Australian Government
Department of Health

Application to Amend the Poisons Standard by Retaining Psilocybine In Scheduling 9 But also having a Schedule 8 Entry for Restrictive Medical Use with Appendix D and Appendix F Controls

2nd 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 Psilocybine in Schedule 9 But Also Having a Schedule 8 Entry for Restrictive Medical Use

We are attaching our second application for the rescheduling of psilocybin 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 psilocybin assisted psychotherapy continue to show that this treatment can be used safely and achieve high remission and response rates for patients with treatment resistant conditions 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.

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.

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.

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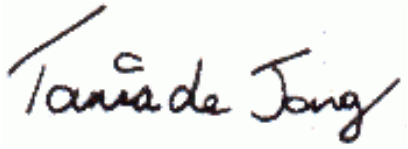
We are available to meet with the Therapeutic Goods Administration, the Advisory Committee on Medicines Scheduling and the nominated Delegate of the Secretary of the Department of Health at your convenience to discuss all aspects of our Application.

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

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DETAILS OF THE APPLICATION

Confidentiality

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

Medicine Details

1. **Name of Medicine Requiring Scheduling:** Psilocybine* (on restrictive basis)
2. **Active Ingredient:** Psilocin
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

- The Poisons Standard spells psilocybin with an “e” at the end (i.e. as psilocybine). All the literature reviewed uses the spelling “psilocybin” (i.e. without an “e” at the end). For the purposes of this Application and to align with the published literature we have used the spelling “psilocybin”.

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**; 2 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: 2 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 Psilocybin as detailed below.

PSILOCYBINE (OR PSILOCYBIN)
Schedule 9
Schedule 8
Appendix D, Item 3
Appendix D, Item 5
Appendix F, Part 1, Item 36

SCHEDULE 9 – Proposed Amended Entry
PSILOCYBINE **except** when separately specified in Schedule 8.

SCHEDULE 8 – Proposed New Entry
PSILOCYBINE 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*.

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 psilocybin are set out in Table 1 below.

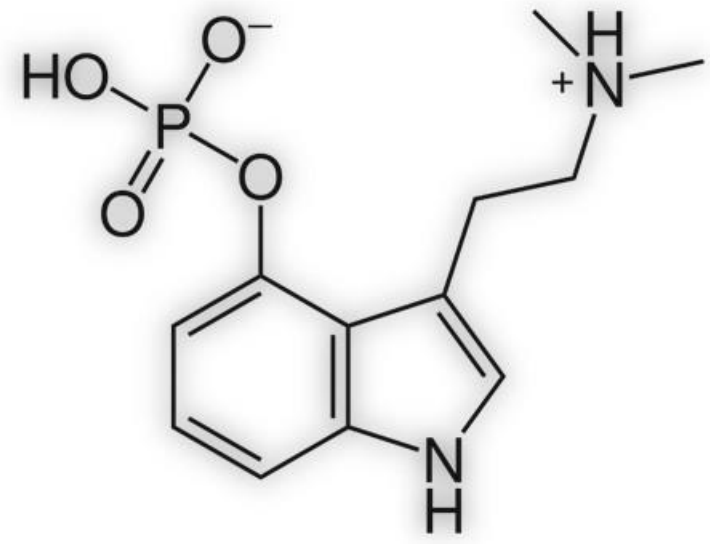
Table 1. Chemical properties of psilocybin

Property	Value
Chemical Formula	$C_{12}H_{17}N_2O_4P$
CAS Number	620-52-5
IUPAC Name	[3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate
Molar Mass	248.25 g/mol
Boiling Point	220-228°C

(2) Chemical Structure

The chemical structure of psilocybin is set out in Figure 1 below.

Fig 1 Chemical structure of Psilocybin



(3) Description of Substance

Psilocybin is a member of the tryptamine chemical family and presents as a white crystalline solid. It is stable over extended periods at room temperatures. It is a major psychoactive constituent in mushrooms of the Psilocybe genus**.** Psilocybin is classed as a

psychedelic, sometimes called a hallucinogen. Psychedelics are chemical compounds which temporarily create changes in brain function including shifts in perception, thinking, and feeling, which temporarily produces an 'altered state of consciousness'. Psilocybin is a non-chiral molecule.

(4) Toxicity

The toxicity of psilocybin is very low. Based on the results of animal studies, the lethal dose of psilocybin has been extrapolated to 6 g in humans,[3] which is 240 times the typical therapeutic dose of 25 mg. The lethal doses for animals are set out in Table 2 below:

Table 2. Acute toxicity of psilocybin

Species	ROA	LD_{50}
Mouse	IP	285 $mg.kg^{-1}$
Rat	IP	280 $mg.kg^{-1}$
Rabbit	IV	12.5 $mg.kg^{-1}$

2.2. PHARMACOLOGY

(1) Pharmacokinetics

Absorption

When administered orally, the absorption of psilocybin is 50%.[4] Psilocybin is converted rapidly and effectively in the gastrointestinal tract into psilocin.[4] The effects of psilocybin are wholly from psilocin. In fact psilocybin is 48 times less efficacious than psilocin.[5]

Distribution

Psilocin is evenly distributed throughout the whole body. Psilocin is detected in plasma after 2,040 minutes, but drug onset is generally 70-90 minutes. Plasma C_{max} for psilocin (as psilocybin administrated in humans at a therapeutic dose of 0.3 mg/kg) is average 16 µg/L (between 14.5-17.2 µg/L).[6] The T_{max} for the C_{max} is average 121 minutes (between 69-124 minutes).

Metabolism

Psilocybin is a prodrug for its active metabolite psilocin (4-OH-DMT; 4-hydroxy-*N*,*N*=dimethyltryptamine).[4]

Elimination

The elimination half-life of psilocin is 163 minutes. The psychoactive effects of psilocybin at therapeutic dose levels can last 6-8 hours.

(2) Pharmacodynamics

Biomechanisms

Psilocybin and its metabolite psilocin exert their primary psychoactive action through partial agonism of the serotonin 5-HT_{2A} receptor, a G-protein-coupled receptor.[7] Pre-treatment with 5-HT_{2A} receptor antagonist, ketanserin, was found to block most of the experiential effects of psilocybin. Serotonin 5-HT_{2A} receptors increase in number within the brain under conditions of depression and states of high stress, such as sleep deprivation and hypoxia.[8] Activation of the 5-HT_{2A} receptor causes downstream effects such as changes in the expression of early growth protein 1 (ERG1) and β-arrestin 2.[9] These findings suggest that the 5-HT_{2A} receptor is involved in processes related to adaptivity, sensitivity to context, learning and unlearning, and synaptogenesis (new neuronal connections).[10] Although 5-HT_{2A} agonism is recognised as the primary mechanism of psilocybin and other classical psychedelics, psilocybin has affinity for an array of pre and postsynaptic serotonin and dopamine receptors.[11] For example, it has been found that classical psychedelics inhibit TNF-α signalling through activation of serotonin receptor 5-HT_{2B}, a potential anti-inflammatory mechanism of classical psychedelics.[12]

Figure 2. Receptor assay of psilocin

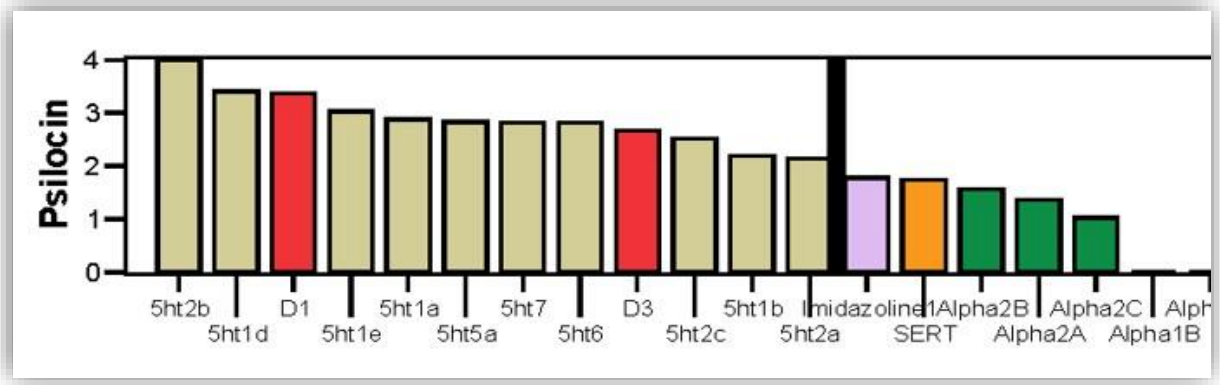


Figure 2 shows the receptor binding affinities of psilocin. The receptors before the black line contribute to the psychoactive effects.[11]

Neurological Mechanisms

Several theories have been put forward to account for the therapeutic effects of psilocybin. The most prominent theories are based on recent brain imaging data.[10] In the past decade, brain imaging technologies have come to describe multiple "hubs" of functional connectivity in the brain called resting-state networks (RSN).[13] The analysis of functional connectivity (FC) can illuminate how brain regions are coupled (RSFC). fMRI studies have opened a window into the mechanisms of psilocybin-assisted therapy and the study of consciousness itself. The way psilocybin changes brain network dynamics, or

RSFC may help explain its observed efficacy in the treatment of mental illnesses. Psilocybin reduces the activity of a brain network, an area of FC, called the Default Mode Network (DMN).

The DMN is associated with rumination about the past, daydreaming and autobiography and is known to be tightly correlated, or overactive, in several mental illnesses. By temporarily decoupling the activity of the DMN, psilocybin appears to enable communication among more diverse brain regions.[14] In this way, psilocybin may facilitate a more plastic, receptive brain state. This hypothesis, along with the proposed effects of $5HT_{2a}$ receptors, accounts for the importance of the environment or therapeutic context.[14] It has been proposed that integration occurs in a window after treatment where the patient is more open to change.

2.3. PHARMACOTHERAPEUTICS

(1) Positive Psychological Effects

Psilocybin exhibits its therapeutic effects during psychotherapy through positive psychological outcomes:[4, 14-16]

- Enhancement of emotions
- Enhanced ability for introspection
- Increased awareness of sub-conscious processes
- Induction of hypnagogic experience and dream-like experiences
- Synaesthesia
- Labile brain state
- Alterations of thought and sense of time
- Enhances 'emotional breakthroughs'

(2) Adverse Effects

No drug related serious adverse events (SAE) have been reported from any previous research investigating psilocybin's effects in healthy participants.[17] In clinical trials there have been no reported significant adverse events either pre or post prohibition. In its Final Decision the Delegate concluded that "*… the safety profile of psilocybin under tightly supervised psychotherapy conditions used in clinical trials is quite reasonable"* and acknowledged that "*...the risk of addiction is low in a highly controlled environment for psilocybin assisted therapy."*

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 below.

All adverse effects in the studies were appropriately managed with safeguards in a clinical setting. The most common psychological adverse experiences have been anxiety and negative mood.[6] The most common physical adverse events are cardiovascular (mild to moderate increases in blood pressure and heart rate), occasional nausea and headache.

There have been a number of recent trials that confirm the strong safety profile of psilocybin when used as part of therapy in properly controlled environments including:

The Compass Pathways randomised Phase 1 double-blind placebo-controlled healthy persons trial

The Compass trial was conducted by King's College London with results published in the *Journal of Psychopharmacology* January 4th, 2022. Psilocybin was administered to healthy adult volunteers.[18] In this double-blind study, 89 healthy volunteers were randomised in a 1:1:1 ratio to receive 10 mg of psilocybin (*n* = 30), 25 mg of psilocybin (*n* = 30), or placebo (*n* = 29), with 1:1 support from a trained assistant therapist during a session lasting six hours. In total, 25 dosing sessions were completed, with up to six participants per session. The study involved a 12-week follow-up period. Key results were**:**

As seen in the Table below, there were no serious adverse events. The most frequent adverse events were seen with 10 mg and 25 mg doses and involved changes in sensory perception and positive mood orientation. There were no negative effects on cognition and emotional functioning.

Table 2. Most frequently reported TEAEs (occurring in >15% of participants in any treatment arm and ordered according to incidence in the 25 mg psilocybin arm) and summary of TEAEs of special interest (Safety Population).

	Psilocybin 25 mg (*N*=30)		Psilocybin 10 mg (*N*=30)		Placebo (*N*=29)	
	n (%)	Events	*n* (%)	Events	*n* (%)	Events
Most frequently reported TEAE (MedDRA Preferred Term)						
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Illusion	18 (60.0)	26	19 (63.3)	25	4 (13.8)	5
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Headache	15 (50.0)	16	9 (30.0)	12	5 (17.2)	5
Fatigue	8 (26.7)	8	9 (30.0)	10	3 (10.3)	3
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Tension headache	6 (20.0)	6	3 (10.0)	3	3 (10.3)	3
Time perception altered	6 (20.0)	6	2 (6.7)	2	3 (10.3)	3
Emotional disorder	5 (16.7)	6	2 (6.7)	2	0	0
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
TEAEs of special interest (MedDRA System Organ Class/Preferred Term)						
Any TEAE of special interest	26 (86.7)	80	25 (83.3)	81	10 (34.5)	19
Nervous system disorders	0	0	2 (6.7)	2	0	0
Memory impairment	0	0	1 (3.3)	1	0	0
Psychomotor skills impaired	0	0	1 (3.3)	1	0	0
Psychiatric disorders	26 (86.7)	80	25 (83.3)	79	10 (34.5)	19
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
Change in sustained attention	0	0	2 (6.7)	2	0	0
Depressed mood	2 (6.7)	2	1 (3.3)	1	1 (3.4)	1
Dissociative identity disorder	2 (6.7)	2	1 (3.3)	2	0	0
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Hallucination[a]	2 (6.7)	2	3 (10.0)	3	0	0
Hallucination, auditory	4 (13.3)	4	4 (13.3)	4	1 (3.4)	1
Hallucination, gustatory	0	0	1 (3.3)	1	0	0
Hallucination, olfactory	1 (3.3)	1	1 (3.3)	1	0	0
Hallucination, tactile	4 (13.3)	4	2 (6.7)	2	0	0
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Substance-induced psychotic disorder	1 (3.3)[b]	1	0	0	0	0

TEAEs were coded post hoc to MedDRA Version 21.0 Preferred Terms. TEAE: treatment-emergent adverse event; MedDRA: Medical Dictionary for Regulatory Activities.
[a]All TEAEs coded to the MedDRA preferred term 'Hallucination' were described as 'kinaesthetic hallucinations'.

Source: https://journals.sagepub.com/doi/pdf/10.1177/02698811211064720

The Johns Hopkins Phase 2 Trial investigating psilocybin-assisted therapy for anxiety and depression exacerbated by a recent cancer diagnosis

The trial results published in the *Journal of Psychopharmacology* in 2016 showed Psilocybin to be well tolerated even in more at-risk patient groups, such as those facing a cancer diagnosis.[19]

Table 3. Adverse events reported in Johns Hopkins study investigating psilocybin assisted therapy for anxiety and depression exacerbated by recent cancer diagnosis.

Adverse event description†	Low dose (*n* = 52)	High dose (*n* = 53)
Elevated Diastolic Blood Pressure (> 100)*	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)*	9 (17%)	18 (34%)
Elevated SBP (> 160) and/or DBP (> 100)	10 (19%)	18 (34)
Elevated Heart Rate (> 110)*	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11(21%)
Anxiety during session	8 (15%)	14. (20%)

† In all cases, the adverse effect had resolved by the end of the session day.

* In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes and returned to normal levels by the end of the session

The Imperial College Phase 2 Trial comparing Psilocybin assisted psychotherapy with a leading SSRI plus therapy published in the New England Journal May 2021

A Phase 2 study completed in 2021, shows that psilocybin has similar primary efficacy at treating depression when compared to escitalopram (an SSRI antidepressant) and more favourable secondary effects, with twice as many patients going into remission from the psilocybin group and significantly less side effects.[20]

This trial again showed Psilocybin to be well tolerated, this time amongst depression patients.

Table 4. Adverse events reported during the 6-week trial period and on dosing-day 1.

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

* These were the most prevalent adverse events that were reported during the trial.
† Whether an adverse event was related to the therapeutic intervention was determined by the study clinician through dialogue with each patient. Events deemed "probably" or "definitely" related were counted.

