MIND MEDICINE
AUSTRALIA

Submission to the Delegate of the Secretary of the Commonwealth Department of Health on the Interim Decision (announced on 3rd February 2021) not to amend the Poisons Standard in relation to;

N, a-Dimethyl-3,4-(methylenedioxy)phenylethylamine (MDMA)

3 March 2021

Mind Medicine Australia Limited
Level 1/ 10 Dorcas St
South Melbourne VIC 3006

MIND MEDICINE AUSTRALIA

The Delegate of the Secretary of the Department of Health
Medicines Rescheduling Unit
Therapeutic Goods Administration
Canberra, ACT.

3 March 2021

Dear Sir/Madam

> ***"I had severe PTSD for 34 years since the age of 19, following a childhood of physical, emotional and sexual abuse. Over that period, I had been treated by 18 therapists, including 3 psychiatrists, and had been hospitalised following a failed suicide attempt.***
>
> ***3 years ago I moved to Amsterdam where I was able to receive MDMA-assisted therapy for PTSD following the MAPS protocol. I had 3 such sessions and experienced a complete cessation of all PTSD symptoms.***
>
> ***The psychedelic experiences themselves were the most profound healing experiences of my life and relieved me of the burden of pain, terror and shame I had been carrying. I am now re-assessing my life from a "post-PTSD" perspective, something I never thought I would see. It has been like giving me a new life."***
>
> **(Steve Ball, Australian living and working in Amsterdam)**

We receive letters like this on a daily basis from people who have treatment resistant post-traumatic stress disorder (PTSD) and/or substance abuse associated with trauma and who are suffering terribly from their misfortune. It's a cry for help because **our current mental health system has failed them.** We have attached some other powerful extracts from the submissions that have been made to the TGA in the Appendix to this letter. Yet, even all of these and all of the submissions supporting our original applications cannot begin to express the unbearable pain and the **avoidable suffering and suicides**.

These people are desperate as they plead with the TGA to give them a chance to receive a "Breakthrough Therapy", using just 2-3 doses of medical grade synthesised MDMA as part of psychotherapy. A therapy that has been shown to be safe and non-addictive in clinical environments, and which offers them hope for healing and the potential of living a life free from the debilitating nature of treatment resistant PTSD. More and more people are hearing about the extraordinary remission rates being achieved in overseas trials and by people who receive these therapies in other ways.

It is time to give all Australians, who live with multiple failed attempts at recovery, the opportunity to access treatments that can improve and save lives. This should be personal for all of us.

The quote from Steve is the right place to start the discussion of whether the medicinal use of MDMA as part of therapy should be moved into Schedule 8 of the Poisons Standard. At the moment this therapy is not legally available in Australia despite the

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www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

fact that the TGA has been authorising its use by doctors on a patient-by -patient basis though its Special Access Scheme. This is because even with such an approval the treatment would be illegal under State and Territory law (with the possible exception of Victoria) whilst this medicinal use of MDMA in medically controlled environments remains in Schedule 9.

In recognising that our mental health system is failing so many people with treatment resistant conditions we are in no way criticising our wonderful mental health professionals who work so passionately to try and heal their patients. Unfortunately, they just don't have the range of treatment options available to get these patients well. Tragically, some of these patients will give up hope and take their own lives.

As a nation that aspires to be innovative, part of the problem has been the lack of effective and scaleable treatment innovation in this country for over 50 years.

There are two ways for the Delegate to look at our Application for Rescheduling:

1. **From the perspective of politics and the history from 50 years ago,** when these substances were unfairly vilified without reference to scientific facts or data, and a clear distinction was not drawn between the medicinal use of medical grade GMP standard MDMA in a medically controlled environment and its recreational use (often mixed with other substances) in an uncontrolled environment; or

2. **From the perspective of the patient suffering from treatment resistant PTSD** who desperately wants to have the chance to get well. The patient understands that these treatments are safe when conducted by trained professionals in medically controlled environments and provide a very real opportunity (but not a guarantee) for that person to get well.

We hope and trust that the Delegate will put aside the politics of 50 years ago and **focus on the data and science that will save lives.**

As you will see from our Submission (and our earlier Rescheduling Application) there is now plenty of evidence to show that **the use of medical grade GMP standard MDMA as part of psychotherapy**:

A. has an **established therapeutic value** as evidenced by the high remission rates being achieved in overseas trials, in comparisons with other substances listed in Schedule 8 of the Poisons Standard and its use as part of expanded access schemes in a number of overseas countries as well as TGA Approvals in Australia under Special Access Scheme-B; and
B. **is safe when used in a medically controlled environment by trained professionals**.

See in particular the supporting views of Professor Arthur Christopoulos set out in his submission to the TGA (reproduced in Appendix M) on established

therapeutic value and safety. Professor Christopoulos is Professor of Analytical Pharmacology and Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University (which ranks second in the World in its field) and one of the most credentialed people in Australia in relation to these subjects.

We recognise that part of the problem that the Delegate has faced are the views of risk-averse peak bodies that have not properly analysed the safety and efficacy of these therapies within a medically controlled environment. We deal directly with this failure in our Submission.

We also deal with each of the statements made by the ACMS and the Delegate and highlight:

1. the terrible and worsening mental health statistics in Australia and the lack of effective treatments for many Australians, including our Veterans and First Responders;
2. the overwhelming support that our rescheduling application received from Health Experts and World-leading researchers in this field including from a large number of psychiatrists;
3. the recent results of a new clinical trial from Imperial College London where MDMA assisted therapy was used for alcohol abuse with outstanding results in terms of both safety and efficacy;
4. the lack of diversion risk and misuse;
5. the very real risks associated with delay and deferral;
6. the infrastructure that is being put in place at world's best practice standards in training, protocols, standard operating practices and training manuals;
7. the fact that down scheduling the medicinal use of MDMA to Schedule 8 is entirely consistent with Australia's obligations under UN Conventions and follows the lead of other reschedulings relevant to those conventions in Australia, New Zealand and other oversea countries;
8. the safety of these therapies for patients, both at the time of the therapy and over the medium to long term (including the absence of psychosis risk);
9. the human rights and ethical arguments associated with the position taken by the Delegate in the Interim Decision raised by human rights lawyer Scott Leckie and Executive Director of The Ethics Centre, Dr Simon Longstaff; and
10. the Canadian example where the Government is taking a pragmatic and compassionate approach to the use of psychedelic assisted therapies.

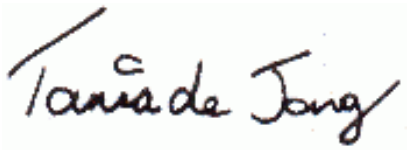
Rescheduling the medical use of MDMA as part of therapy in medically controlled environments will not open "the flood gates" to the use of these therapies in Australia. The prescribing doctor will have to convince both the TGA and the relevant State/Territory Government that the needs of the particular patient warrant this therapy.

Within those strictures we believe that **the choice to use this therapy should be between the treating doctor and the patient suffering from the treatment resistant condition.**

Australians are suffering and dying, and this treatment finally offers an opportunity for true healing. Our community needs your support.

We are available to meet with the ACMS and the Delegate at your convenience to discuss all aspects of our Submission. Mind Medicine Australia has access to an extraordinary Advisory Panel of leading psychiatrists, psychologists, pharmacologists, psychotherapists and researchers in this field (https://mindmedicineaustralia.org/advisory-board/) and we will make sure that the appropriate experts are available for that meeting.

Yours faithfully,



Peter Hunt AM
Co-Founder, Chairman
Mind Medicine Australia

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

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

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TGA Interim Decision Patient Submission Excerpts

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.
T. Mason-Smith

It is appalling to think that psychiatric patients such as my eighteen-year-old daughter face having to take years' worth of 'suck it and see' medication with associated side effects including gastrointestinal, mental, increased anxiety, affected libido, fatigue and others, when psilocybin treatments only involve 2-3 sessions with the medicine and that they are safe and non-addictive when used in this way as part of therapy.
J. Castran

I have 15 years' experience in the Community Services Sector. I also now suffer from treatment resistant Depression and PTSD. If I had access to these medicines, my quality of life and that of my family could be so much better and could possibility have full remission. I do not want to be a burden to the system, I want my life back, I want to be an active member of my community and don't want to end up taking things into my own hands.
J. Banks

It is disappointing for many sufferers, such as myself that the committee has made the interim decision to not reschedule the medicinal use of Psilocybin and MDMA. I do not use the term 'sufferers' lightly, some of us have literally been suffering for our living memory. I have existed, I cannot call it living, with Complex PTSD, depression, anxiety and the chronic health conditions these untreatable conditions have wrought.
C. Stratton

It should be considered that people who would participate in the therapy (ie. patients looking for relief from end-of-life distress, addictions or severe depression) are much more likely to die from suicide due to lack of effective treatment options.
A. Chmist

Please, please, please, give my relatives and thousands like them the opportunity to legally access this treatment and have a good chance of finally receiving relief from their suffering, enabling then to live full lives and contribute to society.
S. Grant

Please don't give up, as a lifelong sufferer of mental illness I have been on every pill known to man all with the same band-aid results. I have no doubt in my mind that this therapy is the way forward. The old way hasn't and won't work. I am now approaching 50 years old very fast and would like just a few years of my life to be peaceful and not filled with crippling depressive episodes and constant anxiety and I'm sure there are a heap more just like me. Please keep fighting - this may be our last hope!
S. Farrington

I've been under treatment for approximately the last 20 years. While I have achieved some normality, I often have debilitating periods where my depression wins as I say. I have a tough time doing anything other than just existing. I am on medications such as Effexor XR, Mirtazapine and Olanzapine and seeing a clinical psychologist for the last 20 of those years as well. My GP has concluded with my psychologist and psychiatrist's assistance that I have Treatment-Resistant Depression…Not having safe and regulated access to these treatment options means I will continue to experience the rollercoaster of mental health illness for the rest of my life, which as I'm sure you would agree is not a pleasant prospect.
A. Marchant

We are in the midst of a mental health epidemic and urgently need solutions. Psilocybin should be made available as an option for people who need it.
R. Mateer

MDMA enabled me to view my trauma through different eyes, without actually going through the trauma with all the bad emotion. The emotion was still there, but different. Over time, I was able to lessen my PTSD, anxiety and self-destructive habits simply by taking MDMA and gaining a greater understanding of the traumatic situation and my response to it.

MDMA also enabled me to forgive my perpetrator. I didn't understand the power of forgiveness at the time and that enabled me to move through the world without the oppressive nature of my trauma dragging me down. MDMA lessened my fear.
L. Ryan

As someone still living with treatment resistant depression and anxiety after 10+ years, I don't understand why therapeutic use of psylocibin and MDMA would not be made legal in Australia when it has proven to be effective overseas.
S. Hazelman

I have had severe PTSD for 34 years since the age of 19, following a childhood of physical, emotional and sexual abuse. Over that period, I had been treated by 18 therapists, including 3 psychiatrists, and had been hospitalised following a failed suicide attempt.

3 years ago I moved to Amsterdam where I was able to receive MDMA-assisted therapy for PTSD following the MAPS protocol. I had 3 such sessions and experienced a complete cessation of all PTSD symptoms.

The psychedelic experiences themselves were the most profound healing experiences of my life and relieved me of the burden of pain, terror and shame I had been carrying.

I am now re-assessing my life from a "post-PTSD" perspective, something I never thought I would see. It has been like giving me a new life.
S. Ball

I have tried numerous conventional treatments over the years provided by expert psychiatrists, psychologists and other doctors. I have been suicidal in the past and recently my condition has declined during covid this year having faced numerous suicides in my social network while living in Melbourne during the lockdown. These two treatments, psilocybin assisted psychotherapy and also MDMA assisted psychotherapy have shown great promise in the number of worldwide clinical trials and could provide great easing of my suffering and even the possibility of being cured.
Yoshi L.

“Trauma creates a prison in the mind, leaving countless Australians shackled by mental illness…I believe psychedelic therapy, responsibly administered in a safe and supported environment, is the key to unlocking those prison doors… In desperation, from a place of abject hopelessness, I turned to safe and supported Ayahuasca psychedelic therapy. One week of intensive treatment provided transformational healing. I’m honoured to be an example of what is possible with guided psychedelic therapy, and it is my passion to help my brothers and sisters in arms find their own healing journey.”
J. Harrop, (Veterans of War, ex-ADF Veteran)

As a recently retired Australian Airforce Electrical Engineering Officer of 16 years. I have spoken on ABC radio and published an article on Medium regarding the profound healing both Psilocybin and MDMA have provided me. Suffering from PTSD, Anxiety and Depression, traditional psychotherapy and anti-depressants did not work. I would not be writing this today if it were not for these psychedelic medicines.

These medicines, have been a light in my darkness, helping me once again gain a sense of purpose, self-love and acceptance I never thought possible.

Other Western nations are progressively rolling out legalisation of psychedelic medicines with the safety and efficacy being no longer in question.

Unfortunately, I believe we will look back on the unnecessary delays in access to these healing modalities as a sad part of history where many Australian families lost loved ones that could still be with them.
M. Raymond (Veteran)

I am one of those fortunate enough to have received psilocybin legally in Jamaica and experienced a considerable, but slowly diminishing, reduction in the symptoms of treatment resistant depression and social anxiety
T. Edney

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

Table of Contents:

1. INTRODUCTORY COMMENTS

In the statement released on 3rd February 2021 the Delegate of the Secretary of the Department of Health ("**the Delegate**") gave reasons to support the Delegate's interim decision not to amend the Poisons Standard in relation to MDMA.

The material used by the Delegate to support the interim decision included:

1. A list of materials that the Delegate considered;
2. A summary of the advice received by the Delegate from the ACMS; and
3. The reasons given by the Delegate for making its decision.

We respectfully believe that the materials considered, the summary of advice received from the ACMS and the reasons given by the Delegate contains many serious errors and omissions. As we discuss below these errors and omissions are particularly serious given:

1. The crisis in mental illness that we have in Australia and the lack of treatment effectiveness for many Australians suffering from Post-Traumatic Stress Disorder (PTSD) and/or Substance Abuse associated with trauma; and
2. The prejudice, stigma and risks often associated with the recreational use of MDMA which should have no relevance to a consideration of its medical use as an adjunct to psychotherapy in a medically controlled environment.

There are plenty of examples (discussed in Section 6.3 below) of substances that are **legally prohibited** for recreational use but **legally permitted** when used by medical professionals to treat specific patient illnesses in our medical system. Indeed, as we will show, many of the substances already in Schedule 8 (and even some of the substances in Schedule 4) are significantly more dangerous than MDMA.

Based on the evidence contained in this Submission and in our earlier Application we respectfully submit that:

1. There are strong grounds for the Delegate to reschedule the ***medical use*** of MDMA as part of psychotherapy from Schedule 9 to Schedule 8 of the Poisons Standard with appropriate controls and in the manner set out in our Rescheduling Application. ***All other uses of MDMA would remain in Schedule 9.***

2. Appropriate controls would include:
   i) for oral use as part of psychotherapy under the authorization of the treating psychiatrist or specialist addiction physician; and
   ii) in a medically controlled environment.

3. Such a rescheduling would be entirely consistent with other medicines listed in Schedule 8.

4. Schedule 8 is the appropriate schedule for the medical use of MDMA under the Poisons Standard.

2. THE MENTAL HEALTH CRISIS IN AUSTRALIA

2.1 Introductory Comments

We respectfully submit that our Rescheduling Application (and the need for new treatment options) should be carefully viewed within the context of the mental health crisis that we have in Australia, which continues to deteriorate.

***Please note that in making this statement we are not suggesting that safety standards associated with new treatments should be compromised*.**

According to the Productivity Commission's Report on Mental Health dated 30 June 2020 (released by the Commonwealth Government publicly on 16 November 2020):

- One in 5 Australian adults (4.8 million people) have a chronic mental illness.
- On a conservative basis, the cost of mental illness to the Australian economy is about $200-$220 billion each year (equivalent to $550 million to $600 million each day).
- Australians with severe mental illness on average die 10 to 15 years earlier than other Australians, usually as a result of physical comorbidities.
- About three quarters of adults with mental illness first experienced mental illness before the age of 25 years and about 25% of all people suffering from mental illness are 25 years old or younger.
- 3,046 people died by suicide in 2018 (which is the leading cause of death in the 15-to-44-year-old age group) and about 65% of people who died by suicide had a mental illness.

