Most 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.[8]

2.2 PHARMACOLOGY

(1) Pharmacokinetics

Absorption

MDMA's onset of action is 30-45 minutes after administration.[12]

Distribution

MDMA reaches peak concentrations in plasma at T_{max} 2.4 hours after administration.[13]

Table 3. Peak blood flow concentrations of MDMA by dose.

PO dose	C_{max}
50 mg	0.106 mg/L
75 mg	0.131 mg/L
125 mg	0.236 mg/L

Metabolism

MDMA is broken down in the liver, principally by the cytochrome P450 isozyme CYP2D6.[14]

Elimination

The elimination half-life for MDMA is eight hours.

(2) Pharmacodynamics

Biomechanisms

MDMA stimulates release of pre-synaptic serotonin, norepinephrine, and dopamine in multiple brain regions.[15] MDMA, like selective serotonin reuptake inhibitors (SSRIs), binds with the pre-synaptic sodium-dependent serotonin transporter (SERT), as well as the norepinephrine transporter (NET), and the dopamine transporter (DAT). This binding blocks the reuptake of 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 that MDMA does not display as strong an affinity for DAT as methamphetamine.[16]

At high doses, well above the therapeutic range, MDMA has been observed to inhibit monoamine oxidase-A (MAO-A) *in vitro*.[17] 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 the serotonin subtype receptors 5-HT_{2A}, 5-HT_{1A} and 5-HT_{2B}, as well as dopamine receptor type-2 (D_2).[15] Catecholamine activation by MDMA also produces downstream effects, including the release of neurohormones such as oxytocin, prolactin, and vasopressin.[13, 18] Oxytocin, prolactin, and vasopressin are implicated in attachment and bonding processes and may contribute to the prosocial effects of MDMA.

Thermoregulatory Effects

Across Phase 2 trials, body temperature elevations above 1 °C from pre-drug readings occurred in 44-50% of participants.[5] 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 °C. All values returned to normal after treatment. During Phase 3 trials, the highest transient temperature recorded was 38.1 °C [19].

Cardiovascular 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.[5] Most individuals do not experience rises in BP and HR beyond that seen during moderate exercise. Greater elevations were observed in people with specific catechol-O-methyltransferase (COMT) and SERT genotypes. However, these genotypes were not severe enough to warrant contraindication. In a study of MDMA, in 166 psychologically healthy individuals, transient severe hypertension of systolic blood pressure (SBP) > 180 mmHg was observed in 5% of participants on a 125 mg dose of MDMA.[20] 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.[7]

2.3 PHARMACOTHERAPEUTICS

(1) Positive Psychological Effects

Under the influence of MDMA, patients can more readily experience and process their emergent psychological material in a state of psychological ease and safety.[15] In a controlled setting, MDMA supports patients in reprocessing traumatic and painful memories, making MDMA efficacious for treating PTSD and addictions associated with trauma.[21] 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

(2) Adverse Effects

In a study of 166 psychologically healthy participants given MDMA, the most frequent complaints were low appetite, dry mouth, difficulty concentrating, sweating, and bruxism.[20] It is noted that there are some mild potential side-effects observed 24 hours post-dose, headache being the most common.[20] See Table 4 below for a full analysis of adverse effects reported in the trial

Table 4. Acute and subacute adverse effects of MDMA total *n* = 166.

Adverse event description[†]	Placebo			MDMA		
	0 hours *n* (%)	Acute < 6 hours *n* (%)	Subacute *24 hours* *n* (%)	0 hours *n* (%)	Acute < 6 hours *n* (%)	Subacute *24 hours* *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 flushes	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 the Multidisciplinary Association of Psychedelic Studies (MAPS) sponsored Phase 2 trials, spontaneously reported reactions were observed upon drug administration, but were generally transient and decreased as MDMA was metabolised. Reactions did not significantly detract from the therapeutic process.[5] Only nausea (6.9%), tight jaw (5.2%), dizziness (3.4%), 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 seven-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.

Table 5. Summary of observed toxic effects of MDMA in animals, clinical research and in epidemiological setting.

Pathology	Mechanism	Clinical use[†]	Epidemiological settings
Cardiotoxicity	Sympathomimetic elevation of blood pressure and heart rate.[11]	Changes in trials safe for those without CV disease.	Some toxicity observed in those with over 900 exposures to MDMA (and other drugs).[22] Other studies did not find any toxic effects with fewer exposures.[23] Individuals with CV or pulmonary disease are more at risk of SAE and morbidity.
Hyponatremia	MDMA may reduce plasma sodium causing electrolyte imbalances.[24] 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 particularly in individuals with certain variations of COMT and CYP2D6 genotypes.[25]
Neurotoxicity	High doses (5-300 mg/kg) cause neurotoxicity to serotonergic and possibly dopaminergic axon terminals.[26, 27]	Not observed in clinical settings.	Mild cognitive effects observed in poly-drug users (including memory, impulsivity, and executive functions.[28, 29] Reduction of serotonin in the post- mortem brain of a chronic user.[30] No significant evidence of cognitive changes for moderate MDMA-only users.[31] Chronic primarily MDMA poly-drug users show decreased declarative memory performance.[32]
Hepatotoxicity	A dose of 20 mg/kg in rats was capable of causing cell death in the liver. High body temperature is implicated.[33]	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.[34]
Hyperthermia/ Hyperpyrexia	Raised body and cerebral temperature combined with vasoconstriction.[27]	Temperature remains in normal bounds in clinical settings.	Major contributor to harm and morbidity.[35] 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)[5]

Data from the recent MAPS Phase 3 trial results confirmed that the MDMA-assisted psychotherapy treatment used for PTSD was safe and well-tolerated with adverse events for the MDMA group being significantly better than for the placebo group.

As shown in the Table taken from the published study in Nature Medicine adverse events (and in particular suicidality) were much lower in the MDMA group than the placebo group.

Table 2 | Participants with treatment-emergent SAEs and AESIs

	MDMA (*n* = 46), *n* (%)	Placebo (*n* = 44), *n* (%)
SAEs	–	2 (4.5)
Suicide attempts	–	1 (2.3)
Suicidal ideation resulting in self-hospitalization	–	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	–
Suicidal behavior (suicide attempts and preparatory acts) and self-harm	–	1 (2.3)
Suicidal behavior (preparatory acts), self-harm and suicidal ideation	–	1 (2.3)
Cardiac events that could indicate QT prolongation (total)	–	1 (2.3)
Irregular heartbeats and palpitations	–	1 (2.3)
Abuse potential for MDMA (total)	–	–

The number of participants experiencing one or more SAEs or AESIs relating to suicidality, cardiovascular symptoms that could indicate QT prolongation, and abuse potential following the first experimental session.

Source: ***MDMA Assisted therapy for Severe PTSD: a randomised, double-blind, placebo-controlled phase 3 study,*** Jennifer Mitchell et al, Nature Medicine Journal, Vol 27, June 2021 at page 1030.

2.4 SPECIAL CONSIDERATIONS

Patients must undergo appropriate counselling and education in preparation for MDMA-assisted psychotherapy. This normally takes 6-8 hours of the therapist's time. Dosing with MDMA requires the patient to be in a safe, clinical environment, and supported by at least one but ideally two treating therapists for the duration of the 6-8 hour therapeutic session.[36] The key therapeutic effects of MDMA lasts 4-6 hours.[37]

2.5 RANGE OF USE

The principal focus to date has been as a therapeutic adjunct in the treatment of PTSD.[38] A highly successful Phase 3 trial has now been completed for treating Post-Traumatic Stress Disorder (PTSD) and another Phase 3 trial is now in progress. The following conditions are also currently being investigated in clinical studies:

- Social Anxiety Disorder (SAD) and emotional processing in adults with Autism
- General Anxiety Disorder (GAD)
- Addictions

2.6 THERAPEUTIC DOSE RANGE

Therapeutic doses in current Phase 3 studies are standardised to 80 mg for the first therapeutic session with an optional supplemental half-dose during the therapeutic session.[7] 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 48 kg for patients following this dosage protocol.

2.7 MDMA-ASSISTED PSYCHOTHERAPY PROTOCOL

MDMA-assisted therapy involves 'talk-therapy' alongside the ingestion of medicinal MDMA.[39] 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** 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
- **Preparation sessions** before medicine-assisted therapy to support development of a therapeutic bond and patient education.
- **Acute medicinal experience** provides an opportunity for therapy while patients are in a receptive, flexible, open 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 to further integrate the experience into their lives.

In the Phase 3 clinical trials, a flexible dosing regimen was chosen to mimic proposed clinical practice and better adapt to risk benefit considerations.[7] 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 seven 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.

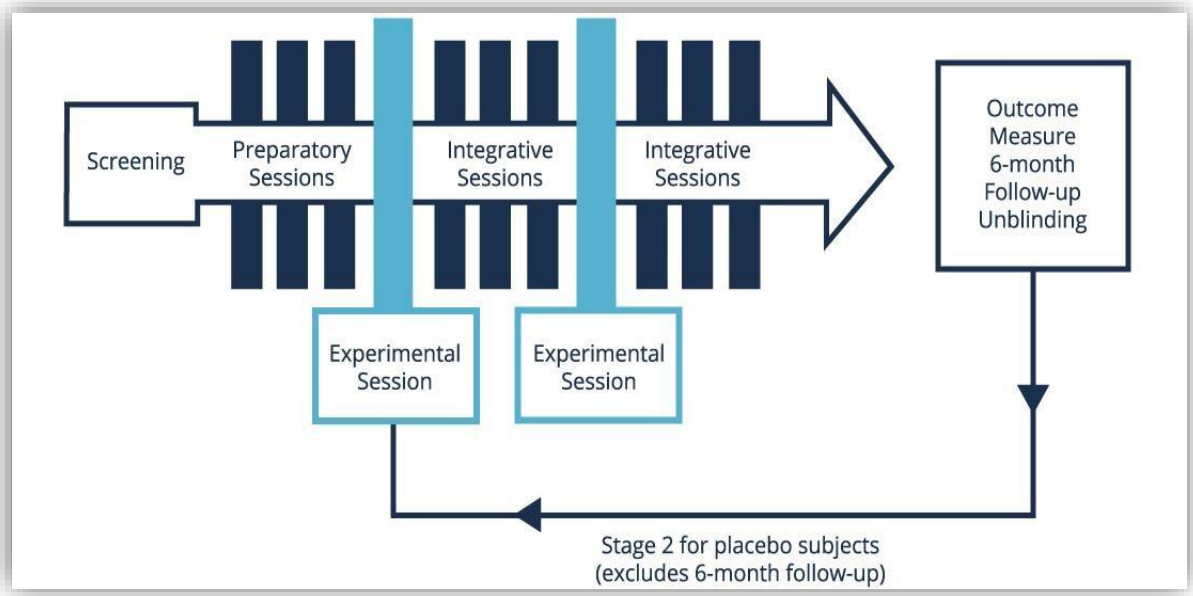
MDMA-assisted psychotherapy occurs within a clinical, aesthetic, and private space. The medicinal sessions generally last 6-8 hours, with two trained specialist therapists working together.

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.[40]

Figure 2. MDMA-assisted therapy protocol.



Mind Medicine Institute is running a 14-week course for health practitioners on how to provide psychedelic assisted psychotherapy within a regulated environment. The course is led by senior clinicians and the teaching faculty contains leading researchers, psychiatrists, clinicians and pharmacologists from around the World. The course was recently described on ABC National Radio by Professor David Nutt (Head of Neuropsychopharmacology at Imperial College London and one of the leading researchers in the World) as "*the best course of its kind in the World*".

During 2021, 88 practitioners graduated from the course. The professional backgrounds of these graduates are set out in the Table below.

Professional Background of CPAT Graduates for Calendar Year 2021

Professions:	Intake 1	Intake 2
Psychologist	13	14
Psychiatrist	8	15
GP	8	5
Psychotherapist	4	2
Nurse	2	1
Social Worker	3	2
Counsellor	5	1
Chiropractor	1	0
Art Therapist	1	0
Jungian Psychoanalyst or other	1	2
Total:	46	42

For calendar year 2022 Mind Medicine Institute has increased the number of places available for qualifying health practitioners by a further 200 places (4-intakes). The background of participants will be similar to the 2021 intake.

To date graduates can only legally provide these therapies as part of clinical trials. However, the limited rescheduling envisage in our application would enable graduates to also practice on a limited basis where approvals are given by the TGA under Special Access Scheme -B and corresponding approvals are given by the State/Territory Government where the treatment is to occur.

The protocols around these treatments provide for appropriate supervision of the treating therapists.

3. OVERVIEW

3.1. Restrictive Proposal

In preparing this application Mind Medicine Australia has considered:

(i) The findings and concerns of the Delegate acting for the Secretary of the Department of Health in its Notice of Final Decision to Not Amend the Current Poisons Standard for Psilocybin and MDMA dated 15 December 2021 ("**the Notice of Final Decision**").

(ii) The views of the Independent Expert Panel in its report to the TGA on the therapeutic value, risks and benefits of MDMA and psilocybin for the treatment of mental, behavioural or development disorders published in November 2021 ("**the Independent Expert Panel Report**").

(iii) The views of the Royal Australian and New Zealand College of Psychiatrists in letters to the TGA responding to our first rescheduling application dated 15 July 2020.

(iv) The views of the Australian Medical association in a letter to the TGA responding to our first rescheduling application dated 15 July 2020.

As a result, Mind Medicine Australia has made this application for rescheduling significantly more restrictive than its previous application lodged in July 2020 (see Part 1 Section 1.1)

We have also reviewed developments in this field to incorporate further evidence supporting the proposed rescheduling that has become available since our last application was lodged in July 2020

3.2. Specific Matters Considered in Relation to the Delegate's Final Decision and the Independent Panel Report

Whilst the Delegate decided against Mind Medicine Australia's application to amend the Poisons Standard the reasons given has enabled us to understand the Delegate's concerns and to take them into account in preparing this revised application.

As required by Section 52E of the Therapeutic Goods Act, the Delegate is required to weigh up the risks and benefits of the use of medical grade MDMA as part of therapy in a medically controlled environment. In ruling against our application, the Delegate applied three key factors in making the decision.

(1) <u>The First Factor – Whether MDMA is in Schedule 1 of the UN Convention of Psychotropic Substances.</u>

Whilst MDMA is a substance in Schedule I of the UN Convention of Psychotropic Substances its quite clear from previous decisions of the Delegate that this does not, of itself, prevent a rescheduling. As dealt with in detail in Part 2.1 Section (A)2.15 below:

- The Convention itself contains a specific exemption for limited medical use approved by Government (this is exactly what the TGA's Special Access-B pathway provides); and
- The TGA has rescheduled substances in the past in exactly these circumstances.

Other countries comparable to Australia also use the exemption in the Convention to support the right to apply for access (e.g., the United States, Canada, Israel and Switzerland). There are also other UN Conventions to which Australia is a signatory which support access in these limited circumstances (e.g., the UN Convention on Economic, Social and Cultural Rights which provides in Article 12 that people have rights to "*the enjoyment of the highest standard of physical and mental health"*).

(2) <u>The Second Factor- Whether the use of MDMA as part of therapy has an established therapeutic value</u>

The Delegate expressed the view in the Final Decision that this requirement had not been met and that MDMA studies indicated only potential therapeutic value. The Delegate also cast doubt on "*the quality of completed studies".* We contend that there is an enormous amount of evidence to support this fact that MDMA when used in medically controlled environments does have an established therapeutic value and we bring together the evidence in Part 2.1 Section (A)1.1 below.

The Independent Expert Panel itself concluded that there were statistically significant differences for MDMA doses of greater than 100mg when used as part of psychotherapy in comparison with active placebos in the trials which they reviewed and MDMA was well tolerated in all of these trials. To use the Panel's exact words "*Effect sizes were large in all comparisons but with wide confidence levels", "MDMA was well tolerated in all the studies"* and *"Serious events such as suicidal ideation were rare and occurred almost entirely in the placebo arm or were otherwise unrelated to the therapy".*

Whilst the trials to date have been of varying quality (this is often the case with substances being reviewed for rescheduling) we would contend that it is wrong to cast doubt on "*the quality of [all] completed studies"* as the Delegate did in the Delegate's Final Report. The most recent trials of note have been conducted by MAPS as a pathway to registration of MDMA assisted therapy in the United States and Europe and written up in prestigious journals. The latest trial was a Phase 3 trial. The quality of this trial (and earlier Phase 2 trials sponsored by MAPS) has not been questioned in extensive reviews.

As you will see in Part 2.1 Section (A) 1.1 below, we review the data supporting our contention that MDMA when used as part of therapy in medically controlled environments does have an established therapeutic value. Our conclusion from this data that MDMA when used as part of therapy in a clinical environment does have an established therapeutic value is also supported by Drug Science in the United Kingdom (Chaired by Professor David Nutt from Imperial College London who is one of the leading researchers in this field in the World) and leading pharmacologists Professors Arthur Christopoulos and Chris Langmead from Monash University's Faculty of Pharmacy and Pharmaceutical Sciences. Professor Christopoulos is also the Dean of this Faculty which is the highest globally ranked faculty in any discipline amongst all Australian universities and is ranked Number 2 in the World in pharmaceutical sciences.

(3) The Third Factor – Whether the benefits of down scheduling outweighs the risks to patients and public health from increased access

The **benefits** of down scheduling are obvious. Patients with treatment resistant conditions (by definition existing treatments don't work for them) get the chance to receive a treatment which has been shown in trials to date to be safe to use in controlled environments and where remission and response rates have generally (and particularly in the latest trials) have been strong.

For many patients with treatment resistant post-traumatic stress disorder, this is likely to be their last chance.

The risks identified by the Delegate were twofold;

The First Alleged Risk (Diversion Risk) was that medical grade MDMA could be illegally diverted by unscrupulous pharmacists and doctors into the recreational area. We deal with this argument in detail in Part 2.1 Section (A)2.1 below. In our view diversion is highly unlikely for two reasons:

- Schedule 8 medicines as the name suggests are *controlled* medicines. They have to be kept in a safe when not in use and specifically accounted for under government controls. The Health System is used to dealing with Schedule 8 medicines. Far more dangerous medicines such as morphine, cocaine, methadone and ketamine are all in Schedule 8.
- Medical grade synthesised MDMA is much more expensive than the substance that is used in the recreational drug scene and which is readily obtainable on the Black Market (synthesised medical grade MDMA is more expensive by a factor of at least 20 times).

The Second Alleged Risk (Translation Risk) was that translation from a trial setting to a clinical setting would make it "*hard to achieve adherence to strict protocols outside of clinical trials*" and that there was a need for "*adequate expertise, procedures and ethical standards".* We deal with this argument in Part 2.1 Section (A)2.2 below but in summary:

- We have made the current application much more restrictive so that not only will this treatment have to be prescribed by the patient's psychiatrist with fully informed patient consent and conducted in a medically controlled environment, but the treating psychiatrist will also have had to have had specific training in this form of therapy and the patient's diagnosis and treatment plan will have had to have been specifically confirmed by two other psychiatrists.
- Our Health System is used to managing the translation of Schedule 8 unregistered medicine from a trial environment to a clinical environment.
- Protocols are easily available from recent trials.
- **Mind Medicine Institute (MMI)** is already training psychiatrists, psychologists and psychotherapists in the application of these therapies and our course was recently described on ABC National Radio by one of the leading researchers in this field (Professor David Nutt, Heat of Neuropsychopharmacology at Imperial College London) as "*the best course of its kind in the World*" – something that Australia should be proud of.