The Compass Pathways Phase 2b multi-site trial using psilocybin for treatment resistant depression released in November 2021

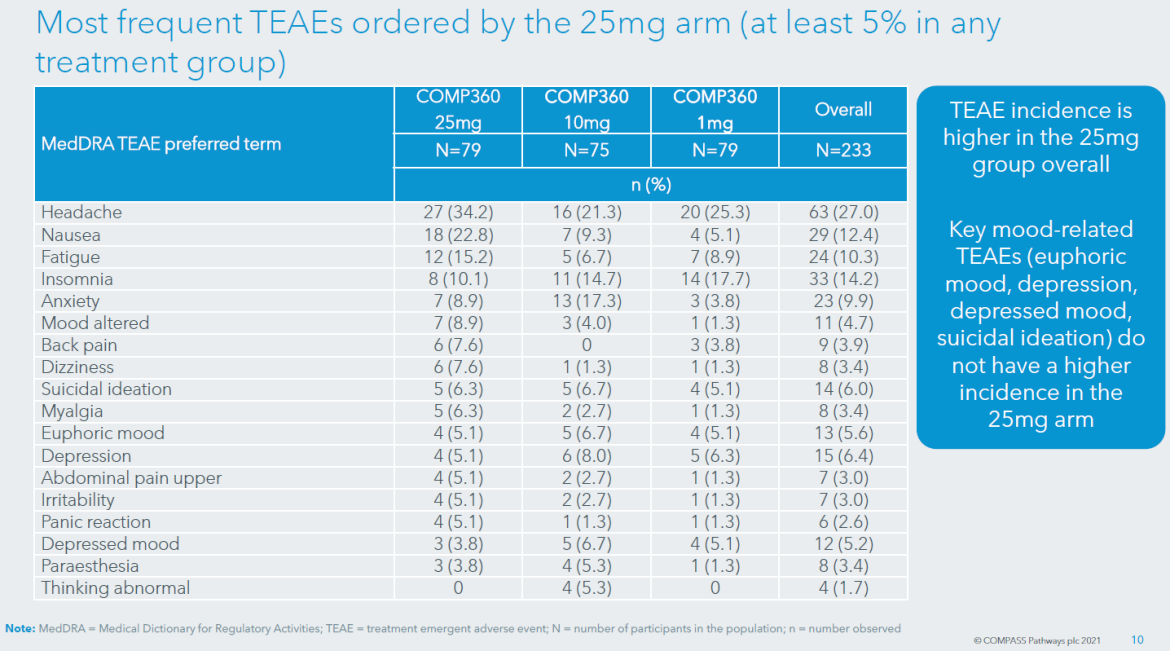
The COMPASS Pathways Phase 2b trial was the largest in history for the use of psilocybin assisted therapy, in this case for treatment resistant depression. The key findings of the trial were:[21]

- Psilocybin-assisted therapy 25mg vs 1mg: a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6
- Psilocybin-assisted therapy 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)
- At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3
    - 36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group
    - 29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group

- 24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group

Psilocybin-assisted therapy was generally well tolerated, with more than 90% of treatment-emergent adverse events (TEAEs) mild or moderate in severity. The majority of TEAEs occurred on the day of the dosing session or the day after (77.4%) and most of these were mild or moderate in nature e.g., headache, nausea, fatigue. All TEAEs of the psilocybin groups which involved hallucination resolved on the same day. TEAs of suicidal ideation, suicidal behaviour and intentional self-injury were seen in all groups, as is regularly observed in the Treatment Resistant Depression population.

Table 5.



Most frequent TEAEs ordered by the 25mg arm (at least 5% in any treatment group)

MedDRA TEAE preferred term	COMP360 25mg N=79	COMP360 10mg N=75	COMP360 1mg N=79	Overall N=233
	n (%)			
Headache	27 (34.2)	16 (21.3)	20 (25.3)	63 (27.0)
Nausea	18 (22.8)	7 (9.3)	4 (5.1)	29 (12.4)
Fatigue	12 (15.2)	5 (6.7)	7 (8.9)	24 (10.3)
Insomnia	8 (10.1)	11 (14.7)	14 (17.7)	33 (14.2)
Anxiety	7 (8.9)	13 (17.3)	3 (3.8)	23 (9.9)
Mood altered	7 (8.9)	3 (4.0)	1 (1.3)	11 (4.7)
Back pain	6 (7.6)	0	3 (3.8)	9 (3.9)
Dizziness	6 (7.6)	1 (1.3)	1 (1.3)	8 (3.4)
Suicidal ideation	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Myalgia	5 (6.3)	2 (2.7)	1 (1.3)	8 (3.4)
Euphoric mood	4 (5.1)	5 (6.7)	4 (5.1)	13 (5.6)
Depression	4 (5.1)	6 (8.0)	5 (6.3)	15 (6.4)
Abdominal pain upper	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Irritability	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Panic reaction	4 (5.1)	1 (1.3)	1 (1.3)	6 (2.6)
Depressed mood	3 (3.8)	5 (6.7)	4 (5.1)	12 (5.2)
Paraesthesia	3 (3.8)	4 (5.3)	1 (1.3)	8 (3.4)
Thinking abnormal	0	4 (5.3)	0	4 (1.7)

TEAE incidence is higher in the 25mg group overall

Key mood-related TEAEs (euphoric mood, depression, depressed mood, suicidal ideation) do not have a higher incidence in the 25mg arm

Note: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event; N = number of participants in the population; n = number observed

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Source:
https://j8g9v7z6.rocketcdn.me/wp-content/uploads/2021/11/COMP001_-_topline_data.pdf

In total there have been over 32 completed trials using psilocybin involving over 1,131 participants with only a minimal number of significant adverse events associated with these trials. See Table 12 in Appendix B.

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**"); and

(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 its letter to the TGA responding to our first rescheduling application dated 15 July 2020.

As a result, we have made this application for rescheduling significantly more restrictive than its first application lodged in July 2020 (see Part 1 Section 1).

As you will see, we have also reviewed developments in this field since our first application was lodged to incorporate further evidence supporting the proposed rescheduling that has become available since July 2020.

3.2. Specific Matters Relied on by the Delegate in the Delegate's Final Decision

Whilst the Delegate decided against Mind Medicine Australia's first application to amend the Poisons Standard the reasons given by the Delegate 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 psilocybin 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) The First Factor – Whether Psilocybin is in Schedule 1 of the UN Convention of Psychotropic Substances

Whilst Psilocybin 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) 2.10 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 access (e.g., The United States, Canada 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) The Second Factor- Whether the use of Psilocybin as part of therapy has an established therapeutic value

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

In particular, psilocybin has been administered to 1,131 participants in 32 trials since prohibition (and an additional 1,196 participants before prohibition) so that the data that we have is far more comprehensive than for most other unregistered medicines at the time they were placed in Schedule 8 of the Poisons Standard. The Independent Panel itself concluded that there were statistically significant differences in most of the limited number of trials which they reviewed which favoured psilocybin against the placebo group (and favouring psilocybin in one recent trial against a leading SSRI) and psilocybin was well tolerated in all of these trials.

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".* The most recent trials of note have been conducted by leading global institutions such as **Imperial College London** and **Johns Hopkins** in the United States and written up in prestigious journals. The latest trial (which the Delegate wasn't able to review for timing reasons) was a Phase 2b Trial sponsored by **Compass Pathways** as part of the FDA and EMA registration pathways in the United

States and Europe. The quality of these trials has not been questioned in extensive reviews.

As you will see in Part 2.1 Section (A) 1.1 below we review the data which we believe strongly supports our contention that psilocybin when used as part of therapy in medically controlled environments does have an established therapeutic value.

Our conclusion from this data that psilocybin 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) <u>The Third Factor – Whether the benefits of down scheduling outweigh the risks to patients and public health from increased access</u>

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) been strong.

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

The risks identified by the Delegate were twofold;

<u>The First Alleged Risk (Diversion Risk)</u> was that medical grade psilocybin 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 psilocybin is much more expensive than the psilocybin that is used in the recreational drug scene and which is readily

obtainable on the Black Market (synthesised medical grade psilocybin is more expensive by a factor of at least 20 times). Psilocybin for recreational purposes can also be obtained for free by simply picking psilocybin containing mushrooms in the wild or at low cost by growing the mushrooms at home (kits and instructions are readily available on the internet).

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 psychiatrist will also have to have received specific training in this form of therapy and the patient's diagnosis and treatment plan will have 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 (see Part 2.1 (F)3 below) and our course was recently described on ABC National Radio by one of the leading researchers in this field in the World (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 Previous Submissions made by The Royal Australian and New Zealand College of Psychiatrists (RANZCP) and The Australian Medical Association (AMA)

Specific Matters Raised by the RANZCP

RANZCP based its submission to the TGA in relation to Mind Medicine Australia's 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 trials conducted by Imperial College London, Johns Hopkins in the United States and from the Compass Pathways Phase 2b Trial (see Part 1 Section 2.3(2) and 3.6 and part 2.1 Section (A) 1.1).
2. The mental health situation in Australia has deteriorated.
3. Mind Medicine Australia has restricted its 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 Perkins, D. et al. (2021) '*Medicinal psychedelics for mental health and addiction: Advancing research of an emerging paradigm*', Australian & New Zealand Journal of Psychiatry, 55(12), pp. 1127–1133. doi: 10.1177/0004867421998785.)
   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 the treating psychiatrist having received specific training for this form of medicinal therapy (See Part 1 Section 1).
5. Mind Medicine Institute has started Australia's first course in psychedelic assisted therapies 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 (see letter

following) which 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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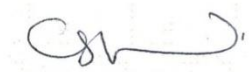
MONASH University

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 on 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 (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 psilocybin more readily available to medical practitioners other than in the very limited way 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.

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 psilocybin. The proposed Schedule 8 entry of psilocybin recognises that psilocybin 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 Australia for the use of psilocybin 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 also require confirmation that the patient is treatment resistant, that the patient'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 psilocybin assisted psychotherapy.

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 current 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 $180 billion estimated annual cost to the Australian economy due to mental illness.[22] 1 in 5 adults were diagnosed with a chronic mental illness, with 48% of all Australians experiencing a mental illness in their lifetime.[23]

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

With current pharmacotherapy treatments, only an estimated 35% of people diagnosed with depression experience remission from using antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs) and/or psychotherapy.[24] Adverse side-effects of using SSRIs are common and they can become a daily reinforcement to the patient that they suffer from a mental illness. Before the current COVID 19 pandemic 1 in 8 adults and 1 in 4 older people were being treated with SSRIs[25]and this is likely to have significantly worsened. In the 15-year period up to 2019 there was a 95% increase in SSRI prescriptions in Australia.

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

The key point we would emphasise here is that a 'more of the same' approach 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 a different result".*

As a nation we need to 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"[26]

It's easy for us all to get tied up with academic arguments and 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 depression (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 treatment resistant 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 Person Suffering from Treatment Resistant Depression

"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

3.6. 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 illnesses in Australia on a highly controlled basis to improve the mental health outcomes of suffering Australians.

Psilocybin has been granted two Breakthrough Therapy Designations by the Food and Drug Administration (FDA) in the United States - the first to Compass Pathways Limited in 2018 for psilocybin as part of therapy for Treatment Resistant Depression and the second in 2019 to Usona Institute for psilocybin as part of therapy in the treatment of Major Depressive Disorder.[18, 27] This designation from the FDA acknowledges both the unmet medical need in these broad populations and the potential for these therapies to offer significant improvements over existing therapies. In a medically controlled environment psilocybin-assisted therapy is safe, non-addictive, and there is no increase in risk for mental ill health in a clinically controlled environment.[28]

Effect sizes of remission rates for psilocybin vs SSRIs

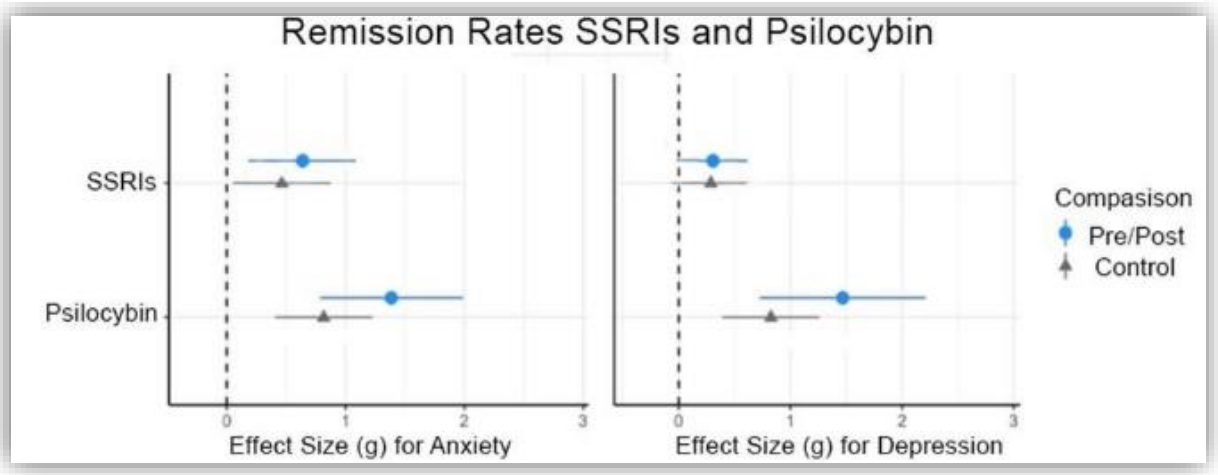


Figure 1. The data in the figure above was collated from meta-analyses of antidepressants and psilocybin.[29-31] The psilocybin data combines outcomes from four studies (*n* = 117); one uncontrolled and three randomised with placebo control.[19, 32-34]

A Phase 2 study sponsored by Imperial College London and published in May 2021, shows that psilocybin has similar primary efficacy at treating depression when compared to escitalopram (an SSRI antidepressant) and more favourable secondary effects, with twice as many patients going into remission from the psilocybin group and significantly less side effects.[20]

The data in the figure below shows the differences in primary and secondary outcomes in depression for parallel treatments of psilocybin vs escitalopram.[20]

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

COMPASS Pathways has finished the largest Phase 2 trial in history on the use of psilocybin assisted therapy, in this case for treatment resistant depression with the results announced in November 2021. The key findings were as follows:[21]

- Psilocybin-assisted therapy 25mg vs 1mg: a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6
- Psilocybin-assisted therapy 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)
- At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3
    - 36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group
    - 29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group
    - 24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group
- Psilocybin-assisted therapy was generally well tolerated, with more than 90% of treatment-emergent adverse events (TEAEs) mild or moderate in severity

Psilocybin-assisted therapy has yielded remarkable clinical results for depression and anxiety in numerous trials at leading universities internationally.[35] The proportion of participants who show positive clinical improvements, and the degree to which they improve, are substantially higher than clinical outcomes associated with currently available treatments.[36] Psilocybin-assisted therapy can lead to remission in up to 60-80% of cases of anxiety and depression, whereas current existing treatments lead to remission

in a maximum of 35-42% of cases.[19, 32, 33] There are over 40 current or recently completed clinical trials in humans.[37] Clinical trials are also underway for an increasing number of treatment indications in addition to depression, including OCD, anorexia, addiction, and dementia.

The safety of this form of therapy in clinical trials has already been summarised in Part 1 Section 2.3(2) above.

We believe that the highly restrictive rescheduling of psilocybin from Schedule 9 to Schedule 8 proposed in this Application with all other uses remaining in Schedule 9 will provide an important treatment option for Australians suffering from treatment resistant depression and treatment resistant anxiety disorders. This will enable patients who fall within these categories to access psilocybin-assisted therapy on a highly controlled basis through the TGA's Special Access Scheme and patient specific State and Territory Government approval processes on the recommendation of their treating psychiatrist who has received specific training in this form of therapy and whose diagnosis and treatment plan has been confirmed by two other psychiatrists.

We believe there is sufficient evidence to justify a Schedule 8 restricted entry of psilocybin (with the strict controls envisaged) to facilitate its use under the Special Access Scheme for compassionate use. The TGA's Special Access Scheme was specifically designed for this purpose.

3.7. Satisfaction of Rescheduling Requirements

We believe that this application for Rescheduling the medical use of psilocybin 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 (A)1.1);
- Translation risks (see Part 2.1 Section (A) 2.2);
- Diversion risks (see Part 2.1 Section (A)2.1); and
- Public health and safety requirements generally (see Part 2.1(F)).

3.8. The Approach is Consistent with Government Policy Statements

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

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

3.9. The Approach is a Pragmatic Response to Problems Associated with Australia's Federal System and is Based on Precedent

The TGA has already granted several approvals under the Special Access Scheme for medical practitioners to treat patients who are treatment resistant and "at risk" with psilocybin as part of psychotherapy. However, despite these approvals, medical access to psilocybin 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 psilocybin 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.[38] 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 psilocybin).

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 psilocybin) 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 US, Switzerland and Canada have restrictive schemes for patient access under compassionate use for psilocybin for Treatment Resistant Depression and for the anxiety and depression often associated with a terminal diagnosis. The US states of Oregon, Colorado and Washington DC have also legalised and regulated the medical use of psilocybin and Health Canada has given a number of regulatory exemptions for the use of psilocybin as part of therapy to patients over the last few years. Health Canada has also recently expanded its Special Access Program (SAP) to provide medical access to 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.**

3.10. 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, patient's being treated, and the research findings being written up. Patient selection is highly selective, and participants have to fall

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

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 and because of funding and other commitments individual patient follow up can be challenging. 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 psilocybin assisted therapy only requires two to three medicine dosing sessions rather than years of taking the medicine daily as occurs with SSRI's.

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 psilocybin for compassionate use is not inconsistent with ongoing trials and will also provide valuable data on the translation of these therapies into a medical (rather than trial) domain (see in particular the independent registry proposal outlined in Part 1 Section 3.3).

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 psilocybin on the limited basis envisaged in this application.

3.11. Rescheduling on the Limited Basis Proposed will 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 psilocybin 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 is considered (see Part 1 Section 2.3 and Part 2.1 Section (A)1.1), the proposed requirement for patient review by two other psychiatrists (see Part 1 Section 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.

3.12. Overwhelming support from Australian Health Practitioners

Health sector participants overwhelmingly supported our first application for the rescheduling of psilocybin as part of psychotherapy. This included many psychiatrists, psychologists, psychotherapists, general practitioners and pharmacologists. These front line practitioners are people who directly see the limitations of current treatments and the desperate need for innovation in this 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 psilocybin as a Schedule 9 substance and doesn't differential between medical and recreational use.