According to other Government sourced statistics:

- I in 8 Australians are now being prescribed anti-depressants despite their relatively low effect size and adverse side effects (a rate which increases to 1 in 4 in older Australians) - this represents an enormous increase in use of 95% over 15 years.
- 1 in 30 children are being prescribed anti-depressants, some as young as 4 years old.
- The incidence and complexity of mental illness is far worse in discrete populations including Australian Defence Force Veterans and First Responders.
- Alcohol dependence (and substance abuse generally) continues to be a massive problem; and
- There is a strong correlation between mental illness and many of Australia's entrenched social problems including domestic violence, homelessness and suicide.

2.2 The Socioeconomic Impact of the Current COVID-19 Pandemic

Please note that all the above statistics related to the period before the current COVID pandemic and there is a lot of data to suggest that the incidence of mental illness in Australia is now getting significantly worse.

The following Australian statistics were reported in the International Journal of Community and Social Development on July 1, 2020 (O'Sullivan et al, 2020):

- COVID-19 stress is straining familial relationships, and family violence has increased. Eighty domestic violence frontline workers and service providers reported a 40 per cent increase in client numbers since the introduction of statewide isolation measures.
- Parent-related disputes in providing safety and care to Australian children have seen a sharp increase.
- The Family Court of Australia has reported a 39 per cent increase in parenting-related disputes, while the Federal Circuit Court of Australia has reported a 23 per cent increase.
- The Family Court has also noted advice from the Women's Legal Services of an increase in the number of enquiries related to parenting matters.
- The COVID-19 lockdown coincided with a sharp increase in alcohol consumption. A national YouGov Galaxy poll commissioned by the Foundation for Alcohol Research and Education (FARE) revealed that 20 per cent of Australians purchased more alcohol, and 70 per cent of them were drinking more alcohol than usual. One-third were now using alcohol daily. One-third of the people who purchased more alcohol were concerned about their own drinking, or that of someone in their household. About 28 per cent reported that they were drinking alcohol to cope with anxiety and stress (FARE, 2020).
- COVID-19 has exposed the socioeconomic gap across social groups. People who were already poor, unemployed or underemployed, with high levels of existing debt, suffering homelessness, or facing existing difficulties with access to health and social services, and people with disabilities, were likely to be further marginalised by increased vulnerability to both physical and mental illness (Friel & Demaio, 2020).
- The risk for higher suicidality rates is backed by historical research. As unemployment jumped 1.22 per cent during the years of the global financial crisis 2007-2009, suicide increased in economically inactive/unemployed males and females.
- COVID-19 also instigated an increase in complaints of racism to the Human Rights Commission. One-third of all complaints since the beginning of February have been related to the virus. These included complaints of verbal and physical abuse, and vandalism (Human Rights Commission, 2020), with Chinese people especially targeted and, consequently, suffering insecurity, fear and mental ill-health.

These figures are alarming. Standard mental health policy measures may provide short-term relief during the COVID-19 pandemic. However, without a more lateral approach, rates of mental illness, particularly amongst vulnerable populations, are likely to get worse.

Perhaps related in part to the pandemic environment there have been alarming numbers of recent suicides involving past and present Defence Force members, with at least 67 suspected suicides in the past 12 months (*Australian Defence Force Facing "Mental Health Crisis" 7News.com.au, 14/2/21)* reproduced in Appendix A).

2.3 The Lack of Treatment Effectiveness

Despite these appalling statistics, treatment options for a large number of people suffering from mental illness remain inadequate and there has been minimal scalable treatment innovation in the mental health sector for over 50 years.

Specifically:

- With Depression only 30-35% of sufferers are estimated to experience remission (i.e. to get fully well) from pharmacotherapy (mainly antidepressants) and/or psychotherapy and the benefits for many patients lapse after treatment stops.
- With Post-Traumatic Stress Disorder (PTSD) the remission rates are even lower (somewhere between 5 and 10%.
- Many of the psychiatric medicines currently used can have bad side effects (such as insomnia, blurred vision, dry mouth, fatigue, GI distress, weight gain, nausea, cognitive decline and sexual dysfunction) and can cause changes in the human brain.
- Virtually all currently marketed medicines to treat psychiatric illnesses are based on discoveries that were made over 50 years ago.

A short article by leading psychiatrist Professor Paul Fitzgerald drawing together research on just how ineffective antidepressants can be as a treatment for Depression can be found here: https://blog.usejournal.com/the-challenges-of-depression-treatment-in-2020-abd74269764. (This article is reproduced in Appendix B). As mentioned above psychiatric medicines are even more ineffective in the treatment of PTSD.

We therefore believe that the reality of Australia's mental health crisis and the lack of treatment effectiveness for many people suffering from PTSD and/or Substance Abuse associated with trauma should cause the Delegate and the TGA to proactively seek to make new treatments available for treatment-resistant conditions where proper controls can be put in place.

We respectfully believe that the Delegate and the TGA should not be reacting adversely to potential barriers to implementation that are more than capable of being resolved.

3. MATERIALS CONSIDERED BY THE ACMS AND THE DELEGATE

3.1 Our Application

Our Application for the Rescheduling of the medical use of MDMA from Schedule 9 to Schedule 8 of the Poisons Standard contained a substantial amount of peer reviewed information on the pharmacology, therapeutic effects, human studies, safety data, toxicity and benefits and risks (among other things) of using medical MDMA as part of therapy for treatment resistant PTSD, anxiety disorders and substance abuse (particularly alcoholism) associated with trauma.

We made it clear that under the terms of the proposed rescheduling that:

i) The use of MDMA as part of therapy would have to be authorized by the treating psychiatrist or specialist addiction physician;
i) The therapy would have to be conducted in a medically controlled environment by trained professionals.
ii) That all other uses of MDMA would remain in Schedule 9.

We also made it clear that rescheduling the medical use of MDMA as part of psychotherapy to Schedule 8 of the Poisons Standard would still mean that:

i) The prescribing doctor would have to provide a clinical justification to the TGA for the use of MDMA as part of psychotherapy under Special Access Scheme – B or be authorised by the TGA under the TGA's Authorised Prescriber Scheme.
ii) The prescribing doctor would also require the approval of the relevant State or Territory Government where the therapy was to be conducted.

Finally, we also emphasized the need to move away from stigma and prejudice and recognize the difference between the recreational use of ecstasy (which may or may not contain MDMA in its pure form) and the medical use of medical grade GMP standard MDMA (which is synthesized in a regulatory controlled laboratory).

As mentioned below, our rescheduling application was supported and endorsed by at least 295 Health Sector Experts. This should be relevant to the Delegate as a key consideration under Section 52E and particularly subsections (1)(a), (b), (c), (e) and (f) of the Therapeutic Goods Act 1989.

3.2 Submissions, Responses and Endorsements Received from Health Sector Experts

3.2.1 Health Sector Experts are Overwhelmingly in Favor of Our Rescheduling Application

We note the comment by the Delegate that the responses given to the TGA about our rescheduling Application "*indicate significant public support for rescheduling*".

In fact, the support was overwhelming and much of the support came from Health Sector Experts.

The TGA received in total 478 responses which came through the TGA portal of which 453 (95%) were supportive, 14 (3%) partially supportive and only 11 (2%) were opposed. Of the overwhelming number of supportive responses, a majority came from Health Sector Experts.

Our Rescheduling Application listed a further 70 leading Australian and International psychiatrists, psychologists, pharmacologists, researchers and other scientists who authorized Mind Medicine Australia to advise the TGA that they had read our Rescheduling Application and supported the proposed rescheduling.

This overwhelming support amongst Health Sector Experts is summarised in Table 1 below;

Table 1: Health Sector Experts Support for Rescheduling of MDMA

Profession	**Fully Support***	**Support with Qualifications**	**Don't Support**
Psychiatrists	47		1
Psychologists/psychotherapists	45	1	
Medical Doctors	33	2	
Researchers/scientists/academics	73	1	3
Counsellors and Social Workers	26		
Other medical by category / Health Professionals (incl nurses)	31	1	1
Pharmacologists and Pharmacists	11		
Dr Nigel Strauss Signatories		1**	
RANZCP			1
AMA			1
PRISM		1	
Drug Free Australia			1
Entheogenesis Australis		1	
Total	**266**	7**	8
*Includes direct endorsement contained in MMA's rescheduling application and all supporting public submissions from Health Experts **Signatories redacted so numbers unclear but not greater than 21. Likely to be a mixture of psychiatrists and psychologists			

In Table 2 we identify as many as possible of the Health Sector Experts summarized in Table 1 who supported our Rescheduling Application.

Table 2: Named Health Sector Experts Supporting the MMA Application to Reschedule MDMA from Schedule 9 to Schedule 8 of the Poisons Standard

Title	First Name	Surname	Position
Dr	Dima	Abdulrahim	**Researcher: employed by Central and North West London NHS Foundation Trust and is the lead researcher and programme manager of the NEPTUNE clinical guidance and learning and development programme on the management of the harms of club drugs and novel psychoactive substances**
Dr	Tanveer	Ahmed +	**Australian Psychiatrist and Author based in NSW.**
Mr	Ben	Atkinson	**Researcher - healthcare**
Mr	Mark	Baxter	**Psychologist and Director of group private practice**
Dr	Steve	Bazire	**Academic: Honorary Professor, School of Pharmacy, University of East Anglia in Norwich, a Director of Mistura Enterprise**
Dr	Christopher	Bench	**Australian Psychiatrist in private practice in Newcastle, NSW.**
Ms	Hannah	Biddell	**Researcher**
Dr	Brigitta	Brander	**Scientist: Consultant in Anaesthesia and Pain Management at University London Hospital Trusts**
Dr	Simon	Brandt	**Researcher: Chemistry, analytical and pharmacological properties of psychoactive substances, "legal highs", drugs of abuse and so-called designer drugs, within the context of (psycho)pharmacology, medicinal chemistry, psychiatry, forensic science and public health.**
Dr	Jillian	Broadbear	**Adjunct Clinical Associate Professor, Monash University; Senior Research Fellow, Spectrum - State-wide Service for Personality Disorder, Eastern Health.**
Prof	Ashley	Bush +	**NHMRC Senior Principal Research Fellow, Director of the Melbourne Dementia Research Centre.**
Mr	Roderick	Campbell	**Researcher**
Dr	Robin	Carhart-Harris (UK)* +	**Head of the Centre for Psychedelic Research - Imperial College London. Leading published researcher in psychedelic assisted therapies. Holds a PhD in Psychopharmacology.**

Dr	Ted	Cassidy +	**Australian psychiatrist. Chief Medical Officer and Co-Founder of TMS Australia, Australia's largest provider of outpatient Depression and PTSD treatment using transcranial magnetic stimulation technology.**
Dr	Juthica	Chaudhary	**Australian Psychiatrist in private practice in South Australia.**
Dr	Lukas	Cheney	**Australian consultant psychiatrist in Victoria.**
Mr	Victor	Chiruta	**Researcher - manufacturing/research and development consultant**
Prof	Arthur	Christopoulos*	**Dean, Faculty of Pharmacy and Pharmaceutical Sciences and Head of the Analytical and Structural Neuropharmacology Laboratory, Monash Institute of Pharmaceutical Sciences at Monash University. World leading molecular Pharmacologist.**
Dr	Mark	Cross +	**Psychiatrist, Senior Conjoint Lecturer at the Universities of NSW and Western Sydney, and SANE Board Director.**
Prof	Val	Curran	**Researcher: psychopharmacology**
A/Prof	Mark	Daglish	**BSc MBChB MD FRANZCP Associate Professor in Addiction Psychiatry, University of Queensland.**
Ms	Caroline	Dale	**Clinical Psychologist**
Dr	Rick	Doblin	**BSc, Ph. D Founder and Executive Director of the Multidisciplinary Association for Psychedelic Studies (MAPS), USA. MAPS ae sponsoring the current Phase 3 global multi-site trials and secured Breakthrough Therapy Designation for MDMA from the FDA.**
Prof	Colin	Drummond	**Scientist: Professor of Addiction Psychiatry at the National Addiction Centre, Institute of Psychiatry, King's College London**
Mr	Niamh	Eastwood	**Academic: Executive Director of Release – the UK's centre of expertise on drugs and drug laws**
Prof	Barry	Everitt	**Scientist: Professor of Behavioural Neuroscience at the University of Cambridge**
Dr	James	Fadiman (USA) +	**American Psychologist, Author and Researcher. Co-founder, Institute of Transpersonal Psychology, which later became Sofia University.**
Ms	Amanda	Fielding (UK) +	**Founder and Executive Director of The Beckley Foundation in the UK, which has been a major funder of research into psychedelic assisted therapies.**

Prof	Paul	Fitzgerald +	**Professor of Psychiatry at Monash University and Director of the Epworth Centre for Innovation in Mental Health.**
Prof	David	Forbes +	**Director of Phoenix Australia - Centre for Posttraumatic Mental Health and Professor in the Dept of Psychiatry, Melbourne University.**
Dr	Nick	Ford	**Australian Psychiatrist in private practice in South Australia, specializing in PTSD.**
Mr	Jack	Gerboni	**Researcher**
Ms	Roz	Gittins	**Researcher: Director of Pharmacy for a national third sector substance misuse treatment provider. She is the Registrar for the College of Mental Health Pharmacy and a credentialed member**
Dr	Robert	Gordon	**Australian Psychiatrist in private practice in Sydney, NSW.**
Dr	Al	Griskaitis	**Australian Psychiatrist in private practice in Wollongong, NSW.**
Ms	Kyle	Hammond	**Researcher - prescription medicines**
Mr	Patrick	Hargreaves	**Educator: school inspector, and a regional PSHE adviser. For 10 years, he was the Drugs and Alcohol Adviser with County Durham Children & Young Peoples' Services where he was responsible for the delivery of drug and alcohol education to children and young people**
Prof	Graeme	Henderson	**Scientist: professor of Pharmacology at the University of Bristol**
Prof	Gregg	Henriques	**Licenced psychologist and professor of clinical psychology**
Dr	Walter	Hipgrave	**Psychiatry Registrar at Alfred Hospital, VIC**
Dr	Karen	Hitchcock	**Specialist medical doctor (Acute and general medicine)**
Dr	Karen	Hitchcock +	**Specialist Physician (acute and general medicine) based in Melbourne and Author.**
Dr	Justine	Hoey-Thompson	**Psychiatrist**
Prof	Malcolm	Hopwood +	**Ramsay Health Care Professor of Psychiatry, University of Melbourne, specialising in clinical aspects of mood and anxiety disorders, psychopharmacology and psychiatric aspects of acquired brain injury and epilepsy. Past President of RANZCP.**
Dr	Pieter	Hurter	**Psychiatrist at Eastern Health, Melbourne.**
Dr	Linda	Kader +	**Psychiatrist and Senior Lecturer at the Department of Psychiatry, University of Melbourne.**

Mr	Michael	Kornhauser +	**Australian Pharmaceutical and Clinical Trial Research Specialist.**
Dr	Eli	Kotler +	**Psychiatrist and Director of Medicine at Malvern Private Hospital, Melbourne, specialising in addictions.**
Dr	Chris	Letheby	**Researcher - philosophy of cognitive sciences**
Mr	Nicholas	Levy	**Researcher**
Dr	Maria	Leonard	**Psychiatrist with FRANZCP**
Dr	Michael	Lynsky	**Researcher: epidemiologist and addiction researcher who has held academic appointments in New Zealand**
Dr	Beth	Mah	**Perinatal Psychiatrist**
Dr	Sonja	Mahs	**Clinical Psychologist**
Dr	John	Marsden	**Academic: Reader in Addiction Psychology at the Institute of Psychiatry, King's College London**
Dr	Raya	Mayo	**GP**
Dr	Catherine	Mccarthy	**Clinical Psychologist**
Prof	Fiona	Measham	**Academic: Chair in Criminology at the University of Liverpool in 2019**
Mr	Ian	Millar	**Academic: methods of drug research, giving lectures and presentations on all aspects of homelessness and drug use**
Dr	Anish	Modak	**Psychiatry Registrar, Adult Mental Health Unit Canberra Hospital, ACT Health.**
Prof	Rob	Moodie AM +	**Professor of Public Health – University of Melbourne and Advisor to World Health Organisation (WHO).**
Mr	Ajdin	Mujezinovic	**Psychologist**
Prof	Jo	Neill	**Scientist: Professor of Psychopharmacology at the University of Manchester**
Mr	James	Neville - Kennard	**Researcher**
A/Prof	David	Nichols (USA) +	**Adjunct Professor of Chemical Biology and Medicinal Chemistry - University of North Carolina, Chapel Hill. Published over 300 scientific articles. Major focus on psychedelic chemistry.**
Professor	David	Nutt (UK) #	**BA, MB BChir, MRCP, MA, DM, MRC Psych, FRCPsych, FMedSci, FRCP, FSB Head of Neuropsychopharmacology at Imperial College London, one of the world's foremost psychedelic research laboratories, publishing landmark research on psychedelic therapies and neuroimaging studies of the psychedelic state.**
Dr	Nikola	Ognyenovits +	**Australian Addiction Medicine Specialist Physician, QLD.**