- **MMI** is also providing a post certificate structure of supervision and ongoing professional development to ensure that therapists trained in this program are adequately supported by a peer network and exposed to ongoing evidence based best practice in the field.
- **MMI** has initiated a register of trained professionals to establish an open and peer supported network of suitably qualified and verified professionals.
- **MMI** has initiated a strong position on harm reduction and is defined in the containment of this work to suitably qualified and medically and ethically governed treatment. MMI is focussed on ensuring that there is clear definition and public psychoeducation around the dangers and risks of unsupervised use of these medicines.

Given the above (and particularly the results of recent trials and the more restrictive nature of this application) we believe there are strong grounds for the Delegate to approve the proposed rescheduling.

3.3. Specific Matters Considered from the Submissions made by the Royal Australian and New Zealand College of Psychiatrists ("RANZCP") and the Australian Medical Association ("AMA")

Specific Matters Raised by RANZCP

RANZCP based its submissions to the TGA in relation to our previous application on the views expressed in a Clinical Memorandum that the College prepared in May 2020. Since that time a number of things have happened:

1. Further (and strong) evidence of safety and efficacy has emerged from a multisite Phase 3 trial sponsored by MAPS in North America and Europe (see Part 1 Sections 2.3(2) and 3.7 and Part 2.1 Section (A)1.1).
2. The mental health situation in Australia has deteriorated still further.
3. We have restricted our application so that the prescribing psychiatrist would need to have been specifically trained in these therapies and the patient's diagnosis and treatment plan would need to have been confirmed by two other psychiatrists.
4. Leading psychiatrists associated with RANZCP and other mental health specialists have acknowledged that *"….an access pathway, such as SAS-B may be appropriate in judicious case for the use of medicinal psychedelics….."* if such approvals include the following additional conditions, namely that (a) the administering clinician has undertaken specific training in psychedelic–assisted therapies; (b) the drug is administered according to a manualised treatment approach used within clinical trials and (c) patients with a history of risk of psychosis are excluded (see "*Medicinal psychedelics for mental health and addiction: Advancing research of an emerging paradigm"* by Daniel Perkins et al, Australian and New Zealand Journal of Psychiatry 2021 1-7). These conditions are all central to our revised application with additional conditions relating to confirmation of the treating psychiatrist's diagnosis and treatment plan by two other psychiatrists and specific training for the treating psychiatrist in the application of MDMA assisted therapy

5. Mind Medicine Institute has started Australia's first course in psychedelic assisted therapies (which includes MDMA assisted psychotherapy) led by outstanding clinicians and a World-leading faculty – see Part 2.1 Section (F)3.
6. As seen from the letter below, the new Neuromedicines Discovery Centre at Monash University has indicated its willingness to host an independent registry to collate treatment data from the treating psychiatrists and their patients that will add significantly to our knowledge base and Mind Medicine Australia has agreed to provide funding for that registry.

Offer from the Neuromedicines Discovery Centre at Monash University to Host an Independent Clinical Registry to Collate Treatment Data

MONASH University

Neuromedicines Discovery Centre
Monash University
381 Royal Parade
Parkville
Victoria, 3052
Australia
28th February 2022

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

Further to the application to the TGA to reschedule psilocybin and MDMA to Schedule 8 of the Poisons Standard, we write in support of establishing an appropriate Clinical Registry to ensure best practice and value for the proposed limited use of these drugs.

The limited use rescheduling application, to which this letter is appended, is for the use of psilocybin and MDMA:

- as part of psychotherapy in medically controlled environments; and
- under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
- where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and
- where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967and/ or; imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

Our view is that should such a limited use application under Schedule 8 be approved, that a voluntary Clinical Registry be established to record the following:

- the nature of the treatment administered;
- the diagnosis or indication being treated;
- a summary of treatment outcome(s); and
- any treatment-emergent side effects or adverse events

We are all of the strong opinion that the level of unmet medical need for mental health disorders warrants the use of these medicines in such well-regulated environments and that a Clinical Registry of such would add value and integrity to their use as well as providing a means to evaluate both long term efficacy and safety.

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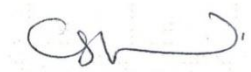
MONASH University

It is for this reason that, in late 2021 with significant financial support of Monash University, we founded the Neuromedicines Discovery Centre (https://www.neuromedicines.monash/) to engage in comprehensive research into the discovery, development, clinical evaluation and rollout of novel medicines for the treatment of mental health disorders.

With some of the world's best pharmacologists, psychiatrists and psychologists with expertise in this space, we offer the Neuromedicines Discovery Centre as a host for a Clinical Registry for the use of psilocybin or MDMA as an adjunct to psychotherapy.

Yours sincerely,

Arthur Christopoulos, B.Pharm., Ph.D., F.A.A., F.A.H.M.S.
Professor of Analytical Pharmacology, Dean & Director, Neuromedicines Discovery Centre
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University



Christopher J. Langmead, M.A., Ph.D., F.B.Ph.S.
Professor & Deputy Director, Neuromedicines Discovery Centre
Faculty of Pharmacy and Pharmaceutical Sciences
Monash University

Christopher Davey, MBBS (Hons) MPsychiatry, Ph.D., FRANZCP
Professor, Head of Department of Psychiatry, Melbourne Medical School, Faculty of Medicine, Dentistry & Health Sciences
Editor-in-Chief, Australian and New Zealand Journal of Psychiatry
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Specific Matters Raised by the AMA

Like the RANZCP the AMA acknowledged in its submission to the TGA in relation to Mind Medicine Australia's last application that "*research has reported positive outcomes with minimal risk".* However, the AMA went to argue the need for *"...more high- quality research using larger scale studies".* We trust that the new information and latest trials outlined in this application will be viewed positively by the AMA (particularly the information and Expert Letters in Part 2.1 Section (A) 1.1 (established therapeutic value) and Part 1 Section 2.3 (2) (adverse events). As noted elsewhere in this application (see Part 2.1 Section (A)1.8) there have been no cases of patients developing psychosis or Hallucinogen Perception Disorder in any of the trials.

We also note that the limited down-scheduling proposed in this application will not make MDMA more readily available to medical practitioners other than in the very limited circumstances envisaged by this application. We also note that the access envisaged through Special Access Scheme -B will be restricted to patients that are treatment resistant and "at risk" and that limited access through the Special Access Scheme was something that appeared to be envisaged by the AMA in its submission.

3.4. The Nature of Our Proposed Rescheduling

Mind Medicine Australia requests an amendment to the *Poisons Standards*, to include a Schedule 8 restricted entry– with appropriate Appendix controls – for the Schedule 9 substance MDMA. The proposed Schedule 8 restricted entry of MDMA recognises that MDMA should satisfy the requirements for a Schedule 8 listing only in the restrictive circumstances set out in this Application.

A Schedule 8 listing will create a basis for uniform access throughout Australian for the use of MDMA as part of psychotherapy but only where specific approval is given to the treating psychiatrist for a particular patient by the Therapeutic Good Administration (TGA) (on a case-by-case basis) under its Special Access Scheme for unregistered medicines and the psychiatrist also obtains the necessary approvals from the State or Territory Government where the treatment is to occur. These approvals will require confirmation that the patient is treatment resistant, that the psychiatrist's diagnosis and treatment plan has been confirmed by two other psychiatrists and that the treating psychiatrist has been specifically trained in the application of MDMA assisted therapy.

3.5. The Need for New and Improved Treatments for Treatment Resistant Patients

We believe that our restrictive rescheduling application needs to be viewed within the context of Australia's mental health crisis which has significantly worsened since we lodged our first rescheduling applications in July 2020 because of the mental pressures and uncertainties associated with the COVID-19 pandemic

Australia worsening mental health crisis is leading to ever increasing social and economic costs. Before the current COVID-19 pandemic there was an approximately $180 billion estimated annual cost to the Australian economy due to mental illness.[41] 1 in 5 adults were diagnosed with a chronic mental illness, with 48% of all Australians experiencing a mental illness in their lifetime.[42]

All these figures will have substantially worsened over the last two years because of the COVID-19 pandemic.

The most common mental illnesses are depression, anxiety disorders and Post Traumatic Stress Disorder (PTSD). Trauma is also at the heart of a significant amount of substance abuse.

With current pharmacotherapy treatments less than 10% of PTSD sufferers go into remission. Whilst response rates are higher at around 20-30% this still means that most PTSD sufferers do not experience significant benefits from current treatments.

With depression an estimated 1 in 8 adults and 1 in 4 older people were being treated with SSRIs[43] in 2019 (i.e. before the current COVID-19 pandemic). Adverse side effects of using SSRIs and other psychiatric medicines are common and they can become a daily reinforcement to the patient that they suffer from a mental illness. In the 15-year period up to 2019 there was a 95% increase in SSRI prescriptions in Australia with no noticeable reduction in the overall rates of depression.

On a per capita basis Australia is the second-highest prescriber of SSRIs worldwide of the 30 countries with available data.

All these figures will have significantly worsened over the last two years.

The key point that we want to make here is that a 'more of the same' approach with only incremental change is not going to alleviate the high levels of mental illness in Australia and the enormous suffering (and in some cases suicide) associated with mental illness. As Albert Einstein is often quoted as saying "*Insanity is doing the same thing over and over and expecting different results"*

As a nation we must focus much more on treatment innovation.

The need for new treatments was specifically recognised by the Independent Expert Panel in their report when they commented that:

> *"The conditions being explored for potential therapeutic efficacy with MDMA and psilocybin are serious. For instance, a significant proportion of people living with PTSD or depression and anxiety in the face of a serious illness do not obtain adequate relief from existing therapeutic strategies ……. More effective treatments are needed" (*See page 18 of the Independent Expert Panel Report)

3.6. PTSD is Notoriously Hard to Treat

It's easy for us all to get tied up with academic arguments, medical terms and trial methodologies but we would ask the TGA, the Medicines Scheduling Committee and the Delegate to all take a moment to imagine what it's like living with treatment resistant PTSD (either for the person suffering or as a family member of that person).

As a mental health charity Mind Medicine Australia constantly receives emails from people suffering from severe mental illness and their families. Regrettably sometimes we are informed that a loved one who has suffered in this way over many years has committed suicide. An extract from an email that we received is set out below to give context to what this application is all about. We have many more communications of this nature that we could provide to the TGA.

Extract from Email Received from Mother of Daughter Suffering from Treatment Resistant Mental Illness

"I am a mother who lives with the daily fear that I will lose my child to her illness. I have journeyed the tortured path of mental illness with my daughter for the past 15 years. I have seen the agony and desperation in her eyes, and I have struggled to maintain the stability of my family as we have all been overwhelmed by the pain she suffers. I need answers. I need help. I need treatment. And I need it now! So, its time. Enough time wasting and enough politics. It's time to ask yourself what is the real agenda and reason behind drugs such as Psilocybin and MDMA being denied to Australian patients. It's time to ask yourself who you are responsible to? Who should you be caring for? The answer is MY DAUGHTER. She is not a number; she is a real person, and she WILL NOT be a suicide statistic. I need your help. I can't save her without your help, understanding and willingness to give her every possible treatment option. It's time to make a shift in Australia's approach to the use of all drugs and to show we are not under the influence of the large drug companies or driven by conservative political or hidden agendas. But most of all it is time to save the life of my daughter and potentially thousands like her. I am relying on you, please do not let me down."

The need for new treatment innovation is highlighted by the letter of consultant psychiatrist Dr Stuart Saker to the TGA reproduced below.

Letter from Dr Stuart Saker, Consultant Psychiatrist, Highlighting Importance of Limited Rescheduling Proposed for his Treatment Resistant patients

healthe.mind clinic

Dr Stuart Saker
Consultant Psychiatrist
MBBS (Syd.), BA, MPH, MHA, MRCpsych. (UK)
Provider No. 214830PA

28th February 2022

The Medicines Rescheduling Unit
Therapeutic Goods Administration
CANBERRA ACT

Dear Sir/Madam

Proposed Rescheduling of Psilocybin and MDMA

I am a psychiatrist practising in the Newcastle region of New South Wales with 21 years of experience. I am also an Australian Defence Force Veteran with 5 years of service and most of my patients are also Veterans.

I am writing to highlight why it's so importance for MDMA and Psilocybin to be rescheduled to Schedule 8 of the Poisons Standard on the limited basis envisaged in the applications being lodged with the TGA by the registered charity Mind Medicine Australia.

I am a Medicinal Cannabis prescriber and was familiar with the process of applying for Special Access Scheme (SAS-B) approvals for my patients from the TGA. I thought that the TGA were offering a legitimate pathway for my patients to access Psilocybin and MDMA in strictly medically controlled environments and as part of psychotherapy for treatment resistant mental illnesses. That this has not become a legitimate pathway to access these medications because of barriers at the State level caused by the current scheduling of these substances has been a cruel and painful "joke" on my patients.

I applied for and received 9 SAS-B approvals to prescribe Psilocybin and MDMA as part of psychotherapy for my patients in a controlled medical environment. In contrast to Medicinal Cannabis my patients would never be allowed to take the substances home.

My patients all have extreme treatment resistant Major Depressive Disorder and/or Post Traumatic Stress Disorder. They have all mainly tried multiple antidepressants, Transcranial Magnetic Stimulation and Electro Compulsive Therapy. Nothing is working for them. They are desperate people who served their country and who have been holding out for many years for access within our medical system to Psilocybin and MDMA assisted therapies. They are also some of my best and most compliant patients.

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Healthe Mind Clinic, Suite 5, Toronto Specialist Medical Centre II, 239 Excelsior Pde, Toronto 2283
Toronto Private Hospital

The risk is that these people could kill themselves if they are again denied the opportunity to access these therapies. This is a very real risk. As you will be aware Australian Defence Force Veterans have very high rates of suicide. The other risk is that they continue to have a disappointing life while they are consumed by mental illness and lose their children, partners and jobs.

It is very urgent if someone could kill themselves and moderately urgent if they are going through the slow process of having their lives dismembered by treatment-resistant mental illness.

I would ask you to act with compassion and expedite the rescheduling of these medicines so that I can commence seeking approval at the State level as soon as possible. I have been specifically trained in the use of these therapies so I know exactly what is required.

Yours Faithfully

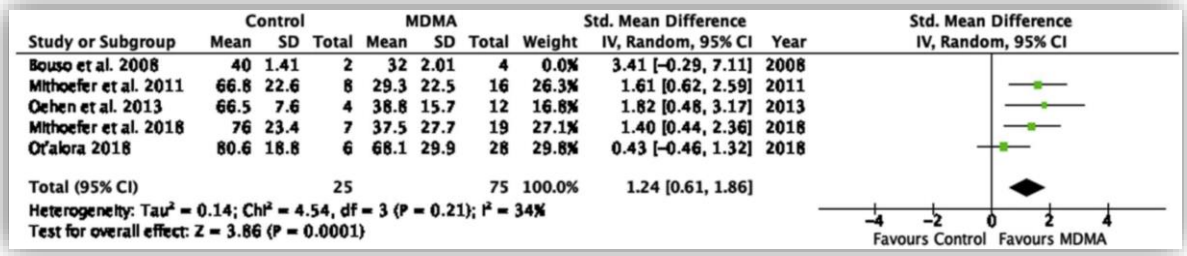
Dr Stuart Saker
MBBS (Syd) BA, MPH, MHA, FRCpsych (UK)
Consultant Psychiatrist

3.7. A Strong Basis to Expand the Treatment Paradigm in a Limited Way

This application supports the opportunity to expand the paradigm for the treatment of treatment resistant mental illness in Australia on a highly controlled basis to improve the mental health outcomes of suffering Australians.

There is strong evidence for the safety and efficacy of MDMA-assisted psychotherapy for the treatment of PTSD.[44] 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.[40] 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.[45]

Figure 3. Forest plot of Standardized Mean Difference (SMD) of effect of MDMA versus control on PTSD symptom score using random-effects meta-analysis.



Through a series of worldwide trials, MAPS has finalised a Phase 3 trial and multiple Phase 2 trials for the use of MDMA-assisted psychotherapy in the treatment of PTSD.[38] 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 Phase 3 and Phase 2 trials was published in *The Journal of Psychopharmacology*, showing that MDMA has a 54.2% remission rate for treatment resistant PTSD sufferers, compared to 23% in the placebo group.[19] Across these Phase 2 and Phase 3 trials the dropout rate was only 7.5% which illustrates MDMA's tolerability and strong patient adherence.[46]

The MAPS Phase 2 trials 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 in their mental wellbeing. This was observed in subsequent follow ups a year later, which showed a 68% rate of remission at this time point.[47, 48]

As seen for the following charts, the MAPS Phase 3 results showed very strong efficacy for the treatment of PTSD.

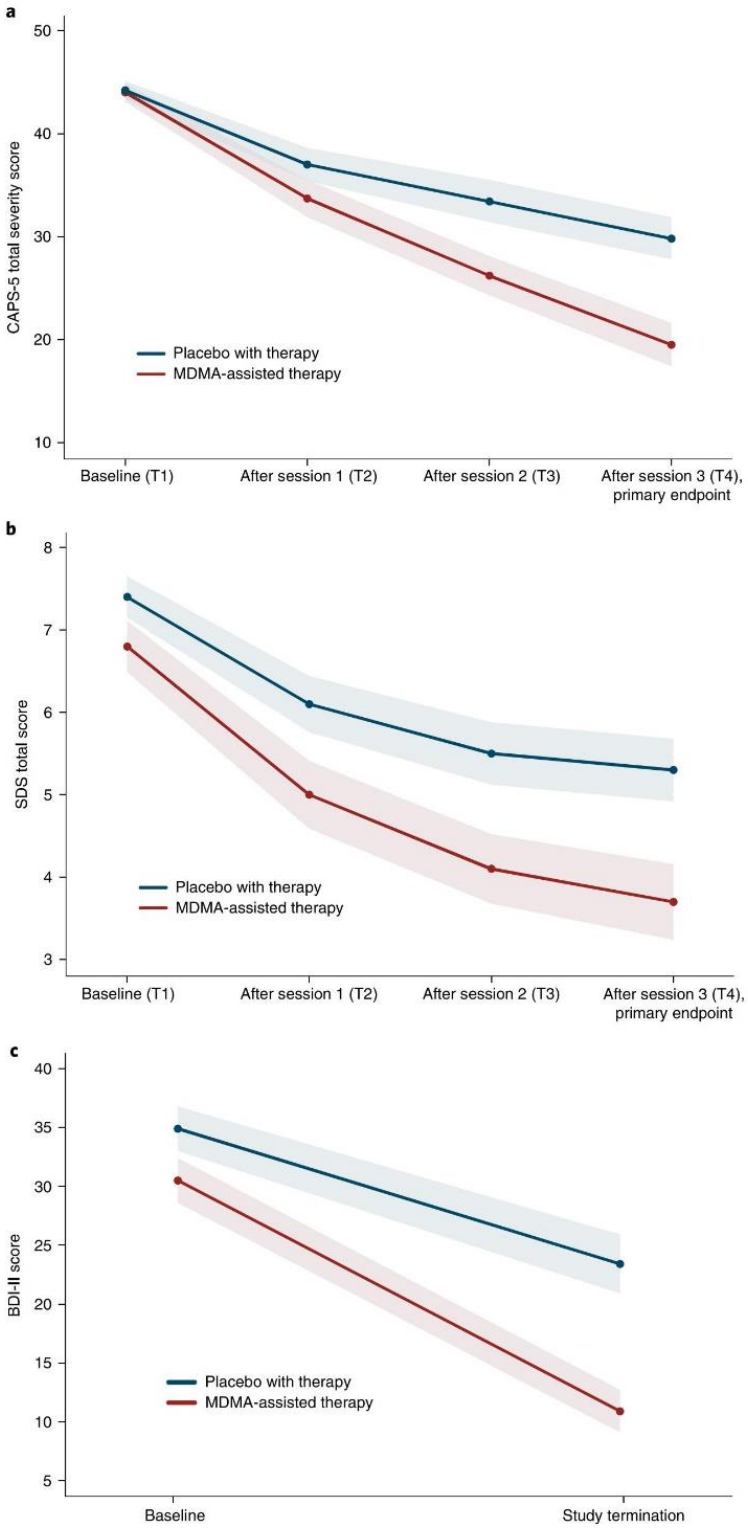


Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an MMRM model. **b**, Change in SDS total score from T1 to T4 ($P = 0.0116$, $d = 0.43$, $n = 89$ (MDMA $n = 46$)), as a measure of the secondary outcome. Primary analysis was completed using least square means from an MMRM model. **c**, Change in BDI-II score from T1 to study termination ($t = -3.11$, $P = 0.0026$, $n = 81$ (MDMA $n = 42$)), as a measure of the exploratory outcome. Data are presented as mean and s.e.m.