2. HISTORICAL CONTEXT

1. Historical Use of Psychedelic Plants

Historians and anthropologists have found that psychedelic plants have been used by humans for thousands of years in various contexts, from the medicinal to the ritualistic. The Eleusinian Mysteries of Ancient Greece (1600 BC to 396 AD) were a ritual attended by thought leaders of the ancient world including Plato, Aristotle, and Cicero. The rites involved what is believed to be a psychedelic drink 'Kykeon', derived from fungus growing on barley.[7] Cicero, stoic philosopher and Roman senator, described the Eleusinian Mysteries as:

"For among the many excellent and indeed divine institutions which your Athens has brought forth and contributed to human life, none, in my opinion, is better than those mysteries. For by their means we have been brought out of our barbarous and savage mode of life and educated and refined to a state of civilization; and as the rites are called 'initiations,' so in very truth we have learned from them the beginnings of life and have gained the power not only to live happily, but also to die with a better hope."

- Cicero, Laws II, xiv, 36

Psychedelic plants have been used by indigenous cultures for millennia.[39] These indigenous cultures have restricted psychedelic plant use to sacramental and healing rituals, in controlled ceremonial environments guided by shamans and healers.

2. Early Scientific Research

Psilocybin was first isolated from Psilocybe mushrooms in 1957 and then synthesised in 1958 by Albert Hoffman.[7] It was then marketed as Indocybin® by pharmaceutical company Sandoz for experimental and psychotherapeutic use. In the 1950s and 1960s, psychedelic-assisted therapy was regarded by a large proportion of psychiatry as the next

big breakthrough for treating mental illness and was used for a range of conditions in thousands of patients.[40]

3. Political Controversy

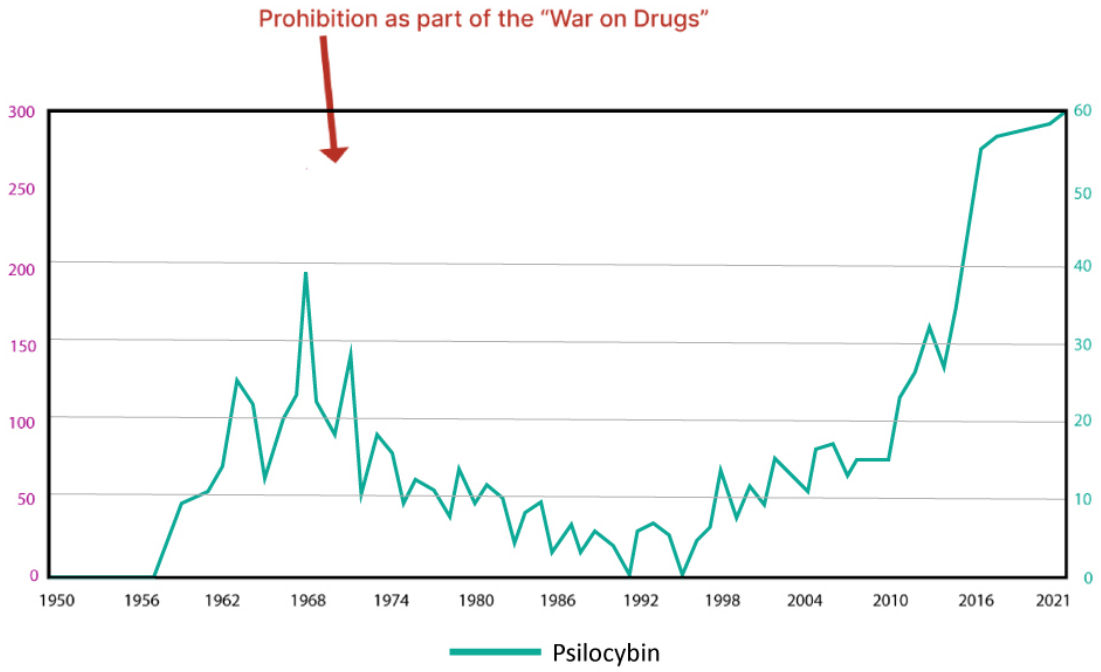
Although strong results were achieved in the 1950s and 1960s research and medical use came to a halt in 1971 as psychedelic substances were rescheduled by the Nixon Administration as part of the US Government's War on Drugs. This change in scheduling for psychedelic substances occurred without any scientific or medical rational or consensus.

The American War on Drugs, which was extended to other members of the United National including Australia through the UN Convention on Psychotropic Substances, was applied without regard to medical benefits of using these medicines as part of psychiatry. Classical psychedelics, including psilocybin, are currently Schedule 9 drugs in Australia (Schedule 1 in the USA). This category is reserved for substances considered by regulators to be without medical value, and with high abuse potential. Research has shown that psychedelics do not meet either of these Schedule 9 criteria.[40] Given that psychedelic-assisted therapy was establishing itself through the 1950s and 1960s as the 'next big thing' in psychiatry, this censoring of inquiry into such a promising line of research severely restricted further research into this area for decades.

4. Psychedelic Research Resurgence and Profile

In the last 20 years well-controlled clinical trials have shown impressive evidence for the clinical use of psychedelics, such as psilocybin, for inducing therapeutically beneficial behavioural change in a variety of mental health conditions. This new data shows that psilocybin-assisted therapy frequently leads to remission from certain mental illnesses within a few doses, when administered with proper psychotherapeutic support before, during and after treatments.

Figure 2. Number of academic publications on psilocybin over the last 70 years



Source: Mind Medicine Australia Analysis

3. RANGE OF USE

The following are taken from completed or current clinical studies:

- Major Depressive Disorder (MDD)
- Treatment-Resistant Depression (TRD)
- Anxiety disorders
- Addiction
- Anorexia nervosa
- Body-dysmorphic disorder
- Cluster and migraine headaches
- Obsessive Compulsive Disorder (OCD)

4. PSILOCYBIN -ASSISTED PSYCHOTHERAPY PROTOCOL

Psychedelic-assisted therapy involves 'talk-therapy' alongside the ingestion of a psychedelic compound such as psilocybin.[36] Importantly, the non-psychedelic elements of this approach are essential for both effectiveness and safety. Medicinal psilocybin is not a complete therapy, but rather acts as a catalyst or accelerator for the therapeutic process. Psilocybin increases mental flexibility and sensitises the patient to the therapeutic environment. Researchers and clinicians often describe three distinct therapy

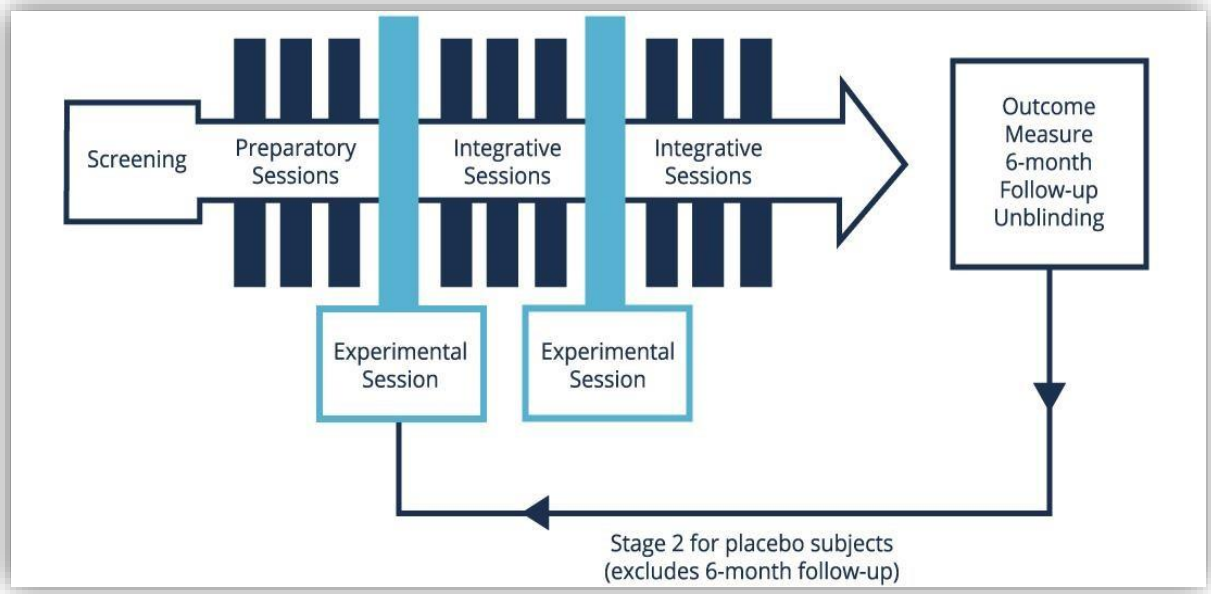
phases that take place over several days: preparation, the psychedelic experience and integration:

- **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.

Psilocybin-assisted psychotherapy occurs within a clinical, aesthetic, and private space. As the dosed sessions generally last 6-8 hours, two trained specialist therapists work together. For 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 put in place to ensure their safety in the unlikely event of a medical complication.

While the therapy can be challenging for some patients and bring up difficult experiences, these may be crucial to the therapeutic process; most participants rate the experience as among the most significant of their lives.[41] Anxiety during the experience can be ameliorated with careful preparation by the individual and therapist as well as support during the active session.

Figure 2. Psilocybin-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 of its kind in the World*".

During 2021, 88 practitioners graduated from the course. The professional backgrounds of these graduates is 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.

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 PSILOCYBIN

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 therapeutic available in the market, the definition is framed in the concept of added therapeutic value"[42]

2. We then 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 a listing in Schedule 8 of the Poisons Standard.

3. Given that our proposed listing on Schedule 8 of the Poisons Standard is restricted to patients that are treatment resistant the need for innovation is obvious. SSRIs have low effect size and can also have harmful side effects (see 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 the clinical efficacy and health outcomes associated with the use pf psilocybin 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 psilocybin assisted therapy is used in clinical trials (see Part 1 Section 2.3(2)). Further anecdotal evidence to support this can also be drawn from uncontrolled environments but we acknowledge that whilst helpful it also less relevant.

There is also strong efficacy information coming from clinical trials (see Part 1 Section 3.6). 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 the appropriateness of this form of therapy for a treatment resistant patient where the patient is fully informed and has given informed consent and the medicine dosing sessions are given in medically controlled environments. This is reinforced by the proposed scheduling requirement that the treating psychiatrist must have received training in the use of psilocybin as part of therapy and the psychiatrist's diagnosis and treatment plan must be supported by two other psychiatrists.

Our view that the use of psilocybin as part of therapy has an established therapeutic value is supported by leading researcher in this field, Professor David Nutt from Imperial College London, by Drug Science in the UK and by leading Australian based pharmacologists, in Australia, 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 as 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 explaining why they believe psilocybin as part of psychotherapy on the basis set out in this application has met the Schedule 8 test of established therapeutic value are reproduced below and also appear in Appendix C. These experts would be prepared to discuss their views with the TGA, the Medicines Scheduling Committee and 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,

The Chair of Mind Medicine Australia, Mr Peter Hunt AM, has asked Drug Science to directly address the question of whether medical grade psilocybin 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 psilocybin 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 in its application is very restrictive;

SCHEDULE 9 – Proposed Amended Entry

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

SCHEDULE 8 – Proposed New Entry

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

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

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

- Between the late 1950s and prohibition, psilocybin was administered to 1,960 participants and was well tolerated in 19 trials without complications and with useful efficacy;

- Since prohibition, psilocybin has been administered to 1,131 participants in 32 trials and has been shown to be well tolerated without complications and with useful efficacy;

- There have been 14 long-term follow up studies of 232 participants which have shown sustained efficacy in a significant portion of participants with no psychosis, HPPD, or other health complications;

- People taking psilocybin as part of therapy in countries such as the Netherlands, Jamaica, some US States and cities, the Bahamas and a number of South America countries (where the laws permit usage) and under compassionate access schemes in Canada, the United States, Switzerland and Israel; and

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

Although there have been over 51 psilocybin trials in total, we will focus on the two most recent in this letter as these were placebo controlled and randomised.

Compass Pathways released its Phase 2b results in November 2021. This was a multi-site parallel, randomised, double-blinded, placebo controlled trial with 216 participants taking either a 25 or 10 mg active dose of psilocybin as part of psychotherapy vs a 1 mg active placebo in patients with treatment-resistant depression. We believe that the sample size was demonstrably statistically relevant with and effect size of over 0.5 and the trial was of high quality. The results were robust and confirmed the results achieved in earlier trials;

Key Findings of the Compass Pathways Phase 2b Trial
Psilocybin 25mg vs 1mg:a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6
Psilocybin 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)
At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3
36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group
29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group
24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group

The adverse events were manageable and consisted of:
Psilocybin was generally well tolerated, with more than 90% of treatment-emergent adverse events (TEAEs) mild or moderate in severity
Treatment-emergent adverse event (TEAE) incidence:
83.5% (66 patients) in 25mg group
74.7% (56 patients) in 10 mg group
72.2% (57 patients) in 1 mg group
Treatment-emergency serious adverse event (TESAE) incidence:
6.3% (5 patients) in 25mg group
8.0% (6 patients) in 10 mg group
1.3% (1 patient) in 1mg group

A second trial that published its results in the New England Journal of Medicine in May 2021 compared the use of psilocybin assisted psychotherapy with a leading SSRI (escitalopram). This trial was led by one of the authors of this letter Professor David Nutt, and Dr Robin Carhart-Harris from Imperial College London. The results also demonstrated that psilocybin when used as part of psychotherapy had a powerful therapeutic value that for almost all measures exceeded that of escitalopram (see table below).

Table 2. Primary and Secondary Outcomes.*

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

Adverse events were also low and easily manageable.

Table 3. Adverse Events Reported during the 6-Week Trial Period and on Dosing-Day 1.*

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

A further important trial was published in 2021 by the Johns Hopkins group[b] showing psilocybin to have clear antidepressant effects. They have just reported the one year follow up which revealed the effect of a single 25mg dose of psilocybin persisted this long in the majority of patients with over half still in remission and three quarters showing good response[c].

A 2017 Imperial College trial of psilocybin used fMRI scans to show the effects of medical doses of psilocybin on the brain in the treatment of depression. As a result, we know the nature of the brain changes in during the acute psychedelic state and in the days following psilocybin-therapy. A persistent enhancement of brain activity was found in the days following psilocybin-therapy, which explains the importance of using psychotherapy for integration.

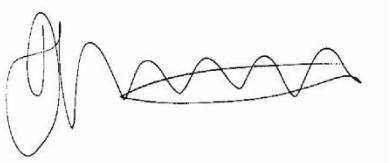
In our view it is now clear that psilocybin when used as part of psychotherapy for patients suffering from treatment-resistant depression or Major Depressive Disorder has an established therapeutic value.

[b] Davis AK, Barrett FS, May DG, et al. (2021) Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 78(5): 481–489. DOI: 10.1001/jamapsychiatry.2020.3285.

[c] Gukasyan N, Davis AK, Barrett FS, et al. (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of Psychopharmacology* 36(2). SAGE Publications Ltd STM: 151–158. DOI: 10.1177/02698811211073759.

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.
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.

MONASH University

Monash Institute of Pharmaceutical Sciences
Monash University
381 Royal Parade
Parkville
Victoria, 3052
Australia
27th February 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 re-scheduling of psilocybin from Schedule 9 to Schedule 8 of the Poisons Standards**. **Simply put, the science does not support the current classification of psilocybin as a Schedule 9 poison.**

There is substantial and growing body of overseas clinical trial evidence that psilocybin possesses *significant therapeutic potential* in the treatment of depression, end-of-life distress, addiction and obsessive-compulsive disorder[3-7]. These datasets have now been augmented by recent *major phase 2 clinical studies* in both major depressive disorder[8] and treatment resistant depression[9], which have substantially expanded both the quality and quantity of clinical data, as well as increased the breadth of patients receiving such treatment.

Given that clinical trials are increasing in size, quality, and consistency (e.g., a dose of 25 mg psilocybin was determined as an effective therapeutic dose for both the phase 2 trials cited) and yet still show the treatment to be highly effective, **collectively we can only conclude that psilocybin-assisted psychotherapy has established itself as a regimen with significant therapeutic value**.

At the molecular level, psilocybin is converted by the liver to its active metabolite, psilocin, which then acts on the same class of receptor proteins (G protein-coupled receptors) as the majority of existing marketed medicines[10,11]. We are world-leaders in the study of the biology of G protein-coupled receptors[11-14], including the serotonin receptor sub-class for which psilocybin has highest selectivity[16-18].

Importantly, there is clear evidence that, when used in a clinical environment under direct monitoring by a trained clinician, psilocybin is safe[19] (significantly more so than Schedule 8 opioids and Schedule 4 medicines such as benzodiazepines[20]). Indeed, the therapeutic index (TI; the ratio of

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toxic dose to therapeutic dose) for psilocybin is 1000[21], which is significantly better than that for heroin (TI=6[21]) and even paracetamol (TI=10[22]).

The most commonly anticipated side effects in a clinical setting would be a transient elevation in blood pressure or some acute anxiety, which can be readily dealt with through appropriate patient pre-screening/exclusion and/or acute clinical supervision[19]. In contrast to many other restricted psychotropic substances, psilocybin is not known to induce dependence[23,24] and, indeed, has medicinal potential to actually treat addiction[7]. Psilocybin is also fast-acting, with reports of patients having experienced rapid and sustained rates of remission of symptoms after psilocybin-assisted psychotherapy sessions[3-7].

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. Based on current overseas data, psilocybin-assisted psychotherapies would also likely require only a single administration (by clinicians) of the medicine only up to 2-3 times over a period of a few months to complete a course of therapy[3-9].

Such a closely controlled dosing regimen would severely mitigate any risk, perceived or otherwise, of multi-drug drug toxicity. Furthermore, the protocol under which psilocybin would be administered (with clinical supervision) provides an environment closest to that used in the successful clinical trials; there is significantly lower risk for the misuse of psilocybin 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 psilocybin abuse or misuse by way of access outside of strictly controlled medical and scientific research settings is low, noting that a rescheduling would place psilocybin 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.