Dr	Larry	Phillips	**Scientist: Emeritus Professor of Decision Science**
Dr	Prash	Puspanathan +	**Previously a Medical Doctor at the Alfred Hospital where he most recently held the position of Neuropsychiatry Fellow.**
Dr	Braham	Rabinov	**GP, MB.BS, Fellow of the Australasian College of Nutritional and Environmental Medicine, Diploma of Health Education**
Dr	John	Ramsey	**Scientist: analytical toxicologist and Director of TICTAC Communications Ltd. at St. George's University of London**
A/Prof	Sathya	Rao	**Executive Clinical Director of Spectrum, Personality Disorder Service for Victoria, Australia. He is also the Deputy President of Australian Borderline Personality Disorder Foundation, Adjunct Associate Clinical Professor at Monash University and a Consultant Psychiatrist at Delmont Private Hospital.**
Mr	Steve	Rolles	**Academic: Senior Policy Analyst for Transform Drug Policy Foundation**
Ms	Jodie	Rosenberg	**Researcher**
Dr	Alana	Roy *	**Dr in Psychology (PhD), Mental Health Social Worker, Counsellor, Advocate, Researcher and Lecturer. Over the last 13 years has worked and remain active in a range of settings including sexual assault, domestic violence, suicide prevention, schools, disability, mental health services, and the Deaf and Deafblind community.**
Dr	James	Rucker (UK) +	**Consultant Psychiatrist & Senior Clinical Lecturer at Kings College London where he leads the Clinical Trials Group which is currently undertaking clinical trials using psilocybin in healthy volunteers and patients with resistant depression.**
Dr	Stuart	Saker	**Psychiatrist**
Dr	Ramsay	Sallis	**GP**
Dr	Harsumeet	Sandhu	**Doctor - Medical Officer**
Dr	Nicola	Santarossa	**Doctor and Master of Counselling student**
Dr	Anne	Schlag (UK) *	**Head of Research at Drug Science, UK and Honorary Fellow at Imperial College London.**
Dr	Ben	Sessa (UK) #	**MBBS, B.SC, MRC PSYCH** **Psychiatrist and researcher at Bristol and Imperial College London University, He is currently conducting the world's first clinical study using MDMA to treat alcohol addiction.**

Dr	Joanne	Shannon	**Psychiatrist**
Prof	Ilina	Singh	**Scientist: Professor of Neuroscience and Society at Oxford University**
Dr	Steven	Stankevicius	**Australian Consultant Psychiatrist and Accredited TMS Clinician at Toowong Private Hospital, QLD.**
Prof	Alex	Stevens	**Health worker: worked on issues of drugs, crime and health in the voluntary sector, as an academic researcher and as an adviser to the UK government**
Dr	Jorg	Strobel	**Senior Consultant Psychiatrist / Clinical Lead Mental Health Informatics Research Unit, SA Health and Flinders University.**
Dr	Polly	Taylor	**Veterinary Doctor: veterinary surgeon who graduated in 1976**
Prof	John	Tiller +	**MD, MBCHB, BSC, DPM, FRACP, FRANZCP, GAICD Professor Emeritus Psychiatry, University of Melbourne and Albert Road Clinic. Past President of RANZCP. His primary research interests have been in the assessment and treatment of depressive and bipolar disorders, anxiety disorders including PTSD and psychoses.**
Dr	Emile	Touma	**Senior Addiction Psychiatrist and Addiction Medicine Specialist, Senior Lecturer, School of Clinical Medicine University of Queensland.**
Mr	Graeme	Van Tongerloo	**Clinical Psychologist**
Dr	Paul	Verris	**Interventional Pain Management Physician**
Mr	Rob	Wainwright	**AHPRA Registered Psychologist, AHPRA Registered Pharmacist**
Dr	John	Webber +	**Australian Psychiatrist in private practice in Melbourne.**
Dr	Tim	Williams	**Psychiatrist: consultant addiction psychiatrist within the NHS and honorary clinical lecturer with the University of Bristol**
Dr	Stephen	Willott	**GP at the Windmill practice in the inner city of Nottingham & has worked there for the past 20 years**
Dr	Michael	Winlo	**Medical Doctor, CEO and managing director of Emyria Clinics**
Prof	Adam	Winstock	**Psychiatrist: Consultant Addiction Psychiatrist and Addiction Medicine specialist based in London.**

Dr	Alex	Wodak AM +	**Physician with expertise in addiction. Previously Director of the Alcohol and Drug Service at St Vincent's Hospital in Sydney.**

Table Key
+ Member of MMA Advisory Panel (honorary position)
* Provided detailed letter of support appearing in Appendix A of our Rescheduling Application
# Ambassador of MMA (honorary position)

You will note that the supporting experts include:

- **Mr. Rick Doblin**, the Founder and Executive Director of the Multidisciplinary Association for Psychedelic Studies (**MAPS)** in the USA which is the sponsor of the current Phase 3 multi-site trials and which secured Breakthrough Therapy Designation for MDMA assisted psychotherapy from the US regulator, the FDA.
- **Professor David Nutt,** Psychiatrist and Professor of Neuropsychopharmacology at Imperial College London, one of the World's foremost psychedelic research laboratories publishing landmark research on psychedelic therapies and associated neuroimaging studies. Founding Chair of Drug Science.
- **Dr Robin Carhart-Harris,** the Head of the Centre for Psychedelic Research at Imperial College London and one of the most cited researchers in this field;
- **Professor Arthur Christopoulos,** Professor of Analytical Pharmacology and Dean of the Faculty of Pharmacy and Pharmaceutical Sciences (the second highest rated faculty of its kind in the World) at Monash University, Melbourne;
- **Professor David Forbes,** the Director of the Phoenix Australia Centre for Posttraumatic Mental Health;
- **Dr James Fadiman,** a leading American psychologist with a focus on the treatment effectiveness of psychedelic medicines as part of therapy;
- **Associate Professor David Nichols,** leading American pharmacologist specializing in the way psychedelics work in the human brain;
- **Dr James Rucker,** the leader of clinical trials at Kings College London using psilocybin assisted psychotherapies in healthy volunteers and patients suffering from treatment resistant depression; and
- leading Australian psychiatrists including **Professor John Tiller, Professor Mal Hopwood and Professor Paul Fitzgerald**

Our Rescheduling Application also included detailed letters of support from World leading experts in this field.

Table 3: Letters of Support from World Leading Experts Attached to our Rescheduling Application

1. **Letter of Support from Dr Robin Carhart-Harris, Head of Centre for Psychedelic Research, Imperial College London**

Dr Carhart-Harris is the head of the Centre for Psychedelic Research at Imperial College London. He is also one of the leading researchers in this field in the World and has the highest annual citation rate in the field.

In his letter Dr Carhart - Harris specifically says in relation to our Rescheduling Application that:

"*Peter Hunt had forwarded to me the applications by Mind Medicine Australia (MMA) to reschedule psilocybin and MDMA in Australia and I have reviewed the rescheduling applications. The argument to reschedule psilocybin is compelling… I support the same rescheduling [i.e. from Schedule 9 to Schedule 8] for MDMA therapy, as the evidence for its efficacy as a tool to facilitate trauma-focused psychotherapy is compelling.*"

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

2. **Letter of Support from Professor Arthur Christopoulos, Professor of Analytical Pharmacology and Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University**

Professor Christopoulos is the Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University which is ranked No 2 in the World (after Oxford) in Pharmacy and Pharmacology (QS World Rankings 2020). He is a World leader in novel modes of drug discovery, with a particular focus on neuropharmacology, neuropsychiatric diseases and protein targets for psychoactive medicines, including those modulated by mind-altering compounds like psilocybin and MDMA and has published over 320 peer reviewed articles.

Professor Christopoulos has received the highest Pharmacology awards from the Australian, American, British and International Pharmacological Societies, is a member of the Australian Academy of Health and Medical Sciences and is rated in the top 1% of all cited scientists worldwide in his field.

In supporting our application for the rescheduling of MDMA from Schedule 9 to Schedule 8 of the Poisons Standard, Professor Christopoulos notes that:

"**Safety and Efficacy of Psilocybin and MDMA in a Medically Controlled Environment**.

There is now a substantive body of highly compelling scientific evidence to support the fact that both psilocybin and MDMA offer superior efficacy to existing psychotherapies in treating major mental health conditions, including depression, PTSD, substance abuse disorders and anxiety, to name a few. In addition and given the short dosing regimens

associated with clinical application of the substances, there is minimal likelihood of any safety concerns or addiction liabilities."

"***Proposed Change of Scheduling***

Based on my professional experience and a review of the international data I believe that psilocybin and MDMA should be rescheduled from Schedule 9 of the Poisons Standard to Schedule 8 of the Poisons Standard. There is simply no reasonable scientific rationale for the current scheduling of either substance as Schedule 9; in a clinical environment, they present minimal risks of harm, adverse events or addictive liability compared to the majority of other psychoactive medicines currently listed as either Schedule 8 or even Schedule 4. I therefore support the applications for rescheduling being made by Mind Medicine Australia Limited."

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

3. Letter of Support from Drug Science (signed by 25 leading health sector specialists)

Drug Science is the leading independent scientific body on drugs in the UK with a focus on providing clear, evidenced based information without political or commercial interference.

The Drug Science letter was signed by 25 leading health sector specialists including Professor David Nutt, who is the Deputy Head of the Centre for Psychedelic Research at Imperial College London (https://www.imperial.ac.uk/psychedelic-research-centre). Professor Nutt has extensive experience and scientific understanding of MDMA being used in a clinical setting and has led, amongst other areas, MDMA trials for the treatment of alcoholism.

In the Drug Science letter, the signatories note, among other things, that:

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

Taken together there were 295 Health Experts supporting our rescheduling application (of which up to 27 did so on a qualified basis) from the directly relevant fields of psychiatry, psychology, pharmacology, addiction specialists, researchers and other health professionals.

The Health Experts that gave qualified support wanted the right infrastructure in place (particularly training, protocols, standard operating procedures and training manuals) before these therapies became available. We deal with this need specifically in Section 5.6 below.

Only 11 parties at most opposed are application (there appears to be some doubling up) and a number of those were not prepared for their identity to be made public (which calls into question the veracity and integrity of their views). We discuss the opposing submissions in Sections3.2.3, 3.4 and 6.12 below.

In total 48 psychiatrists supported our rescheduling application, and no individual psychiatrists were opposed. The supporting figure could be as high as 69 depending on the composition of the signatories of Dr Strauss' letter (in which the signatories were redacted).

We note that neither the Summary of ACMS's Advice to the Delegate or the Delegate's Reason's for the Interim Decision made any mention of the overwhelmingly strong support that our Rescheduling Application received from Health Sector Experts. This must be a key factor for consideration by the Delegate under Section 52E of the Therapeutic Goods Act (and particularly subsections (1)(a), (b), (c), (e) and (f)).

3.2.2 Health Sector Experts and Other Parties that only Partially Supported our Rescheduling Application

According to the Delegate there were 14 groups who only partially supported our Rescheduling Application. These were:

1. Psychedelic Research in Science and Medicine (PRISM)
2. Entheogenesis Australis (EGA)
3. Dr Nigel Strauss' group of what appear to be up to 21 psychiatrists and psychologists (we don't know the actual number or composition because all the names other than the name of Dr Nigel Strauss were redacted)
4. 11 anonymous

As mentioned above, the general tenor of these submissions is that rescheduling should occur and access to these medicines is important, but that we need to develop the right protocols and infrastructure in place to manage these medicines. As described in Section 5.8 there are key initiatives in place to deal with this requirement.

We comment specifically on the published submission of PRISM in Section 6.12 below as the Delegate specifically referred to the views of PRISM in the Delegate's Interim Decision. We also note that there is a significant overlap of Directors between PRISM and Entheogenesis Australis, which has a major focus on the recreational use and preservation of plant-based medicines including naturally growing psychedelic plants and fungi.

3.2.3 Parties Who Opposed our Application

According to the Delegate only 11 parties actually opposed our Rescheduling Application. These were:

1. The Royal Australian and New Zealand College of Psychiatrists (**RANZCP**)
2. The Australian Medical Association (**AMA**)

3. Drug Free Australia
4. 5-7 Anonymous (3 of which appear to be written by the same person)

The identified parties are each discussed below.

The RANZCP Submission

In the RANZCP submission the President, Associate Professor John Allan, draws heavily upon a clinical memorandum prepared by RANZCP entitled "*Clinical Memorandum on the therapeutic use of psychedelic substances (May 2020) (*the **Clinical Memorandum***).* The President argued that, whilst there is emerging evidence that psychedelic therapies (which were defined in the Clinical Memorandum to include MDMA assisted therapies) may have therapeutic benefits in the treatment of mental illnesses, more evidence was needed to comprehensively assess the efficacy, safety and effectiveness of these therapies.

As set out in Section 3.4, the Clinical Memorandum contains many errors and misleading statements and ***does not*** provide RANZCP with a reliable basis for opposing the rescheduling of MDMA.

The President goes on to say in the RANZCP submission that, *"There is a range of effective and evidenced-based treatments currently available in psychiatry for the treatment of mental disorders…".* Unfortunately, this statement doesn't (by definition) apply to people with treatment resistant conditions and doesn't highlight the low effect size and adverse side effects of a number of psychiatric medicines, particularly those used in the treatment of PTSD (see Section 2 above).

The President goes on to say that whilst psychiatrists can apply for approvals from the TGA under the Special Access Scheme they also would need additional State or Territory permissions which, for Schedule 9 substances, are rarely if ever granted. This statement by the President is misleading because (with the possible exception of Victoria) there ***are no legislative access pathways*** under current State and Territory legislation which would enable the relevant government to grant approval to the medical use of MDMA as part of therapy whilst MDMA (for medical use) remains a Schedule 9 substance.

The President then says, somewhat remarkably, that *"Opening access to psychedelic therapy outside of clinical trials may impact the ability to recruit patients for clinical trials of psychedelic therapies to contribute further to this dataset".* How a person with treatment resistant PTSD or substance abuse associated with trauma who can't get on to a clinical trial (where numbers are always very limited and the timeline normally takes years) would feel about this argument can only be imagined! This is made even worse by the lack of MDMA assisted therapy trials in Australia to date.

The President continues by saying that whilst such *"…data may be recorded and evaluated outside of clinical trials, the RANZCP suggests that appropriate treatment methodologies, adequate training, and an ethical and legal framework that provides appropriate safeguards are not sufficiently developed to inform this".* For the reasons set out in Section 5.8 Mind Medicine Australia reiterates that this can all be accommodated within a short timeframe and should not be a reason for deciding not to reschedule the medical use of MDMA to Schedule 8.

Finally, the President also argues that the medical use of psychedelics such as MDMA could somehow encourage recreational use. There is absolutely no evidence to support this claim. Not only does this statement ignore the fact that many Schedule 8 substances can be abused (see Section 6.3) but it also ignores the exceptionally low diversion risk associated with medical grade MDMA (see Section 5.7) and the fact that unlike so many legal and recreational drugs MDMA is not addictive.

The Australian Medical Association (AMA)

In the its submission the AMA comment that "*…the treatment of certain medical conditions with MDMA… is an emerging field and research has reported positive outcomes with minimal risk to the patient …. However, more high-quality research using larger scale studies are needed before it can be used more widely by medical practitioners. High quality research would determine the safety and efficacy of using these drugs for mental illness. Currently long-term side effects are not known. For example, the potential to develop psychosis, Hallucinogen Persisting Perception Disorder have not yet been investigated".*

As mentioned in this Submission;

i) We are proposing that the use of MDMA will have to be authorised by a treating psychiatrist or specialist addiction physician for use as part of psychotherapy in medically controlled environments;
ii) As an unregistered medicine access will have to be through the TGA's Special Access or Authorised Prescriber Schemes and an essential part of those schemes is the fact that use is restricted to patients suffering from treatment resistant conditions; and
iii) Under Australia's dual State Federal system, a specific approval would be required from the State or Territory Government where the treatment is to be provided.