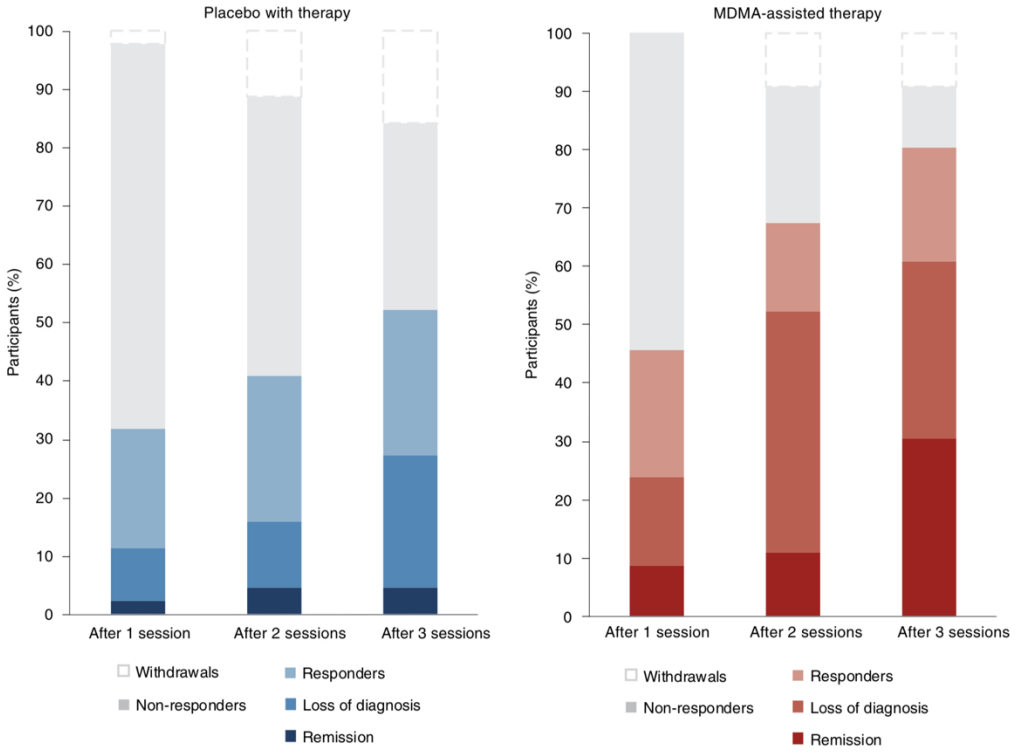


Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of ≤11) were tracked in both groups. Non-response is defined as a <10-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.

Source: ***MDMA Assisted therapy for Severe PTSD: a randomised, double-blind, placebo-controlled phase 3 study,*** Jennifer Mitchell er al, Nature Medicine Journal, Vol 27, June 2021 at page 1030.

As described in Part 1 Section 2.3, adverse events (and in particular suicidality) were much lower in the MDMA group than the placebo group adding to enormous benefits of this therapy for patients who are unable to get relief from existing modalities.

MDMA-assisted therapy has been granted 'Breakthrough Therapy' status by the US Food and Drug Administration (FDA), expediting its transition to a prescription medicine, subject to the Phase 3 trial results (one of which has already been completed with positive results).[49] This designation by the FDA indicates the FDA's view that MDMA-assisted therapies may offer substantial advantage over current treatments.

If the second Phase 3 trial results confirm the first Phase 3 trial results, MDMA may become available as a registered medicine in the United States for the treatment of PTSD in 2024.

MDMA has recently been approved for expanded access under compassionate use in Israel for patients who have not improved with current treatment modalities.[50] Likewise, MDMA has received approval for use under a similar expanded access program in the United States,[51] and Switzerland and access may also now be available in Canada under their Special Access Scheme. Patients have also been approved by the TGA to use MDMA in Australia as part of therapy for patients with treatment resistant PTSD under Special Access

Scheme-B but unfortunately the Australian States and Territories continue to prohibit access because of MDMA's current Schedule 9 scheduling. There seems to be an inability to differentiate between recreational use and medical use for treatment resistant patients in controlled medical environments.

3.8. Satisfaction of Rescheduling Requirements

We believe that this application for rescheduling the medical use of MDMA on the limited basis envisaged satisfies the requirements of Section 52E of the Therapeutic Goods Act and the Scheduling Policy Framework in relation to the key components of:

- Established therapeutic value and safety (see Part 2.1 Section (A)1.1));
- Translation risks (see Part 2.1 Section (A)2.2);
- Diversion risks Part 2.1 Section (A) 2.1); and
- Public health and safety requirements generally (see Part 2.1 Section (F))

3.9. The Approach is Consistent with Government Policy Statements

The Federal Government and State and Territory Governments around Australia have a major focus on mental health and reducing suicide rates. However, despite this focus and all of the work and considerable funds invested, rates of mental illness continue to increase around Australia and rates of suicide remain stubbornly high.

Governments recognise the need for innovation in this sector and the rescheduling of MDMA assisted therapy in the limited manner set out in this application would be consistent with Government policy.

3.10. Our Approach is a Pragmatic Response to Resolving Problems Associated with Australia's Federal System

The TGA has already granted a number of approvals under the Special Access Scheme for medical practitioners to treat patients who are treatment resistant and "at risk" with MDMA as part of psychotherapy. However, despite these approvals, medical access to MDMA as part of psychotherapy remains prohibited at the State and Territory level because of its current Schedule 9 listing. These prohibitions at the State and Territory level of our Federal System fail to distinguish between the medical use of MDMA in a controlled environment and the uncontrolled recreational use of that substance.

The problem caused by Australia's Federal system where both the Federal and State/Territory Governments have responsibility for the control of medicines and poisons was specifically addressed by the National Drugs and Poisons Schedule Committee (NDPSC) when it considered the rescheduling of nabiximols at its 57Th meeting on the 20-21 October 2009.[52] Nabiximols is the United States proprietary name for *Cannabis sativa* whole plant extracts – including psychoactive components. As a consequence of the NDPSC's recommendation the TGA restructured the scheduling of nabiximols so that they appeared

in both Schedule 8 for limited medical purposes and remained in Schedule 9 for all other purposes. This enabled States and Territories to provide approvals for limited medical use in accordance with policies which they then developed where the medical practitioner had already secured approval from the TGA under the Special Access Scheme.

In 2010, nabiximols had no established therapeutic value and were included in Schedule 4 of the *United Nations Single Convention on Narcotic Drugs 1961 (equivalent to Schedule 1* of the UN Convention on Psychotropic Substances which currently applies to MDMA). The direct quote below from the NDPSC's recommendations to the TGA are highly relevant here:

"…the Committee noted that there had been enquiries to jurisdictions regarding the availability of a THC+CBD preparation. The Committee noted that there had been approvals for THC+CBD through the TGA's Special Access Scheme (SAS) but it had been difficult for jurisdictions to also approve access.

"With regard to the current confusion as to whether jurisdictions could allow access to a nabiximols product that had been given a Special Access Scheme approval, some Members reiterated that it was appropriate that this uncertainty be resolved so that jurisdictions could allow restricted access. The Committee generally agreed that this uncertainty could be clarified by creating a new parent entry in Schedule 8 for nabiximols. Members also agreed, however, that this entry would need to be supplemented with additional controls…….Members agreed that it…. was necessary to have safeguards in place to make it clear that the Committee was allowing tightly restricted access to nabiximols only, this was to in no way be extended to other cannabis extracts.".

This advice given by the NDPSC to the TGA highlights that:

- The *Poisons Standard* is for scheduling substances with appropriate controls and is not indicative of a medical approval; and.
- Appropriate Appendix controls can be applied to a limited Schedule 8 entry of a Schedule 9 substance to create further safeguards and restrictions.

The NDPSC's pragmatic approach was also adopted by the TGA for ibogaine (a much more dangerous substance when misused than MDMA) but in that case the TGA agreed to a Schedule 4 listing (see the 16-17 February record of reasonings of the NDPSC in relation to this rescheduling).[a]

Other countries, including the United States, Israel and Switzerland have restrictive schemes for patient access under compassionate use for MDMA for Treatment Resistant PTSD. Health Canada has also recently expanded its Special Access Program (SAP) to provide medical access to both psilocybin and MDMA (and potentially other psychedelic medicines). Unlike Australia a separate approval is not required in Canada from the provincial government where the treatment is to occur.

[a] https://www.tga.gov.au/sites/default/files/ndpsc-record-58.pdf

3.11. Participation in Trials is Not a Solution for a Treatment Resistant "At Risk" Patient

Trials in Australia offer very limited places to people suffering from treatment resistant mental illnesses. They tend to take a least 4 years from inception of the idea through funding, ethics approval, patient selection, patients actually being treated, and the research findings being written up. Patient selection is highly selective (for example in the recent MAPS Phase 3 trial the investigators reduced 1,331 applications to just 90 participants) and participants have to fall within what are often narrow and singular guidelines. Trial requirements (often supported by limited funding) also don't enable treatments to be tailored to a patient's specific needs. In contrast patients being treated by psychiatrists in their clinical practices often have several co-morbidities and are therefore normally ineligible for trials.

Furthermore, the funding of trials is expensive and to date traditional pharmaceutical companies have not shown any interest in funding these trials. The challenge with the business model of a pharmaceutical company is that MDMA assisted therapy only requires two to three medicine dosing sessions rather than years of taking the medicine on a daily basis as often occurs with SSRI's and most other psychiatric medicines and patents aren't available.

Mind Medicine recognises the importance of ongoing research trial work in Australia in the development of medical knowledge and the improvement of outcomes. However, we believe that a limited rescheduling of MDMA for medical and compassionate use is not inconsistent with ongoing trials and will also provide valuable data on translation into a medical (rather than trial) domain. See our comments on the setting up of an independent registry in Part 1 Section 3.3 to collate treatment information and outcomes.

The suffering that people with treatment resistant mental illness go through (with some committing suicide) combined with the strong safety and efficacy data supports the need to reschedule the medical use of MDMA on the limited basis envisaged in this application.

3.12. Rescheduling on the limited basis proposed would highlight and support the Importance of the Psychiatrist Patient Relationship

This is obviously subject to appropriate controls being put in place which is the basis of the limited rescheduling of MDMA being sought. However, where the limited basis of the proposed rescheduling is considered against the safety and efficacy data achieved in overseas trials to date (see Part 1 Section 2.3 and Part 2.1Section (A)1.1), the proposed requirement for patient review by two other psychiatrists (see Part 1) and the training being provided to practitioners (see Part 2.1 Section (F)3) we believe that psychiatrists should be able to provide these treatments subject to the controls envisaged and the patients informed consent.

3.13. Overwhelming Support from Australia's Health Practitioners

Health sector participants overwhelmingly supported our first application for the rescheduling of the medical use of MDMA as part of psychotherapy. This included many psychiatrists, psychologists, psychotherapists, general practitioners and pharmacologists. These afront line practitioners are people who directly see the limitations of current treatments and the desperate need for innovation in the sector.

This application is even stronger because of the further restrictions incorporated into the application in specific response to concerns raised by the Delegate, RANZCP and the AMA.

PART 2 - BACKGROUND

1. CURRENT SCHEDULING

The Poisons Standard currently schedules MDMA as a Schedule 9 substance and doesn't differential between medical and recreational use.

2. 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.[15] 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*'.[53] It is estimated that between 1976 and 1986, over 150 therapists used MDMA-assisted psychotherapy to treat over 4,000 patients with remarkable results.[54] 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.[40] Over 90% of patients described improvements at the 19-month follow up.

2. Early Scientific Research

Subsequent research focused on the potential harms of MDMA. Several studies indicated that MDMA had neurotoxic effects in animals and in human recreational users.[15] 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.[55]

3. MDMA is Much Safer Than Early Research Suggests

Researchers have written extensively on the neurocognitive effects produced by the recreational drug Ecstasy (which often contains adulterants and is taken in uncontrolled environments), which includes:[22, 28]

- Deficits in retrospective memory
- Higher cognition
- Reduced serotonin transporter levels in the cerebral cortex
- Disturbed sleep architecture
- Other behavioural and psychiatric problems

However, the majority of the studies exploring the above effects in humans have many methodological flaws:[56]

- 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, 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 the recreational drug Ecstasy in participants who had an average lifetime exposure of 15-2000 tablets.[57] 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.[58] 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.[31]

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.[5]

4. Political Controversy

In 1984, in response to rising population use and police seizures of the recreational drug Ecstasy, the Drug Enforcement Administration in the United States announced the intention to ban MDMA.[40] Research into the therapeutic use of MDMA as a therapeutic agent was ceased in 1985 when MDMA was scheduled under the *Controlled Substances Act*.

5. Research Resurgence and Profile

In 1996, the FDA approved the first Phase 1 clinical trial with MDMA post-prohibition. 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.[45] 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.

3. RANGE OF USE

The principal focus to date has been as a therapeutic adjunct in the treatment of PTSD.[38] A highly successful Phase 3 trial has now been completed for treating Post-Traumatic Stress Disorder (PTSD) and another Phase 3 trial is now in progress. The following conditions are also currently being investigated in clinical studies:

- Social Anxiety Disorder (SAD) and emotional processing in adults with Autism
- General Anxiety Disorder (GAD)
- Addictions

4. MDMA-ASSISTED PSYCHOTHERAPY PROTOCOL

This is outlined in Part 1 Section 2.7 above.

PART 2.1 DETAILED CLAIMS AGAINST THE SCHEDULING POLICY FRAMEWORK REQUIREMENTS

PART 2.1 SECTION (A) - RISKS AND BENEFITS ASSOCIATED WITH THE MEDICAL USE OF MDMA

1. WHAT ARE THE BENEFITS?

1.1 Established Therapeutic Value

We have interpreted the "established therapeutic value" requirement for a listing in Schedule 8 of the Poisons Standard in the following way:

1. We start by reviewing the meaning in the literature of **therapeutic value** as follows.

   "The concept of therapeutic value is related to the therapeutic purposes of medications, their clinical effectiveness and health outcomes. When these characteristics are compared with other therapeutic alternatives available in the market, the definition is framed in the concept of added therapeutic value".[59]

2. We conclude that "established" requires clinical evidence to support that therapeutic value but not to the level of the support required for the registration of a medicine on the Therapeutic Good Register because registration of a medicine is not a prerequisite for listing on Schedule 8 of the Poisons Standard.

3. Given that the proposed listing on Schedule 8 of the Poisons Standard is restricted to patients that are treatment resistant the need for innovation is obvious. Current treatments for PTSD have very low remission rates and can also have harmful side effects (Part 1 Section 3.5 and Part 2.1 Section F(2)).

4. Therefore, in relation to the present case, we conclude that "established therapeutic value" requires reasonable evidence to support both safety and efficacy and health outcomes associated with the use of MDMA as part of psychotherapy in controlled medical environments but not to the standard required for registration. In other words, the evidence is sufficient for a psychiatrist to believe, on reasonable grounds, that it could be appropriate to prescribe this treatment for a patient that is treatment resistant.

The evidence to support the patient safety is strong when MDMA assisted therapy is used in clinical trials (Part 1 Section 2.3(2)).

There is also strong efficacy information coming from clinical trials (see Part 1 Section 3.7 and Part 2.1 (A) 1.1) although not yet at the level required for registration of this medicinal therapy on the Australian Register of Therapeutic Goods.

There is therefore a strong basis for a psychiatrist to consider recommending this form of therapy to a treatment resistant patient provided that the patient is able to give fully informed consent and the medicine dosing sessions are conducted in a medically controlled environment. This is reinforced by the proposed scheduling requirement that the treating psychiatrist must have received training in the use of MDMA as part of therapy and the psychiatrist's diagnosis and treatment plan must be confirmed by two other psychiatrists.

Our view that the use of MDMA as part of therapy has an established therapeutic value is supported by World leading researcher in this field, Professor David Nutt from Imperial College London, by Drug Science in the UK and by leading Australian based pharmacologists, Professors Arthur Christopoulos and Chris Langmead from the new Monash University Neuromedicines Discovery Centre in Melbourne. Professor Christopoulos is also Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University which is the leading globally ranked faculty in any discipline of any Australian University and ranked second in the World in Pharmaceutical Sciences.

The letters from these experts are reproduced here and also appear in Appendix C. These experts would be prepared to discuss their views with the TGA, the Medicines Scheduling Committee and with the Delegate.

We can also obtain confirmatory letters from many other experts in this field if that would be helpful.

Drug Science

The Secretary

Medicines Scheduling Unit

Therapeutic Goods Administration

Canberra, ACT.

London, 23/02/2022

Dear Sir/Madam,

Application to Reschedule MDMA – Assisted Psychotherapy to Schedule 8 of the Poisons Standard

The Chair of Mind Medicine Australia, Mr Peter Hunt AM, has asked Drug Science to directly address the question of whether medical grade MDMA when used as part of psychotherapy has an established therapeutic value. We are aware that this is one of the factors to be considered by the Medicines Scheduling Committee and the Delegate in addressing whether MDMA when used as part of psychotherapy should be rescheduled to Schedule 8 of the *Poisons Standard*.

We note that the rescheduling proposed by Mind Medicine Australia is very restricted in its application.

The Mind Medicine Australia Proposal

SCHEDULE 9 – Proposed Amended Entry

MDMA **except** when separately specified in Schedule 8.

SCHEDULE 8 – Proposed New Entry

MDMA for use in the treatment of treatment resistant mental illness when:

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists: and

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d) where the substance has been manufactured in accordance with the *Narcotic Drugs Act 1967and/ or* ;
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
f) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*.

MDMA places the patient in a 'zone of optimal arousal', enhancing access to, and control of, emotions, increasing a perceptible sense of ease, and expanding a patient's therapeutic window.[1]

We are of the view that MDMA when used as part of psychotherapy for the treatment of PTSD in the limited manner proposed clearly has an established therapeutic value. This is demonstrated by;

- Between the late 1960s and prohibition, MDMA was administered in approximately 500,000 doses across 20 years of psychotherapy without complications and with useful efficacy;

- When MDMA was being scheduled in 1982 in the US the US Supreme Court Federal Judge who was overseeing the expert witness data recommended that MDMA be placed in Schedule III of the Controlled Substances Act by the Drug Enforcement Agency ("the DEA"). The DEA ignored expert testimonies and placed MDMA in Schedule 1. Harvard psychiatrist Lester Grinspoon then sued the DEA for ignoring the medical benefits of MDMA. Dr Grinspoon won the case and the US Federal Supreme Court overruled the DEA and declassified MDMA. However, less than a month later, the DEA reclassified MDMA as a Schedule 1 drug.

- Since prohibition, MDMA has been shown to be well tolerated in a significant number of trials and with useful efficacy.

All long-term follow up studies have shown sustained efficacy in a significant portion of participants with no adverse mental health effects, dependence or physical health

[1] Nutt DJ and de Wit H (2021) Putting the MD back into MDMA. *Nature Medicine* 27(6): 950–951. DOI: 10.1038/s41591-021-01385-8

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complication, even in patient groups such as alcohol dependence where physical health is often compromised[2]

- People have been able to access MDMA as part of therapy in countries under compassionate access schemes in the United States, Switzerland and Israel.