With respect to the perceived risks of psilocybin inducing psychosis, although an association between hallucinogen administration and psychosis has long been discussed[25], the actual determination of a causal link remains arguable and the risks of developing any psychosis during or subsequent to a short-term clinical regimen are actually extremely rare[26].

Importantly, two recent peer-reviewed large population studies[26,27] found *no* link between psychedelic use and mental health problems. The former study used a dataset of over 135,000 randomly selected United States adults, while the latter included over 190,000 United States respondents.

These striking results were of such significant international interest in the field that they were the subject of a Commentary in the leading science journal, *Nature*[28]. Although such population studies cannot exclude the potential for a negative effect on mental health for a specific *individual*, the same can be said for *any* psychoactive substance, and this would be addressed through appropriate

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patient pre-screening/selection (as would be the case for a prescription of any other medicine by a clinician).

Collectively, these facts strongly mitigate any likelihood of major risk or abuse liability of psilocybin in the clinical setting. It should also be noted that the USA FDA has granted psilocybin-assisted therapies for treatment-resistant depression "breakthrough therapy" status, paving the way for availability of this as a form of prescribed medicine (under psychiatric supervision) pending further clinical trial results.

The application for rescheduling psilocybin 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
- 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 psilocybin, 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 these data **strongly support the contention that medicinal psilocybin already has established therapeutic potential when used as part of psychotherapy,** with the potential to represent a possible 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 psilocybin 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 psilocybin as Schedule 9 prevents States or Territories providing a permit for use by psychiatrists, even when they have met the criteria above and access has approved 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,

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financial and bureaucratic restrictions specific to Schedule 9 substances[29]. This would not be the case if psilocybin were re-scheduled as a Schedule 8 substance.

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 psilocybin.

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

Yours sincerely,

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References

1. https://www.pc.gov.au/inquiries/completed/mental-health/report
2. Whitaker, R. (2011) Anatomy Of An Epidemic. Crown Publishers, NY. ISBN: 9780307452429.
3. Grob et al. (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psych.* 68: 71.
4. Carhart-Haris et al. (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility. *Lancet Psych.* 3: 619.
5. Ross et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J. Psychopharmacol.* 30*:* 1165.
6. Griffiths et al. (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J. Psychopharmacol.* 30*:* 1181.
7. Johnson and Griffiths (2017) Potential therapeutic effects of psilocybin. *Neurotherapeutics*. 14*:* 734.
8. Carhart-Harris et al. (2021) Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* 384:1402-1411
9. Compass Ph2b clinical trial results: https://ir.compasspathways.com/static-files/0f9fbce8-2619-438b-a6ba-5bbe2ba08cf6
10. Passie et al. (2002) The pharmacology of psilocybin. *Addiction Biol.* 7: 357.
11. Nichols, D.E. (2016) Psychedelics. *Pharmacol. Rev.* 68: 264.
12. Christopoulos, A. (2002) Allosteric binding sites on cell-surface receptors: Novel targets for drug discovery. *Nature Rev. Drug Disc.* 1: 198.
13. Kenakin and Christopoulos (2013) Signaling bias in new drug discovery: Detection, quantification and therapeutic impact. *Nature Rev. Drug Disc.* 12: 205.
14. Changeux and Christopoulos (2016) Allosteric modulation as a unifying mechanism for receptor function and regulation. *Cell* 166: 1084.
15. Thal et al. (2018) Structural insights into G-protein-coupled receptor allostery. *Nature* 559: 45.
16. Devlin et al. (2004) Regulation of serotonin 5-HT_{2C} receptors by chronic ligand exposure, *Eur. J. Pharmacol*., 308: 59.
17. Werry et al. (2005) Characterization of serotonin 5-HT_{2C} receptor signaling to extracellular signal-regulated kinases 1 and 2. *J. Neurochem.* 93: 1603.
18. Werry et al. (2008) RNA editing of the serotonin $5HT_{2C}$ receptor and its effects on cell signalling, pharmacology and brain function. *Pharmacol. Ther.* 119: 7.
19. Aday et al. (2020) Long-term effects of psychedelic drugs: A systematic review. *Neurosci. Behav. Rev.* 113: 179.
20. Bonomo et al. (2019) The Australian drug harms ranking study. *J. Psychopharmacol.* 33*:* 759.

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21. Gable, R.S. (2004) Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*. 99: 686.

22. Bertolini et al. (2006) Paracetamol: new vistas of an old drug. *CNS Drug Rev*. 12: 250.

23. Rucker, J.J.H. (2015) Psychedelic drugs should be legally reclassified so that researchers can investigate their therapeutic potential. *BMJ*. 350: h2902.

24. Johnson et al. (2018) The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharm*. 142: 143.

25. Strassman (1984) *J. Nerv. Ment. Dis.*, 172: 577

26. Johnson et al. (2008) *J. Psychopharmacol.,* 22: 603

27. Johansen and Krebs (2015) *J. Psychopharmacol.,* 29: 270

28. Cormier (2015) No link found between psychedelics and psychosis, doi:10.1038/nature.2015.16968

29. Nutt et al. (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Rev. Neurosci.* 14: 577.

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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.

1.2 Psilocybin Produces No Dependency at its Therapeutic Dose

Psilocybin does not produce dependency at its established therapeutic dose, nor at any dose (see Section 1.6 of this Part).

1.3 Psilocybin Produces No Toxicity at its Therapeutic Dose

Psilocybin has very low risks of toxicity.[3]

1.4 No Negative Health Outcomes with Synthetic Psilocybin

Synthetic psilocybin has only been used in clinical trials and has had no negative health outcomes associated with its use.[43]

1.5 Safe and Non-Toxic

The therapeutic index of psilocybin is 1000.[40] The therapeutic index is the quantitative measurement of a drug's safety; the TD_{50} (toxic dose) divided by the ED_{50} (effective dose). An index of 1000 is very high. This gives psilocybin a therapeutic index of very high efficacy to toxicity. For a comparison, the therapeutic index of other schedule 8 drugs, such as cocaine and diamorphine, is 15 and 6 respectively. Psilocybin (and psilocin) does not accumulate in the body, its metabolites are non-toxic, and the body is easily able to excrete them rapidly and completely.

1.6 Non-Addictive and No Dependence

Tolerance builds rapidly to psilocybin limiting the ability for it to be used regularly and there is no evidence of physical dependence.[28] Providing psilocybin to patients in clinical studies has not resulted in reported instances of subsequent illicit abuse.[44] The finding that psilocybin did not serve as positive reinforcers in rhesus monkeys shows that primates do not find the psychoactive effects of the $5HT_{2A}$ receptor agonists rewarding.[45] All available evidence suggests psilocybin is non-addictive. Moreover, psilocybin has profound effects for facilitating remission from addiction in people with alcohol and tobacco addiction,[46] and is currently in Phase 2 clinical trials for cocaine, methamphetamine, alcohol, and opioid addiction.

1.7 No Negative Long-Term Effects

There have been no negative health outcomes found from psilocybin clinical trials in long-term follow ups. In no long-term follow up did any participant who took psilocybin experience any negative health outcomes and there were no recorded developments of psychosis or HPPD.

Table 4. Negative health outcomes assessed in long-term follow ups of psilocybin clinical trials*

Year study published	Follow up timeframe	*n*	Psychosis developed?	HPPD developed?	Negative health outcomes developed?
		24	No	No	No
2020[41]	4.5 years	15	No	No	No
2017[47]	3.2-4.5 years	12	No	No	No
	12 months	15	No	No	No
2016[32]	6.5 months	29	No	No	No
2014[48]	6 months	15	No	No	No
2008[49]	14 months	36	No	No	No
1998-2008[50]	8-16 months	110	No	No	No
1998[51]	34 years	21	No	No	No
Total patients screened for follow up		**277**			

*References are cited within the table in the 'Year study published' column.

1.8 No Risk of HPPD, Psychosis, or Schizophrenia

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

Table 3. 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 psilocybin?
1998-2017[52]	50	No
1995-2017[53]	45	No
1998-2008[50]	8	No
1997-2007[54]	64	No

1.9 Historical Medical Use Without Complication

Early therapeutic use of synthetic psilocybin developed by the pharmaceutical sector (Indocybin®Sandoz) was without complication.[4] A review on psilocybin and psychedelic

drugs found little to no significant adverse reactions, if used within a controlled setting.[55] In more recent trials there have been no significant adverse event [56] and psilocybin assisted therapy has been generally well tolerated (Part 1 Section 2.3(2)).

1.10 Benefits in Population Use

An analysis of information from the National Survey on Drug Use and Health showed that the use of psilocybin is associated with significantly reduced odds of:[57]

(iv) Past month psychological distress
(v) Past year suicidal thinking
(vi) Past year suicidal planning
(vii) Past year suicide attempt

In 2016, a study was completed at Johns Hopkins by 1993 individuals in an online survey, in which 84% of participants endorsed psychologically benefiting from the psilocybin-containing mushroom experience.[58]

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 (e.g. Methamphetamines, Cocaine, Morphine and all analogues, Cannabis, Ketamine, Fentanyl and other narcotics/opioids, Opium, Prescription Amphetamines) and which (unlike psilocybin) carry with them substantial risks of addiction if used inappropriately (e.g. Methamphetamines, Morphine, Opium).

We have set out in Table 6 below the way that psilocybin as a Schedule 8 medicines 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 assumed below that the medical grade synthesised psilocybin is imported into Australia as there is as yet no manufacturing of this substance occurring in Australia.

Table 4. Managing Psilocybin 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 licence 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 are imported such as narcotics and cannabinoids, the supply chain is tightly controlled by Australian Border Force and the need to have all relevant permits and licences in place – otherwise goods are confiscated at the point of importation
API is stored	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 int product in labs	Pharmacy receives legal drug order on a patient-by-patient basis from a psychiatrist with approvals under Special Access Scheme – B and meeting local State/Territory requirements. Bona 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 moving 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 show 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. **Continued on Next Page**

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 synthesised medical grade psilocybin from a legally controlled medical setting to an uncontrolled setting.

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

The price equation also does not provide an incentive. Psilocybin containing mushrooms can be picked in the wild in country areas and are readily identifiable through published material. Psychedelic organisations also publish online how to grow psilocybin containing mushrooms. As a result, the supply of psilocybin 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 psilocybin is at least 20 times higher than this on global markets) and carries with it further supply costs for secure carriage, safekeeping and stabilisation testing.

Given the plentiful availability of psilocybin for illegal use and the pricing differential the diversion risk for medical grade synthesised psilocybin is actually far lower than for other Schedule 8 medicines (where the diversion risk for the reasons given above 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).

2.3 The Vital Importance of Environment and Context

There are several factors which influence psychological reactions to psilocybin. In trials, occasionally temporary anxiety can occur which alleviates as psilocybin is metabolized. Clinical usage is undertaken in a controlled context also described as adhering to a 'set and setting' protocol.[59] This approach diminishes adverse experiences and enhances trial outcomes.[60]

2.4 Risks of Psilocybin in an Uncontrolled Setting

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

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

- Vulnerable individuals in uncontrolled settings may experience complications from the psychological effects of psilocybin.
- Analysis of harms caused by a range of psychotropic substances ranked psilocybin containing mushrooms as among the least harmful to the user and least harmful to others in population use.[2]
- When compared to psilocybin-containing mushrooms, the following drugs and medicines were ranked as causing more harm to the user and more harm to others in uncontrolled settings. This research was recently repeated in Australia at St Vincent's Hospital Melbourne.[61]
    - **Schedule 8 drugs** within the *Poisons Standard*; ***buprenorphine***, ***methadone***, ***cannabis***, ***ketamine*** and ***amphetamines***.

- **Schedule 4 drugs** within the *Poisons Standard*; ***anabolic steroids***, ***benzodiazepines***.
- **Unscheduled drugs** within Australia; ***tobacco*** and ***alcohol***.

With unexpected or accidental ingestion of psilocybin-containing mushrooms in uncontrolled settings, panic reactions can occur in some cases. Reported negative effects include confusion, anxiety, violent behaviour, suicidal thoughts,[62] and temporary experiences of delusion.[63]

The risks are therefore much more prevalent for a person who ingests psilocybin in an uncontrolled setting (ie. non-medical, illegal underground medical or recreational environment) but still much less than for a number of legal drugs and existing Schedule 8 and Schedule 4 substances.[60]

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 3. **The Australian Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.[64]**