With respect, this paragraph is inconsistent with the truth because the Special Access and Authorised Prescriber Schemes are designed to enable medical practitioners to access unregistered medicines at the Commonwealth level with the approval of the TGA in the *Poisons Standard*. Yet the AMA are suggesting this be resolved outside the *Poisons Standard*, thus new legislation and regulation should be used instead of implementing the current regulatory framework. The use of unregistered medicines for trials is dealt with at the Commonwealth level though the TGA's CTN and CTA schemes.

To suggest that studies and experience to date haven't established that MDMA can be used safely in a medically controlled environment is incorrect – see Sections 5.3 and 5.8. Note also that studies to date have shown extremely high rates of efficacy compared to traditional treatments using current psychiatric medicines and without the attendant adverse side effects that are so often associated with current psychiatric medicines (Section 5.3). Long term side effects have been studied and are known (see Section 5.3).

There is also no evidence in any of the trials that a patient undergoing MDMA assisted psychotherapy could face the potential risk of developing psychosis or Hallucinogen Persisting Perception Disorder In addition, as part of the therapy, patients will be screened for any personal or family history of psychosis or other potential precursors (see Section 5.8) and the treatment protocols only provide for 2-3 dosing sessions with MDMA in a medically controlled environment.

We do not understand the AMA's suggestion that studies to date may not have been of a "high quality". There is no basis for that statement.

The AMA go on to say that "*The AMA appreciates the barriers to research as raised by the* applicant*. However, these barriers should be addressed outside of the Poisons Standard Framework. The AMA believes that the need to reduce research barriers does not warrant making psilocybin and MDMA more readily available to practising medical practitioners as it would through down-scheduling. For example, a review of the barriers to MDMA and psilocybin through the Special Access Scheme or the Authorised Prescriber Scheme might be more appropriate."*

With respect, this paragraph does not make any sense because the Special Access and Authorised Prescriber Schemes are designed to enable medical practitioners to access unregistered medicines at the Commonwealth level with the approval of the TGA. However, these Schemes can only work at the State and Territory level if the medical use of MDMA is moved to Schedule 8 of the Poisons Standard. The use of unregistered medicines for trials is dealt with at the Commonwealth level through the TGA's CTN and CTA schemes.

The down scheduling of the medical use of MDMA as part of psychotherapy does not remove the requirement for medical practitioners to seek approvals under the Special Access or Authorised Prescriber Schemes at the State/Territory level.

The Drug Free Australia Submission

The Drug Free Australia submission only focuses on the pathway through to registration of medicines on the Australian Register of Therapeutic Goods. The comments of Drug Free Australia therefore have no relevance to the rescheduling of an unregistered medicine substance on the Poisons Standard.

Other Parties

8 of the parties who opposed our submission refused to allow their names to be publicly identified. It's apparent that at least 3 of these are likely to have been written by the same person. The problem with not disclosing the writer's name is that we can't assess and comment on the credentials of that person or on whether that person may also not be disclosing conflicts of interest that should have been disclosed (such as links to pharmaceutical companies with competing but not very effective psychiatric medicines or the link of a researcher working with a commercial company seeking a monopoly route to register a psychedelic medicine on the ARTG for use in the treatment of specific mental illnesses).

3.2.4 Concluding Comments about the Views of Health Sector Experts

Our Application for Rescheduling has had overwhelming support from Health Sector Experts and this support came from leaders in the fields of expertise directly relevant to the Delegate's decision. This is clearly relevant to Section 52E of the Therapeutic Goods Act 1989 and should have been stated and its importance emphasized in both the summary of the AGSM's advice to the Delegate and in the Delegate's reasons.

In our opinion, both the AGSM and the Delegate should have given the views of these Health Sector Experts much more weight than is apparent from the Interim Decision (where they aren't even mentioned).

We request that these expert views be fully considered in the final decision.

3.3 Reviews by Illingsworth et al and Bahji et al

These reviews mentioned in the Interim Decision are not inconsistent with a down scheduling of MDMA from Schedule 9 to Schedule 8 of the Poisons Standard. As seen in Table 4, these reviews refer to the safety of MDMA when used in a clinical environment, which is a critical aspect of the TGA's rescheduling requirements.

Table 4: Key Points from the Reviews Referred to in the Interim Decision

Bahji et al

- Five study inclusions spanning 13 years from (2004-2017) of 56 experimental participants and 92 overall participants (including control) were used in the review.
- MDMA-assisted psychotherapy was associated with a high rate of treatment response.
- MDMA-assisted psychotherapy also resulted in a significant reduction in the number and intensity of PTSD symptoms with the completion of treatment.
- MDMA-assisted psychotherapy also retained its therapeutic effect (for reducing PTSD symptoms) in follow-up, highlighting its durability.
- Only one out of 56 participants faced adverse events due to the MDMA-psychotherapy (and this was quickly resolved).
- MDM-assisted psychotherapy for treatment resistant PTSD indicates a potential therapeutic benefit with minimal physical and neurocognitive risk.

Illingworth et al

- Four trials since 2013 using 85 participants were used in the meta-analysis.
- The results of this meta-analysis suggest that the use of MDMA in conjunction with psychotherapy is associated with a significant decrease in PTSD.
- Only one out of 85 participants faced adverse events due to the MDMA-psychotherapy.
- MDMA-assisted psychotherapy for treating treatment-resistant PTSD indicates a potential therapeutic benefit with minimal physical and neurocognitive risk.

Note that these points should all be viewed within the context of:

i) the announcement relating to the completion of the first part of the Phase 3 trials (see Section 4 below);

ii) the views of the Health Sector Experts listed in Section 3;

iii) the Breakthrough Therapy Designation granted to these therapies by the FDA referred to in the Interim Decision;

iv) the safety and efficacy data set out in our Rescheduling Application and in this Submission;

v) the current state of mental illness in Australia and the lack of effective treatments for many people suffering from trauma related mental illnesses;

vi) the fact that this is a rescheduling application and not an application to register MDMA on the Australian Register of Therapeutic Goods; and

vii) The very real risks of patients going to underground therapists if their medical practitioners can't access these therapies for their treatment resistant patients under Special Access Scheme – B because of State and Territory prohibitions of the use of Schedule 9 substances, even where the use is for medical purposes.

3.4 A Clinical Memorandum prepared by the Royal Australian and New Zealand College of Psychiatrists called Therapeutic Use of Psychedelic Substances (2020)

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) published a Clinical Memorandum entitled *Therapeutic Use of Psychedelic Medicines* in May 2020 (the Clinical Memorandum). Mind Medicine Australia (MMA) has advised RANZCP that this Clinical Memorandum contains many significant factual errors and misleading statements.

In January 2021 MMA sent the President of RANZCP, Associate Professor John Allan, an article on the Clinical Memorandum entitled *Critique of the Royal Australian and New Zealand College of Psychiatrists psychedelic therapy clinical memoranda* dated *May 2020* written by 9 researchers – https://papers.ssrn.com/abstract=3757891. The Critique is set out in Appendix C.

In the Critique the researchers noted that RANZCP had positioned itself in the Clinical Memorandum against medically controlled patient access to MDMA and psilocybin assisted therapies because of safety concerns and the need for more trials.

The Critique argued that RANZCP's position was based on "*…outdated, irrelevant misinterpreted and misinformed evidence"* and concluded that contrary to the views expressed by RANZCP in the Clinical Memorandum "*There is no scientific or medical evidence from the last 70 years to suggest that either psilocybin or MDMA when administered as an adjunct to therapy in a controlled clinical setting are linked to either mental illness or negative health outcomes. On the contrary, MDMA and psilocybin have been shown to be safe, non-toxic, non-addictive, and efficacious when administered in a medically-controlled environment. All associated risks are apparent in an uncontrolled setting".*

Some of the errors and misleading statements in RANZCP's Clinical Memorandum highlighted by the researchers are summarized in Table 5 below.

TABLE 5: Mistakes and Misleading Statements in the RANZCP Clinical Memorandum

Incorrect RANZCP statement	**What the literature and legislation say (see the detail critique for more information and references)**
Psychedelic substances are illicit and are not registered for any use by the Therapeutic Goods Administration (TGA) in Australia or by Medsafe in New Zealand	Ketamine is an ingredient in many Australian approved medicines. Harmalas have therapeutic indication for use designated by the TGA. Ibotenic acid is approved for use in medicine. DMT containing plants are approved for use in medicines by the TGA. Medsafe NZ has classified MDMA as equivalent of Schedule 8.
Currently psychedelic therapy is not regulated for use in any country	Ketamine-assisted psychotherapy is occurring in Australia. Ibogaine-assisted psychotherapy is occurring in New Zealand. Multiple countries including US, Canada, Switzerland, Israel, Brazil, South Africa, Peru, Gabon, Bahamas, Mexico, Caribbean have either fully legalised and regulated different psychedelics or have regulated expanded access schemes.
Clinical trials have demonstrated safety profile, for example 760 individuals have participated in the MAPS' MDMA trials	Actually, 1,916 participants have participated in MAPS' MDMA trials. But, a further 1,431 participants have participated in non-MAPS' MDMA rials. Further, approximately 500,000 patients participated in MDMA-psychotherapy pre-prohibition.
Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics in various non-psychotic psychiatric disorders	Excluding ketamine, www.clinicaltrials.gov reports over 50 completed psychedelic completed trials since 2006. MAPS report 77 complete MDMA trials post-prohibition.
Psychedelics when misused can cause psychosis (hallucinogen induced psychotic disorder) as well as Hallucinogen Persisting	Both cited reviews [18, 19] by the RANZCP do not refer to either MDMA or psilocybin causing HPPD or psychosis. They refer to

Perception Disorder (HPPD). [18, 19] This is a potential long- term risk factor following psychedelic therapy, though this has not been investigated in research trials.	alcohol, cannabis, PCP, LSD, as well as many other very commonly prescribed psychiatric medications including antidepressants, anxiolytics, and anti-psychotics. Long-term risks and effects of both MDMA and psilocybin-assisted psychotherapies is well studied and documented.
Much about the neuroscience of psychedelics remains unknown, although there are theories that they heighten emotional responses and encourage people to confront their disorder actively, which can prompt enduring shifts in mind-set.	The neuroscience and neuropharmacology of psilocybin, MDMA, and other psychedelics is well studied and documented.

The Clinical Memorandum has also been criticised by members of RANZCP "*for its childish representation of data"* with accusations that the College ignored expert advice and that the Clinical Memorandum did not disclose any authors and was released for political purposes rather than as a statement of scientific fact (Article in the Australian entitled *"Psychedelic Drug Memo sparks uproar" (9/2/21)* reproduced in Appendix D).

TABLE 6: KEY Quotes from Psychiatrists in the Australian Article

"Both (the RANZCP and the TGA) statements appear to unfortunately perpetuate the stigma around these treatments by conflating illicit substances with medicines. They also appear to have been selective with the data used for their respective conclusions." "There's a lot of objections to what they've written. And it's not a good reflection of the literature. There's some misrepresentation around numbers of people, some almost clownish, childish misrepresentation of numbers of people who've been in clinical trials. And they've substantially misrepresented that to the TGA. I don't even know whose produced the memorandum because its pitiful, really".

We also asked Professor David Nutt, a psychiatrist and Professor of Neuropsychopharmacology at Imperial College London and one of the World's foremost researchers in this field to comment on the veracity of RANZCP's Clinical Memorandum and the quality of the Critique. Professor Nutt's letter is set out in Table 7 below.

Table 7: Letter of Professor David Nutt on the Critique of the RANZCP clinical memorandum

Professor David Nutt DM FRCP FRCPsych FMedSci DLaws
The Edmond J Safra Chair in Neuropsychopharmacology
Head Centre for Neuropsychopharmacology
Imperial College London
Burlington-Danes Building
Hammersmith Hospital
Du Cane Rd
London
W12 0NN
•
d.nutt@imperial.ac.uk
Phone +44 207 5946628
Mobile *+447590250428*
•
Feb 22nd 2021

1) I am psychiatrist and professor of Neuropsychopharmacology at Imperial College London. I have worked for almost all my professional life in psychiatry with a particular interest in the addictions and on the effects, both beneficial and harmful, of drugs on the brain. I have extensive clinical and research experience in this field. I am a Fellow of the Royal Colleges of Physicians and of Psychiatrists and of the Academy of Medical Sciences of the UK. In 2004/5 I was the medical lead on the UK government's Foresight committee that provided a 25-year future vision of addiction and brain science.

2) I have published over 500 research papers as well as several hundred specialist reviews and 34 books largely on the effects of drugs on the brain. For over 25 years I have acted as the editor of the Journal of Psychopharmacology one of the top journals in the world on the effects of drugs and the brain. My expertise has been recognised with a number of prestigious appointments including Presidencies of the European Brain Council (2013-2017) and of the European College of Neuropsychopharmacology, the British Association of Psychopharmacology and the British Neuroscience Association.

3) I have also served on the MRC Neuroscience board, and for 16 years I held programme grant funding from the MRC for the study of addictions. With this and other funding I have conducted more human studies on the brain mechanisms of psychedelics and MDMA than anyone else in the world, and have also pioneered studies of their use in depression and in alcoholism. Around half of the top-cited psychedelic research papers in the past decade have come from my group. This expertise has led to my being asked to recently write editorial in leading science [Cell] and medical [JAMA psychiatry] journals. Our new paper showing remarkable efficacy of MDMA in maintaining abstinence in alcoholics has just been published. All three papers are attached to this email.

4) I have been asked to provide an expert opinion on the RANZCP Clinical Memorandum on Psychedelic Therapies (May 2020), the critique of that memorandum by Chiruta et al and on the

TGA's Interim Decision in relation on the rescheduling of Psilocybin and MDMA on the Poisons Standard announced on February 3rd 2021

5) I find the Chiruta et al analysis to be impressive. The Authors have given a comprehensive overview of the issues and the considerable amount of clinical data that now exists to support the use of these medicines. Their conclusions on safety accord well with:

a) Historical evidence of safety and efficacy of LSD and psilocybin from over 40,000 patients studies in many countries – including Australia – in the 1950s and 1960s

b) My own clinical experience of over 200 people administered either psilocybin or MDMA – some of whom were patients with treatment resistant depression and some with significant medical problems occasioned by alcoholism

c) The fact that both psilocybin and MDMA have investigators brochures that supply pre-clinical safety data of pharmaceutical research standards and that have been approved by the UK MHRA and the US FDA

d) There is outstanding evidence of the neuroscience behind the therapeutic effects of these medicines. It should be noted that my group's decision to use psilocybin for resistant depression was based on the imaging data showing it attenuates activity in the brain circuits that drive this disorder. – see CELL review

e) A major review of the safety of psychedelic therapy that our group is finalising that shows the following