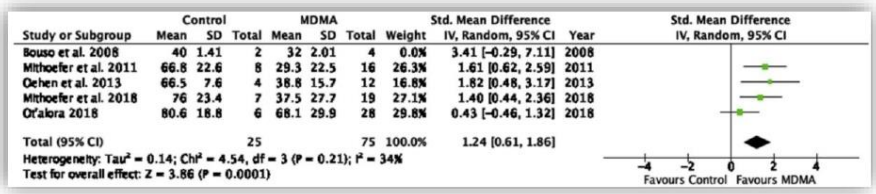
- Significant media and online anecdotal evidence from people who have taken MDMA-therapy outside of the legal medical system.

- But most importantly the trial results achieved in the MAPS sponsored multisite Phase 2 and Phase 3 trials which we deal with below.

As a result, we believe there is strong evidence for the safety and efficacy of MDMA-assisted psychotherapy for the treatment of PTSD.

The following meta analysis was completed before the recent Phase 3 results were published and was already compelling.

Forest plot of Standardized Mean Difference (SMD) of effect of MDMA versus control on PTSD symptom score using random-effects meta-analysis.



Source:Bahji at al, Efficacy of MDMA assisted psychotherapy for post traumatic stress disorder; A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry 2020; 96:109735*

[2] Sessa B, Higbed L, O'Brien S, et al. (2021) First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *Journal of Psychopharmacology* 35(4). SAGE Publications Ltd STM: 375–383. DOI: 10.1177/0269881121991792.

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Through a series of worldwide trials, MAPS has finalised a Phase 3 trial and multiple Phase 2 trials for the use of MDMA-assisted psychotherapy in the treatment of PTSD. 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 Phase 3 and Phase 2 trials showed that MDMA assisted psychotherapy had a 54.2% remission rate for treatment resistant PTSD sufferers, compared to 23% in the placebo group. Across these Phase 2 and Phase 3 trials the dropout rate was also low which illustrates MDMA's tolerability and strong patient adherence.

The MAPS Phase 2 trials 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 assisted psychotherapy, patients continued to improve in their mental wellbeing.

In the MAPS Phase 3 results patients with severe PTSD in the MDMA group also achieved strong efficacy results. Figures 2 and 3 below are taken directly from the published results (Jennifer Mitchell et al, MDMA-assisted therapy for severe PTSD: a randomised, double-blind, placebo-controlled phase 3 *Nature Medicine Vol 27, June 2021 1025-1033*).

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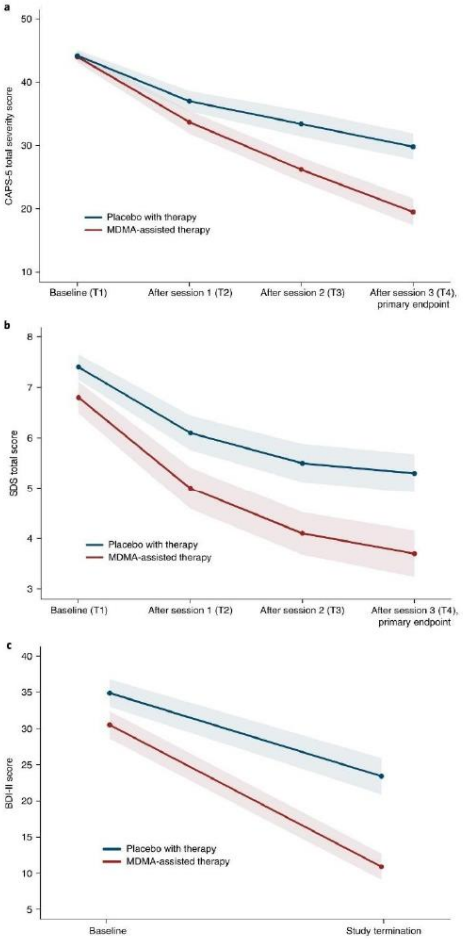

Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an MMRM model. **b**, Change in SDS total score from T1 to T4 ($P = 0.0116$, $d = 0.43$, $n = 89$ (MDMA $n = 46$)), as a measure of the secondary outcome. Primary analysis was completed using least square means from an MMRM model. **c**, Change in BDI-II score from T1 to study termination ($t = -3.11$, $P = 0.0026$, $n = 81$ (MDMA $n = 42$)), as a measure of the exploratory outcome. Data are presented as mean and s.e.m.

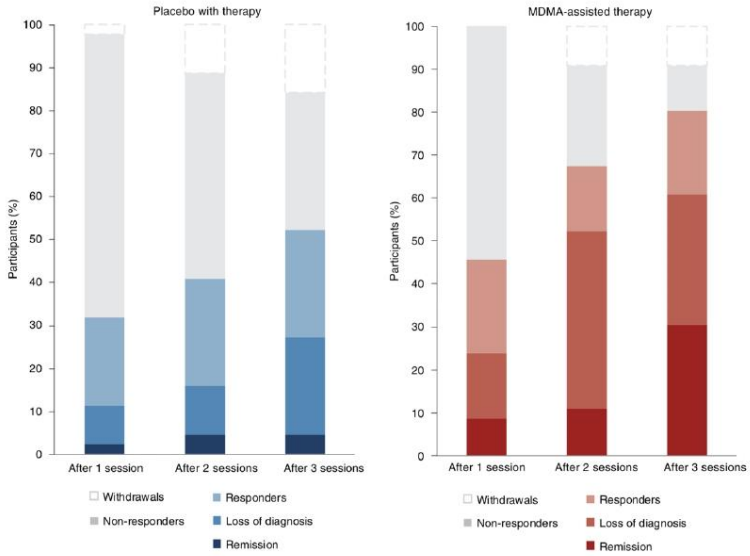

Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of ≤11) were tracked in both groups. Non-response is defined as a <10-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.

As shown in Table 2 from the same study, adverse events (and in particular suicidality) were also lower in the MDMA group than the placebo group.

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Table 2 | Participants with treatment-emergent SAEs and AESIs

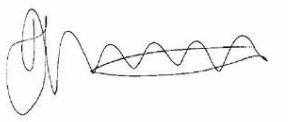
	MDMA ($n=46$), n (%)	Placebo ($n=44$), n (%)
SAEs	-	2 (4.5)
Suicide attempts	-	1 (2.3)
Suicidal ideation resulting in self-hospitalization	-	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	-
Suicidal behavior (suicide attempts and preparatory acts) and self-harm	-	1 (2.3)
Suicidal behavior (preparatory acts), self-harm and suicidal ideation	-	1 (2.3)
Cardiac events that could indicate QT prolongation (total)	-	1 (2.3)
Irregular heartbeats and palpitations	-	1 (2.3)
Abuse potential for MDMA (total)	-	-

The number of participants experiencing one or more SAEs or AESIs relating to suicidality, cardiovascular symptoms that could indicate QT prolongation, and abuse potential following the first experimental session.

In our view it is now clear that MDMA when used as part of psychotherapy for patients suffering from treatment-resistant Post-Traumatic Stress Disorder has an established therapeutic value.

We would be more than happy to answer any questions that you might have.

Yours sincerely



Prof David Nutt and the Drug Science Scientific Committee

Prof Jo Neill

Dr David Erritzoe

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.

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Prof David Nutt, Chair of Drug Science, is Head of the Centre for Psychedelic Research at Imperial College London, Prof Jo Neill is Chair of the Drug Science Medical Psychedelics Working Group, and Dr David Erritzoe leads the CiPPRes Clinic, London, UK. All have extensive experience and scientific understanding of psilocybin being used in a clinical setting.

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MONASH University

Monash Institute of Pharmaceutical Sciences
Monash University
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Victoria, 3052
Australia
1st March 2022

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

The statistics associated with the burden of chronic mental health in Australia are staggering. Over 45% of Australians will experience a mental illness during their lifetime, and approx. 20% of Australians at any one time are suffering from a chronic mental health issue.

The Australian Government Productivity Commission's 2020 Report into Mental Health[1] conservatively estimates that the cost to the Australian economy of mental ill-health and suicide is in the order of $43-51 billion per year. The largest costs within this are for the loss of workforce participation and productivity ($9.8-18.1 billion p.a.), for the additional informal care provided by family and friends ($15 billion p.a.), and for government expenditure on health and services ($16.2 billion p.a.).

Notably, all three of these major cost categories have come under increased strain during the COVID-19 pandemic. On top of this economic burden, there is also an additional $130 billion per year associated with diminished health and reduced life expectancy for those living with mental ill-health.

These sobering data reinforce previous work by the Commission, which estimated that mental health has the highest economic cost burden in terms of workforce participation and productivity out of any disease category. In this context of large and rising costs, it is notable that the Productivity Commission found "despite the rising expenditure on healthcare, there has been no clear indication that the mental health of the population has improved"[1].

As international neuropharmacology researchers with >25 years' experience in the field, this pessimistic outlook is not surprising to us. Despite the massive strides that we have made in destigmatising and understanding mental illness, in developing patient access gateways, support systems and advocacy – all championed by the Australian government – these advances have not been accompanied by a commensurate increase in the clinical development of truly novel, efficacious and safe medicines.

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Indeed, an often-unappreciated fact is that all current medicines prescribed to treat psychiatric diseases are based on science that is at least 50 years old[2]. We cannot think of any other realm of medical or scientific research where such a decades-long lack of innovation would be deemed acceptable. This is why most current psychiatric medicines have similar (limited) success rates; require long-term dosing; are difficult to cease; have significant side-effects that affect both compliance and quality of life.

We wholeheartedly believe that improving our mental health outcomes requires a holistic, systemic, approach – which is why we feel that the current lack of medicinal treatment breakthroughs has been a crucial inhibitor of the clinical and social progress that we are trying to achieve in our community.

It is for this reason that in late 2021, with significant financial support of Monash University, we founded the Neuromedicines Discovery Centre (https://www.neuromedicines.monash/) to engage in comprehensive research into the discovery, development, clinical evaluation and rollout of novel medicines for the treatment of mental health disorders.

We urgently require new approaches to break the current bottleneck in psychiatric drug discovery, which is why we are writing **in strong support of the limited re-scheduling of MDMA from Schedule 9 to Schedule 8 of the Poisons Standards, to facilitate its medical use as a vital and effective part of psychotherapy**. **Simply put, the science does not support the current classification of MDMA (when used in this way) as a Schedule 9 poison.**

There is a substantial and growing body of overseas clinical trial evidence that MDMA possesses *significant therapeutic benefit* when used as part of psychotherapy in the treatment of otherwise drug-resistant psychiatric diseases, particularly PTSD[3-5]. These datasets have now been augmented by a recent *major phase 3 clinical study* in PTSD[6], which has substantially expanded both the quality and quantity of clinical data, increased the breadth of patients receiving such treatment and *validated* the therapeutic effectiveness of MDMA in treating PTSD as part of psychotherapy.

At the molecular level, MDMA acts on similar classes of brain transporter proteins that are targeted by the existing Schedule 8 medicines, methylphenidate (Ritalin) and dexamphetamine (Adderall; Dexedrine)[7-10].

Moreover, when used in a clinical environment under direct monitoring by a trained therapist, MDMA is very safe[5] (significantly more so than Schedule 8 opioids and Schedule 4 medicines such as benzodiazepines[11]); the most commonly anticipated side effect in a clinical setting would be a transient elevation in blood pressure[12] that can be monitored for and/or used as an exclusion criterion depending on the patient's existing health.

MDMA is also fast-acting, with reports of patients having experienced rapid and sustained rates of remission of symptoms after MDMA-assisted psychotherapy sessions[4]. This is in contrast to the majority of existing psychiatric medicines, which often take weeks to start showing an effect and then need to be taken by the patient for long periods of time.

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Based on current overseas data, MDMA-assisted psychotherapies are also likely to only require a single administration (by clinicians) of the medicine 2-3 times over a period of a few months to complete a course of therapy[4].

Such a controlled and limited dosing regimen markedly mitigates any likelihood of abuse liability or risk of adverse effects induced by longer term dosing (such as sleep disturbances, depression, heart disease or decreased cognitive function). As evidenced by a recent meta-analysis of five MDMA clinical trials[5], there were no serious adverse events observed in four of the five clinical studies; in the fifth trial where some serious adverse events were observed, it was concluded that the majority of these events were not due to MDMA[5]. Indeed, in the more recent and comprehensive Phase 3 clinical trial of MDMA in PTSD[6], the researchers found that the adverse effects were actually worse in the placebo group than they were in the MDMA group.

The severe adverse effects listed by the Delegate in previous communications regarding MDMA, specifically loss of consciousness and seizures, have never been reported (to our knowledge) in a clinical setting; rather, they are associated with the unsupervised, recreational use of MDMA of unknown purity.

It should also be noted that the USA FDA has recently granted MDMA-assisted therapies for PTSD "breakthrough therapy" status[13], paving the way for availability of this as a form of prescribed medicine (under psychiatric supervision) pending further clinical trial results.

Furthermore, the protocol under which MDMA would be administered (with clinical supervision) as part of psychotherapy provides an environment closest to that used in the successful clinical trials; there is significantly lower risk for the misuse of MDMA by this approach than for most medicines that, once prescribed, are subject to patient compliance at home.

The risk of acute and long-term effects of MDMA abuse or misuse by way of access outside of strictly controlled medical and scientific research settings is low, noting that a rescheduling would place the medical use of MDMA as part of psychotherapy at the same level as drugs such as morphine, methadone, and ketamine, which are used therapeutically and securely stored in accordance with Schedule 8 requirements.

The application for rescheduling MDMA to Schedule 8 of the Poisons Standard, to which this letter is appended, is for limited clinical use, namely:

- when used as part of psychotherapy in medically controlled environments; and
- under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
- where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and

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- where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967and/ or; imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

When this strictly limited use application is considered with a) the strong evidence base supporting extant therapeutic effectiveness of MDMA, b) the minimal risk/abuse liability in such controlled settings and c) the establishment of training courses in psychedelic-assisted therapies both in Australia and overseas, we believe that the data **strongly support the contention that medicinal MDMA already has an established therapeutic value when used as part of psychotherapy,** and could represent a front-runner in a new class of psychiatric medicines that are safe, fast-acting, with minimal adverse effects and minimal abuse liability.

Please note that we categorically do not support the use of MDMA in any setting that does not involve appropriate patient screening prior to clinically supervised administration and observation, with the same policies and guidelines as applied to Schedule 8 medicines for manufacture, storage and disposal.

Whilst the Federal Government's recent Medical Research Future Fund announcement of support for clinical studies of psychedelic medicines is welcome, the current classification of MDMA as Schedule 9 prevents States or Territories providing a permit for use by psychiatrists, even when they have met the criteria above set out in the rescheduling application and access has been approved by the TGA via the Special Access Scheme-B.

Furthermore, the current classification places extremely prohibitive barriers in allowing even fundamental research to proceed, let alone appropriately sized clinical trials, due to practical, financial and bureaucratic restrictions specific to Schedule 9 substances[14]. This would not be the case if MDMA were re-scheduled as a Schedule 8 substance in the manner proposed.

Based on our long-term experiences, industry research, and successful collaborations on major NIH, Wellcome Trust, NHMRC, ARC and industry-sponsored grants, we can attest that Australia has some of the world's best pharmacologists, psychiatrists and psychologists with expertise in this space who would benefit enormously from improved access to MDMA when used in the way proposed.

Collectively, based on the extant and growing evidence base, we are satisfied that MDMA use as an adjunct to psychotherapy has an established therapeutic value and meets the requirements for a revised Schedule 8 listing.

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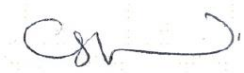

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We comment specifically on translation risk from clinical trial environments to medically controlled environments in Part 2.1 Section (A) 2.2 below.

1.2 Safe and Non-Toxic at its Therapeutic Dose

See Part 1 Section 2.1 (4) and Part 2.1 Section (B)4

1.3 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.[60] PTSD patients are described as having a narrow therapeutic window, meaning psychotherapy can trigger patients outside the zone of optimal arousal and into an overwhelmed state, leading to dissociation or re-traumatisation.[45]

MDMA releases the social bonding neurohormones of oxytocin, prolactin and vasopressin as well as serotonin.[13] 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.[15] 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.

1.4 Reduction of Fear Response and Memory Reconsolidating

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.[61] 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.[62] 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.[21]

A leading trauma therapy approach, Exposure Therapy, relies on slowly enabling a patient to extinguish their fear response to allow processing of traumatic memory.[37] MDMA may accelerate this process by diminishing the fear response, enhancing the ease by which a patient can tolerate and reprocess traumatic memory.[63] MDMA- assisted therapy was compared to exposure therapy in a 2016 meta-analysis.[64] 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.[47, 48]

1.5 Strong Results from Phase 2 Clinical Trials and the first Phase 3 Trial

Of those diagnosed with PTSD, 20-30% respond to pharmacotherapy.[65] SSRI's are considered a second line treatment.[66] Current psychotherapy treatments provide 44% of those entering treatment to experience some clinical relief from PTSD but remission rates are much lower.[67] 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.[38] These remission rates increased to 68% at the 12 month follow up.

The first Phase 3 trial also demonstrated strong safety and efficacy results. At the primary study end point 67% of the participants in the MDMA group no longer met the diagnostic criteria for PTSD compared to 32% of those in the placebo group and 80% of the MDMA group participants responded to treatment. **Interestingly, MDMA was equally effective in participants with comorbidities that are often associated with treatment resistance**. Based on the Phase 2 12-month outcomes, the Phase 3 MDMA group outcomes are expected to further increase over the next 12 months (see Part 1 Section 3.7 and Part 2.1 Section(A)1.1).

1.6 Non-Addictive and No 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*.[8] Following a therapeutic protocol, the administration of MDMA will be limited to in clinic treatments, with minimal risk of dependence. Therapeutic treatment with MDMA has not be shown to increase illicit drug use.

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.[68]

1.7 No Negative Long-Term Effects

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). There have been no negative health outcomes found from MDMA clinical trials.

Table 6. Negative health outcomes assessed in long-term follow ups of MDMA clinical trials.

Year study published	Follow up timeframe	*N*	Psychosis developed?	HPPD developed?	Negative health outcomes developed?
2021[69]	3 and 6 months	12	No	No	No
2020[46]	6x Phase 2 studies of PTSD averaging 3.8 years follow-up	107	No	No	No
2020[70]	3x Phase 2 studies of 12 months	60	No	No	No
2019[71]	12 months	19	No	No	No
2018[72]	6 months	12	No	No	No
2015[73]	2 years	96	No	No	No
2004[74]	18 months	17	No	No	No

1.8 No Risk of HPPD, Psychosis, or Schizophrenia

In the scientific literature, MDMA use is not associated with the development of HPPD, psychosis, and schizophrenia.

Table 7. Meta-analysis and systematic reviews of development HPPD, psychosis, and schizophrenia associated with drug use

Years of studies included	*n* of studies included	Development of HPPD, psychosis, or schizophrenia associated with MDMA?
1998-2017[81]	50	No
1995-2017[82]	45	No
1997-2007[83]	64	No

1.9 Historical Medical Use Without Complication

Early therapeutic use of MDMA was without complication.[84] In more recent trials, adverse events have been rare and there have been no life threatening or unpredicted 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 125 mg MDMA treatment.[5] The individual was observed in a hospital setting and all readings returned to normal ranges. The adverse events in the MAPS Phase 3 trial were also not serious (see Part 1 Section 2.3(2)).