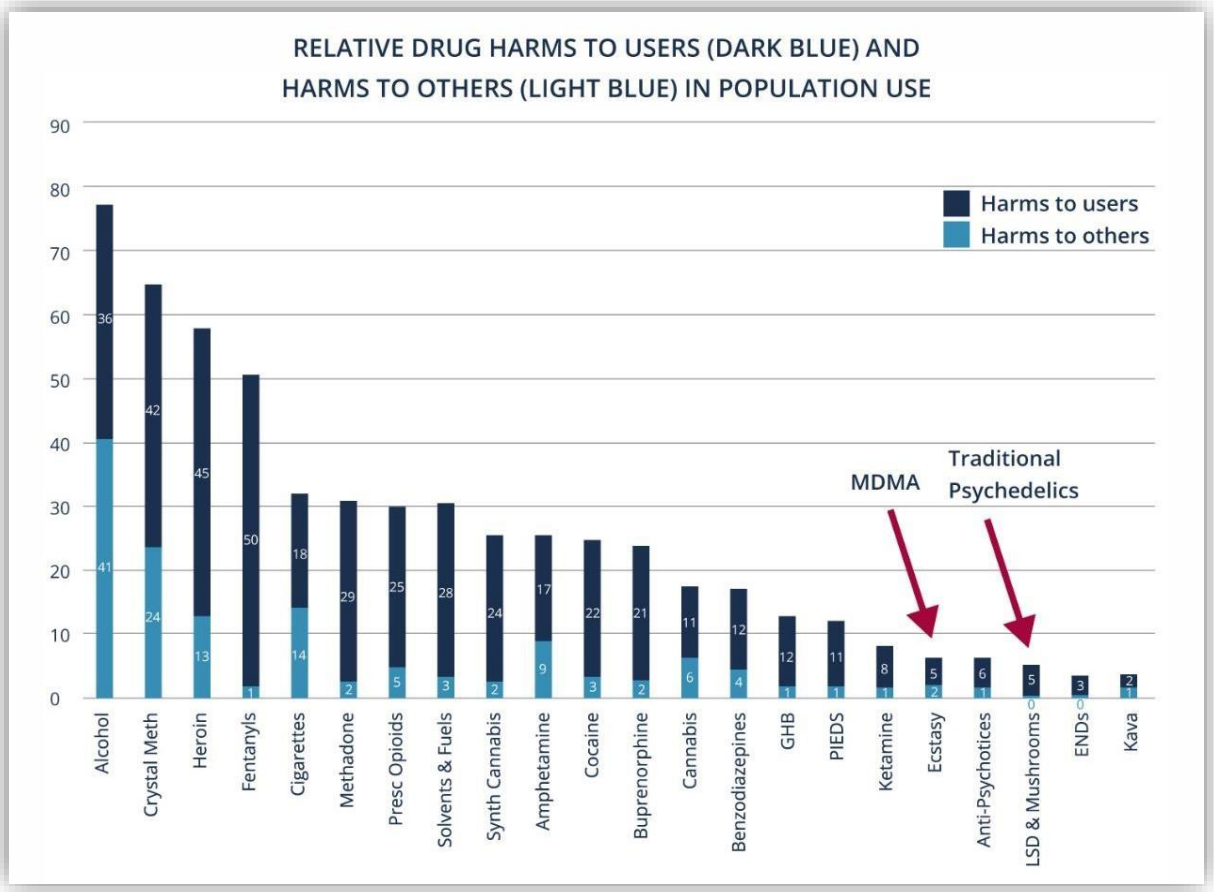


Figure 4. **The UK Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.[2]**

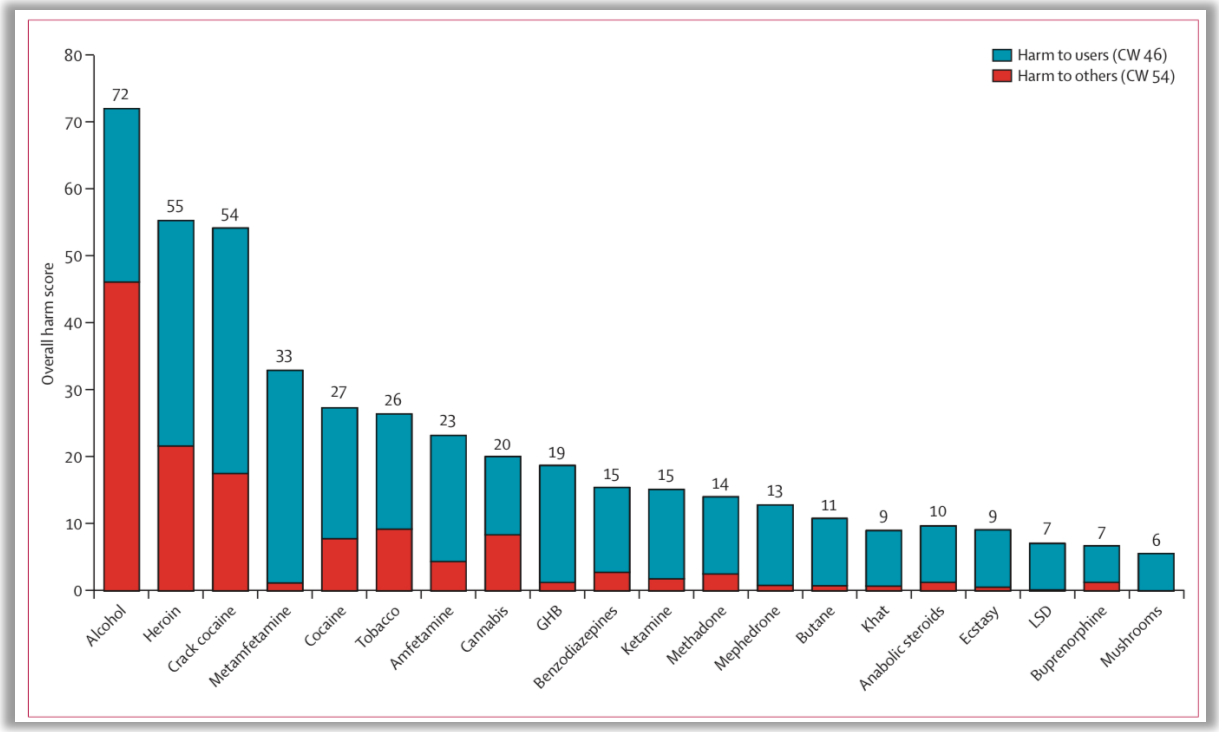
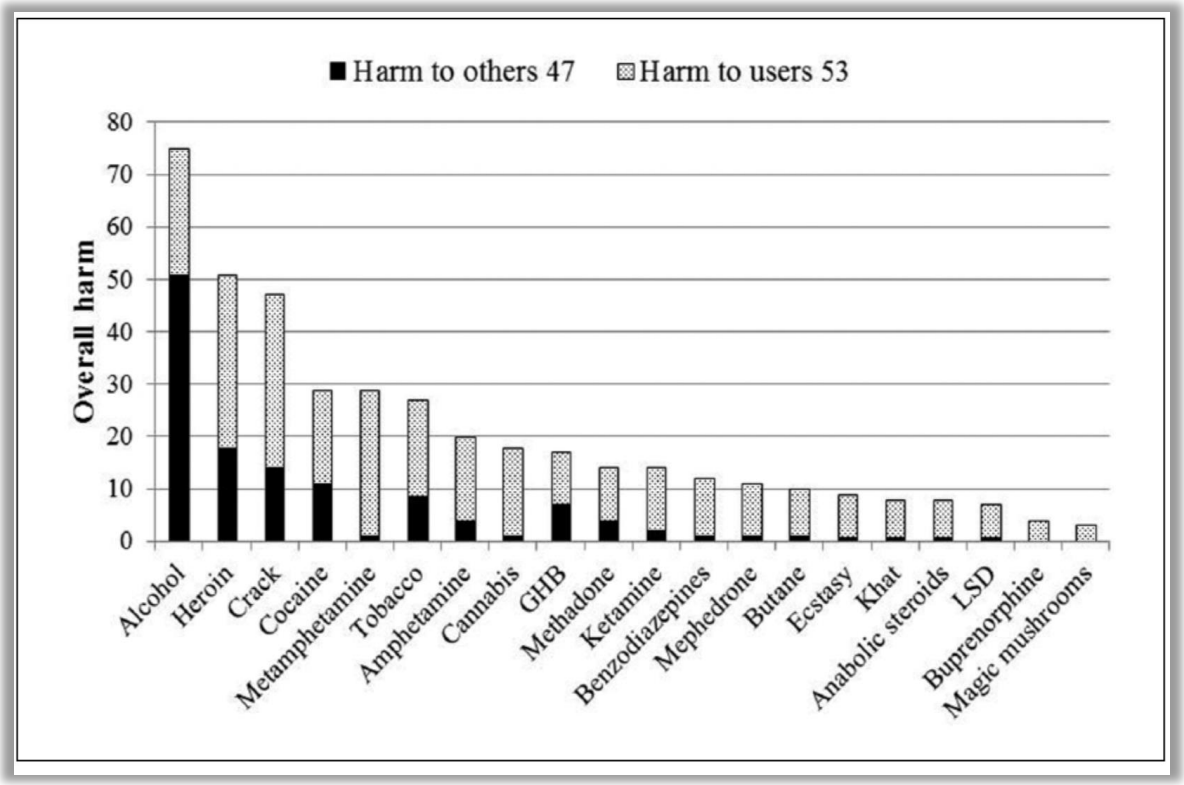


Figure 5. **The European Drug Harms Ratings Study examined the psychological, medical, and social harms of substances in population use.**[1]



2.5 In What Circumstances can the Risks Arise?

Risks can arise if there is unexpected or accidental psilocybin ingestion or use in an **uncontrolled or recreational setting**. Risks can also arise in vulnerable people . However, management of these sorts of risk are normal part of our medical system and additional safeguards have been inserted into the proposed Schedule 8 restricted listing.

2.6 What is the Likelihood of the Hazards Occurring?

Whilst psilocybin is a powerful psychedelic substance, and can produce challenging experiences without appropriate support, there is no evidence that psilocybin use is linked to either mental illness or negative health outcomes when used in controlled environments.

However, the evidence is even stronger than this because information is also available from recreational or medically uncontrolled settings.

A meta-analysis found no link between psychedelic use (outside of a clinical context) and psychosis across a cohort of 135,000.[65] The researchers found that individuals who had taken psychedelics were not at increased risk of developing 11 indicators of mental-

health problems, including: schizophrenia, psychosis, depression, anxiety disorders and suicide attempts.

The incidence of risky behaviour or enduring psychological distress is therefore extremely low when psilocybin is administered in a controlled setting; where participants are screened, prepared and supported.[58]

2.7 Who is at Risk?

The risks are mitigated in a medically controlled environment 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.[39] To date, research trials have produced impressive levels of safety. These same exclusions would be applied by the treating and reviewing psychiatrists in applying for and using psilocybin assisted therapy under the Special Access Scheme with appropriate State/Territory approvals.

2.8 What are the Consequences of these Risks?

Whilst not strictly relevant to this application we can draw information from recreational usage. In the recreational domain, in terms of severity (morbidity, mortality, and duration), fatal intoxication due to ingestion of psilocybin-containing mushrooms is extremely rare.[66-68]. **This would never occur in a medically controlled environment.** The toxicity is extrapolated to be approximately 17 kg of fresh psilocybin-containing mushrooms in humans.[69] It would be highly unusual and very challenging to consume 17 kg of mushrooms. Ingesting psilocybin-containing mushrooms in an uncontrolled setting could theoretically cause reckless behaviour and/or panic attacks. This could lead to public nuisance and/or violation of traffic rules. These hazards are minimal in a medically controlled environment where common procedures are used to ensure that a patient does not leave the clinical environment until the effects of the medicine abates and is taken home by another person who signs the patient out.

2.9 Contraindications

- Antidepressants can cause down regulation of the 5-HT_{2A} receptor which may limit treatment benefit.[14] A washout period of at least two weeks is advised and is current practice in major clinical trials of psilocybin-assisted therapy.
- Caution should be taken with a Monoamine Oxidase Inhibitor (MAOI) type antidepressants which may increase the effects of psilocybin.
- Some anti-psychotic medications act as antagonists at the 5-HT_{2A} receptor and others (atypical anti-psychotics) can contribute to downregulation.
- Psilocybin has no other major drug-related contraindications.

2.10 Could Australia Breach its Obligations under the UN Convention of Psychotropic Substances 1971?

Psychotropic Substance Scheduling

Psilocybin is included in Schedule 1 of the *United Nations Convention on Psychotropic Substances 1971*.[70]

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 (ie. psilocybin) to have limited use for medical purposes with appropriate pre-approvals and restrictions by Government bodies.[70] This exemption specifically supports the requirement for patients to be able to access psilocybin in Australia in medically controlled environments as part of psychotherapy 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 provisions to access a Schedule 1 substance in the *United Nations Convention on Psychotropic Substances 1971* for medical use through a scheme such as Special Access Scheme-B and is not inconsistent with a Schedule 8 restricted listing in the manner envisaged by this application. It therefore should ***NOT*** inhibit the rescheduling of psilocybin 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 (B)1 below which shows that comparable countries to Australia with highly rated medical systems such as the United States, Canada, Switzerland, the Netherlands and Israel all have compassionate access schemes which give treatment resistant patients access to psilocybin 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 PSILOCYBIN IS TO BE USED

1. INTERNATIONAL COMPASSIONATE USE AND EXPANDED ACCESS SCHEMES

In the US, the FDA has approved an Expanded-Access-Scheme (EAS) for compassionate use for using psilocybin to treat both Treatment Resistant Depression (TRD) and Major Depressive Disorder (MDD). For a treating physician to obtain psilocybin for a patient under EAS, the Institutional Review Board of Usona Institute (a not-for-profit organisation in the US) along with the FDA must approve the patient on a case-by-case basis. If successful, psilocybin treatment is conducted by Usona Institute.[71] An EAS has also commenced between COMPASS Pathways and the FDA.[72]

In Canada, the Minister of Health has granted the use of psilocybin as part of psychotherapy in patients for compassionate use under a regulatory exemption. As of 31 December 2021, over 40 exemptions had been issued and patients treated. On 4th January 2022, the Canadian Government passed a Federal Amendment allowing medical practitioners to access psilocybin and other psychedelics for patient use through the Special Access Program (SAP).[73, 74] 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 5. Global Therapeutic Use of Psilocybin as Part of Psychotherapy

Country	Jurisdiction	Scheme
Australia	Commonwealth	Patients approved by the Therapeutic Goods Administration to use psilocybin therapeutically. However, State and Territory approval is also required and (with the exception of Victoria) no permit systems currently exist for the use of psilocybin as part of psychotherapy whilst it remains a Schedule 9 substance.
Canada	Country wide	Psilocybin can be medically administered under compassionate grounds with approval from Health Canada. **No further approvals are required at the Provincial level.**
US	Federal	Psilocybin can be medically administered as part of psychotherapy under compassionate grounds with no further approvals required at the State level.

We also understand that psilocybin assisted therapy is available on a case by case basis in Switzerland and Israel.

The State of Oregon in the United States has gone further and legalised psilocybin assisted therapy.

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

The TGA has approved psilocybin 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) as no permits are available in those States and Territories for psilocybin whilst its medical use remains in Schedule 9. The National Drugs and Poisons Schedule Committee (now the Medicines Scheduling Committee) has recommended in the past that to bypass the "confusion" between the medical and recreational or illicit use of a drug, a Schedule 9 substance can also have a Schedule 8 Appendix D entry for medical use in the Poisons Standard.[38]

In its response to Mind Medicine Australia's first submission the AMA appeared to support the removal of barriers that restricted access to psilocybin for medical purposes under Special Access Scheme-B.[75]

3. TREATMENT CONDITIONS

(1) Treatment-Resistant Depression (TRD)

TRD is a form of depression that has been unsuccessfully treated with traditional methods used to treat depression. Symptoms include a negative affective state, ranging from unhappiness and discontent to an extreme feeling of sadness, pessimism, and despondency that interferes with daily life. The US Food and Drug Administration (FDA) has granted psilocybin-assisted therapy Breakthrough Therapy status for TRD.[18] In a preliminary trial of TRD, psilocybin-assisted therapy substantially reduced depressive symptoms in over 65% of patients, which remained significant six months post-treatment.[60] COMPASS Pathways has announced the completion of a 216 participant Phase 2b double-blind placebo-controlled trial researching the safety and efficacy of psilocybin in participants with TRD.[76] The results released shows rapid and sustained remission from TRD (see also Part 2.1Section (A)1.1 above).

(2) Major Depressive Disorder (MDD)

MDD is characterised by persistent sadness and other symptoms of a major depressive episode but without accompanying episodes of mania or hypomania or mixed episodes of depressive and manic or hypomanic symptoms. The FDA has granted psilocybin-assisted therapy Breakthrough Therapy status for MDD.[27] Usona Institute is currently in Phase 2 of an 80-participant study using psilocybin for the treatment of MDD.[59] The study is randomised under double-blind conditions to receive a single 25 mg oral dose of

psilocybin or single 100 mg oral dose of niacin (vitamin B_3). Niacin serves as an active placebo. The purpose of this study is to evaluate the efficacy of a single 25 mg oral dose of psilocybin for MDD compared to the active placebo.

Table 6. Details of trials complete and underway for psilocybin treating MDD

#	Phase	Trial Status	*n*	Psilocybin dose	Ctrl	Sponsor	Trial ID
1.	Phase 2b	Recruiting	30	25 mg	Placebo	Northern Stockholm Psychiatry	NCT04630964
2.	Phase 2	Complete	59	25 mg; Escitalopram	Placebo	Imperial College London	NCT03429075
3.		Complete	27	25 mg	No	Johns Hopkins University	NCT03181529
4.		Active	30	25 mg	No	Maryland Oncology Hematology	NCT04593563
5.		Recruiting	100	25 mg	Placebo	Usona Institute	NCT03866174
6.		Recruiting	90	25 mg	Placebo	Johns Hopkins University	NCT04620759
7.	Phase 1	Active	18	0.1 mg/kg; 0.3 mg/kg	Placebo	Yale University	NCT03554174

(3) End-of-Life Anxiety and Depression

End-of-life or existential anxiety and depression is characterised by a general sense of anguish or despair associated with an individual's recognition of the inevitability of death and associated suffering. Psilocybin has been shown to be effective in treating end of life anxiety with long-lived results in two overseas trials and 60-80% of patients reviewed still showed clinically significant improvements at a four-year follow up.[41] End-of-life anxiety and depression affect many Australians in palliative care. The ageing population shows the highest use of anti-depressant medication with Australians over 68 consuming 25% of all antidepressant prescriptions.[25]

Psilocybin for end-of-life anxiety and depression is also currently being trialled in Australia: Psilocybin is currently being used in conjunction with psychotherapy to treat depression and anxiety in terminally ill patients in a trial at St Vincent's Hospital in Melbourne.[77] The trial began in January 2020 with 40 patients recruited from the hospital's palliative care unit who have not responded to anti-depressant or anti-anxiety therapies. This trial is double-blinded and placebo-controlled. Patients will be given 25 mg of synthetic psilocybin in conjunction with psychotherapy sessions.

It is truly ironic that a patient with a terminal disease in Australia can (in certain circumstances) commit legal suicide through State and Territory based euthanasia laws but can't legally access psilocybin assisted psychotherapy which has been shown to be safe and have high efficacy rates in treating the depression and anxiety often associated with a terminal diagnosis.

(4) Other Promising Indications Being Trialed

It has been suggested that psilocybin-assisted therapy is most effective in conditions characterised by rigid thoughts and behaviours such as depression, anxiety, addictions, obsessive compulsive disorder and eating disorders. This is in part due to the neurological change psilocybin facilitates. Recent evidence suggests there may also be application for pain relief, immune function and learning disorders.[13]

Psilocybin is currently also being studied for the treatment of the following conditions:

Table 7. Current indications being investigated by institution

Treatment Indication	Institution
Addictions, including tobacco, opioid, alcohol, cocaine	Johns Hopkins University, University of Zurich, New York University
OCD	Yale University
Anorexia Nervosa	Imperial College London, Johns Hopkins University
Depression associated with AIDS recovery	University of California
Cluster headaches	Harvard University, Yale University
Early-stage cognitive decline	Johns Hopkins University
Lyme Disease recovery	Johns Hopkins University
PTSD	Lieber Institute for Brain Development

4. Hazards and Safety of Psilocybin

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 8. Safety and therapeutic index of common drugs and medicines.[78-80]

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 ranked in terms of safety and therapeutic effect.

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

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

1. TOXICITY

Psilocybin has very low risks of toxicity. **See Part 1 Section 2.3(2) (toxicity) and Part 2.1 Section (B) 3.5 (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 psilocybin's effects in healthy participants.[17] In clinical trials there have been no reported significant adverse events either pre or post prohibition. In its Final Decision the Delegate concluded that "*… the safety profile of psilocybin under tightly supervised psychotherapy conditions used in clinical trials is quite reasonable"* and acknowledged that " *….the risk of addiction is low in a highly controlled environment for psilocybin assisted therapy".* **See Part 1 Section 2.3(2) for more information.**

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 PSILOCYBIN PRODUCE DEPENDENCY AT ITS ESTABLISHED THERAPEUTIC DOSE?

Psilocybin does not produce dependency at its established therapeutic dose (see Part 2.1 Section (A)1.6). One of the benefits of psilocybin 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 PSILOCYBIN FOR LIMITED MEDICAL PURPOSES

Note: Psilocybin in synthetic form is not currently manufactured in Australia and so, for the time being, will need to be imported from overseas. If Psilocybin becomes a Schedule 8 medicine on the restricted 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.

1. DOSAGE

This application is for a very limited rescheduling of psilocybin for medical purposes. The dosage of psilocybin will be specified by the treating psychiatrist on the Special Access Scheme-B form and approved by the TGA on a case-by-case basis. We have extrapolated the following dosages from the literature:

- A single dose of 25 mg of psilocybin for a person weighing under 90 kg but not below 45kg; or
- A single dose of 30 mg of psilocybin for a person weighing between 90 kg and 115 kg; or
- A single dose of 35 mg of psilocybin for a person weighing over 115 kg.

2. FORMULATION

The synthesised psilocybin 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;
b) The name of the dosage form;
c) The quantity of the medicine;
d) The batch number of the medicine preceded by the batch number prefix;
e) The expiry date of the medicine, preceded by the expiry date prefix; and
f) The storage conditions applicable to the medicine;
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 is one capsule of 25 mg of psilocybin (or higher if the patient weighs more than 90 kg). 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 an individual capsule as authorised by the supervising medical practitioner.