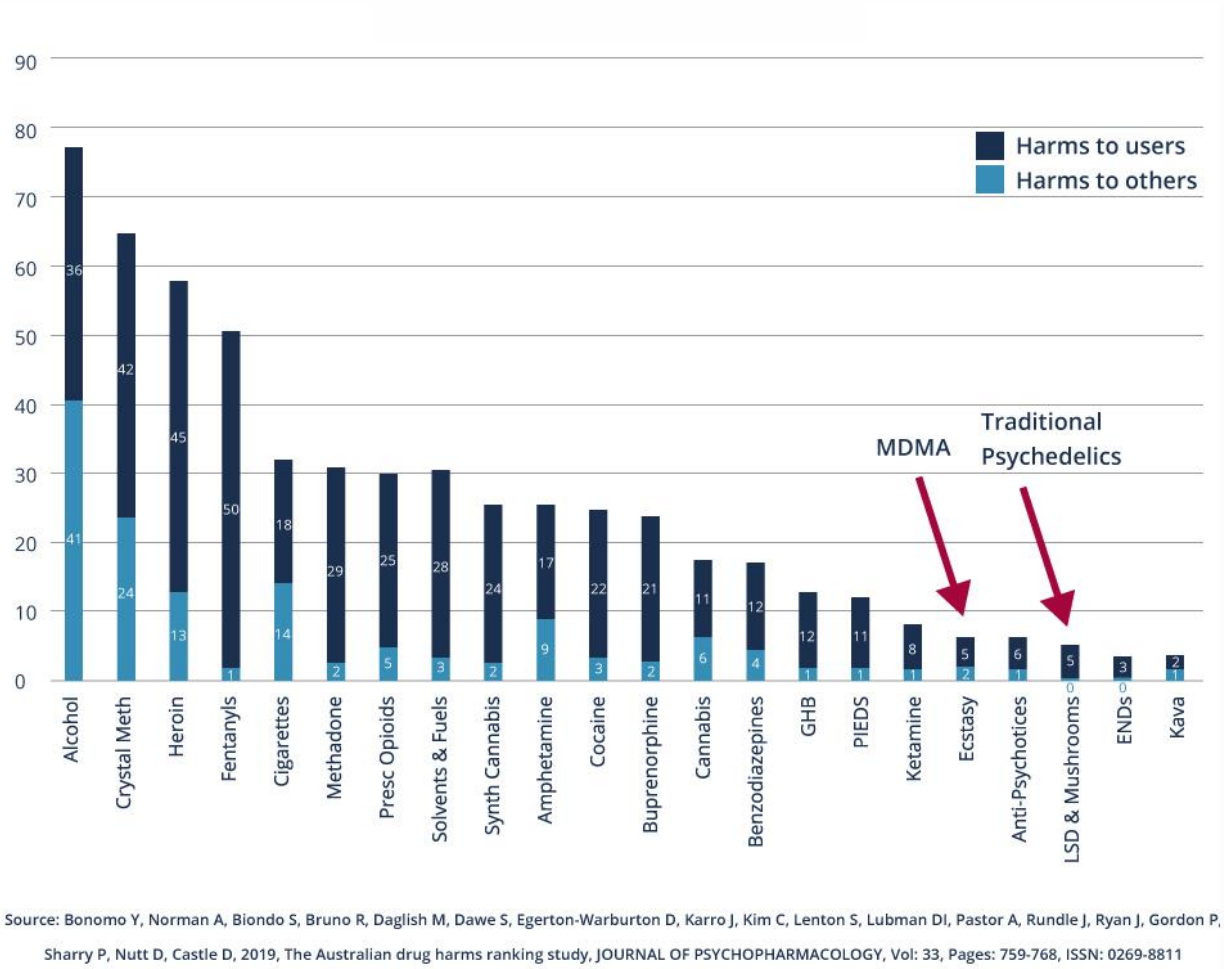
   i) Little evidence of clinically meaningful cardiovascular effects – very minor and totally manageable elevations in heart rate and blood pressure

   ii) Very rare precipitation of psychosis [though we recommend that people with pre-existing psychosis or first degree family relatives with psychosis should not undergo psilocybin treatment at present]

   iii) No deaths when treatment is given in a medical setting, and significant reductions in suicidal behaviour and thinking

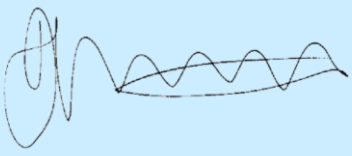
Overall, it seems to me that the TGA's Interim Decision is significantly biased towards historical misinformation regarding the potential harms of these medicines when used in non-medical settings. But even there they are safer than almost all other recreational drugs – see figure from recent Australian analysis. When used in medical settings their safety will easily be within that of other psychiatric medicines and probably safer than most because they are given just once or twice.

The Figure below of the 2019 Australian drug harms survey shows psilocybin and MDMA [ecstasy] to have very low harms to users and society



Source: Bonomo Y, Norman A, Biondo S, Bruno R, Daglish M, Dawe S, Egerton-Warburton D, Karro J, Kim C, Lenton S, Lubman DI, Pastor A, Rundle J, Ryan J, Gordon P, Sharry P, Nutt D, Castle D, 2019, The Australian drug harms ranking study, JOURNAL OF PSYCHOPHARMACOLOGY, Vol: 33, Pages: 759-768, ISSN: 0269-8811

Taken in totality I can see no good reason why psilocybin and MDMA should not be moved into Schedule 8 of the Australian Poisons Standards to facilitate research particularly clinical studies and to enable these treatments to be properly made available around Australia through Australia's Special Access Scheme. We are in the process of making similar requests for re-scheduling in the UK.



Prof David Nutt FMedSci

Attached – Cell JAMA and BIMA papers [See Appendix E for these papers]

The other problems with the Clinical Memorandum are:

1. That the author(s) name(s) are not given making it impossible for the reader to assess their relevant qualifications and expertise of the writer(s) of the Clinical Memorandum.
2. That there is no disclosure statement in the Clinical Memorandum about the author(s) conflicts or potential conflicts – this sort of disclosure should be a normal part of a peak body's governance practices given the impact and credibility that practice notes normally have.
3. That it is not apparent that the Clinical Memorandum was peer reviewed in accordance with normal practice (see comments of psychiatrists in press article reproduced in Table 6 and Appendix D).

Based on the above, MMA strongly believes that the RANZCP Clinical Memorandum ***is not*** a document that either the ACMS or the Delegate can properly use to support an Interim Decision against down scheduling the medical use of MDMA as an adjunct to therapy from Schedule 9 to Schedule 8 of the Poisons Standard.

4. MATERIALS THAT MAY NOT HAVE BEEN CONSIDERED BY THE DELEGATE

Since Mind Medicine Australia submitted its Rescheduling Application to the TGA in July 2020 for MDMA to be used as part of therapy in medically controlled environments, further developments around the World with MDMA assisted psychotherapies highlight the continuing positive momentum:

- MAPS have completed the first of two randomised, double-blind placebo controlled multi-site Phase 3 clinical trials with 100 participants with severe PTSD required by the FDA as part of the medicine registration process in the United States. The paper summarizing the results of this first phase 3 clinical trial is currently being peer reviewed and is expected to be published in a leading journal in the next few months. The results are expected to be robustly significant with a large effect size and show an excellent safety record. They are also understood to be better than the Phase 2 results which showed remission in 52% of cases immediately after the therapy increasing to 68% in the 12 month follow up. We understand that the TGA can easily verify this Phase 3 trial information through their direct connections with MAPS in the United States.

- Results for the first study of safety and tolerability of MDMA-Assisted Psychotherapy in Patients with Alcohol Use Disorder have been published in the Journal of Psychopharmacology – (https://doi.org/10.1177/0269881121991792) – and reproduced in **Appendix F.** The study showed that MDMA was well tolerated by all participants with no unexpected adverse events observed. At 9 months post detox the average units of alcohol consumption of participants were 18.7 units per week compared to 130.6 units per week before the detox.

- Australia's TGA has granted approximately 10-15 approvals for the use of MDMA as part of psychotherapy under Australia's Special Access Scheme – B for the treatment of patients suffering from Treatment Resistant PTSD.

- Health Europa has recommended that MDMA be rescheduled to Schedule 2 of the *United Nations Convention* (https://www.healtheuropa.eu/why-mdma-must-be-reclassified-as-a-schedule-2-drug/95780/).

- Expanded access schemes for MDMA assisted therapies continue to be available for patients and their doctors in the United States, Switzerland, Israel and Australia (although in Australia the Schedule 9 listing of MDMA for medical use means that these therapies remain prohibited at the State and Territory level even where the prescribing doctor has received approval from the TGA under Special Access Scheme – B or as a TGA approved Authorised Prescriber.

- The for-profit sector and investor interest around the World, focused on the development and application of psychedelic assisted-therapies for the treatment of key classes of mental illness, has continued to rapidly expand with the potential size of the market globally estimated to worth up to US$200 billion. There are now over 50 for profit companies working on developing and applying these therapies in the United States and Europe compared to just one company 2 years ago.

- The Icahn School of Medicine at Mount Sinai has just launched the Centre for Psychedelic Psychotherapy and Trauma Research to pursue a multi-pronged clinical and research approach to discovering novel and more efficacious therapies for post-traumatic stress disorder (**PTSD)**, depression, anxiety and other stress-related conditions in the veteran and civilian populations.

- Mind Medicine Australia has commenced its Certificate Course in Psychedelic-Assisted Therapies (CPAT) to train medical and health practitioners in the safe use of these therapies - discussed later in this Submission (See Section 5.8). The first course of 47 involving students started in January 2021.

- The work being done by clinical group Emyria Limited in conjunction with Mind Medicine Australia to develop protocols, standard operating procedures and training manuals for the clinical application of MDMA (and psilocybin) assisted therapies in Australia (see Section 5.8)

The Delegate made the comment in the Interim Decision that no comparable country has classified MDMA as equivalent of Schedule 8 of our Poisons Standard (See Section 6.9 below). This is not correct. MDMA has been classified in New Zealand as a Class B1 substance since 2015. Class B substances are equivalent to Schedule 8 substances in Australia. Other Class B1 substances include morphine, amphetamines, medicinal cannabis and THC.

5. THE SUMMARY OF THE ACMS ADVICE TO THE DELEGATE

5.1 The Advice Received by the Delegate Should be Publicly Released in Full.

We believe that public confidence in the TGA's Scheduling System necessitates that the TGA's briefing papers and the ACMS advice to the Delegate should be released publicly in their entirety.

We believe that this is necessary because of the prejudice and stigma associated with MDMA as a substance, the confusion between recreational use and its use as a medicine, the profound need for new and more effective treatment options, the strong safety and efficacy data supporting MDMA assisted psychotherapy set out in our Rescheduling Application, the high remission rates to date in overseas trials, , the overwhelming number of submissions supporting the rescheduling and the fact that the TGA's briefing papers and the ACMS advice cannot possibly be commercial-in-confidence.

We therefore respectfully request that the TGA's briefing papers and the ACMS advice to the Delegate is released to the public in full as a matter of urgency so that we can all properly review these materials for accuracy and completeness.

5.2 Advice under (a) Benefits of the use of a substance

The ACMS notes that:

"There is limited but emerging evidence that MDMA-assisted psychotherapy may have therapeutic benefits in the treatment of PTSD. These benefits are currently under investigation in clinical trials.

Our Response

The large number of trials that have been completed with MDMA assisted psychotherapy both pre prohibition and over the last 20 years have shown high remission rates for treatment resistant conditions. This demonstrates that the therapeutic benefit of MDMA has been clearly shown.

There have been over 70 completed post-prohibition trials over the last 30 years including many Phase 1, Phase 2, and one Phase 3 trial MAPS Investigator's Brochure 2020, p. 56, https://mapscontent.s3-us-west-1.amazonaws.com/research-archive/MDMA+IB+12th+Edition+Final+17AUG2020.pdf). All trials have been successful. This is excluding the approximately 500,000 doses administered MDMA therapeutically pre-prohibition (MAPS Investigator's Brochure 2020, p. 57).

PTSD (post-traumatic stress disorder) is notoriously hard to treat, with current antidepressant pharmacotherapy achieving relief from symptoms in only about 20%-30% of sufferers (Stein et al. 2009). While 44% of patients experience some clinical improvement in their PTSD symptoms from trauma focused psychotherapies, 60-72% still retain the PTSD diagnosis, with 35% still experiencing debilitating symptoms (Bradley, 2005; Lee et al. 2016; Steenkamp et al; 2015). A significant impediment to the treatment of PTSD is the high drop-out rate ranging from 30-50%

across clinical trials, significantly higher than for other mental health disorders (Schottenbauer et al., 2008). Therapeutic efficacy is limited by a PTSD patient's 'narrow therapeutic window', caused by the anxious arousal associated with traumatic memory (Thal & Lommen 2018). This means psychotherapy can be confronting for patients and can lead to traumatisation and/or dissociation symptoms.

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

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

MDMA-assisted therapy has been granted 'Breakthrough Therapy' status by the US Food and Drug Administration (FDA), expediting its transition to prescription medicines subject to positive outcomes from current Phase 3 trials (MAPS PR, 2017). This designation highlights the FDA's anticipation that MDMA-assisted therapies may offer substantial advantage over current treatments. An interim report on the MAPS Phase 3 trial revealed a 90% or greater chance that the completed trial will show significant results (MAPS PR3, 2020). Release of the final data is expected early in 2021 and is understood to demonstrate even stronger safety and efficacy benefits than the Phase 2 trials.

MDMA has recently been approved for advanced access "Compassionate Use" in Israel for patients who have not improved with current treatment modalities (MAPSPR2, 2020). Likewise, MDMA has received approval for use under a similar program (Expanded Access) in the USA (MAPS PR1, 2020), Switzerland and, more recently, Australia (under Special Access Scheme-B).

Key aspects of the therapeutic benefit of MDMA as part of therapy are summarised below.

1. **Positive Psychological Effects**

Outcomes for psychotherapy rely on a strong therapeutic alliance between patient and therapist which can be challenging for many patients with PTSD (Schottenbauer et al., 2008). PTSD patients

are described as having a narrow therapeutic window, meaning psychotherapy can trigger patients outside the zone of optimal arousal and into overwhelm, leading to dissociation or re-traumatisation (Mithoefer, 2011).

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

2**. Reduction of Fear Response and Memory Reconsolidation**

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

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

There is a lot more information in our Rescheduling Application about the established therapeutic value of the use of MDMA as part of psychotherapy for treatment resistant PTSD. Further support is given in the Expert Letters contained in Appendix A of our Rescheduling Application and extracted in Table 3 in Section 3.2 above.

We believe that there is ample evidence to show that MDMA has an established therapeutic value when used as part of psychotherapy for treatment resistant PTSD.

See in particular the supporting views of Professor Arthur Christopoulos set out in his submission to the TGA (reproduced in Appendix M) on established therapeutic value and safety. Professor Christopoulos is Professor of Analytical Pharmacology and Dean of the Faculty of Pharmacy and Pharmaceutical Sciences at Monash University (which ranks second in the World in its field) and one of the most credentialed people in Australia in relation to these subjects.

It should be noted that we are not applying for MDMA to be listed as a publicly available medicine on the Australian Register of Therapeutic Goods, where vigorous efficacy must be proven. MDMA

is seeking to have the Poisons Standard Scheduling of MDMA changed by moving the medicinal use of MDMA when used as part of therapy from Schedule 9 to Schedule 8.

Nabiximols and Cannabis have Schedule 8 controls in place for medical use whilst remaining in Schedule 9 when used recreationally. They are mentioned because much less clinical evidence was available for Nabiximols and Cannabis when they were rescheduled then would have been the case if registration on the ARTG had been sought. It should also be noted that at the time of rescheduling both medicines were in Schedule 1 of the *United Nations Convention on Psychotropic Substances 1971*.

Despite the period that has elapsed since the rescheduling of Nabiximols and Cannabis neither have enough efficacy data to be listed on the ARTG. Yet a significant number of patients have been able to access these medicines under Special Access Scheme-B or through the TGA's Authorised Prescriber Scheme.

Some Schedule 4 and Schedule 8 medicines have no clinical data and have even failed Phase 3 trials Examples include SARMs, ibogaine, synthetic cathinones, synthetic cannabinomimetics, and cannabis. Yet these medicines are still available for prescription. Applying an ARTG registration standard to the rescheduling of MDMA is not a required rescheduling parameter under the Poisons Standard.

5.3 Advice under (a) Risks of the use of a substance

The ACMS notes that:

"Acute effects include high blood pressure and pulse rate, faintness and panic attacks. In severe cases, MDMA can cause loss of consciousness and seizures."

Our Response

We refer the ACMS and the Delegate to the views of leading experts in this field set out in Section 3.1 of this Submission to the effect that these medicines can be used safely as part of therapy in medically controlled environments.

See also the supporting views on safety of Professor Arthur Christopoulos in Appendix M and Professor David Nutt in his letter reproduced in Table 7 in Section 3.4

MDMA-assisted psychotherapy has been conducted since the 1960s. There is an extraordinary amount of evidence about side-effects both short and long-term.

There is no evidence that the medicinal use of MDMA as part of therapy in a controlled medical environment has caused loss of consciousness and seizures.

Cardiovascular (CV) Effects

As a sympathomimetic, MDMA can cause increases in Blood Pressure (BP) and Heart Rate (HR). No participants required medical intervention in MAPS sponsored studies (MAPS, 2019). Most individuals do not experience rises in BP and HR beyond that seen during moderate exercise.