2. WHAT ARE THE RISKS?

2.1 Is there a Realistic Diversion Risk?

Australia's medical system is used to managing Schedule 8 medicines, many of which are far more dangerous than the medical use of MDMA (e.g. fentanyl, benzdiazepam) and which (unlike MDMA) carry substantial risks of addiction if used inappropriately (e.g. opioids).

We have set out in Table 8 below the way MDMA as a Schedule 8 medicine would be controlled in our medical system to minimise any diversion risk. This is based on Schedule 8 controls that already exist for other medicines. We are advised by practitioners that this system provides for a very high level of safeguards. We have also assumed below that the medical grade MDMA is imported into Australia as there is as yet no manufacturing of this substance for medical use in Australia.

Table 8. Managing MDMA as A Schedule 8 Medicine to Minimise Diversion Risk

Supply Step	Description	Comment re diversion risk
API is ordered from overseas by the Pharmacist with a Schedule 8 license and shipped to the pharmacist's secured premises in Australia where it is kept in a safe that satisfies Schedule 8 requirements	Pharmacy obtains importation permit from the office of Drug Control and storage permits from the relevant State Department of Health	Nil – As for other drugs that we import such as narcotics and cannabinoids, the supply chain is tightly controlled by Australian Border Force and the need to have all relevant permits and licenses in place – otherwise goods are confiscated at the point of importation
API is stored in labs which have been licensed to store Schedule 8 medicines	Pharmacy labs have relevant licensing and DD safes. Safes are compliant to the relevant State's Pharmacy Authority Standard. Only Pharmacists registered to deal with Schedule 8 substances have access. Premises are monitored via alarm and video after hours.	NIL – access to API is tightly controlled.
API is made into product in labs	Pharmacy receives legal drug order on a patient-by-patient basis from a psychiatrist with Special Access Scheme-B approval and meeting local State/Territory requirements. Bone fides of each patient checked as well as prescriber. Safe Scripts platform ensures dr/patient permit is in place prior to dispensing	Nil – products cannot be made until legal drug order is in situ and relevant permits are in place

Product is shipped to medical clinic for patient dosage	Dangerous medicine couriers are used to move patient orders to each clinic (i.e. by hand in person). Staff at medical clinic sign in goods into Medical Practice DD books which are audited by the local State/Territory Health Department	Nil – DD records in place. Items stored in practice DD safe securely with limited access – as for other DD's like opiate injections. Product only held on site for 72 hrs. max, otherwise sent back to pharmacy
Product is not dosed as planned	Patient no shows for a variety of reasons. Practice staff send product back to pharmacy after 72 hours via same dangerous medicines courier – DD book return of stock entry completed	Nil – in person transport back to pharmacy and handed to Pharmacist. DD entries completed as inwards items.
Destruction	Stock destroyed and counter signed by 2 Pharmacists – VPA standard.	Stock entered as destroyed in DD book

The other way of assessing diversion risk is to understand the incentives, the demand for and the risk reward equation for diverting medical grade MDMA from the legally controlled medical setting to an uncontrolled setting.

A doctor or pharmacist caught illegally diverting MDMA would face criminal charges and almost certainly lose their licence to practice.

The price equation also does not provide an incentive. Despite Australia's War on Drugs MDMA is readily available on the Black Market. Unfortunately, this means that the supply of MDMA for illegal use is plentiful and the costs low (the current black-market cost is about $30 per dose. By comparison the cost of medical grade GMP synthesised MDMA is much higher (currently around $1,000 per dose depending upon the amount purchased on global markets) and carries with it further supply costs for obtaining required permits, secure carriage, safekeeping and stabilisation testing.

Given the availability of MDMA for illegal use and the pricing differential, the diversion risk for medical grade synthesised MDMA is actually far lower than for many other Schedule 8 medicines (where the diversion risk for the reasons given is already low).

2.2 Is there a Realistic Translation Risk?

As mentioned in Part 1 Section 3.2 above this was a concern of the Delegate in relation to Mind Medicine Australia's previous application. Translation risk is an issue with all medicines as they move from trial environments to clinical environments. We have deliberately structured our revised scheduling application to minimise this risk.

Firstly, we have made the current application much more restrictive so that not only will this treatment have to be prescribed by the patient's psychiatrist with fully informed consent but in addition;

(i) the psychiatrist will have had to have received specific training in this form of therapy;

(ii) the patient's diagnosis and treatment plan will have to have been confirmed by two other psychiatrists; and

(iii) The medicinal dosing sessions will have to take place in medically controlled environments with the medicines being held under strict Schedule 8 controls and the patients never being allowed to take the medicines home.

Secondly, our Health System is used to managing the translation of Schedule 8 unregistered medicine from a trial environment to a clinical environment.

Thirdly, protocols for this treatment are easily and readily available from recent trials.

Finally, **Mind Medicine Institute** is already training psychiatrists, psychologists and psychotherapists in the application of these therapies and our course was recently described by one of the leading researchers in this field on ABC National Radio (Professor David Nutt, Head of Neuropsychopharmacology at Imperial College London) as "*the best course of its kind in the World*" – something that Australia should be proud of (see Part 2.1 Section (F)3 below).

2.3 Cardiovascular and Cerebrovascular Risks

Current clinical trials exclude individuals with uncontrolled blood pressure.[7] In a therapeutic setting cardiovascular health will be assessed prior to use and a physician is to be always on premises.

2.4 Thermoregulatory Risks

Although body temperatures remain stable in clinical settings, in uncontrolled settings there is a greater risk of hyperthermia.[35] A physician is recommended to assess patients for thermoregulatory risk.

2.5 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.[25] It is recommended to assess patients for osmoregulatory risk and to have electrolyte supplements available on premises.

2.6 Increased Health Risks with High Doses

Adverse effects increase with higher non-therapeutic doses.[85] It is therefore recommended that prescription of MDMA follow an assigned dosing protocol. Increased risk can occur in uncontrolled non-clinical settings. Morbidity and mortality have only occurred in uncontrolled, non-clinical settings.[40] This application is for the prescription of MDMA for in clinic settings only as part of therapy.

2.7 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. The most common are nausea, jaw clenching, muscle aches, numbness, dizziness, headache, sweating, and decreased appetite.[37] These reactions are not considered to be significant hazards.

2.8 The Vital Importance of Environment and Context

There are several factors which influence psychological reactions to MDMA. In trials, occasionally temporary anxiety can occur which alleviates as MDMA is metabolised. Modern clinical research is undertaken in a controlled context also described as adhering to a 'set and setting' protocol.[86] This approach diminishes adverse experiences and enhances outcomes[87] and would be continued in the clinical environment under standard protocols.

2.9 Risks of MDMA in Uncontrolled Settings

Whilst not relevant to medical use in a controlled setting the following information is provided for completeness.

All following risks of MDMA use are only apparent in an uncontrolled setting:

- Vulnerable individuals in uncontrolled settings may experience complications from the psychological effects of MDMA.
- Analysis of harms caused by a range of psychotropic substances ranked MDMA containing mushrooms as among the least harmful to the user and least harmful to others in population use.[2]
- When compared to MDMA, the following drugs and medicines ranked as causing more harm to the user and more harm to others.[1] This research was recently repeated in Australia.[88, 89]
    - Schedule 8 drugs within the *Poisons Standard*; buprenorphine, methadone, cannabis, ketamine, amphetamine.
    - Schedule 4 drugs within the *Poisons Standard*; anabolic steroids, benzodiazepines.
    - Unscheduled drugs within Australia; tobacco and alcohol.

Three separate studies in the UK, Europe, and Australia, ranked both MDMA (evaluated as ecstasy) and psilocybin (evaluated as magic mushrooms) in their pure form as amongst the recreational drugs that cause minimal and least harm to the user and society when compared to other drugs (both legal and illicit) with little to no dependence. However, purity and lack of adulteration are key problems in the recreational scene.

Figure 4. The Australian Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.[89]

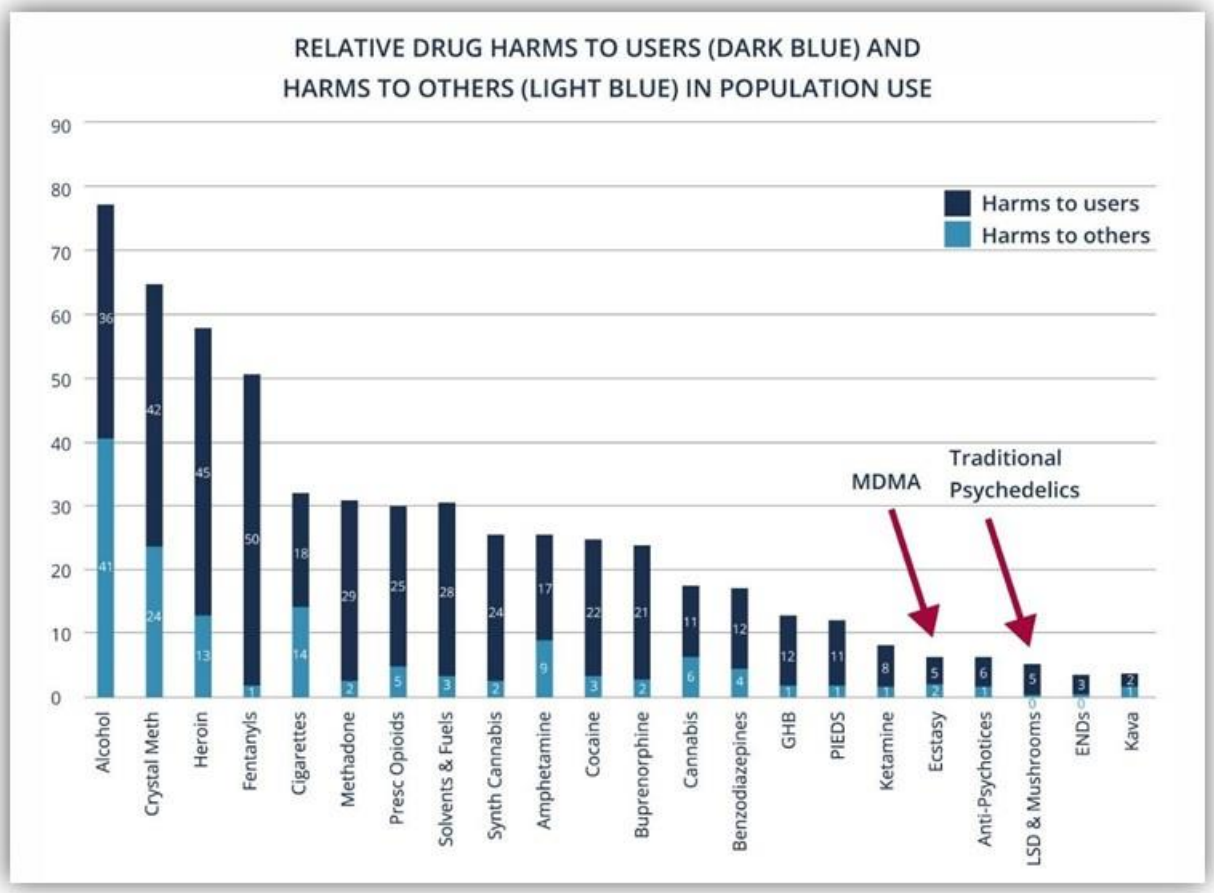


Figure 5. The UK Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.[2]

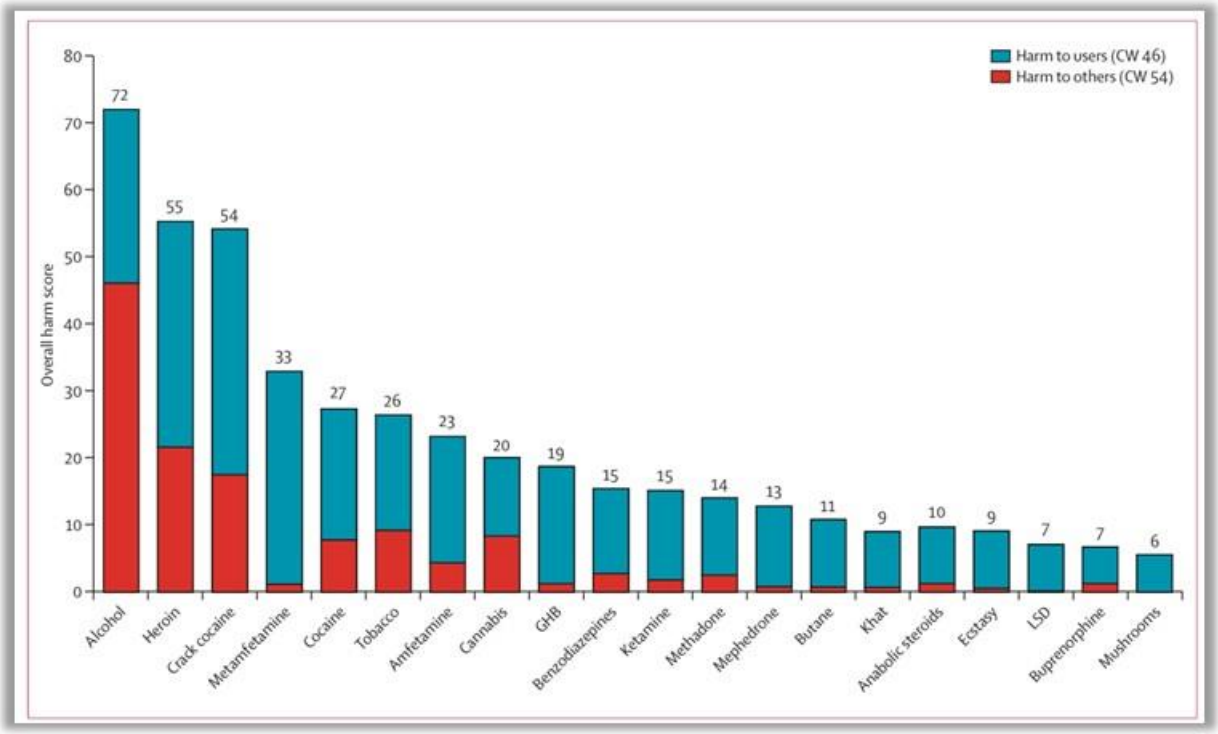
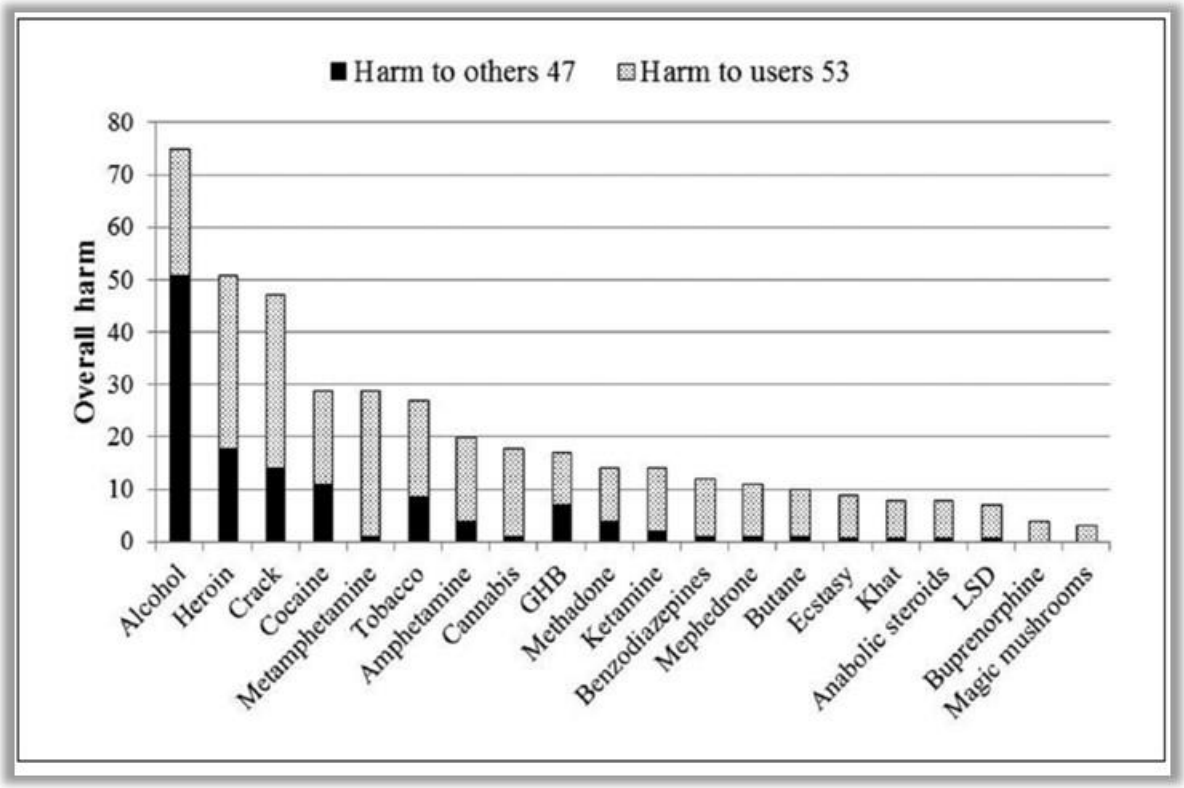


Figure 6. The European Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.[1]



2.10 In What Circumstances can the Risks Arise?

Risks can arise if there is MDMA ingestion or use in an uncontrolled or recreational setting. Risks can also arise in vulnerable people. However, management of these sorts of risks are a normal part of our medical system and additional safeguards have been inserted into the proposed Schedule 8 restricted listing. In controlled settings there have been no major adverse events and minor side effects related to MDMA resolve within a few days.[5]

2.11 What is the Likelihood of the Hazards Occurring?

As mentioned above, hazards have only occurred in recreational settings.

The following is a summary of mortality where the recreational drug Ecstasy was found in the individual's system at the time of the autopsy.[90]

Table 9. Cause and intent of Ecstasy-related deaths in Australia between 2000-2018.

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-only toxicity	14 (55)	33 (24)	10 (31)
Other cause	38 (148)	24 (18)	41 (130)
Traumatic accident	29 (115)	19 (14)	31 (101)
Violent suicide	6 (23)	3 (< 5)	7 (21)
Disease	3 (10)	3 (< 5)	3 (8)

In Australia between the years 2000 to 2018, 56% of recreational Ecstasy-related toxicity occurred in private locations whereas 44% occurred in public places.[90] The most common public places were streets/roadways, followed by outdoor places (parks, beaches, countryside).

2.12 Who is at Risk?

The risks are mitigated in a clinical environment under standard protocols by exclusion of potential participants with schizophrenia, other psychotic disorders, bipolar I and II disorders, and first or second-degree family relations to these psychiatric disorders as well as cardiovascular health problems and individuals who do not cease use of contraindicated drugs.[91] To date, research trials have done well to select appropriate participants and conduct trials in such a way as to produce impressive levels of safety.

2.13 What are the Consequences of the Risks?

Individuals who take MDMA in a recreational or uncontrolled setting in combination with other drugs are also at risk.[90] 86% of recreational users reported consuming alcohol at the same time as Ecstasy.[68] In cases of Ecstasy toxicity alone, deaths among women are more likely to be attributed to drug toxicity.[90]

These risks associated with the recreational drug Ecstasy are obviously not relevant to the medical use of MDMA as part of psychotherapy as envisaged in our rescheduling application. See Part 1 Section 1.