Psilocybin 25 mg (or specified higher level if the patient weighs over 90 kg) Caps (1): Take one capsule only in the presence of your psychiatrist or designated medical professional. For in-clinic use only. Do not take this medicine at home. Do not drive a motor vehicle or consume alcohol within 24 hours of taking this capsule.

8. PRESENTATION

To be given to a patient by a treating psychiatrist or medical professional designated by that psychiatrist in a clinical setting after they have read and signed a patient informed consent form specifically applicable to psilocybin-assisted therapy.

9. PHARMACY PROCEDURE

The intermediary importation pack will be held at a pharmacy under Schedule 8 regulations with a reporting register of mg use. Each primary pack will be compounded and provided to the designated medical practitioner only under an authorised Schedule 8 prescription. The supply pathway is explained in detail in Part 2.1 Section (A)2.2.

10. PSILOCYBIN PRODUCES NO DEPENDENCY AT ITS THERAPEUTIC DOSE

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

11. PSILOCYBIN PRODUCES NO TOXICITY AT ITS THERAPEUTIC DOSE

Psilocybin has very low risks of toxicity (see Part 2.1 Section (A) 1.7).

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

1. BACKGROUND

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

All information in this section is therefore of psilocybin-containing mushrooms in an uncontrolled setting and is provided for completeness.

The Australian Bureau of Statistics (ABS) has never reported on misuse, abuse, illicit use, or anything with the keyword, psilocybin, Psilocybe, or magic mushrooms.[81]

2. DIVERSION RISK

For the reasons set out in Part 2.1 Section (A)2.1, we believe that the diversion risk of psilocybin 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 psilocybin on the limited basis set out in this application as a Schedule 8 medicine in a medically controlled environment is extremely low.

4. AUSTRALIAN DRUG TRENDS

The 2019 Australian Drug Trends published by the National Drug & Alcohol Research Centre (NDARC) from the University of New South Wales reports no overdose, misuse, or abuse of psilocybin or psilocybin-containing mushrooms between the years 2000 and 2019.[82]

5. MISUSE

In the recreation drug scene misuse can occur when psilocybin is used in combination with other drugs:[69]

- In 2005, a 31-year-old English male died from falling from heights after combined use of psilocybin-containing mushrooms and alcohol.

- In 2006, a 33-year-old Irish male died from falling from heights after combined use of psilocybin-containing mushrooms and alcohol.
- In 1999, young French female died falling from a window with the combination of psilocybin-containing mushrooms and cannabis.
- A 20-year-old Dutch male died after he became sick following the use of psilocybin-containing mushrooms, ecstasy, and alcohol.

Suicide:[69]

- In 2004, a suicide was reported in the Czech Republic, in which the presence of psilocybin containing mushrooms was confirmed by autopsy.
- Two young foreign male tourists died after they jumped out of the window of an Amsterdam hotel after the consumption of magic mushrooms.
- An 18-year-old Dutch male died after he jumped out of a window following ingestion of psilocybin-containing mushrooms.

Circumstantial:[69]

- In 2002, a 27-year-old male was found dead in a canal who had ingested a large amount of *Psilocybe cubensis*.

6. ABUSE

Australia has never conducted an official governmental investigation into psilocybin abuse. However, with psilocybin having no dependency and significant tolerance build-up, repeat and multiple dosing becomes ineffective. Abuse potential even in recreational environments is low.

7. ILLICIT USE

Australia has never conducted an official governmental investigation into psilocybin illicit use. Internationally though, in 2007, the Dutch National Criminal Intelligence Service (DNCIS) conducted an inquiry into the criminal involvement of psilocybin-containing mushrooms.[69] The DNCIS found no evidence of public nuisance as a result of sale or use of psilocybin-containing mushrooms. The 2007 briefing of the DNCIS reported no criminal acts related to psilocybin-containing mushrooms in relation to:

- Psilocybin-containing mushroom growers and criminals
- No offenders of law regarding users (except for one shop for selling dried magic mushrooms)
- The police intercepted postal mailings containing illegal dried psilocybin-containing mushrooms on occasion.

The DNCIS also reported the following:

- The border police at the Belgium border regularly observed the export of dried mushrooms
- The customs at the Schiphol airport, Amsterdam, occasionally confiscated small amounts of psilocybin-containing mushrooms
- In 2007, the German customs confiscated one large mailing of 27 kg of psilocybin-containing mushrooms.

8. OVERDOSE

There are only two fatal cases described in literature, in 1996 and 1961, due to overdosing with psilocybin-containing mushrooms.[69] As the same paper estimates that the lethal dose of fresh psilocybin containing mushrooms is likely to be 17 kg. it is not clear how this over-dosing could have occurred. The authors go on to say that:

" …normally people do not die from a magic mushroom overdose, because they are not very toxic and the potential victim will spontaneously vomit keeping the final dose low."

9. ACCIDENTAL INGESTION

A six-year-old child in 1962, developed hyperthermia and status epilepticus following accidental ingestion of *Psilocybe baeocystis*.[69]

Note: All of the cases in this section refer to the recreational use of mushrooms or truffles containing psilocybin. We are proposing a limited rescheduling to Schedule 8 on the basis that the medicine will only be able to be authorised by psychiatrists supported by a review of the patient's diagnosis and treatment plan by two independent psychiatrists and will only be given to the patient for use in medically controlled environments under strict supervision. Two specifically trained therapists will always be with the patient during the medicine sessions. The medicine will never be available to the patient to take home.

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

1. RISKS OF PSILOCYBIN COMPARED TO COMMON SCHEDULE 4 MEDICINES

There is self-reported evidence that 0.15% of the psilocybin-containing mushroom users in an uncontrolled setting attempted to commit suicide. There is one death of intentional reported suicide in the literature. In 1999, 2007, and 2016, the ABS reported that in Australia there were 2,227, 2,392, and 2,862 suicide cases in total respectively.[83] The ABS points out that benzodiazepines and antidepressants are more common in intentional self-harm drug deaths. A total of 12 deaths are reported in the literature to be associated with (but not always necessarily due to) psilocybin-containing mushrooms internationally between 1961-2011.[69]

This can be compared with current Schedule 4 drugs. In 1999, 2007, and 2016, the ABS reported that in Australia there were 503, 354, and 663 cases of the Schedule 4 drug benzodiazepine causing direct deaths respectively. In 1999, 2007, and 2016, the ABS reported 441, 127, and 361 cases of prescription antidepressant-induced deaths. The difference is even more striking when it is recognized that the psilocybin associated figure comes from a global search whereas the figures relating to benzodiazepines and anti-depressants relate only to Australia.

2. META-ANALYSIS OF ANTIDEPRESSANT MEDICATIONS

There is academic debate on the extent of efficacy of conventional antidepressant classes of SSRIs and SNRIs and the increased risk of suicide that these medications may cause.[84] Below are the findings from three meta-analyses, one population study and one review on the evidence against SSRIs having antidepressant efficacy. Although the analysis is of SSRIs, it is noted that there does not appear to be significant difference in effectiveness between SSRIs and SNRIs.[85]

In 2008, a meta-analysis of 47 studies concluded that, SSRIs provide no clinically significant benefit in the treatment of depression (Kirsch et al., 2008).[86] No effect on mild or moderate depression and relatively small efficacy for severe depression. A small percentage of severely depressed people get noticeable benefit from SSRIs. The researchers attributed SSRI efficacy for severely depressed people, to a decrease in placebo effect rather than an increase in the efficacy of SSRIs. In 2010, another meta-

analysis confirmed the results of SSRIs having no effect on mild or moderate depression and relatively small to noticeable effect on severe depression (Fournier et al., 2010).[87]

In 2009, the UK National Institute of Health and Care Excellence (NICE), conducted a comprehensive review on antidepressants.[88] They concluded that antidepressants have no advantage over placebo in treating mild depression.

There is available evidence supporting antidepressant treatment for persistent depressive disorder and other forms of mild chronic depression. In 2009, the population study, the STAR*D trial, found that all anti-depressants led to remission from depression in only 3% of the over 4,000 participants surveyed.[24] In 2018, the largest meta-analysis of 21 antidepressants was conducted reviewing 522 individual trials with 116, 477 patients. It was found that while antidepressants were more effective than placebo in adults with MDD, the effect sizes was modest (g = 0.30).[30]

We provide this analysis because the conventional medical treatments for depression, antidepressants, show low effect size. There is therefore a strong need to increase the treatment paradigm available to patients in Australia through medical specialists for patients suffering from depression.

3. 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 psilocybin. 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 psilocybin-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 psilocybin, psilocybin's very low toxicity, and psilocybin's 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 2.1 Section (A).**

2. PURPOSES AND EXTENT OF USE

Psilocybin-assisted psychotherapy for depression and anxiety disorders (and potentially other indications) in a controlled medical setting**. See Part 2.1 Section B**

3. TOXICITY

Psilocybin has extremely low toxicity and a therapeutic index of 1000. Psilocybin has no history of severe adverse effects in a clinical setting. **See Part 1 Section 2.1(4) and Part 2.1 Section (A) 1.5.**

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 2.1 Section E).** Even in the recreational area there is no record of synthetic psilocybin being abused in Australia or internationally. Australia has no official record of psilocybin abuse or psilocybin-containing mushroom abuse. There are very few recorded cases internationally of overdose, misuse, and abuse.

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 Schedule 4 drugs for anxiety and depression (antidepressants and benzodiazepines) have more hazards, greater suicide risk, abuse potential, and toxicity than psilocybin. Psilocybin-assisted therapy 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 antidepressants. 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 psilocybin (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 reducing suicide rates.

We acknowledge and accept the premise that the use of psilocybin 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 psilocybin in the manner set down in this application as a Schedule 8 substance with all other uses remaining in Schedule 9.

BIBLIOGRAPHY

[1] van Amsterdam J, Nutt D, Phillips L, van den Brink W. European rating of drug harms. J Psychopharmacol. 2015;29(6):655-60.

[2] Nutt DJ, King LA, Phillips LD, Independent Scientific Committee on D. Drug harms in the UK: a multicriteria decision analysis. Lancet. 2010;376(9752):1558-65.

[3] Gable RS. Comparison of acute lethal toxicity of commonly abused psychoactive substances. Addiction. 2004;99(6):686-96.

[4] Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. Addict Biol. 2002;7(4):357-64.

[5] Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metab Rev. 2017;49(1):84-91.

[6] Brown RT, Nicholas CR, Cozzi NV, Gassman MC, Cooper KM, Muller D, et al. Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults. Clin Pharmacokinet. 2017;56(12):1543-54.

[7] Nichols DE. Psychedelics. Pharmacol Rev. 2016;68(2):264-355.

[8] Moya EA, Powell FL. Serotonin and Adenosine G-protein Coupled Receptor Signaling for Ventilatory Acclimatization to Sustained Hypoxia. Front Physiol. 2018;9:860.

[9] Maple AM, Zhao X, Elizalde DI, McBride AK, Gallitano AL. Htr2a Expression Responds Rapidly to Environmental Stimuli in an Egr3-Dependent Manner. ACS Chem Neurosci. 2015;6(7):1137-42.

[10] Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, et al. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep. 2017;7(1):13187.

[11] Ray TS. Psychedelics and the human receptorome. PLoS One. 2010;5(2):e9019.

[12] Yu B, Becnel J, Zerfaoui M, Rohatgi R, Boulares AH, Nichols CD. Serotonin 5-hydroxytryptamine(2A) receptor activation suppresses tumor necrosis factor-alpha-induced inflammation with extraordinary potency. J Pharmacol Exp Ther. 2008;327(2):316-23.

[13] Nichols DE, Johnson MW, Nichols CD. Psychedelics as Medicines: An Emerging New Paradigm. Clin Pharmacol Ther. 2017;101(2):209-19.

[14] Carhart-Harris RL, Goodwin GM. The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. Neuropsychopharmacology. 2017;42(11):2105-13.

[15] Roseman L, Haijen EC, Idialu-Ikato K, Kaelen M, Watts RR, Carhart-Harris RL. Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory. J Psychopharmacol. 2019;33(1):1-11.

[16] Kraehenmann R. Dreams and Psychedelics: Neurophenomenological Comparison and Therapeutic Implications. Curr Neuropharmacol. 2017;15(7):1032-42.

[17] Aday JS, Bloesch EK, Davoli CC. 2019: A year of expansion in psychedelic research, industry, and deregulation. Drug Sci, Policy Law. 2020;6:1-6.

[18] COMPASS Pathways. COMPASS Pathways receives FDA Breakthrough Therapy designation for psilocybin therapy for treatment-resistant depression: COMPASS Pathways; 2018

[Available from: https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapydesignation-for-psilocybin-therapy-for-treatment-resistant-depression/.

[19] Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol. 2016;30(12):1181-97.

[20] Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of Psilocybin versus Escitalopram for Depression. NEJM. 2021;384:1402-11.

[21] COMPASS Pathways. COMPASS Pathways announces positive topline results from groundbreaking phase IIb trial of investigational COMP360 psilocybin therapy for treatment-resistant depression: COMPASS Pathways; 2021 [Available from: https://ir.compasspathways.com/node/7516/pdf.

[22] Productivity Commission. Mental Health Inquiry Report: Australian Government Productivity Commiission; 2020 [Available from: https://www.pc.gov.au/inquiries/completed/mental-health/report.

[23] Australian Bureau of Statistics. National Health Survey First Results; cat no 4364.0.55.001. Australian Government; 2018.

[24] Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, et al. STAR*D: revising conventional wisdom. CNS Drugs. 2009;23(8):627-47.

[25] Organisation for Economic Cooperation and Development (OECD). *Antidepressant drugs consumption, 2000 and 2015 (or nearest year)*. Health at a Glance 2017: OECD; 2017 [Available from: https://doi.org/10.1787/health_glance-2017-en.

[26] Kisely S, Connor M, Somogyi A. An evaluation of the therapeutic value, benefits and risks of methylenedioxymethamphetamine (MDMA) and psilocybin for the treatment of mental, behavioural or developmental disorders Therapeutic Goods Administration, Australian Government Department of Health: Feb 2022; 2021 [Available from: https://www.tga.gov.au/sites/default/files/mmda-and-psilocybin-independent-expert-panel-review-final-report.pdf.

[27] Businesswire. FDA grants Breakthrough Therapy Designation to Usona Institute's psilocybin program for major depressive disorder: Businesswire; 2019 [Available from: https://www.businesswire.com/news/home/20191122005452/en/FDA-grantsBreakthrough-Therapy-Designation-Usona-Institutes

[28] Passie T, Halpern JH, Stichtenoth DO, Emrich HM, Hintzen A. The pharmacology of lysergic acid diethylamide: a review. CNS Neurosci Ther. 2008;14(4):295-314.

[29] Goldberg SB, Pace BT, Nicholas CR, Raison CL, Hutson PR. The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. Psychiatry Res. 2020;284:112749.

[30] Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):P1357-66.

[31] Locher C, Koechlin H, Zion SR, Werner C, Pine DS, Kirsch I, et al. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2017;74(10):1011-20.

[32] Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol. 2016;30(12):1165-80.

[33] Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry. 2016;3(7):619-27.

[34] Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry. 2011;68(1):71-8.

[35] Johnson mW, Griffiths RR. Potential Therapeutic Effects of Psilocybin. Neurother. 2017;14:734-40.

[36] Schenberg EE. Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. Front Pharmacol. 2018;9:733.

[37] Williams W. Campaigners believe using psychedelic medicines – including magic mushrooms and MDMA – to treat mental illnesses could be life changing: Probono; 2020 [Available from: https://probonoaustralia.com.au/news/2020/08/were-experiencing-a-growing-mental-health-crisis-we-need-more-innovative-solutions/.

[38] National Drugs and Poisons Scheduling Committee. Record of Reasons of Meeting 57 – October 2009: Therapeutic Goods Admiinistration, Australian Government Department of Health; 2009 [Available from: https://www.tga.gov.au/sites/default/files/ndpsc-record-57.pdf.

[39] Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. J Psychopharmacol. 2008;22(6):603-20.

[40] Rucker B, Browning DM. Practicing End-of-Life Conversations: Physician Communication Training Program in Palliative Care. J Soc Work End Life Palliat Care. 2015;11(2):132-46.

[41] Agin-Liebes GI, Malone T, Yalch MM, Mennenga SE, Ponte KL, Guss J, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. J Psychopharmacol. 2020;34(2):155-66.

[42] Prieto-Pinto L, Garzón-Orjuela N, Lasalvia P, Castañeda-Cardona C, Rosselli D. International Experience in Therapeutic Value and Value-Based Pricing: A Rapid Review of the Literature. ViHRI. 2020;23:37-48.

[43] Chiruta V, Zemla PK, Miller P, Santarossa N, Hannan JA. Critique of the Royal Australian and New Zealand College of Psychiatrists Psychedelic Therapy Clinical Memorandum, Dated May 2020. JMHS. 2021;2(2):145-60.

[44] Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218(4):649-65.

[45] Heal DJ, Gosden J, Smith SL. Evaluating the abuse potential of psychedelic drugs as part of the safety pharmacology assessment for medical use in humans. Neuropharmacology. 2018;142:89-115.

[46] Burdick BV, Adinoff B. A proposal to evaluate mechanistic efficacy of hallucinogens in addiction treatment. Am J Drug Alcohol Abuse. 2013;39(5):291-7.

[47] Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse. 2017;43(1):55-60.

[48] Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol. 2014;28(11):983-92.

[49] Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J Psychopharmacol. 2008;22(6):621-32.

[50] Studerus E, Kometer M, Hasler F, Vollenweider FX. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J Psychopharmacol. 2011;25(11):1434-52.

[51] Doblin R. Dr. Leary's Concord Prison Experiment: a 34-year follow-up study. J Psychoactive Drugs. 1998;30(4):419-26.