Greater elevations were observed in people with specific COMT and SERT genotypes but these were not severe enough to warrant contraindication. In a study of MDMA in 166 psychologically healthy individuals, transient severe hypertension (systolic blood pressure > 180 mmHg) was observed in 5% of participants on a 125mg dose of MDMA (Vizeli and Liechti et al, 2017). The duration of these Adverse Events (AE) was not long enough to require medical intervention. Individuals with cardiovascular disease that is poorly controlled by medication are contraindicated in current studies (MAPS, 2018).

Historic Use also Without Incident

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

1. Page 90 of the MAPS Investigator's Brochure does not list that any participant in MDMA trials within the last three decades has ever experienced faintness or panic attacks. There will inevitably be cardiac changes because of MDMA's affinity with the andrenergic system.
2. It is a well-documented fact that antidepressants can cause:
    a. Nausea
    b. increased appetite and weight gain
    c. loss of sexual desire and other sexual problems, such as erectile dysfunction and decreased orgasm
    d. fatigue and drowsiness
    e. insomnia
    f. dry mouth
    g. blurred vision
    h. constipation
    i. dizziness
    j. agitation
    k. irritability
    l. anxiety

The ACMS also notes that:

> ***"Secondary effects include involuntary jaw clenching, lack of appetite, depersonalization, illogical or disorganized thoughts, restless legs, nausea, hot flashes or chills, headache, sweating and muscle/joint stiffness."***

Our Response

That is all correct and it should be seen as positive that potential secondary effects are already established. Usually Phase 3 and 4 trials need to be completed for this data but MDMA has now been extensively used in psychotherapy, clinical trials and recreationally for over 50 years. It should also be noted that side-effects data are a requirement for medicine registration on the ARTG but is not part of the requirements for poisons classification.

All of these secondary side effects are transitory and can be easily managed in a medically controlled environment.

The ACMS goes on to say;

"Long-term use can result in sleep disturbances, difficulties with concentration, depression, heart disease, impulsivity and decreased cognitive function."

Our Response

The obvious starting point to make here is that these therapies only involve two to three medicinal sessions with medical grade GMP standard MDMA. We are not talking about long-term use. The obvious contrast here is antidepressants which are often given to people with PTSD and which ***can*** cause each of the above adverse side effects listed above and many others including suicidal ideation (See Section 2 above).

Finally, the ACMS notes that:

"MDMA can reduce the ability to perceive and predict motion and can therefore result in accidents."

Our Response

This point also confuses the recreational and medical use of MDMA. Under the proposed therapies MDMA is only given to the patient two to three times in a medically controlled environment with two therapists in attendance during the therapy session. The patient does not leave the clinic or hospital whilst still under the influence of MDMA.

There are Appendices in the Poisons Standard that are specifically designed to address this issue.

5.4 Advice under (b) The purposes for which a substance is to be used and the extent of use of a substance

We agree with the comments of the ACMS under this heading but note that these therapies are also being trialed for substance abuse (particularly alcoholism).

5.5 Advice under c) The Toxicity of a Substance

According to ACMS the lethal dose of MDMA is:

"…10 – 20mg/kg"

Our Response

It's very positive that a lethal dose has been established, as the establishment of a lethal dose is not a requirement for Scheduling under Schedule 8. However, it is a requirement for listing a medicine on the ARTG, which we are not seeking to do in our application.

We should also add that plenty of medicines have far worse medical dose to lethal dose ratios including fentanyls which are used in medicine to treat pain - see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311234/figure/f1/

We should also add that plenty of medicines have far worse therapeutic dose to lethal dose ratios including fentanyls which are used in medicine to treat pain - see https://www.ncbi.nim.nih.gov/pmc/articles/PMC4311234/figure/f1/

Table 8A: Safety index (between the lowest effective dose of a drug and its highest tolerated dose) or the therapeutic index (effective dose of a drug in comparison with its lethal dose), ranking from safest ratio downwards, displayed as safety and therapeutic index.

Drug	Safety Index	Therapeutic Index
Psilocybin	1000	1000
Paracetamol	10	10
MDMA	10	10
Heroine (Diamorphine)	10	6
Methadone	5	-
Cocaine	4	15
THC	4	-
Nicotine	3	-
Methane	3	-
Diazepam	2	-
Alcohol	1.5	-

- https://dx.doi.org/10.1038%2Fsrep08126
- https://doi.org/10.1136/bmj.h2902
- https://doi.org/10.1177%2F102490790200900305

The ACMS goes on to say that:

"The potential adverse effects are unknown in the context of psychotherapy."

Our Response

This is not correct. 76 Phase 1 and 2 trials have been completed post prohibition and one Phase 3 trial, totaling over 3,000 participants. 500,000 individuals received MDMA in psychotherapy pre-prohibition. Adverse effects are very well documented in the literature.

Table 8B: MAPS Reported trial participants who have received MDMA

Year	# of participants	Source
Pre-1987	> 500,000	Investigator's Brochure 2020, p.56
2000-2012	811	Investigator's Brochure 2013, p.54
as of 2015	1,180	Investigator's Brochure 2016, p.92

as of 2016	1,280	Investigator's Brochure 2017, p.133
as of 2018	>1500	Investigator's Brochure 2018, p.127
as of 2019	(MAPS) 1,837	Investigator's Brochure 2019, p.63
as of 2020	(non-MAPS) 1,431	Investigator's Brochure 2020, p.14
in 2020	79	Safety Update Report 2020, p.29

Chiruta et al. 2021, p. 5, https://papers.ssrn.com/abstract=3757891

5.6 Advice under (d) The dosage, formulation, labelling, packaging and presentation of a substance

According to the ACMS,

"Optimal dosages have not been established, especially outside of PTSD treatment."

Optimal dosage of a drug is not relevant to a Poisons Standard reclassification. An 'optimal dose' is only ever defined when the TGA has approved a dose for a medicine listed on the ARTG. We have ***not*** applied for MDMA to be listed as a medicine on the ARTG. Our Rescheduling Application would limit the use of MDMA to psychiatrists and specialist addiction physicians treating patients with treatment resistant mental illnesses associated with trauma and these treatments would only be available on a case-by-case basis with specific TGA and relevant State Government approvals. Medicinal cannabis has even less of an established dose. Many other unregistered Schedule 4 and Schedule 8 have no 'optimal dose'.

In the MAPS Phase 3 trials an initial does of between 80 -120mg is being used with a supplemental dose of between 40–60mg if the initial dose is well tolerated and with clinician judgement. MDMA is dose dependent like many Schedule 8 medicines. Generally, when an established dose of a pharmaceutical is defined, a pharmacokinetic calculation is created on the C_{max} in comparison with efficacy, which can present challenges for dose-dependent medicines. Furthermore, most available medicines have a recommended dose based on patient weight, tolerance, P450 expression or other drug inhibition/induction, genetics, age, sex, diet, and other factors.

Based on the above factors, trials to date have used an 85, 100, or 125mg initial dose with a 50% dose booster if needed. In other words, a therapeutic dose has been clearly established from evidence based on the last 30 years in over 70 clinical trials. (MAPS Investigator's Brochure 2020, p. 57)

The ACMS goes on to say:

"***A typical dose in the context of psychotherapy is 1-2 mg. This is often followed by an optional half-dose 1.5 to 2.5 hours into the session."***

Our Response

This statement is not correct. We assume that ACMS meant 1 – 1.5 mg ***per kg of body weight***.

AS mentioned above, MAPS are using two different dosing formats in their Phase 3 trials:

- 120mg with a 60mg optional supplement; and
- 80 mg with a 40mg optional supplement.

5.7 Advice under (e) The potential of abuse of a substance

According to ACMS:

"***It is not clear whether MDMA causes dependence. However, it affects many of the same neurotransmitter systems in the brain that are targeted by drugs with an abuse and dependence liability, and some studies report symptoms of dependence in users."***

Our Response

Recreational misuse and abuse have been linked in some cases with psychological dependence. However, these comments by the ACMS are not relevant to the use of MDMA as a medicine and as part of therapy in a medically controlled environment with only 2-3 dosed sessions being required.

Medicinal MDMA does not produce dependence as defined in the contemporary versions of the *Diagnostic and Statistical Manual of Mental Disorders* or the *International Statistical Classification of Diseases* (Kalant, H. 2001)1. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *CMAJ*, 165(7), pp. 917-928).

It should also be noted that the DSM-IV criteria were inconclusive on whether recreational MDMA causes dependence (https://doi.org/10.1016/j.drugpo.2014.07.004).

1. Nutt DJ King LA Phillips LD (2010) Drug harms in the UK: a multicriteria decision analysis Lancet 376: 1558-65 http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2810%2961462-6/abstract
2. van Amsterdam J, Nutt D, Phillips L, van den Brink W (2014) European rating of drug harms. Journal of Psychopharmacology 2015 Apr 28. pii: 0269881115581980

3. Bonomo Y, Norman A, Biondo S, Bruno R, Daglish M, Dawe S, Egerton-Warburton D, Karro J, Kim C, Lenton S, Lubman DI, Pastor A, Rundle J, Ryan J, Gordon P, Sharry P, Nutt D, Castle Det al., 2019, The Australian drug harms ranking study, *JOURNAL OF PSYCHOPHARMACOLOGY*, Vol: 33, Pages: 759-768, ISSN: 0269-8811

In three separate studies in the UK, Europe, and Australia, both MDMA (evaluated as ecstasy) and psilocybin (evaluated as magic mushrooms) ranked as the drugs that cause minimal and least harm to the user and society with little to no dependence.

Drug Harms in the UK (Nutt et al. 2010, Lancet, 376, pp. 1558-1564)

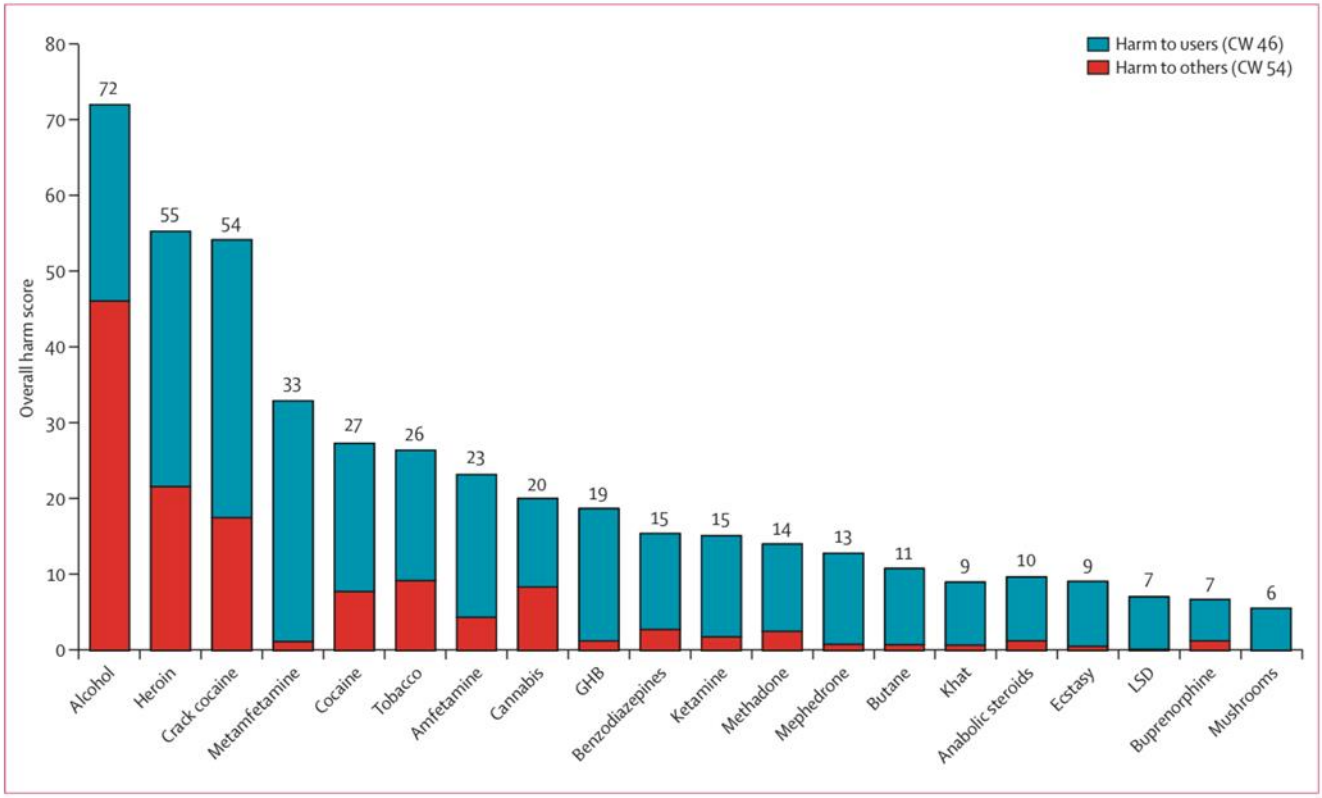


Figure 2: **Drugs ordered by their overall harm scores, showing the separate contributions to the overall scores of harms to users and harm to others**
The weights after normalisation (0–100) are shown in the key (cumulative in the sense of the sum of all the normalised weights for all the criteria to users, 46; and for all the criteria to others, 54). CW=cumulative weight. GHB=γ hydroxybutyric acid. LSD=lysergic acid diethylamide.

European Rating of Drug Harms (van Amsterdam et al. 2015, *J Psychopharm*, 29(6), pp. 655-660)

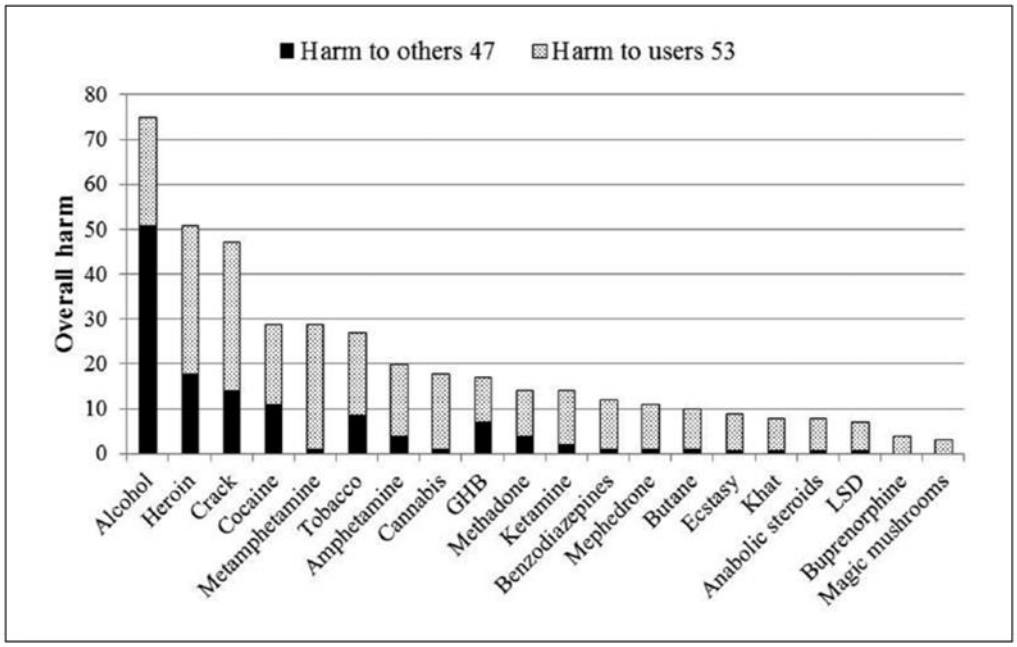


Figure 2. The drugs ordered by their overall harm scores, with the stacked bar graphs showing the contribution to the overall score of harm to others and harms to users with a cumulative weight of 47 and 53, respectively. GHB; gamma-hydroxy-butyric acid; LSD: lysergic acid diethylamide.

The Australian Drug Harms Ranking (Bonomo et al. 2019, *J Psychopharm*, 33(7), pp. 759-768).