2.14 Contraindications

- Monoamine Oxidase Inhibitor (MAOI) combination with MDMA predisposes individuals to serotonin syndrome and has been the cause of some fatalities.[17] A washout period of at least two weeks is advised and is current practice in major clinical trials of MDMA-assisted therapy. Careful consideration of patient safety and monitoring during the washout phase is advised.
- 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.[20]
- Tramadol acts as a serotonin norepinephrine reuptake inhibitor and is metabolised by CYP2D6 enzymes which is known to increase the risk of serotonin syndrome.[92]
- 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.[5]

2.15 Could Australia Breach its Obligations under the UN Convention on Psychotropic Substances?

Psychotropic Substance Scheduling

MDMA is included in Schedule 1 of the *United Nations Convention on Psychotropic Substances 1971*.[93]

The UN Convention on Psychotropic Substances Article 7 Medical Exemption

Article 7 of the *United Nations Convention on Psychotropic Substances 1971* provides an exemption for Schedule 1 substances (including MDMA in this case) for limited use for medical purposes with appropriate pre-approvals and restrictions by Government bodies.[93] This exemption specifically supports the requirement for patients to access MDMA as part of psychotherapy in Australia through Special Access Scheme-B.

"Article 7
SPECIAL PROVISIONS REGARDING SUBSTANCES IN SCHEDULE I

In respect of substances in Schedule I, the Parties shall:

a) Prohibit all use except for scientific and very limited medical purposes by duly authorized persons, in medical or scientific establishments which are directly under the control of their Governments or specifically approved by them;

b) *Require that manufacture, trade, distribution and possession be under a special licence or prior authorization;*
c) *Provide for close supervision of the activities and acts mentioned in paragraphs a) and b);*
d) *Restrict the amount supplied to a duly authorized person to the quantity required for his authorized purpose;*
e) *Require that persons performing medical or scientific functions keep records concerning the acquisition of the substances and the details of their use, such records to be preserved for at least two years after the last use recorded therein; and*
f) *Prohibit export and import except when both the exporter and importer are the competent authorities or agencies of the exporting and importing country or region, respectively, or other persons or enterprises which are specifically authorized by the competent authorities of their country or region for the purpose. The requirements of paragraph 1 of article 12 for export and import authorizations for substances in Schedule II shall also apply to substances in Schedule I..."*

Article 7 provides legal provision to access a Schedule 1 substance in the *United Nations Convention on Psychotropic Substances 1971* for medical use through a scheme such as the TGA's Special Access Scheme – B and is not inconsistent with a Schedule 8 restricted listing in the manner envisaged in this application. It therefore should **NOT** inhibit the rescheduling of MDMA for medical use on the limited basis provided for in our application.

Examples of the TGA Using this Medical Exemption in its Rescheduling Decisions

The conclusions of the previous section are also supported by the fact that the TGA has already rescheduled a number of substances which at the time of rescheduling were in Schedule 1 of the UN Convention of Psychotropic Substances 1971 or the comparable Schedule IV of the UN Convention on Narcotic Drugs 1961

Examples of Substances being Rescheduled from Schedule 9 to Schedule 8 of the Poisons Standard which are either in Schedule 1 of the UN Convention of Psychotropic Substances 1971 or Schedule IV of the UN Convention on Narcotic Drugs 1961

Then Schedule 9 drugs in the Poisons Standard	**Relevant UN Convention scheduling they came under**	**Notes on established therapeutic value**
Cannabis **Scheduled with a S8 provision in 2016**	At the time of rescheduling in 2016, cannabis was in Schedule 4 of the *UN Convention on Narcotic Substances 1961*	At the time of rescheduling cannabis had no relevant Phase 3 studies completed for efficacy or safety (and still doesn't).
Cannabis extracts (nabiximols) **Scheduled with a S8 provision in 2010**	At the time of rescheduling in 2016, cannabis extracts were in Schedule 4 of the *UN Convention on Narcotic Substances 1961*	At the time of rescheduling nabiximols had one Phase 2 study complete and the preliminary results from a Phase 3 study for Multiple Sclerosis.
THC **Scheduled with a S8 provision in 2016**	THC is listed in Schedule 1 of the *UN Convention on Psychotropic Substances 1971*	At the time of rescheduling, THC had three Phase 3 trials complete, two in Multiple Sclerosis and one for Anorexia. However, the TGA has given treatment authorisation for a range of conditions that have no established therapeutic value, i.e. anxiety and sleep.
Dronabinol (THC) **Scheduled with an S8 provision in 1994**	THC is listed in Schedule 1 of the *UN Convention on Psychotropic Substances 1971*	At the time of rescheduling in 1994, dronabinol had no human clinical data. Phase 3 trials for dronabinol were first completed over a decade after rescheduling, in 2008, 2012, 2013, 2018, and 2020.
Nabilone (THC derivative) **Scheduled with an S8 provision in 1984**	THC derivatives are listed in Schedule 1 of the *UN Convention on Psychotropic Substances 1971*	At the time of rescheduling in 1984, nabilone had no human clinical data. Only one Phase 3 trial for Alzheimer's Disease has been completed in 2020.

Australia's Obligations Under Other UN Conventions

There are also other UN Conventions to which Australia is a signatory which support access in these limited circumstances (e.g. the UN Convention on Economic, Social and Cultural Rights which provides in Article 12 that people have rights to "*the enjoyment of the highest standard of physical and mental health"*).

Other Signatory Countries that are Comparable to Australia Clearly Do Not Believe that Limited Clinical Access to Psylocibin in a Controlled Medical Environment Would Breach their Obligations under the UN Convention on Psychotropic Substances

See Part 2.1 Section (B)1 below which shows that comparable countries to Australia with highly rated medical systems such as the United States, Israel and Switzerland (and potentially Canada as well) all have compassionate access schemes which give treatment resistant patients access to MDMA as part of psychotherapy on a limited but workable basis through their medical systems.

PART 2.1 SECTION (B) - THE PURPOSE AND EXTENT FOR WHICH MDMA IS TO BE USED

1. INTERNATIONAL COMPASSIONATE USE AND EXPANDED ACCESS SCHEMES

In the United States, the FDA has approved an 'expanded access' or 'compassionate use' scheme using MDMA assisted psychotherapy for Post-Traumatic stress Disorder (PTSD) in patients who have limited treatment options.[51] Israel launched a Compassionate Use program for MDMA-assisted therapy for PTSD in 2019.[50] The use of MDMA in treatment is as directed by the open-source MAPS's Manual of MDMA-Assisted Psychotherapy.[39] Switzerland also has a compassionate use program for MDMA with individual authorizations by the Federal Office of Public Health.[40]

On 4th January 2022, the Canadian Government passed a Federal Amendment allowing medical practitioners to access MDMA and other psychedelics for patient use through the Special Access Program (SAP).[94, 95] This a similar scheme to Australia's Special Access Scheme-B**. However, the big difference between Canada and Australia is that in Canada an approval given by Health Canada does not require a further approval from the provincial government where the treatment is to occur.**

Table 10. Global Therapeutic Use of MDMA as part of Psychotherapy

Country	Jurisdiction	Scheme
Australia	Commonwealth	Patients approved by the Therapeutic Goods Administration to use MDMA therapeutically, but State and Territory approvals also required
Canada	Country wide	
		MDMA can be medically accessed through Health Canada's SAP without any provincial government approvals being required
US	Federal	MDMA is medically administered under compassionate grounds
Israel	Country wide	
Switzerland	Country wide	

2. COMPASSIONATE USE IN AUSTRALIA UNDER SPECIAL ACCESS SCHEME-B

The TGA has approved MDMA for use as part of therapy on a case-by-case basis under Special Access Scheme-B. However, a doctor with such an approval would currently face criminal sanctions under the recreational drug laws of the State or Territory where the treatment is to occur as (with the exception of Victoria) no permits are available in those States and Territories for MDMA whilst its medical use remains in S9. The National Drugs and Poisons Scheduling Committee (now the TGA's Advisory Committee on Medicines Scheduling) recommended that to bypass this 'confusion' a Schedule 9 substance can have a Schedule 8 Appendix D entry in the *Poisons Standard*.[52]

The Australian Medical Association appeared to support removing barriers to MDMA access under Special Access Scheme -B in its response to Mind Medicine Australia's earlier application but didn't focus on the fact that this wouldn't be possible without moving the medical use of MDMA as part of therapy on a restricted basis into Schedule 8.

3. TREATMENT CONDITIONS

(1) 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 with low remission and response rates. 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 several symptoms including:

- Hypervigilance, anxiety, and sleep disturbance.
- Intrusive memories, nightmares, or flashbacks.
- Avoidance symptoms, including emotional numbing and withdrawal (Sherin, 2011).

Over the past decade, 13 Phase 2 trials testing MDMA-assisted psychotherapy for the treatment of PTSD have been conducted with significant results. 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.[5] 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. In the Phase 3 trial 46 participants went through the same MDMA treatment program with 44 participants being randomised to the placebo group. At the primary study end point 67% of the participants in the MDMA group no longer met the diagnostic criteria for PTSD compared to 32% of those in the placebo group and 80% of the MDMA group participants responded to treatment. **Interestingly, MDMA was equally effective in participants with comorbidities that are often associated with treatment resistance**. Based on the Phase 2 12-month outcomes, the Phase 3 MDMA group outcomes are expected to further increase over the next 12 months.

Table 11. Details of trials complete and underway for MDMA treating PTSD*.

#	Phase	Trial Status	*n*	MDMA dose	Ctrl.	Sponsor	Trial ID
1.	Expanded Access	Complete	50	80, 120 mg + ½ dose	n/a	MAPS	
2.		Complete	7			MAPS	
3.		Complete	200			Swiss Medical Society for Psycholytic Therapy	
4.	Phase 3	Complete	100	80-120 mg + ½ dose	Placebo	MAPS	NCT03537014
5.	Phase 2	Complete	4	100-125 mg + ½ dose	None	MAPS	NCT03485287
6.		Complete	38	80-120 mg + ½ dose	None	MAPS	NCT03282123
7.		Complete	18	125 mg	Placebo	MAPS	NCT02427568
8.		Complete	12	100, 125 mg	Placebo	MAPS	NCT02008396
9.		Complete	29	100, 125 mg	Active placebo	MAPS	NCT01793610
10.		Complete	10	125 mg	Placebo	MAPS	NCT01689740
11.		Complete	26	75, 125 mg	Active placebo	MAPS	NCT01211405
12.		Complete	3	125 mg + ½ dose	None	MAPS	NCT01458327
13.		Complete	14	125 mg	Active placebo	MAPS	NCT00353938
14.		Complete	3	125 mg + ½ dose	Placebo	MAPS	NCT00090064
15.	Phase 1/2	Complete	12	75 mg + ½ dose	None	MAPS	NCT02876172

*Extrapolated from trial ID.

(2) Other Promising Indications Being Trialled

The use of MDMA as part of psychotherapy is currently being studied for the treatment of the following additional conditions:

Table 12. Current indications also being investigated by institution.

Treatment Indication	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, Los Angeles Biomedical research Institute

4. SAFETY AND THERAPEUTIC INDEX OF MDMA IN A CLINICAL SETTING

The safety index is a ratio between the lowest effective dose of a drug and its highest tolerated dose. The therapeutic index is the effective dose of a drug in comparison with its lethal dose. The table below ranks drugs and medicines from most to least saftest, displayed as safety and therapeutic index.

Table 13. Safety and therapeutic index of common drugs and medicines.[96-98]

Drug or medicine	Safety Index	Therapeutic Index
Psilocybin	**1000**	**1000**
Paracetamol	10	10
MDMA	**10**	**10**
Heroine (Diamorphine)	10	6
Methadone	5	-
Cocaine	4	15
THC	4	-
Methamphetamine	3	-
Nicotine	3	n/a
Diazepam	2	-
Alcohol	1.5	n/a

In this table the higher the number the higher the safety and therapeutic ranking.

The safety of MDMA when used as part of psychotherapy in medically controlled environments by trained practitioners is further described in Part 1 Section 2.3(2).

Part 2.1 Section (C) – TOXICITY AND SAFETY OF THE SUBSTANCE

1. TOXICITY

MDMA has low risks of toxicity. **See Part 1 Section 2.1(4) (toxicity) and Part 2.1 Section (B) 4 (safety and therapeutic index)**.

2. SAFETY AND ADVERSE EVENTS IN CONTROLLED ENVIRONMENTS

No drug related serious adverse events (SAE) have been reported from any previous research investigating MDMA's effects in healthy participants.[17] In clinical trials there have been no reported significant adverse events either pre or post prohibition. **See Part 1 Section 2.3(2) and Part 2.1 Section (A) 1.2 for more information.**

In its Final Decision the Delegate concluded that "*…I agree with the ACMS that MDMA appeared to be well tolerated in all the studies evaluated for the Expert Report and that MDMA appears to have an acceptable adverse effect profile. However, this was in a highly controlled environment with short-term dosing only and cannot be extrapolated to use in environments with less control."(*Australian Government - Department of Health Therapeutic Goods Administration, 2021. *Notice of final decision to not amend the current Poisons Standard - Psilocybin and MDMA*. Canberra: Australian Government - Department of Health Therapeutic Goods Administration, p.15.)

We specifically deal with the translation risk from clinical trials to medically controlled environments in **Part 1 Section 3.2 and Part 2.1 Section (A)2.2**.

3. IS THERE A TRANSLATION RISK?

As discussed in **Part 1 Section 3.2 and Part 2.1 (A) 2.2** we believe that the translation risk from trial environments to clinical environments on the limited basis set out in our application is low.

4. DOES MDMA PRODUCE DEPENDENCY AT ITS ESTABLISHED THERAPEUTIC DOSE?

MDMA does not produce dependency at its established therapeutic dose (see Part 2.1 Section (A)1.6). One of the benefits of MDMA assisted psychotherapy is that the patient only has 2-3 session with the medicines. Unlike most other psychiatric medicines, the patient will never take these medicines outside of the clinical environment and daily dosing isn't required.

Part 2.1 SECTION (D) - DOSAGE, FORMULATION, PACKAGING AND PRESENTATION OF MDMA FOR LIMITED MEDICAL PURPOSES

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 (from overseas. If MDMA becomes a Schedule 8 medicine on the limited basis set out in this application the substance would need to be held securely at a pharmacy with Schedule 8 holding facilities (see Part 2.1 Section (A) 2.2 above) until transferred in small quantities to the treating medical practitioner who would in turn need to hold all requisite approvals

1. DOSAGE

This application is for a poison rescheduling not a medicine listing of MDMA. As such, dosage is not a relevant issue for scheduling. The dosage of MDMA is specified by a medical practitioner on the SAS-B form and approved by the TGA on a case-by-case basis. However, as a guide we have extrapolated the literature:[7]

Table 14. MAPS Phase 3 dosing protocol for full treatment of one patient for a lower weight limit of 48 kg.

Medicinal session	Initial dose	Supplement dose*	Min-max cumulative dose
1	80 mg	40 mg	80 to 120 mg
2	80 or 120* mg	40 or 60* mg	80 to 180 mg
3	80 or 120* mg	40 or 60* mg	80 to 180 mg
Total cumulative dose			**240 to 480 mg**

* If initial dose is well tolerated and with clinician judgement

2. FORMULATION

MDMA for therapeutic purposes has to date been formulated in capsules.

3. LABELLING REQUIREMENTS

a) 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 TGA's requirements.
b) The registration number, which must be in a text size of not less than 1.0 millimetre height as required by subparagraph 15(1)(c)(i) of the Regulations be in a colour or colours contrasting strongly with the background.
c) The expiry date and expiry date prefix must be clearly shown.
d) The batch number and batch number prefix must be clearly shown when the information is embossed or debossed and not printed.
e) Figures shown must be in metric units of measurement.

4. INFORMATION REQUIRED ON LABEL

a) The name of the medicine; and
b) The name of the dosage form; and
c) The quantity of the medicine; and
d) The batch number of the medicine preceded by the batch number prefix; and
e) The expiry date of the medicine, preceded by the expiry date prefix; and
f) The storage conditions applicable to the medicine; and
g) The name and contact details of the sponsor or distributor of the medicine; and
h) Relevant warning statements (see below).

5. STATEMENTS OF CAUTION ON PACKAGING

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

6. STATEMENTS OF QUANTITY, PROPORTION AND STRENGTH

In the manner prescribed by orders made under subsection 10(3) of the Commonwealth *Therapeutic Goods Act 1989*.

7. PACKAGING

The pack size per patient would be a full course of MDMA-assisted therapy (up to 480 mg) with individual capsules to be dispensed by the prescribing doctor in each dosing session and kept at all times in a Schedule 8 safe until required for each dosing 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.

The packaging will read ; MDMA (x) mg # Caps : Take capsule only in the presence of your psychiatrist or other medical professional. For in-clinic use only. This medicine cannot be taken out of the clinic. Do not drive a motor vehicle or consume alcohol within 48 hours of taking this capsule.

8. 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 applicable to MDMA-assisted therapy.

9. 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 or designated medical professionals only under authorised Schedule 8 prescription. The restricted supply pathway is explained in detail in Part 2.1 Section (A)2.2/

10. MDMA PRODUCES NO DEPENDENCY AT ITS THERAPEUTIC DOSE

MDMA does not produce dependency at its established therapeutic dose, nor at any dose (see Part 2.1 – Section(A) 1.6).

11. MDMA PRODUCES NO TOXICITY AT ITS THERAPEUTIC DOSE

MDMA has very low risks of toxicity (see Part 1 Section and part 2.1 Section (B)4.1(4).

PART 2.1 (E) - POTENTIAL FOR MISUSE AND ABUSE OF MDMA

1. BACKGROUND

MDMA has not been abused, misused, accidentally ingested, or had any recorded overdose in a clinical setting.

All information in the Part 2.1(E) relating to misuse or abuse is therefore of MDMA in an uncontrolled and recreational setting.

Mind Medicine Australia is proposing a rescheduling to Schedule 8 on the basis that the medicine will only be able to be authorised by psychiatrists in medically controlled environments under strict supervision, where the treating psychiatrist has been specifically trained in MDMA assisted therapy and where the patient's diagnosis and treatment plan has been confirmed by two other psychiatrists. The medicinal MDMA will never be available to the patient to take home.

2. DIVERSION RISK

For the reasons set out in Part 2.1 Section (A)2.1 we believe that the diversion risk of MDMA as a Schedule 8 medicine from the medical supply chain and the medically controlled environment where the medicine is to be used is extremely low.

3. TRANSLATION RISK

For the reasons set out in Part 2.1 Section (A)2.2 we believe that the translation risk of using MDMA as a Schedule 8 medicine in controlled medical settings on the limited basis set out in this application is extremely low.

4. OVERDOSE

In Australia, between the years 2000 and 2018 there were a total of 392 deaths with Ecstasy present in autopsy. 14 of these deaths were due to MDMA-only toxicity**. All deaths were related to recreational and non-medical use.**[90]

5. MISUSE

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.[68] 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%).

There have been numerous studies of cognitive effects of long-term poly drug users who use Ecstasy.[5] Changes have been observed in SERT receptor density, memory, impulse

control, and executive function when compared to non-drug users. 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.[29] The challenge of these studies is three-fold:[56]

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.[30] 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.

A Harvard study compared the cognitive functioning of 52 moderate to heavy Ecstasy only drug users to 59 non-drug users.[31] 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 over 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.

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.[32] 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.[29]

However, none of this is relevant to the medical use of MDMA as part of psychotherapy on the limited basis set out in this application.

6. ABUSE

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.[99] **Research on Ecstasy appears to be largely inapplicable to establish the potential for misuse, abuse, or toxicity of MDMA in clinical settings.**

7. ILLICIT USE

Across several MAPS sponsored MDMA studies, subsequent Ecstasy use was measured in participants.[5] 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.

PART 2.1 SECTION (F) - ANY OTHER MATTER THAT MAY BE RELEVANT TO THE SCHEDULING OF A SUBSTANCE

1. RISKS OF MDMA COMPARED TO COMMON SCHEDULE 4 MEDICINES

Although recreational use of MDMA in the form of Ecstasy may have potential for abuse, misuse, and overdose in a recreational setting Ecstasy even in a recreational setting 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.[68]

The information below is from the Australian Bureau of Statistics (ABS).[100] The ABS has only published drug-related deaths from three years (1999, 2007, 2018). Ecstasy-related deaths were published across 18 years, the below comparison extrapolates the percentage of 18 years vs 3 years.