[52] Murrie B, Lappin J, Large M, Sara G. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. Schizophr Bull. 2020;46(3):505-16.

[53] Martinotti G, Santacroce R, Pettorruso M, Montemitro C, Spano MC, Lorusso M, et al. Hallucinogen Persisting Perception Disorder: Etiology, Clinical Features, and Therapeutic Perspectives. Brain Sci. 2018;8(3).

[54] Hermle L, Kovar KA, Hewer W, Ruchsow M. [Hallucinogen-induced psychological disorders]. Fortschr Neurol Psychiatr. 2008;76(6):334-42.

[55] Strassman RJ. Adverse reactions to psychedelic drugs. A review of the literature. J Nerv Ment Dis. 1984;172(10):577-95.

[56] Dos Santos RG, Bouso JC, Alcazar-Corcoles MA, Hallak JEC. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews. Expert Rev Clin Pharmacol. 2018;11(9):889-902.

[57] Hendricks PS, Thorne CB, Clark CB, Coombs DW, Johnson MW. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. J Psychopharmacol. 2015;29(3):280-8.

[58] Carbonaro TM, Bradstreet MP, Barrett FS, MacLean KA, Jesse R, Johnson MW, et al. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. J Psychopharmacol. 2016;30(12):1268-78.

[59] Usona Institute. Psilocybin Investigator's Brochure: Usona Institute; 2021 [Available from: https://www.usonainstitute.org/wp-content/uploads/2018/12/psilocybin-ib-v4.pdf.

[60] Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl). 2018;235(2):399-408.

[61] Nutt D. Psychedelic drugs-a new era inpsychiatry? Dialogues Clin Neurosci. 2019;21(2):139-47.

[62] Peden NR, Pringle SD, Crooks J. The problem of psilocybin mushroom abuse. Hum Toxicol. 1982;1(4):417-24.

[63] Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998;9(17):3897-902.

[64] Bonomo Y, Norman A, Biondo S, Bruno R, Daglish M, Dawe S, et al. The Australian drug harms ranking study. J Psychopharmacol. 2019;33(7):759-68.

[65] Johansen PO, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol. 2015;29(3):270-9.

[66] Gonmori K, Yoshioka N. A fatal case of mushroom poisoning by hallucinogenic species. Jpn J Legal Med. 2002;56(1):P-15.

[67] Gonmori K, Yoshioka N. Mushroom Toxins. Drugs and Poisons in Humans. Berlin, Heidelberg: Springer; 2005.

[68] McCawley EL, Brummett RE, Dana GW. Convulsions from psilocybe mushroom poisoning. Proc West Pharmacol Soc. 1962;5:27-33.

[69] van Amsterdam J, Opperhuizen A, van den Brink W. Harm potential of magic mushroom use: a review. Regul Toxicol Pharmacol. 2011;59(3):423-9.

[70] *United Nations Convention on Psychotropic Substances 1971*.

[71] Usona Institute. Expanded Access Policy: Usona Institute; 2020 [Available from: https://www.usonainstitute.org/expandedaccess/?doing_wp_cron=1590465036.2982139587402343750000.

[72] COMPASS Pathways. Compassionate use policy/expanded access policy: COMPASS Pathways; 2021 [Available from: https://compasspathways.com/our-research/psilocybin-therapy/clinical-trials/compassionate-use-policy/#:~:text=More%20about%20compassionate%20use%2Fexpanded%20access&text=Compassionate%20use%20is%20a%20treatment,to%20it%20as%20compassionate%20use.

[73] PSW Editor. Health Canada's New SAP Rules: A Q&A With Numinus' Payton Nyquvest: Psychedelic Stock Watch; 2022 [Available from: https://www.psychedelicstockwatch.com/psychedelic-stock-news/health-canada-s-new-sap-rules-a-q-a-with-numinus-payton-nyquvest.

[74] Health Canada. Health Canada's special access programs: Overview: Government of Canada; 2022 [Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access.html.

[75] Australian Medical Association (AMA). AMA Submission to the Therapeutic Goods Administration – Proposed amendments to the Poisons Standard – November 2020: AMA; 2020 [Available from: https://www.ama.com.au/sites/default/files/documents/AMA_submission_to_the_TGA_proposed_amendments_to_the_Poisons_Standard_November_2020_proposals_FINAL.pdf.

[76] COMPASS Pathways. Phase IIb results in TRD: COMPASS Pathways; 2021 [Available from: https://compasspathways.com/our-research/psilocybin-therapy/clinical-trials/psilocybin-therapy-study-results/.

[77] St Vincent's Hospital Melbourne. Australia's first psychedelic clinical trial commences recruitment: St Vincent's Hospital; 2020 [Available from: https://www.svhm.org.au/newsroom/announcements/australia-s-first-psychedelic-clinicaltrial-commences-recruitment.

[78] Lachenmeier DW, Rehm J. Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. Sci Rep. 2015;5(8126):1-7.

[79] Wong SK. Analysis of Drug Overdose in Teenagers. Hong Kong Journal of Emergency Medicine. 2002;9:144-9.

[80] Rucker JJ. Psychedelic drugs should be legally reclassified so that researchers can investigate their therapeutic potential. BMJ. 2015;350:h2902.

[81] Australian Bureau of Statistics (ABS). Search results: psilocybin OR psilocybe OR "magic mushrooms": ABS; 2022 [Available from: https://search.abs.gov.au/s/search.html?form=simple&collection=abs-search&query=psilocybin+OR+psilocybe+OR+%22magic+mushrooms%22.

[82] Peacock A, Karlsson A, Uporova J, Gibbs D, Swanton R, Kelly G, et al. Australian Drug Trends 2019: Key Findings from the National Ecstasy and Related Drugs Reporting System (EDRS) Interviews: National Drug and Alcohol Research Centre, UNSW Sydney; 2019 [Available from: https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/National%20EDRS%20Interview%20Report%202019_1.pdf.

[83] Australian Bureau of Statistics (ABS). Causes of Death, Australia: ABS; 2018 [Available from: https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/2018.

[84] Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ. 2005;330(7488):396.

[85] Gartlehner G, Hansen RA, Morgan LC, Thaler K, Lux L, Van Noord M, et al. Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. Ann Intern Med. 2011;155(11):772-85.

[86] Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.

[87] Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA. 2010;303(1):47-53.

[88] National Institute for Health and Care Exellence (NICE(Depression in adults: recognition and management: NICE; 2009 [Available from: https://www.nice.org.uk/guidance/CG90.

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/kh7ediq84uhq1x5/AACO5AkpViQho4TF8kzd8j5sa?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 9. Completed psilocybin clinical studies

#	Study type	Condition	End year	Location	Sponsor	*n*	Psilocybin dose	Cntrl	Masking	Trial ID
1.	Phase 2	TRD	2021	US, California	COMPASS Pathways	19	25 mg	Placebo	Open	NCT04739865
2.		TRD	2021	Canada; Czechia; Czech Republic; Denmark; Finland; Germany; Ireland; Netherlands; Norway; Portugal; Spain; UK; US	COMPASS Pathways	216	1 mg; 10 mg; 25 mg	Placebo	Quadrupl	NCT03775200; EUCTR2017-003288-36-PT; EUCTR2017-003288-36-DK; EUCTR2017-003288-36-CZ; EUCTR2017-003288-36-GB
3.		MDD	2021	UK	Imperial College London	59	25 mg; escitalopram	Placebo	Quadrupl	NCT03429075
4.		MDD	2020	US, Maryland	Johns Hopkins University	27	n.d.	None	Single	NCT03181529
5.		Cognitive flexibility, creativity and learning	2020	Netherlands	University Maastricht	60	17 ug/kg	Placebo	Quadrupl	NTR6505
6.		Depression and anxiety, cancer patients	2016	US, Maryland	Johns Hopkins University	56	n.d.	Placebo	Quadrupl	NCT00465595
7.		MDD	2015	UK	Imperial College London	12	25 mg	None	Open	ISRCTN14426797; EUCTR2013-003196-35-GB
8.		Addiction, tobacco	2014	US, Maryland	Johns Hopkins University	15	20 mg; 30 mg	None	Open	10.1177/0269881114548296
9.	Phase 2/ Phase 1	Mechanism	2018	US, Maryland	Johns Hopkins University	13	25 mg	None	Open	NCT02971605
10.	Phase 1	Mechanism, religious leaders	2020	US, New York	NYU Langone Health	12	20 mg/70 kg	None	Open	NCT02421263
11.		Mechanism	2020	Switzerland	University Hospital, Basel	25	10 mg; 20 mg; 25 mg; escitalopram	Placebo	Quadrupl	NCT03912919174
12.		Demoralisation, AIDS survivors	2019	US, California	Joshua Woolley	30	n.d.	None	Open	NCT02950467
13.		Mechanism	2019	US, Maryland	Johns Hopkins University	40	n.d.	Placebo	Double	NCT02145091
14.		Mechanism	2015	US, Wisconsin	University of Wisconsin, Madison	12	0.3, 0.45 mg/kg	Placebo	Open	NCT02163707
15.		Mechanism	2014	US, Maryland	Johns Hopkins University	10	n.d.	None	Open	NCT01988311
16.		Mechanism	2014	US, Maryland	Johns Hopkins University	75	n.d.	Placebo	Quadrupl	NCT00802282
17.		Anxiety, cancer patients	2008	US, California	Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	12	0.2 mg/kg	Placebo	Quadrupl	NCT00302744
18.		Mechanism	2006	US, Maryland	Johns Hopkins University	36	30 mg; 40 mg	Methylphenidate	Double	10.1007/s00213-006-0457-5
19.	Phase 0	Mechanism, microdose	2021	Argentina	National Council of Scientific and Technical Research	34	0.5 g dried Psilocybine mushrooms	Placebo	Double	NCT05160220

20.	Phase 0	Mechanism	2021	Switzerland	University of Zurich	25	n.d.	Placebo	Quadrupl	NCT03853577
21.		Mechanism	2021	Switzerland	University Hospital, Basel	28	15 mg; 30 mg; LSD	None	Open	NCT03604744
22.		Anxiety, cancer patients	2018	US, New York	NYU Langone Health	29	0.3 mg/kg	Placebo	Quadrupl	NCT00957359
23.		Mechanism	2018	Switzerland	University of Zurich	140	0.2, 0.215, 0.25, 0.315 mg/kg	Placebo	Double	NCT03736980
24.		Microdose, creativity	2018	Netherlands	Dutch Psychedelic Society	38	0.22, 0.33, 0.44 g dried Psilocybine truffles	None	Open	10.1007/s00213-018-5049-7
25.	Follow up	Anxiety, cancer patients	2020	US, New York	NYU Langone Health	15	0.3 mg/kg	Placebo	Quadrupl	10.1177/0269881119897615
26.		Addiction, tobacco	2016	US, Maryland	Johns Hopkins University	15	20 mg; 30 mg	None	Open	10.3109/00952990.2016.1170135
27.		Mechanism	2008	US, Maryland	Johns Hopkins University	36	30 mg; 40 mg	Methylphenidate	Double	10.1177/0269881108094300

Table 10. Active psilocybin clinical studies

#	Study type	Condition	Start year	Location	Sponsor	*n*	Psilocybin dose	Cntrl	Masking	Trial ID
1.	Phase 2	TRD	2020	US, California	COMPASS Pathways	19	25 mg	None	Open	NCT04739865
2.		TRD	2020	UK	King's College London	60	25 mg	None	Open	EUCTR2018-003573-97-GB
3.		MDD	2020	US, Maryland	Maryland Oncology Hematology, PA	30	25 mg	None	Open	NCT04593563
4.		MDD	2020	Sweden	SLSO	30	25 mg	None	Open	EUCTR2020-002790-94-SE
5.		TR-MDD	2020	Germany	Central Institute of Mental Health	144	5 mg; 25 mg	Placebo	Quadrupl	EUCTR2019-003984-24-DE
6.		TRD	2020	Czech Republic	Národní ústav duševního zdraví	60	20 mg; ketamine	Placebo	Quadrupl	EUCTR2018-004480-31-CZ
7.		Anorexia Nervosa	2020	UK	Imperial College London	20	25 mg	None	Open	EUCTR2019-004054-28-GB
8.		Headache, cluster	2019	Denmark	NeuroPharm	20	0.14 mg/kg	None	Open	EUCTR2018-003382-34-DK
9.		MDD	2018	UK	Imperial College London	50	25 mg; escitalopram	Placebo	Quadrupl	EUCTR2017-000219-18-GB
10.		OCD	2019	US, Arizona	University of Arizona	1 5	0.1 mg/kg; 0.3 mg/kg	Placebo	Quadrupl	NCT03300947
11.		Headache, migraine	2019	US, Connecticut	Yale University	24	0.1 mg/kg; 0.3 mg/kg	Placebo	Double	NCT03341689
12.		MDD	2018	US, Connecticut	Yale University	18	0.1 mg/kg; 0.3 mg/kg	Placebo	Double	NCT03554174
13.		Headache, cluster	2016	US, Connecticut	Yale University	24	1 mg; 10 mg	Placebo	Triple	NCT02981173
14.		Addiction, alcohol	2014	US, New York	NYU Langone Health	135	25, 30 mg/70 kg	Placebo	Quadrupl	NCT02061293
15.	Phase 1	Mechanism, religious professionals	2015	US, New York	NYU Langone Health	12	20 mg; 30 mg	None	Open	NCT02421263
16.		Mechanism, religious professionals	2015	US, Maryland	Johns Hopkins University	20	20, 30 mg/70 kg	None	Open	NCT02243813
17.	Phase 0	Mechanism	2021	US, Missouri	Washington University School of Medicine	25	25 mg	Methylphenindate	Open	NCT04501653

Table 11. Recruiting psilocybin clinical studies

#	Study type	Condition	Start year	Location	Sponsor	*n*	Psilocybin dose	Cntrl	Masking	Trial ID
1.	Phase 2	TRD	2021	Australia, VIC	Swinburne University of Technology	15	25 mg	None	Open	ACTRN12621001097831
2.		TRD	2021	Canada, Ontario	Brain and Cognition Discovery Foundation	30	n.d.	None	Open	NCT05029466
3.		Addiction, alcohol	2021	Denmark	Psychiatric Centre Copenhagen	100	25 mg	Placebo	Quadrupl	EUCTR2020-000829-55-DK
4.		Addiction, alcohol	2021	US, California	Keith Heinzerling	20	25 mg	Set, setting	Open	NCT04410913
5.		Parkinson's Disease, depression and anxiety	2021	US, California	Joshua Woolley, MD/PhD	10	10 mg; 25 mg	None	Open	NCT04932434
6.		Bipolar 2 Disorder	2021	US, Maryland	Sheppard Pratt Health System	12	25 mg	None	Open	NCT04433845
7.		Anorexia Nervosa	2021	US, California	University of California, San Diego	20	25 mg	None	Open	NCT04661514
8.		TR-MDD	2021	Germany	Central Institute of Mental Health, Mannheim	144	25 mg	Placebo	Triple	NCT04670081
9.		MDD	2021	Sweden	Section for Affective Disorders; Northern Stockholm Psychiatry	30	25 mg	Placebo	Quadruple	NCT04630964
10.		Depression	2021	US, Wisconsin	University of Wisconsin, Madison	12	25 mg + Midazolam	None	Open	NCT04842045
11.		Body Dysmorphic Disorder	2021	US, New York	New York State Psychiatric Institute	12	25 mg	None	Open	NCT04656301
12.		TRD	2021	US, California US, Maryland	Sheppard Pratt Health System	15	25 mg	None	Open	NCT04433858
13.		TRD	2021	Germany	Zentralinstitut für Seelische Gesundheit	144	25 mg	Placebo	Quadrupl	DRKS00024484
14.		Addiction, alcohol	2020	Switzerland	University of Zurich	60	25 mg	Placebo	Triple	NCT04141501
15.		Life-threatening illness, depression and anxiety	2020	Australia, VIC	St. Vincent's Hospital Melbourne	40	25 mg	Placebo	Quadrupl	ACTRN12619001225101
16.		TRD	2020	UK	King's College London	60	25 mg	Placebo	Quadrupl	NCT04959253
17.		MDD	2019	Switzerland	University of Zurich	60	0.215 mg/kg	Placebo	Triple	NCT03715127
18.		MDD	2019	US, Multi-State	Usona Istitute	100	25 mg	Placebo	Triple	NCT03866174
19.		Addiction, cocaine	2014	US, Alabama	University of Alabama at Birmingham	40	0.36 mg/kg	Placebo	Quadrupl	NCT02037126
20.		Addiction, tobacco	2016	US, Maryland	Johns Hopkins University	115	30 mg/70 kg	None	Open	NCT01943994
21.	Phase 2/ Phase 1	Anorexia Nervosa	2021	UK	Imperial College London	20	25 mg	None	Open	NCT04505189
22.		Headache, chronic cluster	2020	Denmark	Gitte Moos Knudsen	20	0.14 mg/kg	None	Open	NCT04280055
23.	Phase 1b	Chronic Short-Lasting Unilateral Neuralgiform Headache Attacks	2021	UK	Beckley Psytech Limited	12	n.d.	None	Open	NCT04905121
24.	Phase 1	Headache, migraine	2021	US, Connecticut	Yale University	24	10 mg ;25 mg	Placebo	Quadrupl	NCT04218539
25.		Mechanism	2021	US, Minnesota	University of Minnesota	75	25 mg	Placebo	None	NCT04424225
26.		Addiction, opioid	2021	US, Wisconsin	University of Wisconsin, Madison	10	n.d.	None	Open	NCT04161066
27.		Mechanism	2020	Switzerland	University Hospital, Basel	30	20 mg; LSD; Mescaline	Placebo	Quadrupl	NCT04227756
28.		Headache, concussion	2019	US, Connecticut	Yale University	24	10 mg ;25 mg	Placebo	Quadrupl	NCT03806985
29.		Anorexia Nervosa	2019	US, Maryland	Johns Hopkins University	18	20 mg	None	Open	NCT04052568
30.		OCD	2018	US, Connecticut	Yale University	30	0.25 mg/kg	Placebo	Quadrupl	NCT03356483