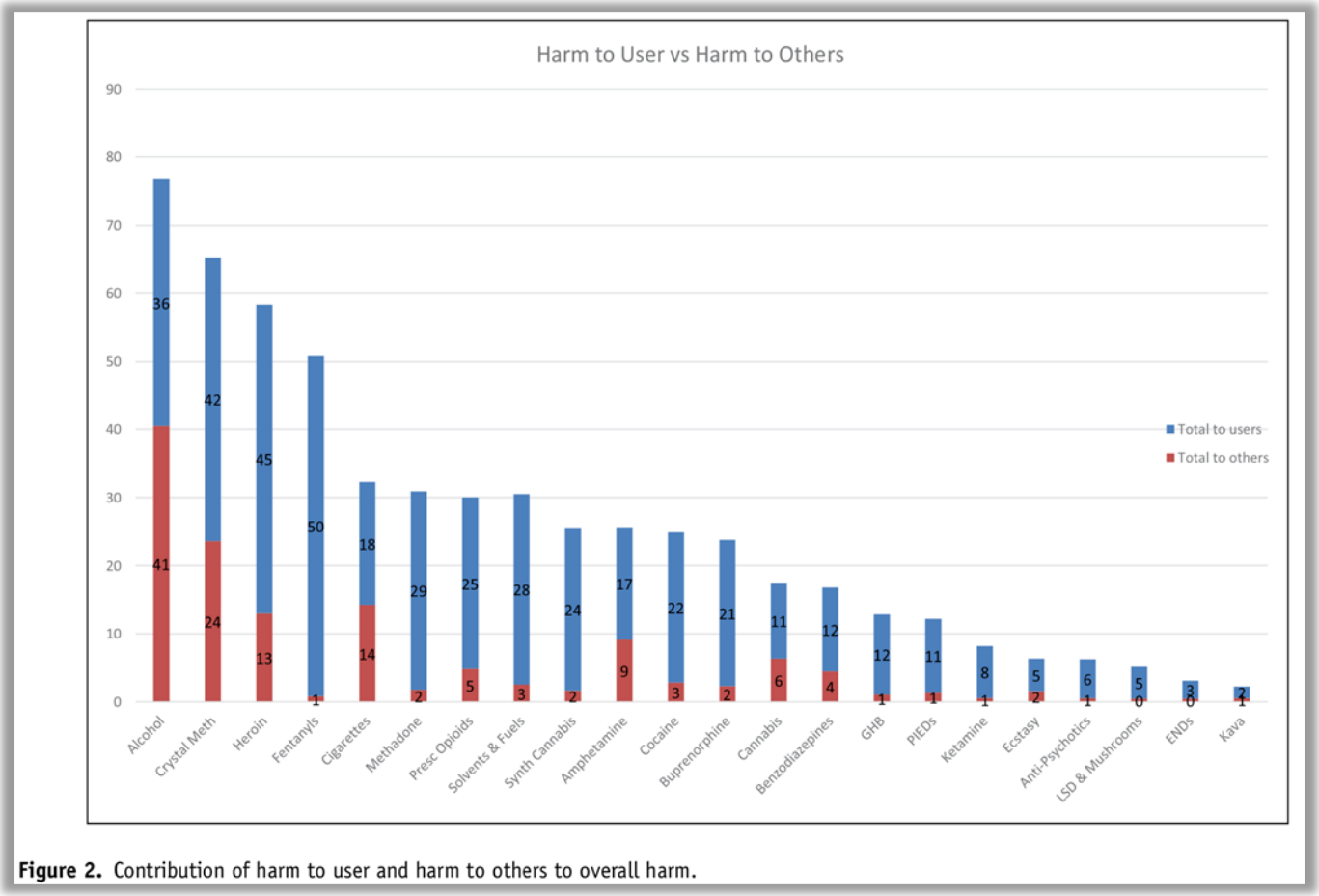


Figure 2. Contribution of harm to user and harm to others to overall harm.

The ACMS go on to say that;

"There is a high risk of diversion for misuse, even in conjunction with Schedule 8 controls."

<u>Our Response</u>

We believe that this is a very simplistic statement for two reasons.

Firstly, there is a potential high risk of abuse of every Schedule 8 substance, many Schedule 4 substances, and some unscheduled substances. All the below mentioned substances carry a greater risk of harm, misuse and/or abuse in comparison to MDMA.

Schedule 8 substances would include:

- Methamphetamines
- Cocaine
- Morphine and all analogues
- Cannabis
- Ketamine
- Fentanyl and other narcotics/opioids
- Opium
- Prescription Amphetamines

Schedule 4 substances would include:

- Anabolic androgenic steroids
- Selective androgen receptor modulators (SARM)
- Non-Amphetamine Stimulants (ADHD/ADD medications)
- Antiepileptics / Anticonvulsants
- Antipsychotics
- Antidepressants
- Anxiolytic medication/Benzodiazepines
- Ibogaine
- Codeine

Unscheduled substances would include:

- Alcohol
- Cigarettes

Most of these substances are much more dangerous than MDMA in a recreational context. They also have much more dependence liability and harms.

Table 9A: All Drug induced Deaths in 2018 by Drug Type

	All drug-induced deaths	Unintentional drug-induced deaths
All opioids	1130	900
Benzodiazepines	899	648
All Pharmaceutical Opioids	647	457
Anti-depressants	591	382
Stimulants	501	442
Oxycodone, morphine, codeine	484	321
Heroin	438	402
Alcohol	435	322
Anti-psychotics	318	223
Cannabinoids	363	328
Fentanyl, pethidine, tramadol	243	189
Methadone	225	207
Anti-convulsants	174	128
Specified anti-convulsants and sedatives	107	65
Cocaine	64	61
Other sedatives	16	12
Succinimides and oxazolidinediones	7	6

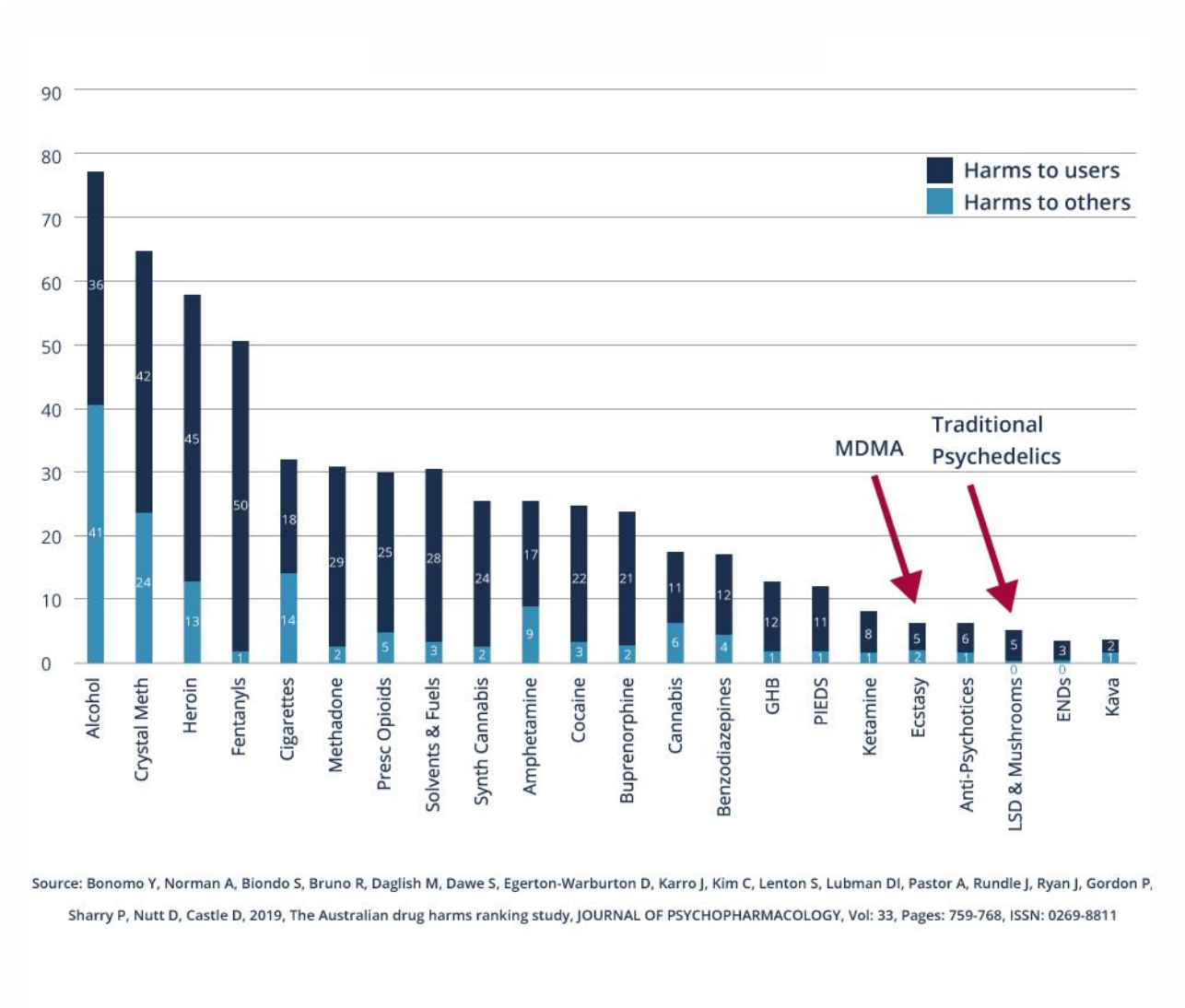
Source: https://www.penington.org.au/wp-content/uploads/Australias-Annual-Overdose-Report-2020.pdf

Table 9B: Hospital separations by drug-related principal diagnosis, 2012–13 to 2016–17

Drug of concern	2012–13	2013–14	2014–15	2015–16	2016–17
Analgesics					
Opioids	7,438	8,153	8,365	8,904	8,615
Non-opioid analgesics	7,525	7,301	7,579	8,545	9,144
Sedatives and hypnotics					
Alcohol	62,359	64,248	65,701	68,239	70,011
Other sedatives and hypnotics	8,919	8,717	9,173	9,857	10,414
Stimulants and hallucinogens					
Cannabinoids	4,314	4,991	5,550	6,020	6,302
Hallucinogens	215	214	241	263	339
Cocaine	444	523	827	776	818
Tobacco and nicotine	60	84	77	72	96
Methamphetamines	1,741	2,782	4,612	7,762	8,652
Other amphetamines	4,644	5,055	6,765	7,302	5,654
Other stimulants	400	434	377	413	391
Antidepressants and antipsychotics	7,924	7,827	8,264	9,104	9,290
Volatile solvents	805	884	901	818	875
Other and unspecified drugs of concern					
Multiple drug use	4,580	4,564	5,294	5,649	5,176
Unspecified drug use and other drugs not elsewhere classified	299	256	295	352	374
Foetal and perinatal conditions	**27**	**27**	**26**	**5**	**12**
Total	**111,910**	**116,337**	**124,483**	**135,001**	**137,203**

Source: https://www.aihw.gov.au/reports/alcohol-other-drug-treatment-services/drug-related-hospitalisations/contents/content

This risk analysis was highlighted in a recent study involving addiction specialists and emergency recreational drug responders – see Relative Drug Harms Table below.



Source: Bonomo Y, Norman A, Biondo S, Bruno R, Daglish M, Dawe S, Egerton-Warburton D, Karro J, Kim C, Lenton S, Lubman DI, Pastor A, Rundle J, Ryan J, Gordon P, Sharry P, Nutt D, Castle D, 2019, The Australian drug harms ranking study, JOURNAL OF PSYCHOPHARMACOLOGY, Vol: 33, Pages: 759-768, ISSN: 0269-8811

Secondly, there are established Schedule 8 controls that are designed to minimise risks associated with Schedule 8 substances, which would also be applied to the rescheduled use of medicinal MDMA. In particular:

i) The unlawful diversion by medical practitioners carries criminal liability.

ii) When delivering schedule 8 substances one/two doctor(s), nurse(s) or pharmacist(s) must sign on receival and each tablet must be accounted for in storage or delivery in a continuously maintained book, in which every single movement of drugs is recorded, including administration, dispensing and deliveries. This is the case in all facilities that hold any schedule 8 substances.

iii) Schedule 8 substances also require constant counting on regular time intervals to ensure no stock is missing and the balances are correct.

iv) Destruction or disposal of schedule 8 substances requires two signatures and an extra entry record to be made in a special schedule 8 destruction book.

v) In many if not all States and Territories it is illegal for a doctor to prescribe a schedule 8 substance for themselves and family members.

vi) All schedule 8 substances must always be stored in a safe that is locked at all times, except when opening the safe to obtain access to the medicines.

vii) Schedule 8 substances also require special labelling, they must feature on the box or bottle label that States, "controlled drug".

Thirdly, (and perhaps most importantly), it's not obvious why any medical practitioner or pharmacist working in a hospital or clinical environment would take the risk of breaching Schedule 8 controls given that MDMA can easily be accessed in Australia in the Black Market at much cheaper prices than the likely price of synthesized medical grade MDMA.

The lack of diversion risk was very clearly set out in the submission given to the TGA by the Australian Institute in Canberra and Fearless in a joint submission (see Appendix H).

5.8 Advice under (f) Any other matters that the Secretary considers necessary to protect public health

According to ACMS:

"There are significant benefits to waiting for the results of the clinical trials. MDMA-assisted psychotherapy may prove to be safe and efficacious, but the evidence does not yet suggest this – especially for conditions outside PTSD."

Our Response

There are a number of very real problems with this advice:

Firstly, we are not suggesting that MDMA be used as part of therapy where the underlying cause is not related to trauma. This applies to both PTSD and most forms of substance abuse.

Secondly, there is already a lot of evidence on the safety and efficacy of MDMA when used as part of therapy in medically controlled environments.

We have already provided evidence that medicinal MDMA, when used as part of psychotherapy, is safe and effective:

1. In the expert letters and endorsements set out in Section 3 above;
2. In detail in our Rescheduling Application – see pages 9-13 and 25-27; and
3. In this Section 5 of this Submission.

We should also add here that efficacy in the context of rescheduling is not relevant. MDMA is not being proposed as an approved medicine registered on the ARTG. The application is for a Poisons Standard rescheduling.

Safety is proven from over 70 clinical studies conducted in the last 30 years (MAPS Investigator's Brochure 2020, p. 57) Our Rescheduling Application thoroughly addresses these issues.

We should also add that many Schedule 8 and Schedule 4 substances do not have proven efficacy or safety data. Examples are given in Table 10 below.

Table 10: Examples of Schedule 4 and 8 substances without substantial human efficacy data

Schedule 4

1) **Selective Androgen Receptor Modulators (SARMs)**

The listed SARMs below do not have proven human efficacy data:

a. MK-2866 (Enbosarm) – only has one Phase 1 and one Phase 2 clinical trials complete, with two failed Phase 3 clinical trials. The FDA have announced a serious adverse warning for using MK-2866, but it is available in Australia at some pharmacies and is still actively prescribed.
b. RAD-140 (Testolone) – still in pre-clinical in vivo studies but is available at some pharmacies and is still actively prescribed.
c. LGD-4033 (Ligandrol) – only has one Phase 1 and one Phase 2 clinical trials complete, with no Phase 3 clinical trials but is available at some pharmacies and is still actively prescribed.
d. AC-262,536 – still in pre-clinical in vitro studies but available for prescription.
e. LGD-2226 – still in pre-clinical in vitro studies but available for prescription.
f. LGD-3303 – still in pre-clinical in vivo studies but available for prescription.
g. S-40503 – still in pre-clinical in vivo studies available for prescription.
h. S-23 – still in pre-clinical in vivo studies but available for prescription.

2) **Ibogaine**

Ibogaine is magnitudes more psychologically difficult, carries far greater risk, mortality, morbidity, lethality, toxicity, and contraindications than both MDMA and psilocybin. Furthermore, ibogaine has no human clinical data and only pre-clinical in vivo and in vitro data. Yet ibogaine is available to doctors for prescription in Australia and is actively being prescribed and administered in New Zealand as an adjunct to psychotherapy

(https://doi.org/10.1080/00952990.2017.1310218;
https://doi.org/10.1080/02791072.2019.1598603;
https://doi.org/10.1080/00952990.2017.1357184).

3) **Nabiximols**

At the time of the rescheduling from Schedule 9 to Schedule 8 nabiximols also had no 'proven' efficacy data. Nabiximols had been rescheduled based on the data of one Phase 2 trial and the preliminary results from a pivotal Phase 3 trial. Refer to page 67 of the NDPSC Record of Reasons 57th Meeting 20-21 October 2009, (https://www.tga.gov.au/sites/default/files/ndpsc-record-57.pdf).