Table 15. Drug related deaths in comparison to MDMA.

Drug	Average deaths per year	Average deaths as percentage annually in Australia compared to Ecstasy
MDMA only	0.78	2,795% deaths less than Ecstasy
Ecstasy	21.8	n/a
Antipsychotics and neuroleptics	96.7	444% deaths more than Ecstasy
Paracetamol	120.7	554% deaths more than Ecstasy
Antidepressants	190.7	875% deaths more than Ecstasy
Alcohol	202	926% deaths more than Ecstasy
Benzodiazepines	506.7	2,324% deaths more than Ecstasy
Prescription opioids	506.7	2,324% deaths more than Ecstasy

Annualised deaths for prescription medications are averaged from ABS across three years; 1999, 2007, 2018. MDMA and ecstasy related deaths are annualised across 18 years, from 2000 to 2018.

2. CERTIFICATE IN PSYCHEDELIC-ASSISTED THERAPIES (CPAT)

Mind Medicine Institute commenced its Certificate Course in Psychedelic-Assisted Therapies (CPAT) in January 2021 to train medical and health practitioners in the safe use of these therapies in regulatory approved and medically controlled environments.

To date 88 health practitioners have graduated from the course including;

- 23 psychiatrists;
- 27 psychologists; and
- 6 psychotherapists.

During 2022 we expect a further 200 to graduate from the course with a similar composition of professional backgrounds. We will then continue to build up capacity as required by the medical and regulatory system.

Applications for the course far exceed available places and all applicants who qualify for the course are screened by clinical psychologists.

Treatment protocols involve two therapists working together and being in the room with the patient for the therapy sessions when the patient takes the medicinal MDMA. This could involve a psychiatrist as one of the therapists if the psychiatrist is available to do this but, because of the length of the session and skills base, we believe that it is more likely to involve psychologists and/or psychotherapists.

There are several world class therapist training courses where participants with experience as therapists are taught to implement these therapies and the associated protocols have been developed internationally by leading organisations such CIIS, Yale, Johns Hopkins and Imperial College London.

There is enormous demand for this training because medical practitioners desperately want to heal patients with key treatment resistant mental illnesses and see this therapy as a way of overcoming the failure of currently available treatments to get their treatment resistant patients well.

The course has been developed primarily to meet the anticipated demand for trained therapists to provide psychedelic-assisted therapies (including MDMA-assisted therapies) for the treatment of mental ill-health in Australia in medically controlled environments as part of clinical practice. In addition, it is also expected that trained therapists will be needed to work in research trials as more occur in Australia.

The academic team developing and leading the course is led by clinicians with extensive experience in the treatment of complex mental health issues and the development of accredited training programs including psychologists Nigel Denning and psychotherapist Dr Tra-ill Dowie. They are supported by a world class Faculty of leading international and national teachers. The course has been modelled on world-leading courses developed by the California Institute of Integral Studies (CIIS), Imperial College, and MAPS. The certificate course combines weekend and week-long intensives with online learning, assessments, and practical sessions.

The high calibre of the Teaching Faculty, which contains many of the leading experts in these therapies from around the World can be found here:
https://mindmedicineaustralia.org.au/certificate-in-psychedelic-assisted-therapies-cpat/

PART 2.2 - CRITERIA WHICH MUST BE ADDRESSED

The application has given medical and scientific justification, reasoning, and critical objective discussion addressing all the legislative requirements set out in Section 52E of the *Therapeutic Goods Act 1989*, which the Secretary must consider in exercising powers.

The following is a brief discussion of the evidence presented in this application:

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

1. RISKS AND BENEFITS OF USE

The therapeutic benefits of MDMA, MDMA's low toxicity, and non-addictive properties outweigh the associated risks which can be fully mitigated with medical use in a medically controlled setting. **See Part 1 Section 2.3(2) and Part 2.1 Section (A).**

2. PURPOSE AND EXTENT OF USE

MDMA-assisted psychotherapy for PTSD and for substance abuse (and potentially other indications) in a controlled medical setting. **See Part 2.1 Section (B).**

3. TOXICITY

MDMA has no history of severe adverse effects in a clinical setting. **See Part 1 Section 2.1(4) and Part 2.1 Section (B)4.1).**

4. DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION

This is all known. **See Part 2.1 Section (D)**

5. POTENTIAL FOR ABUSE

This is minimal when the restricted terms of the proposed rescheduling are considered, and the lack of diversion risk given Schedule 8 controls. **See Part 1 Section 1 and Part 2.1 Section (A)2.1.**

6. OTHER MATTERS THAT THE SECRETARY BELIEVES ARE NECESSARY TO CONSIDER

We have reviewed both the Interim Decision and the Final Decision of the Delegate in relation to our first application and believe that we have addressed all of the Secretary's expressed concerns.

Furthermore, many Schedule 4 drugs used to treat mental illness (e.g. antidepressants and benzodiazepines) have more hazards, greater suicide risk, abuse potential, and toxicity than MDMA when used in the restricted way envisaged by this application. MDMA-assisted psychotherapy in a medically controlled environment would therefore provide a safer and more effective alternative and one that requires only 2-3 sessions with the medicine.

We believe the Secretary should start with an analysis of the suffering of people with treatment resistant mental illnesses, the risk of suicide and actual suicide that this can lead to, and the low effect size and side effects of current psychiatric medicines used for PTSD. The Secretary should then recognise that diversion risk is minimal with Schedule 8 controls, translation risk can be dealt with adequately by psychiatrists and supporting health professionals and that the risk of misuse and abuse in controlled medical settings is minimal. Finally, the Secretary should focus on the efficacy rates to date and the opportunity of giving treatment resistant patients the opportunity though this modality to go into remission and therefore have the chance to lead the lives that they should be entitled to.

CONCLUSION

The application meets all the criteria specified in Section 52E of the Therapeutic Goods Act 1989 and the scheduling requirements.

We have set out the strong results of MDMA (in terms of both safety and efficacy) for treatment resistant depression and anxiety disorders in this application. We believe that it would be detrimental for Australians suffering with treatment resistant conditions ***not*** to have the opportunity (with the support of their treating psychiatrist and therapists involved) to access this form of therapy in a medically supervised setting. These people suffer terribly, and they deserve the opportunity to see if this form of therapy can give them the positive response and remission from their condition that they are so desperate to have. **Over time this would have profound and vastly positive societal implications and reduce suicide rates.**

We acknowledge and accept the premise that medical the use of MDMA should only be able to be authorised by a psychiatrist in the restrictive terms set out in this application and that the patient should never be allowed to take the medicine away from the medically controlled environment.

We therefore believe that it is reasonable to reschedule the limited medical use of MDMA in the manner set down in this application as a Schedule 8 substance with all other uses remaining in Schedule 9.

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SUPPORTING DATA

Appendix A - Copy of Papers Referenced in the Bibliography

Copies of all papers referenced in this application can be found in the following link:

https://www.dropbox.com/sh/4exu6zrk3xbbcuz/AACSaI7rL_TL5xGvlwwEvD8ja?dl=0

We have also posted via Express Mail a USB stick to you containing all the papers in the Drop Box.

Appendix B - Data Summary

Table 16. Completed MDMA clinical studies.

#	Study type	Condition	End year	Location	Sponsor	*n*	MDMA dose	Control	Masking	Trial ID
1.	Expanded Access	PTSD	2021	Israel	MAPS	50	80, 120 mg + ½ dose	n/a	Open	
2.		PTSD	2017	Switzerland	MAPS	7				
3.		PTSD	1993	Switzerland	Swiss Medical Society for Psycholytic Therapy	≈ 200				
4.	Phase 3	PTSD	2020	US, multi-site Canada, multi-site Israel	MAPS	100	80-120 mg + ½ dose	Placebo	Quadruple	NCT03537014
5.		PTSD	2019	Canada, multi-site	MAPS	4	100-125 mg + ½ dose	None	Open	NCT03485287
6.		PTSD	2019	US, multi-site	MAPS	38	80-120 mg + ½ dose	None	Open	NCT03282123
7.		Anxiety	2018	US, California	MAPS	18	125 mg	Placebo	Double	NCT02427568
8.		Autism, Social Anxiety Disorder	2017	US, California	MAPS	12	100, 125 mg	Placebo	Triple	NCT02008396
9.		PTSD	2017	US, Colorado	MAPS	29	100, 125 mg	Active placebo	Triple	NCT01793610
10		PTSD	2017	Israel	MAPS	10	125 mg	Placebo	Triple	NCT01689740
11		PTSD	2016	US, South Carolina	MAPS	26	75, 125 mg	Active placebo	Triple	NCT01211405
12		PTSD	2016	US, South Carolina	MAPS	3	125 mg + ½ dose	None	Open	NCT01458327
13		PTSD	2011	Switzerland	MAPS	14	125 mg	Active placebo	Triple	NCT00353938

14	Phase 1/2	PTSD	2010	US, South Carolina	MAPS	3	125 mg + ½ dose	Placebo	Triple	NCT00090064
15		PTSD	2018	US, South Carolina	MAPS	12	75 mg + ½ dose	None	Open	NCT02876172
16		Mechanism, startle response	2020	US, Georgia	MAPS	34	100 mg	Placebo	Double	NCT03181763
17	Phase 1	Mechanism	2019	US, Maryland	Johns Hopkins University	20	n.d.	Active arm	Triple	NCT02033707
18		Drug interaction, mephedrone	2014	Spain	Parc de Salut Mar	12	100 mg	Placebo	Double	NCT02232789
19		Drug interaction, methylphenidate	2013	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Quadruple	NCT01465685
20		Drug interaction, bupropion	2013	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Quadruple	NCT01771874
21		Mechanism	2012	US, Maryland	National Institute on Drug Abuse	187	1, 1.6 mg/kg	None	Open	NCT01148342
22		Drug interaction, doxazosin	2012	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Quadruple	NCT01386177
23		Mechanism	2011	Spain	Parc de Salut Mar	27	1.5 mg/kg (75-100 mg)	None	Open	NCT01447472
24		Drug interaction, reboxetine	2010	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Double	NCT00886886
25		Drug interaction, duloxetine	2010	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Double	NCT00990067
26		Drug interaction, clonidine	2010	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Double	NCT01136278
27		Drug interaction, pindolol	2002	Switzerland	University Hospital, Basel	16	1.6 mg/kg	Placebo	Double	NCT00895804
28		Mechanism	1996	US			0.25-1 mg/kg	Placebo	Double	
29	Phase 0	Mechanism, Autism	2021	US, Illinois	University of Chicago	24	1.5 mg/kg	Placebo	Triple	NCT04053036
30		Mechanism, fear extinction	2020	Switzerland	University Hospital, Basel	30	125 mg	Placebo	Quadruple	NCT03527316

31		Mechanism, emotional processing	2018	Switzerland	University Hospital, Basel	28	125 mg	Placebo	Quadruple	NCT03019822
32		Mechanism, emotional regulation	2016	US, Illinois	University of Chicago	84	1 mg/kg	Placebo	Triple	NCT03050541
33		Drug interaction, fMRI	2014	Switzerland	University Hospital, Basel	24	125 mg	Placebo	Quadruple	
34		Mechanism, emotional regulation	2013	US, Illinois	University of Chicago	65	0.75, 1.5 mg/kg	Placebo	Double	NCT01849419
35		Mechanism, social cognition	2013	Switzerland	University Hospital, Basel	30	75 mg	Placebo	Quadruple	NCT01616407
36		Drug interaction, carvedilol	2011	Switzerland	University Hospital, Basel	16	125 mg	Placebo	Quadruple	NCT01270672
37		Mechanism	2011	US, Illinois	California Pacific Medical Center Research Institute	12	1.5 mg/kg	Placebo	Double	NCT00838305
38		Discontinuation Syndrome	2011	US, Illinois	California Pacific Medical Center Research Institute	12	1.5 mg/kg	Placebo	Quadruple	NCT01053403
39		Discontinuation Syndrome	2008	Switzerland	University of Zurich	50	n/a	Active control	Triple	NCT01296802
40	Observational	Anxiety, fMRI	2017	US, California	MAPS	12	100, 125 mg	None	Open	NCT02954562
41		PTSD, fMRI	2015	US, South Carolina	MAPS	10	125 mg + ½ dose	None	Open	NCT02102802
42		MDMA hangover	2011	Netherlands	Utrecht Institute for Pharmaceutical Sciences	39	n/a	None	Open	NCT01400204
43		Recreational users, fMRI	2011	Israel	Hadassah Medical Organization	18	n/a	None	Open	NCT00254306
44		Recreational users, neurotoxicity	2005	Netherlands	UMC Utrecht	225	n/a	None	Open	NCT00235768

Appendix C - Expert Letters

Expert Letter A
Offer from the Neuromedicines Discovery Centre at Monash University to Host Independent Clinical Registry to Collate Treatment Data

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Level 1/10 Dorcas St
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Australia

Neuromedicines Discovery Centre
Monash University
381 Royal Parade
Parkville
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Australia
28th February 2022

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

Further to the application to the TGA to reschedule psilocybin and MDMA to Schedule 8 of the Poisons Standard, we write in support of establishing an appropriate Clinical Registry to ensure best practice and value for the proposed limited use of these drugs.

The limited use rescheduling application, to which this letter is appended, is for the use of psilocybin and MDMA:

- as part of psychotherapy in medically controlled environments; and
- under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
- where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and
- where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967and/ or; imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

Our view is that should such a limited use application under Schedule 8 be approved, that a voluntary Clinical Registry be established to record the following:

- the nature of the treatment administered;
- the diagnosis or indication being treated;
- a summary of treatment outcome(s); and
- any treatment-emergent side effects or adverse events

We are all of the strong opinion that the level of unmet medical need for mental health disorders warrants the use of these medicines in such well-regulated environments and that a Clinical Registry of such would add value and integrity to their use as well as providing a means to evaluate both long term efficacy and safety.

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It is for this reason that, in late 2021 with significant financial support of Monash University, we founded the Neuromedicines Discovery Centre (https://www.neuromedicines.monash/) to engage in comprehensive research into the discovery, development, clinical evaluation and rollout of novel medicines for the treatment of mental health disorders.

With some of the world's best pharmacologists, psychiatrists and psychologists with expertise in this space, we offer the Neuromedicines Discovery Centre as a host for a Clinical Registry for the use of psilocybin or MDMA as an adjunct to psychotherapy.

Yours sincerely,

Arthur Christopoulos, B.Pharm., Ph.D., F.A.A., F.A.H.M.S.
Professor of Analytical Pharmacology, Dean & Director, Neuromedicines Discovery Centre
Faculty of Pharmacy and Pharmaceutical Sciences
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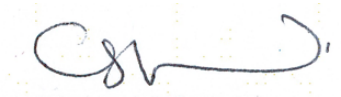

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MIND MEDICINE AUSTRALIA

Expert Letter B

Dr Stuart Saker, Consultant Psychiatrist, Highlighting Importance of Limited Rescheduling Proposed for his Treatment Resistant patients

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Provider No. 214830PA

28th February 2022

The Medicines Rescheduling Unit
Therapeutic Goods Administration
CANBERRA ACT

Dear Sir/Madam

Proposed Rescheduling of Psilocybin and MDMA

I am a psychiatrist practising in the Newcastle region of New South Wales with 21 years of experience. I am also an Australian Defence Force Veteran with 5 years of service and most of my patients are also Veterans.

I am writing to highlight why it's so importance for MDMA and Psilocybin to be rescheduled to Schedule 8 of the Poisons Standard on the limited basis envisaged in the applications being lodged with the TGA by the registered charity Mind Medicine Australia.

I am a Medicinal Cannabis prescriber and was familiar with the process of applying for Special Access Scheme (SAS-B) approvals for my patients from the TGA. I thought that the TGA were offering a legitimate pathway for my patients to access Psilocybin and MDMA in strictly medically controlled environments and as part of psychotherapy for treatment resistant mental illnesses. That this has not become a legitimate pathway to access these medications because of barriers at the State level caused by the current scheduling of these substances has been a cruel and painful "joke" on my patients.

I applied for and received 9 SAS-B approvals to prescribe Psilocybin and MDMA as part of psychotherapy for my patients in a controlled medical environment. In contrast to Medicinal Cannabis my patients would never be allowed to take the substances home.

My patients all have extreme treatment resistant Major Depressive Disorder and/or Post Traumatic Stress Disorder. They have all mainly tried multiple antidepressants, Transcranial Magnetic Stimulation and Electro Compulsive Therapy. Nothing is working for them. They are desperate people who served their country and who have been holding out for many years for access within our medical system to Psilocybin and MDMA assisted therapies. They are also some of my best and most compliant patients.

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The risk is that these people could kill themselves if they are again denied the opportunity to access these therapies. This is a very real risk. As you will be aware Australian Defence Force Veterans have very high rates of suicide. The other risk is that they continue to have a disappointing life while they are consumed by mental illness and lose their children, partners and jobs.

It is very urgent if someone could kill themselves and moderately urgent if they are going through the slow process of having their lives dismembered by treatment-resistant mental illness.

I would ask you to act with compassion and expedite the rescheduling of these medicines so that I can commence seeking approval at the State level as soon as possible. I have been specifically trained in the use of these therapies so I know exactly what is required.

Yours Faithfully

Dr Stuart Saker
MBBS (Syd) BA, MPH, MHA, FRCpsych (UK)
Consultant Psychiatrist

MIND MEDICINE AUSTRALIA

Expert Letter C

Letter from Drug Science in the UK confirming that MDMA as part of psychotherapy on the terms set out in this Application has met the Schedule 8 test of established therapeutic value.

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Drug Science

The Secretary

Medicines Scheduling Unit

Therapeutic Goods Administration

Canberra, ACT.

London, 23/02/2022

Dear Sir/Madam,

Application to Reschedule MDMA – Assisted Psychotherapy to Schedule 8 of the Poisons Standard

The Chair of Mind Medicine Australia, Mr Peter Hunt AM, has asked Drug Science to directly address the question of whether medical grade MDMA when used as part of psychotherapy has an established therapeutic value. We are aware that this is one of the factors to be considered by the Medicines Scheduling Committee and the Delegate in addressing whether MDMA when used as part of psychotherapy should be rescheduled to Schedule 8 of the *Poisons Standard*.

We note that the rescheduling proposed by Mind Medicine Australia is very restricted in its application.

The Mind Medicine Australia Proposal

SCHEDULE 9 – Proposed Amended Entry

MDMA **except** when separately specified in Schedule 8.

SCHEDULE 8 – Proposed New Entry

MDMA for use in the treatment of treatment resistant mental illness when:

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists: and

d) where the substance has been manufactured in accordance with the *Narcotic Drugs Act 1967and/ or* ;
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
f) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*.

MDMA places the patient in a 'zone of optimal arousal', enhancing access to, and control of, emotions, increasing a perceptible sense of ease, and expanding a patient's therapeutic window.[1]

We are of the view that MDMA when used as part of psychotherapy for the treatment of PTSD in the limited manner proposed clearly has an established therapeutic value. This is demonstrated by;

- Between the late 1960s and prohibition, MDMA was administered in approximately 500,000 doses across 20 years of psychotherapy without complications and with useful efficacy;

- When MDMA was being scheduled in 1982 in the US the US Supreme Court Federal Judge who was overseeing the expert witness data recommended that MDMA be placed in Schedule III of the Controlled Substances Act by the Drug Enforcement Agency ("the DEA"). The DEA ignored expert testimonies and placed MDMA in Schedule 1. Harvard psychiatrist Lester Grinspoon then sued the DEA for ignoring the medical benefits of MDMA. Dr Grinspoon won the case and the US Federal Supreme Court overruled the DEA and declassified MDMA. However, less than a month later, the DEA reclassified MDMA as a Schedule 1 drug.