31.	Phase 0	Depression, Alzheimer's Disease	2021	US, Maryland	Johns Hopkins University	20	15 mg; 25 mg	None	Open	NCT04123314
32.		Cancer patients, safety	2021	US, Utah	University of Utah	12	n.d.	None	Open	NCT04522804
33.	Follow up	TRD	2020	US; UK; Ireland; Czechia; Spain; Czech Republic; Netherlands; Portugal	COMPASS Pathways	150	1 mg; 5 mg ;25 mg	Placebo	Quadrupl	NCT04519957; EUCTR2020-001348-25-PT
34.		MDD	2020	US, Florida	Usona Institute	100	25 mg	Placebo	Quadrupl	NCT04353921

Table 12. Registered, but not yet recruiting psilocybin clinical studies

#	Study type	Condition	Start year	Location	Sponsor	*n*	Psilocybin dose	Ctrl	Masking	Trial ID
1.	Phase 2a	Fibromylagia	2022	US, Michigan	TRYP Therapeutics	20	n.d.	None	Open	NCT05128162
2.		Binge Eating Disorder	2022	US, Florida	TRYP Therapeutics	10	n.d.	None	Open	NCT05035927
3.	Phase 2	GAD	2022	Australia, VIC	Monash University	72	25 mg; 30 mg	Diphenhydramine	Quadrupl	ACTRN12621001358831
4.		Hospice Care Demoralisation	2022	US, Massachusetts	Yvan Beaussant	15	25 mg	None	Single	NCT04950608
5.		TRD	2022	Canada; Czechia; Czech Republic; Denmark; Finland; Germany; Ireland; Netherlands; Norway; Portugal; Spain; UK; US	COMPASS Pathways	398	1 mg; 10 mg; 25 mg	Placebo	Quadrupl	EUCTR2017-003288-36-DE; EUCTR2017-003288-36-ES
6.		TRD	2021	US; Ireland	COMPASS Pathways	20	25 mg	None	Open	EUCTR2018-002577-22-IE
7.		Addiction, alcohol	2021	Denmark	Anders Fink-Jensen, MD, DMSci	10	25 mg	None	Open	NCT04718792
8.		Bipolar 2 Disorder	2021	US, California	University of California, San Francisco	14	10 mg; 25 mg	None	Open	NCT05065294
9.		Anxiety and depression	2021	Jamaica	Wake Network, Inc	120	1 mg	Placebo	Double	NCT04989972
10.	Phase 2/ Phase 1	Addiction, Methamphetamine	2022	US, Oregon	Portland VA Research Foundation, Inc	30	25 mg; 30 mg	Placebo	Single	NCT04982796
11.		Palliative care, existential distress	2022	Canada	Ottawa Hospital Research Institute	40	1 mg; 2 mg; 3 mg	None	Open	NCT04754061
12.		OCD	2021	Israel	Beersheva Mental Health Center	15	n.d.	None	Open	NCT04882839
13.	Phase 1	Mechanism	2022	Australia, VIC	Monash University	60	19 mg	None	Open	ACTRN12621001375842
14.		Functional Neurological Disorder	2022	Australia, VIC	Austin Health	15	5 mg; 10 mg; 15 mg	None	Open	ACTRN12621000578808
15.		Functional Neurological Disorder	2022	Australia, VIC	Austin Health	22	5 mg; 10 mg; 15 mg	None	Open	ACTRN12621000560897
16.		Trauma	2022		NWTraumatherapies	30	1 mg; 1.5 mg	SSRIs	Quadrupl	NCT05042466
17.		Mechanism	2021	Netherlands	Maastricht University	18	15 mg; 2C-B	Placebo	Double	NL8813
18.	Phase 0	Chronic Pain	2022	US, Alabama	University of Alabama at Birmingham	30	0.36 mg/kg	DXM	Quadrupl	NCT05068791

Appendix C – Expert Letters

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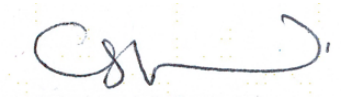
It is for this reason that, in late 2021 with significant financial support of Monash University, we founded the Neuromedicines Discovery Centre (https://www.neuromedicines.monash/) to engage in comprehensive research into the discovery, development, clinical evaluation and rollout of novel medicines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

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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MIND MEDICINE
AUSTRALIA

Expert Letter B

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

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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.

T 02 4956 0149 F 02 4956 0193 E healthemind@healthecare.com.au
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

MIND MEDICINE AUSTRALIA

Expert Letter C

Letter from Drug Science in the UK confirming that psilocybin 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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Level 1/10 Dorcas St
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Drug Science

The Secretary

Medicines Scheduling Unit

Therapeutic Goods Administration

Canberra, ACT.

London, 23/02/2022

Dear Sir/Madam,

The Chair of Mind Medicine Australia, Mr Peter Hunt AM, has asked Drug Science to directly address the question of whether medical grade psilocybin 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 psilocybin 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 in its application is very restrictive;

SCHEDULE 9 – Proposed Amended Entry

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

SCHEDULE 8 – Proposed New Entry

PSILOCYBINE 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*.

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

- Between the late 1950s and prohibition, psilocybin was administered to 1,960 participants and was well tolerated in 19 trials without complications and with useful efficacy;

- Since prohibition, psilocybin has been administered to 1,131 participants in 32 trials and has been shown to be well tolerated without complications and with useful efficacy;

- There have been 14 long-term follow up studies of 232 participants which have shown sustained efficacy in a significant portion of participants with no psychosis, HPPD, or other health complications;

- People taking psilocybin as part of therapy in countries such as the Netherlands, Jamaica, some US States and cities, the Bahamas and a number of South America countries (where the laws permit usage) and under compassionate access schemes in Canada, the United States, Switzerland and Israel; and

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

Although there have been over 51 psilocybin trials in total, we will focus on the two most recent in this letter as these were placebo controlled and randomised.

Compass Pathways released its Phase 2b results in November 2021. This was a multi-site parallel, randomised, double-blinded, placebo controlled trial with 216 participants taking either a 25 or 10 mg active dose of psilocybin as part of psychotherapy vs a 1 mg active placebo in patients with treatment-resistant depression. We believe that the sample size was demonstrably statistically relevant with and effect size of over 0.5 and the trial was of high quality. The results were robust and confirmed the results achieved in earlier trials;

Key Findings of the Compass Pathways Phase 2b Trial

Psilocybin 25mg vs 1mg: a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6

Psilocybin 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)

At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3

36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group

29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group

24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group

The adverse events were manageable and consisted of:

Psilocybin was generally well tolerated, with more than 90% of treatment-emergent adverse events (TEAEs) mild or moderate in severity

Treatment-emergent adverse event (TEAE) incidence:

83.5% (66 patients) in 25mg group

74.7% (56 patients) in 10 mg group

72.2% (57 patients) in 1 mg group

Drug Science

Treatment-emergency serious adverse event (TESAE) incidence:

6.3% (5 patients) in 25mg group

8.0% (6 patients) in 10 mg group

1.3% (1 patient) in 1mg group

A second trial that published its results in the New England Journal of Medicine in May 2021 compared the use of psilocybin assisted psychotherapy with a leading SSRI (escitalopram). This trial was led by one of the authors of this letter Professor David Nutt, and Dr Robin Carhart-Harris from Imperial College London. The results also demonstrated that psilocybin when used as part of psychotherapy had a powerful therapeutic value that for almost all measures exceeded that of escitalopram (see table below).

Table 2. Primary and Secondary Outcomes.*

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

Adverse events were also low and easily manageable.

Table 3. Adverse Events Reported during the 6-Week Trial Period and on Dosing-Day 1.*

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

A further important trial was published in 2021 by the Johns Hopkins group[1] showing psilocybin to have clear antidepressant effects. They have just reported the one year follow up which revealed the effect of a single 25mg dose of psilocybin persisted this long in the majority of patients with over half still in remission and three quarters showing good response[2].

A 2017 Imperial College trial of psilocybin used fMRI scans to show the effects of medical doses of psilocybin on the brain in the treatment of depression. As a result, we know the nature of the brain changes in during the acute psychedelic state and in the days following psilocybin-therapy. A persistent enhancement of brain activity was found in the days

[1] Davis AK, Barrett FS, May DG, et al. (2021) Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry* 78(5): 481–489. DOI: 10.1001/jamapsychiatry.2020.3285.

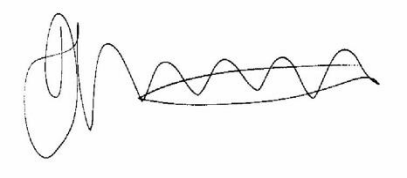
[2] Gukasyan N, Davis AK, Barrett FS, et al. (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of Psychopharmacology* 36(2). SAGE Publications Ltd STM: 151–158. DOI: 10.1177/02698811211073759.

following psilocybin-therapy, which explains the importance of using psychotherapy for integration.

In our view it is now clear that psilocybin when used as part of psychotherapy for patients suffering from treatment-resistant depression or Major Depressive 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.

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 psilocybin 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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Monash Institute of Pharmaceutical Sciences
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Australia
27th February 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 re-scheduling of psilocybin from Schedule 9 to Schedule 8 of the Poisons Standards**. **Simply put, the science does not support the current classification of psilocybin as a Schedule 9 poison.**

There is substantial and growing body of overseas clinical trial evidence that psilocybin possesses *significant therapeutic potential* in the treatment of depression, end-of-life distress, addiction and obsessive-compulsive disorder[3-7]. These datasets have now been augmented by recent *major phase 2 clinical studies* in both major depressive disorder[8] and treatment resistant depression[9], which have substantially expanded both the quality and quantity of clinical data, as well as increased the breadth of patients receiving such treatment.

Given that clinical trials are increasing in size, quality, and consistency (e.g., a dose of 25 mg psilocybin was determined as an effective therapeutic dose for both the phase 2 trials cited) and yet still show the treatment to be highly effective, **collectively we can only conclude that psilocybin-assisted psychotherapy has established itself as a regimen with significant therapeutic value**.

At the molecular level, psilocybin is converted by the liver to its active metabolite, psilocin, which then acts on the same class of receptor proteins (G protein-coupled receptors) as the majority of existing marketed medicines[10,11]. We are world-leaders in the study of the biology of G protein-coupled receptors[11-14], including the serotonin receptor sub-class for which psilocybin has highest selectivity[16-18].

Importantly, there is clear evidence that, when used in a clinical environment under direct monitoring by a trained clinician, psilocybin is safe[19] (significantly more so than Schedule 8 opioids and Schedule 4 medicines such as benzodiazepines[20]). Indeed, the therapeutic index (TI; the ratio of

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toxic dose to therapeutic dose) for psilocybin is 1000[21], which is significantly better than that for heroin (TI=6[21]) and even paracetamol (TI=10[22]).

The most commonly anticipated side effects in a clinical setting would be a transient elevation in blood pressure or some acute anxiety, which can be readily dealt with through appropriate patient pre-screening/exclusion and/or acute clinical supervision[19]. In contrast to many other restricted psychotropic substances, psilocybin is not known to induce dependence[23,24] and, indeed, has medicinal potential to actually treat addiction[7]. Psilocybin is also fast-acting, with reports of patients having experienced rapid and sustained rates of remission of symptoms after psilocybin-assisted psychotherapy sessions[3-7].

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. Based on current overseas data, psilocybin-assisted psychotherapies would also likely require only a single administration (by clinicians) of the medicine only up to 2-3 times over a period of a few months to complete a course of therapy[3-9].

Such a closely controlled dosing regimen would severely mitigate any risk, perceived or otherwise, of multi-drug drug toxicity. Furthermore, the protocol under which psilocybin would be administered (with clinical supervision) provides an environment closest to that used in the successful clinical trials; there is significantly lower risk for the misuse of psilocybin 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 psilocybin abuse or misuse by way of access outside of strictly controlled medical and scientific research settings is low, noting that a rescheduling would place psilocybin 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.

With respect to the perceived risks of psilocybin inducing psychosis, although an association between hallucinogen administration and psychosis has long been discussed[25], the actual determination of a causal link remains arguable and the risks of developing any psychosis during or subsequent to a short-term clinical regimen are actually extremely rare[26].

Importantly, two recent peer-reviewed large population studies[26,27] found *no* link between psychedelic use and mental health problems. The former study used a dataset of over 135,000 randomly selected United States adults, while the latter included over 190,000 United States respondents.

These striking results were of such significant international interest in the field that they were the subject of a Commentary in the leading science journal, *Nature*[28]. Although such population studies cannot exclude the potential for a negative effect on mental health for a specific *individual*, the same can be said for *any* psychoactive substance, and this would be addressed through appropriate

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patient pre-screening/selection (as would be the case for a prescription of any other medicine by a clinician).

Collectively, these facts strongly mitigate any likelihood of major risk or abuse liability of psilocybin in the clinical setting. It should also be noted that the USA FDA has granted psilocybin-assisted therapies for treatment-resistant depression “breakthrough therapy” status, paving the way for availability of this as a form of prescribed medicine (under psychiatric supervision) pending further clinical trial results.

The application for rescheduling psilocybin 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
- 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 psilocybin, 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 these data **strongly support the contention that medicinal psilocybin already has established therapeutic potential when used as part of psychotherapy,** with the potential to represent a possible 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 psilocybin 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 psilocybin as Schedule 9 prevents States or Territories providing a permit for use by psychiatrists, even when they have met the criteria above and access has approved 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,

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financial and bureaucratic restrictions specific to Schedule 9 substances[29]. This would not be the case if psilocybin were re-scheduled as a Schedule 8 substance.

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 psilocybin.

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

Yours sincerely,

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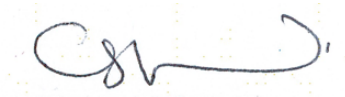

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References

1. https://www.pc.gov.au/inquiries/completed/mental-health/report

2. Whitaker, R. (2011) Anatomy Of An Epidemic. Crown Publishers, NY. ISBN: 9780307452429.

3. Grob et al. (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch. Gen. Psych.* 68: 71.

4. Carhart-Haris et al. (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility. *Lancet Psych.* 3: 619.

5. Ross et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J. Psychopharmacol.* 30*:* 1165*.*

6. Griffiths et al. (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J. Psychopharmacol.* 30*:* 1181.

7. Johnson and Griffiths (2017) Potential therapeutic effects of psilocybin. *Neurotherapeutics*. 14*:* 734.

8. Carhart-Harris et al. (2021) Trial of Psilocybin versus Escitalopram for Depression. *N. Engl. J. Med.* 384:1402-1411

9. Compass Ph2b clinical trial results: https://ir.compasspathways.com/static-files/0f9fbce8-2619-438b-a6ba-5bbe2ba08cf6

10. Passie et al. (2002) The pharmacology of psilocybin. *Addiction Biol.* 7: 357.

11. Nichols, D.E. (2016) Psychedelics. *Pharmacol. Rev.* 68: 264.

12. Christopoulos, A. (2002) Allosteric binding sites on cell-surface receptors: Novel targets for drug discovery. *Nature Rev. Drug Disc.* 1: 198.

13. Kenakin and Christopoulos (2013) Signaling bias in new drug discovery: Detection, quantification and therapeutic impact. *Nature Rev. Drug Disc.* 12: 205.

14. Changeux and Christopoulos (2016) Allosteric modulation as a unifying mechanism for receptor function and regulation. *Cell* 166: 1084.

15. Thal et al. (2018) Structural insights into G-protein-coupled receptor allostery. *Nature* 559: 45.

16. Devlin et al. (2004) Regulation of serotonin 5-HT_{2C} receptors by chronic ligand exposure, *Eur. J. Pharmacol*., 308: 59.

17. Werry et al. (2005) Characterization of serotonin 5-HT_{2C} receptor signaling to extracellular signal-regulated kinases 1 and 2*. J. Neurochem.* 93: 1603.

18. Werry et al. (2008) RNA editing of the serotonin $5HT_{2C}$ receptor and its effects on cell signalling, pharmacology and brain function. *Pharmacol. Ther.* 119: 7.

19. Aday et al. (2020) Long-term effects of psychedelic drugs: A systematic review. *Neurosci. Behav. Rev.* 113: 179.

20. Bonomo et al. (2019) The Australian drug harms ranking study. *J. Psychopharmacol.* 33*:* 759*.*

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21. Gable, R.S. (2004) Comparison of acute lethal toxicity of commonly abused psychoactive substances. *Addiction*. 99: 686.

22. Bertolini et al. (2006) Paracetamol: new vistas of an old drug. *CNS Drug Rev*. 12: 250.

23. Rucker, J.J.H. (2015) Psychedelic drugs should be legally reclassified so that researchers can investigate their therapeutic potential. *BMJ*. 350: h2902.

24. Johnson et al. (2018) The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharm*. 142: 143.

25. Strassman (1984) *J. Nerv. Ment. Dis.*, 172: 577

26. Johnson et al. (2008) *J. Psychopharmacol.,* 22: 603

27. Johansen and Krebs (2015) *J. Psychopharmacol.,* 29: 270

28. Cormier (2015) No link found between psychedelics and psychosis, doi:10.1038/nature.2015.16968

29. Nutt et al. (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Rev. Neurosci.* 14: 577.

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