- Since prohibition, MDMA has been shown to be well tolerated in a significant number of trials and with useful efficacy.

All long-term follow up studies have shown sustained efficacy in a significant portion of participants with no adverse mental health effects, dependence or physical health

[1] Nutt DJ and de Wit H (2021) Putting the MD back into MDMA. *Nature Medicine* 27(6): 950–951. DOI: 10.1038/s41591-021-01385-8

complication, even in patient groups such as alcohol dependence where physical health is often compromised[2]

- People have been able to access MDMA as part of therapy in countries under compassionate access schemes in the United States, Switzerland and Israel.

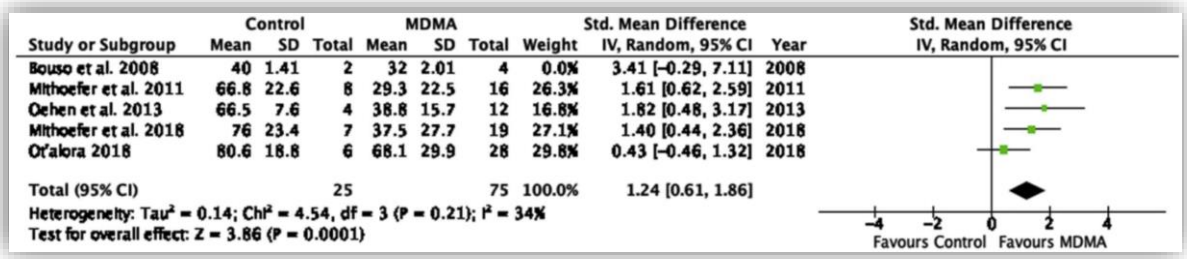
- Significant media and online anecdotal evidence from people who have taken MDMA-therapy outside of the legal medical system.

- But most importantly the trial results achieved in the MAPS sponsored multisite Phase 2 and Phase 3 trials which we deal with below.

As a result, we believe there is strong evidence for the safety and efficacy of MDMA-assisted psychotherapy for the treatment of PTSD.

The following meta analysis was completed before the recent Phase 3 results were published and was already compelling.

Forest plot of Standardized Mean Difference (SMD) of effect of MDMA versus control on PTSD symptom score using random-effects meta-analysis.



Source:Bahji at al, Efficacy of MDMA assisted psychotherapy for post traumatic stress disorder; A systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry 2020; 96:109735*

[2] Sessa B, Higbed L, O'Brien S, et al. (2021) First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *Journal of Psychopharmacology* 35(4). SAGE Publications Ltd STM: 375–383. DOI: 10.1177/0269881121991792.

Through a series of worldwide trials, MAPS has finalised a Phase 3 trial and multiple Phase 2 trials for the use of MDMA-assisted psychotherapy in the treatment of PTSD. 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 Phase 3 and Phase 2 trials showed that MDMA assisted psychotherapy had a 54.2% remission rate for treatment resistant PTSD sufferers, compared to 23% in the placebo group. Across these Phase 2 and Phase 3 trials the dropout rate was also low which illustrates MDMA's tolerability and strong patient adherence.

The MAPS Phase 2 trials 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 assisted psychotherapy, patients continued to improve in their mental wellbeing.

In the MAPS Phase 3 results patients with severe PTSD in the MDMA group also achieved strong efficacy results. Figures 2 and 3 below are taken directly from the published results (Jennifer Mitchell et al, MDMA-assisted therapy for severe PTSD: a randomised, double-blind, placebo-controlled phase 3 *Nature Medicine Vol 27, June 2021 1025-1033*).

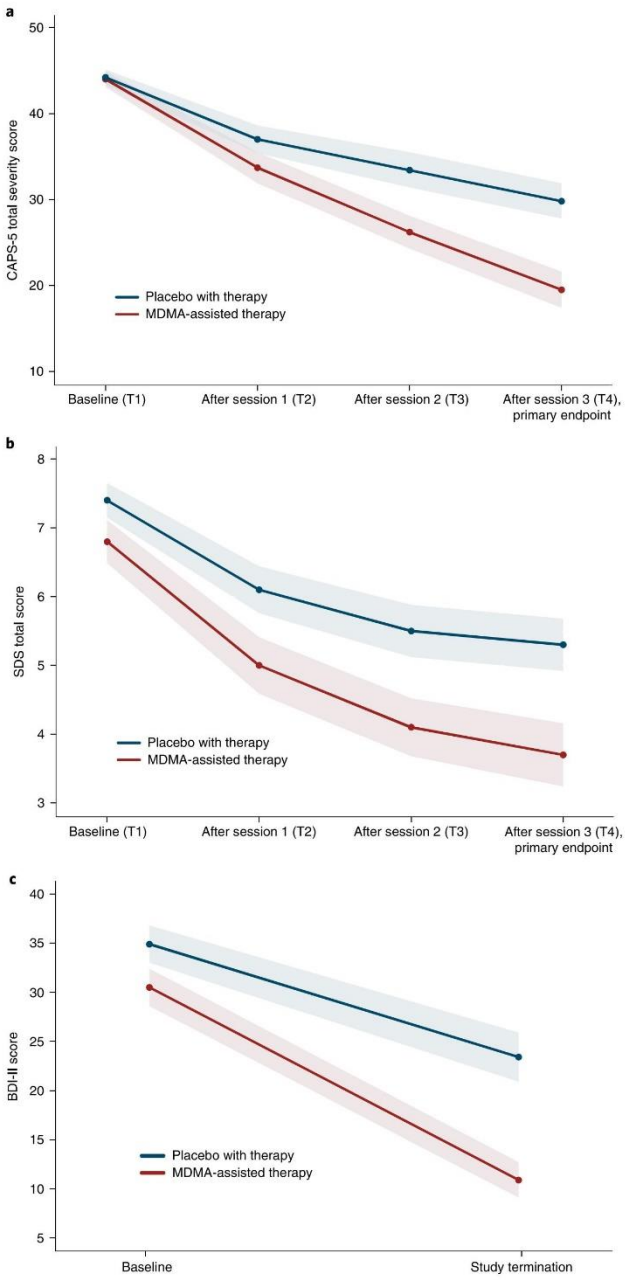


Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an MMRM model. **b**, Change in SDS total score from T1 to T4 ($P = 0.0116$, $d = 0.43$, $n = 89$ (MDMA $n = 46$)), as a measure of the secondary outcome. Primary analysis was completed using least square means from an MMRM model. **c**, Change in BDI-II score from T1 to study termination ($t = -3.11$, $P = 0.0026$, $n = 81$ (MDMA $n = 42$)), as a measure of the exploratory outcome. Data are presented as mean and s.e.m.

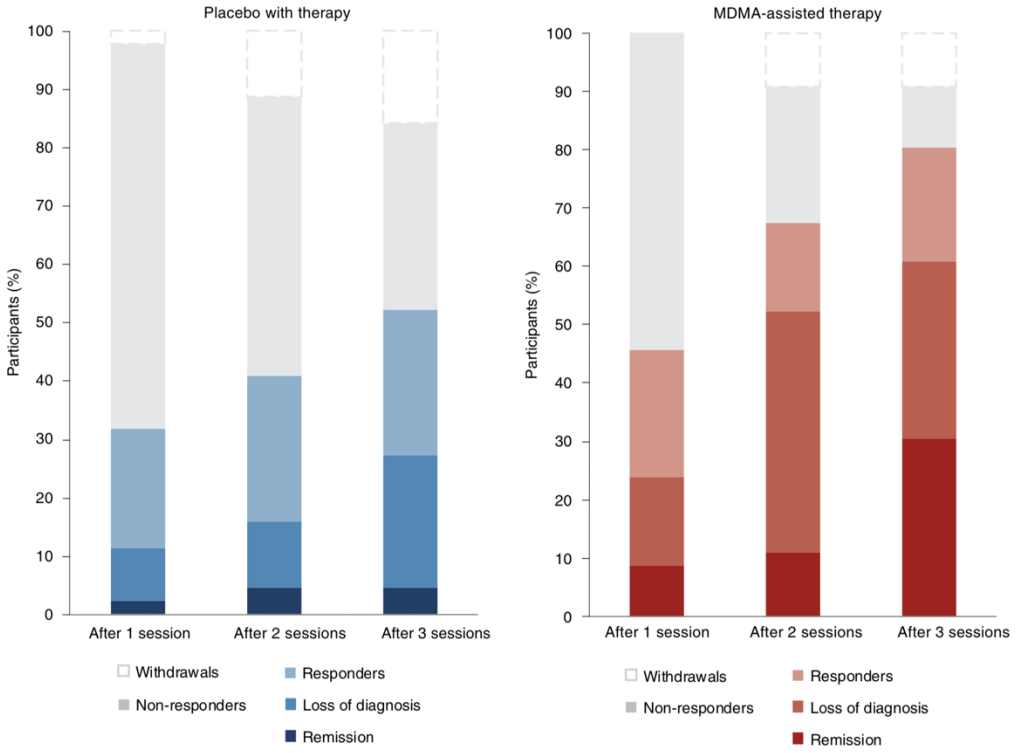


Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of ≤11) were tracked in both groups. Non-response is defined as a <10-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.

As shown in Table 2 from the same study, adverse events (and in particular suicidality) were also lower in the MDMA group than the placebo group.

Table 2 | Participants with treatment-emergent SAEs and AESIs

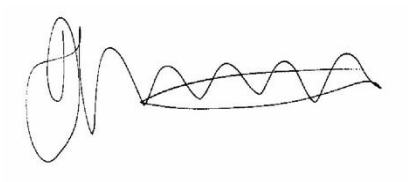
	MDMA ($n=46$), n (%)	Placebo ($n=44$), n (%)
SAEs	–	2 (4.5)
Suicide attempts	–	1 (2.3)
Suicidal ideation resulting in self-hospitalization	–	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	–
Suicidal behavior (suicide attempts and preparatory acts) and self-harm	–	1 (2.3)
Suicidal behavior (preparatory acts), self-harm and suicidal ideation	–	1 (2.3)
Cardiac events that could indicate QT prolongation (total)	–	1 (2.3)
Irregular heartbeats and palpitations	–	1 (2.3)
Abuse potential for MDMA (total)	–	–

The number of participants experiencing one or more SAEs or AESIs relating to suicidality, cardiovascular symptoms that could indicate QT prolongation, and abuse potential following the first experimental session.

In our view it is now clear that MDMA when used as part of psychotherapy for patients suffering from treatment-resistant Post-Traumatic Stress Disorder has an established therapeutic value.

We would be more than happy to answer any questions that you might have.

Yours sincerely



Prof David Nutt and the Drug Science Scientific Committee

Prof Jo Neill

Dr David Erritzoe

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.

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Prof David Nutt, Chair of Drug Science, is Head of the Centre for Psychedelic Research at Imperial College London, Prof Jo Neill is Chair of the Drug Science Medical Psychedelics Working Group, and Dr David Erritzoe leads the CiPPRes Clinic, London, UK. All have extensive experience and scientific understanding of psilocybin being used in a clinical setting.

MIND MEDICINE AUSTRALIA

Expert Letter D

Letter from Professors Arthur Christopoulos and Chris Langmead from the Monash Institute of Pharmaceutical Sciences confirming that MDMA as part of psychotherapy on the terms set out in this Application has met the Schedule 8 test of established therapeutic value.

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1st March 2022

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

The statistics associated with the burden of chronic mental health in Australia are staggering. Over 45% of Australians will experience a mental illness during their lifetime, and approx. 20% of Australians at any one time are suffering from a chronic mental health issue.

The Australian Government Productivity Commission's 2020 Report into Mental Health[1] conservatively estimates that the cost to the Australian economy of mental ill-health and suicide is in the order of $43-51 billion per year. The largest costs within this are for the loss of workforce participation and productivity ($9.8-18.1 billion p.a.), for the additional informal care provided by family and friends ($15 billion p.a.), and for government expenditure on health and services ($16.2 billion p.a.).

Notably, all three of these major cost categories have come under increased strain during the COVID-19 pandemic. On top of this economic burden, there is also an additional $130 billion per year associated with diminished health and reduced life expectancy for those living with mental ill-health.

These sobering data reinforce previous work by the Commission, which estimated that mental health has the highest economic cost burden in terms of workforce participation and productivity out of any disease category. In this context of large and rising costs, it is notable that the Productivity Commission found "despite the rising expenditure on healthcare, there has been no clear indication that the mental health of the population has improved"[1].

As international neuropharmacology researchers with >25 years' experience in the field, this pessimistic outlook is not surprising to us. Despite the massive strides that we have made in destigmatising and understanding mental illness, in developing patient access gateways, support systems and advocacy – all championed by the Australian government – these advances have not been accompanied by a commensurate increase in the clinical development of truly novel, efficacious and safe medicines.

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Indeed, an often-unappreciated fact is that all current medicines prescribed to treat psychiatric diseases are based on science that is at least 50 years old[2]. We cannot think of any other realm of medical or scientific research where such a decades-long lack of innovation would be deemed acceptable. This is why most current psychiatric medicines have similar (limited) success rates; require long-term dosing; are difficult to cease; have significant side-effects that affect both compliance and quality of life.

We wholeheartedly believe that improving our mental health outcomes requires a holistic, systemic, approach – which is why we feel that the current lack of medicinal treatment breakthroughs has been a crucial inhibitor of the clinical and social progress that we are trying to achieve in our community.

It is for this reason that in late 2021, with significant financial support of Monash University, we founded the Neuromedicines Discovery Centre (https://www.neuromedicines.monash/) to engage in comprehensive research into the discovery, development, clinical evaluation and rollout of novel medicines for the treatment of mental health disorders.

We urgently require new approaches to break the current bottleneck in psychiatric drug discovery, which is why we are writing **in strong support of the limited re-scheduling of MDMA from Schedule 9 to Schedule 8 of the Poisons Standards, to facilitate its medical use as a vital and effective part of psychotherapy**. **Simply put, the science does not support the current classification of MDMA (when used in this way) as a Schedule 9 poison.**

There is a substantial and growing body of overseas clinical trial evidence that MDMA possesses *significant therapeutic benefit* when used as part of psychotherapy in the treatment of otherwise drug-resistant psychiatric diseases, particularly PTSD[3-5]. These datasets have now been augmented by a recent *major phase 3 clinical study* in PTSD[6], which has substantially expanded both the quality and quantity of clinical data, increased the breadth of patients receiving such treatment and *validated* the therapeutic effectiveness of MDMA in treating PTSD as part of psychotherapy.

At the molecular level, MDMA acts on similar classes of brain transporter proteins that are targeted by the existing Schedule 8 medicines, methylphenidate (Ritalin) and dexamphetamine (Adderall; Dexedrine)[7-10].

Moreover, when used in a clinical environment under direct monitoring by a trained therapist, MDMA is very safe[5] (significantly more so than Schedule 8 opioids and Schedule 4 medicines such as benzodiazepines[11]); the most commonly anticipated side effect in a clinical setting would be a transient elevation in blood pressure[12] that can be monitored for and/or used as an exclusion criterion depending on the patient's existing health.

MDMA is also fast-acting, with reports of patients having experienced rapid and sustained rates of remission of symptoms after MDMA-assisted psychotherapy sessions[4]. This is in contrast to the majority of existing psychiatric medicines, which often take weeks to start showing an effect and then need to be taken by the patient for long periods of time.

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Based on current overseas data, MDMA-assisted psychotherapies are also likely to only require a single administration (by clinicians) of the medicine 2-3 times over a period of a few months to complete a course of therapy[4].

Such a controlled and limited dosing regimen markedly mitigates any likelihood of abuse liability or risk of adverse effects induced by longer term dosing (such as sleep disturbances, depression, heart disease or decreased cognitive function). As evidenced by a recent meta-analysis of five MDMA clinical trials[5], there were no serious adverse events observed in four of the five clinical studies; in the fifth trial where some serious adverse events were observed, it was concluded that the majority of these events were not due to MDMA[5]. Indeed, in the more recent and comprehensive Phase 3 clinical trial of MDMA in PTSD[6], the researchers found that the adverse effects were actually worse in the placebo group than they were in the MDMA group.

The severe adverse effects listed by the Delegate in previous communications regarding MDMA, specifically loss of consciousness and seizures, have never been reported (to our knowledge) in a clinical setting; rather, they are associated with the unsupervised, recreational use of MDMA of unknown purity.

It should also be noted that the USA FDA has recently granted MDMA-assisted therapies for PTSD "breakthrough therapy" status[13], paving the way for availability of this as a form of prescribed medicine (under psychiatric supervision) pending further clinical trial results.

Furthermore, the protocol under which MDMA would be administered (with clinical supervision) as part of psychotherapy provides an environment closest to that used in the successful clinical trials; there is significantly lower risk for the misuse of MDMA by this approach than for most medicines that, once prescribed, are subject to patient compliance at home.

The risk of acute and long-term effects of MDMA abuse or misuse by way of access outside of strictly controlled medical and scientific research settings is low, noting that a rescheduling would place the medical use of MDMA as part of psychotherapy at the same level as drugs such as morphine, methadone, and ketamine, which are used therapeutically and securely stored in accordance with Schedule 8 requirements.

The application for rescheduling MDMA to Schedule 8 of the Poisons Standard, to which this letter is appended, is for limited clinical use, namely:

- when used as part of psychotherapy in medically controlled environments; and
- under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and
- where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists; and

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- where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967and/ or; imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

When this strictly limited use application is considered with a) the strong evidence base supporting extant therapeutic effectiveness of MDMA, b) the minimal risk/abuse liability in such controlled settings and c) the establishment of training courses in psychedelic-assisted therapies both in Australia and overseas, we believe that the data **strongly support the contention that medicinal MDMA already has an established therapeutic value when used as part of psychotherapy,** and could represent a front-runner in a new class of psychiatric medicines that are safe, fast-acting, with minimal adverse effects and minimal abuse liability.

Please note that we categorically do not support the use of MDMA in any setting that does not involve appropriate patient screening prior to clinically supervised administration and observation, with the same policies and guidelines as applied to Schedule 8 medicines for manufacture, storage and disposal.

Whilst the Federal Government's recent Medical Research Future Fund announcement of support for clinical studies of psychedelic medicines is welcome, the current classification of MDMA as Schedule 9 prevents States or Territories providing a permit for use by psychiatrists, even when they have met the criteria above set out in the rescheduling application and access has been approved by the TGA via the Special Access Scheme-B.

Furthermore, the current classification places extremely prohibitive barriers in allowing even fundamental research to proceed, let alone appropriately sized clinical trials, due to practical, financial and bureaucratic restrictions specific to Schedule 9 substances[14]. This would not be the case if MDMA were re-scheduled as a Schedule 8 substance in the manner proposed.

Based on our long-term experiences, industry research, and successful collaborations on major NIH, Wellcome Trust, NHMRC, ARC and industry-sponsored grants, we can attest that Australia has some of the world's best pharmacologists, psychiatrists and psychologists with expertise in this space who would benefit enormously from improved access to MDMA when used in the way proposed.

Collectively, based on the extant and growing evidence base, we are satisfied that MDMA use as an adjunct to psychotherapy has an established therapeutic value and meets the requirements for a revised Schedule 8 listing.

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Yours sincerely,

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Professor of Analytical Pharmacology & Director, Neuromedicines Discovery Centre
Dean
Faculty of Pharmacy and Pharmaceutical Sciences
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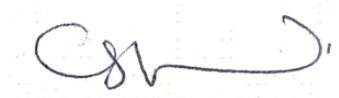

Christopher J. Langmead, M.A., Ph.D., F.B.Ph.S.
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