4) **Schedule 8**

Schedule 8 substances without 'proven' efficacy data include Cannabis. According to www.clinicaltrials.gov, Cannabis has no completed Phase 3 trials for any indication.

Thirdly, there are also major risks associated with delay.

1. The timing of future trials is completely beyond the Government's control

The timing of further clinical trials is completely beyond the control of the Australian Government and waiting will involve more people with Treatment Resistant PTSD and Treatment Resistant Substance Abuse not being offered the chance of accessing MDMA assisted therapy in a safe way through our medical system. This unnecessary suffering may lead to some of these people taking their own lives.

We have an established regime in Australia for the use of unregistered medicines designed to help to treat people with treatment-resistant conditions and the Delegate should explain why the current controls that apply to unregistered Schedule 8 medicines wouldn't adequately work for a schedule 8 listing of MDMA.

2. Delay will cause unnecessary suffering of people with treatment resistant PTSD and treatment resistant Substance Abuse

Delay will mean unbearable suffering for many people with treatment resistant PTSD and treatment resistant substance abuse associated with trauma by preventing them from being able to have access to a therapy that has achieved outstanding remission rates in overseas trials and which many Australian psychiatrists and other experts (see Section 3 above) are supportive of.

This unnecessary suffering may lead to some of these people taking their own lives.

3. Delay will encourage sufferers to access MDMA assisted therapy from underground therapists

As MDMA is easy to access though the underground it will be impossible for the Government to stop people with trauma from accessing MDMA assisted psychotherapy from underground therapists. Patients accessing underground therapies cannot be confidant about the purity of the MDMA being used or whether the therapists have any training in the use of this modality.

This last risk will only get worse as the results of further trials are publicized by mainstream and social media. Note that all trials to date have had very positive results.

Any benefits of waiting (which the Delegate should be required to list and risk weight) needs to be weighed against the safety evidence supporting the use of MDMA as part of therapy and the fact that - by definition - there may be no other viable treatment options available for particular patients suffering from treatment-resistant PTSD or treatment-resistant Substance Abuse.

We would like to see the analysis prepared by the Committee comparing the benefits of waiting for an unspecified and unknown period of time with the benefits of making these treatments available now to people with key classes of treatment-resistant mental illnesses (particularly Depression and Substance Abuse) through our medical system with appropriate controls in place.

Finally, ACMS say that

"It will take time to develop a curriculum and accredited training process for psychiatrist. To protect public health and prevent inappropriate use, MDMA should not be down-scheduled until all necessary safeguards have been established and implemented."

Our Response

There are three major problems with this statement.

1. The role of the Psychiatrist as a psychiatrist

The statement indicates a lack of understanding of the team approach involved with these therapies.

The key role of the psychiatrist is threefold:

a. to diagnose or support the diagnosis that the patient suffers from treatment resistant depression;
b. to confirm in the view of the psychiatrist that this treatment is appropriate to the particular patient; and
c. to screen out patients with psychosis or a family history of psychosis.

This is exactly what psychiatrists are already trained to do.

If the Delegate requires this role to be more controlled the Delegate could easily limit the role above to psychiatrists with experience of diagnosing and treating the particular mental illness that is being treated (e.g. PTSD) and who have experience in identifying psychosis. Most psychiatrists would be perfectly capable of deciding whether or not this treatment was appropriate for a patient (they make such judgements about different treatments all of the time).

2. The Role of the Therapist

Treatment protocols to date involve two therapists working together and being in the room with the patient for the therapy sessions when the patient actually takes the medicinal MDMA. This could involve a psychiatrist as one of the therapists but, because of the length of the session and skills base, is more likely to involve psychologists or psychotherapists.

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

In Australia the first intake of Mind Medicine Australia's Certificate in Psychedelic-Assisted Therapies commenced in January 2021 with a full group of 47 participants including 9 psychiatrists, 8 general practitioners, 13 psychologists, 4 psychotherapists, 2 mental health nurses, 3 social workers, 8 counsellors. The second intake of 50 commences in July and is nearly full. Applications for the course far exceed available places and all applicants who qualify for the course are screened by clinical psychologists.

There is enormous demand for this training because medical practitioners desperately want to heal patients with treatment resistant PTSD and/or trauma related substance abuse and see this therapy as a way of overcoming the failure of currently available treatments to get their patients well.

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

The Academic team developing and leading the course is led by professionals with extensive experience in either or both the treatment of complex mental health issues and the development of accredited training programs including psychologists Nigel Denning and Dr Alana Roy, psychotherapist Dr Tr-ill Dowie and education adviser Mr Brad Seaman. They are supported by a world class Faculty of 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 the Multidisciplinary Association for Psychedelic Studies (MAPS). The certificate course combines weekend and week-long intensives with online learning, assessments and practical sessions.

Please see the website including the world class Faculty here:
https://mindmedicineaustralia.org.au/certificate-in-psychedelic-assisted-therapies-cpat/

More information on the CPAT course and the high calibre of the teaching faculty is set out in the letter from the academic teachers attached as Appendix I.

We note that neither ACMS, the Delegate or any of the small number of parties that either partially supported or opposed our Rescheduling Application (see Section 3) has made any attempt to be briefed by us on the quality of the CPAT course despite the details of the course being on our website, referred to in our Rescheduling Application and the extensive publicity that has been given to the course.

We would be delighted to brief the Delegate generally on the course content and quality. However, please be assured that this course has been developed at world's best practice and it is a course that Australia can be proud of.

We would refer the Delegate in particular to the high caliber of the **teaching Faculty** which contains many of the leading experts in these therapies from around the World. Please see the Faculty here: https://mindmedicineaustralia.org.au/certificate-in-psychedelic-assisted-therapies-cpat/

3. The Need for Appropriate Protocols, Standard Operating Procedures and Training Manuals

Mind Medicine has partnered with clinical group Emyria Limited to co-develop a robust evidence-generating care model for MDMA-assisted psychotherapy, which will be ready for rollout in mid-2021, to coincide with the graduating CPAT cohort.

This care model comprises:

- Controlled documents:
    - An observational study protocol modelled off active Phase 3 clinical trials and incorporating an evidence-based schedule of assessments
    - Detailed schedule of licenced and validated assessments covering clinical and patient-reported outcomes as well as health economic outcomes
    - Training manuals and Standard Operating Procedures covering all clinical interventions
    - Data governance framework to provide a structured approach to reducing risk associated with handling personal health information, and to ensure compliance with all laws and regulations with respect to data.

- Appropriately credentialled clinicians to ensure patient safety at all times, including:
    - Clinical specialists including GPs and psychiatrists to assist with patient screening, review and safety, as well as protocol input as required
    - GCP-trained clinicians to maintain data integrity
    - CPAT-trained therapists including licenced psychologists and social workers to ensure a standardised, consistent experience and help maintain duty of care.

- Additional aspects:
    - Clinical-trial grade data management system and processes
    - Fit-for-purpose facility with close proximity to psychologists, psychiatrists and physicians.

Further details of the work being done with Emyria are set out in Appendix J

Given the points above we see no reason why the necessary safeguards can't be put in place expeditiously, so that treatments can occur safely in medically controlled environments as soon as requisite government approvals can be obtained for each patient at both the Commonwealth and State levels. The reference to "taking years" is not only ***not*** credible but such an attitude, and a lack of belief in the capacity of Australians to progress and innovate, will result in a huge amount of unnecessary suffering (see Section 2 above).

6. REASONS GIVEN FOR THE DELEGATE'S INTERIM DECISION (INCLUDING FINDINGS ON MATERIAL QUESTIONS OF FACT)

6.1 The Delegate's statement that it was not currently appropriate to list to MDMA as a Schedule 8 substance because it fits the scheduling factors set out for a Schedule 9 substance in the Scheduling Policy Framework (SPF 2018)

The Scheduling Policy framework sets out two factors for a Schedule 9 substance:

i) The substance is included in either Schedule IV to the United Nations Single Convention on Narcotics Drugs 1961 or in Schedule I to the United Nations Convention on Psychotropic Substances 1971.
ii) The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use.

It goes on to say that by way of explanation that:

i) A high level of control is required through prohibition of manufacturing, possession, sale or use to prevent abuse, misuse or diversion into illicit activities.
ii) The benefits of use are substantially outweighed by the risks and dangers are such as to warrant limiting use to strictly controlled medical and scientific research.

Starting with the explanation we have already shown that as a Schedule 8 substance the medical use of MDMA as part of therapy in a medically controlled environment would have high levels of safety (see Section 5.3) and a very low diversion risk (see Section 5.7). Combined with Schedule 8 controls the "risks and dangers" are low. They certainly don't outweigh the benefits in terms of the high remission rates for treatment resistant PTSD achieved in trials to date (see Section 5.7).

In a recreational environment opiates (and particularly heroin) are far more dangerous than MDMA (see Section 5.7). Yet opiates in the form of morphine and its analogues (which include heroin) are Schedule 8 substances when used for medical purposes.

The two factors mentioned above can also be distinguished.

To begin with the UN Convention on Psychotropic Substances is 50 years old and doesn't take any account of research findings that have occurred since 1971. Taking account of these research findings is particularly relevant given the enormous suffering that mental illness causes in Australia and the lack of treatment effectiveness for many sufferers.

The Convention also contains a key exemption for the medical use of a Schedule I substance. The exemption reads:

"In respect of substances in Schedule 1 the Parties shall (a) prohibit all use except for…very limited medical purposes by duly authorised persons in medical…establishments which are directly under the control of the government or approved by them".
specifically

This exemption is very appropriate to a Schedule 8 listing of the medicinal use of MDMA as part of psychotherapy.

Unregistered medicines in Australia are - by definition - only used on a limited basis through one or more of the pathways prescribed by the TGA and with the approval of State-based permit systems. In the present case the TGA has already given at least 10-15 approvals for the use of MDMA as part of therapy under Special Access Scheme - B. However, as the Delegate will know, these approvals can't be implemented in any State or Territory of Australia (other than perhaps Victoria) whilst these medicines remain in Schedule 9 of the Poisons Standard.

In other words, MDMA would have to be a Schedule 8 medicine to come within the exemption referred to above.

The Delegate may also be working under the assumption that no comparable country has rescheduled a Schedule 1 substance under the UN Convention on Psychotropic Substances or Schedule IV of the UN Convention on Narcotic Drugs into the equivalent of a Schedule 8 substance.

In fact, Australia itself has rescheduled several substances for medical purposes from Schedule 9 to Schedule 8 of the Poisons Standard that were either in Schedule 1 of the UN Convention on Psychotropic Substances or Schedule IV of the UN Convention on Narcotic Drugs. These rescheduled substances are summarised in Table 11 below.

Table 11: 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 and Schedule IV of the UN Convention on Narcotic Drugs 1961

Schedule 9 drugs with a therapeutic use exemption	**Relevant UN Convention scheduling**	**Notes on having no 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 pivotal Phase 3 study for Multiple Sclerosis.
Cathinones (and analogues) **Scheduled with a S4 provision**	Methcanione and its analogues (this includes cathinones) are in Schedule 1 of the *UN Convention on Psychotropic Substances 1971*	Synthetic cathinones are included in Schedule 4 of the *Poisons Standard* yet have no human clinical data.
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

		give treatment authorisation for a range of conditions that have no established therapeutic value, ie. anxiety and sleep.
Dronabinol (synthetic THC) **Scheduled with an S8 provision in 1994**	Synthetic 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.
Mescaline analogues	Mescaline analogues are listed in Schedule 1 of the *UN Convention on Psychotropic Substances 1971*	The *Poisons Standard* contains a Schedule 9 exemption for mescaline analogues included in other schedules.

Our nearest neighbour, New Zealand, has also reclassified MDMA (a substance listed in Schedule I of the UN Convention on Psychotropic Substances) as a Class B1 substance since 2015. Class B1 substances in New Zealand are equivalent to Schedule 8 substances in Australia. Other Class B1 substances in New Zealand include morphine, amphetamine, medicinal cannabis and THC.

The other Schedule 9 limb that the Delegate seeks to rely on is that MDMA is "*without an established therapeutic value".* This position is even more conservative than the advice given to the Delegate by the ACMS that "*There is limited but emerging evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses".* Notwithstanding *this* more conservative view we have already demonstrated in Section 5.2 that MDMA when used as part of therapy does have a therapeutic value. We discuss this further in Section 6.2 below.

It could be argued that Schedule 4 of the Poisons Standard would be a more appropriate place to list MDMA when used as a medicine as part of therapy because, in contrast to the Schedule 8 requirements, it does not cause either dependency or have a high propensity for misuse, abuse or illicit use (see Section 5.7).

The final point to raise in this section is that there is another equally important convention which we believe the Delegate should consider called the International Convention on Economic, Social and Cultural Rights. Article 12 of that Convention provides for rights to "*the enjoyment of the highest attainable standard of physical and mental health*."

If a person is suffering from treatment resistant depression, there is lots of evidence to support the proposition that MDMA assisted therapy could lead to that person experiencing remission and therefore enjoy "*the highest attainable standards of ...mental health*".

The highest standard of mental health is only possible if people with treatment resistant conditions have access to ALL forms of medicine and medical intervention that can assist in this regard. In the present case this is made even stronger by the fact that the ingestion of medical grade MDMA would be done as part of therapy under strict medical supervision in medically controlled environments.

The Human Rights issues associated with the Delegate's final Decision are set out in the Submission from Human Rights Lawyer, Mr Scott Leckie, reproduced in Appendix K.

The ethical argument strongly supports this position. See the analysis of Dr. Simon Longstaff, the Executive Director of the Ethics Centre in Sydney set out in Appendix L.

Other ethical viewpoints are provided by Dr Simon Longstaff AO, Executive Director of The Ethics Centre and Australia's leading ethicist. Appendix L.

6.2 The Delegate's Reference to MDMA being "Without an Established Therapeutic Value"

Our Response

This is the other limb of the Schedule 9 listing factors mentioned above which we have already dealt with extensively in Section 5.2 and in our Rescheduling Application and show that **MDMA, when used as part of therapy, does have an established therapeutic value.**

In this section we look more at theory and precedents.

Starting with theory, established therapeutic value is not a defined pharmacotherapeutic term. Established therapeutic value is generally in respect of a drug being approved as a medicine and its respective indication. Or alternatively a drug's pharmacodynamics, eg. all opioid agonists may be seen as having an established therapeutic value. If this approach is taken, all serotonin receptor agonists have an established therapeutic value.

However, therapeutic value is an established pharmacological calculation. Therapeutic value can be determined using the Ahlqvist-Rastad's rating system or Motola's rating system. An assessment conducted in 2013 of the therapeutic value of new medicines with TGA approval marketed in Australia, found that out of 59 approved drugs within Australia (during the studies timeframe), on the Ahlqvist-Rastad's system, only one third of the 59 medicines had 'added therapeutic value' (https://link.springer.com/article/10.1186/2052-3211-6-2).

Turning to precedents the following is directly from the National Drugs and Poisons Scheduling Committee (NDPSC) 57th meeting 20-21 October 2009, pp. 65-71 (https://www.tga.gov.au/sites/default/files/ndpsc-record-57.pdf), for the rescheduling of nabiximols (cannabis extracts) for medicinal use. At the time of rescheduling in 2009/2010, cannabis extracts were Schedule 9 in the *Poisons Standard* and in Schedule 4 of the *UN Single Convention on Narcotic Substances 1961*.

Members acknowledged that there was a substantial degree of controversy regarding a therapeutic role for cannabis extracts. However, Members agreed that it was important to clarify that the matter before the Committee at this time was a proposal to consider appropriate scheduling for nabiximols. It was the regulator's role, not the Committee's, to approve particular products for use in Australia.

The Committee recalled the following from Members' discussion at the June 2009 meeting:

1) Certain jurisdictions could not allow access to Schedule 9 substances for medical purposes. Therefore, in the absence of a Schedule 8 (or lower) listing, access could not be granted by these State and Territory health authorities.

2) The Committee agreed that efficacy was a primary consideration, given that this treatment had yet to be assessed by the TGA. While overseas clinical trial data were reassuring, it was noted that no trials have taken place in Australia as yet. This may be partly due to the current Schedule 9 status of this therapy.

With regard to the current confusion as to whether jurisdictions could allow access to a nabiximols product that had been given a SAS 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.

Therefore, according to the TGA, nabiximols must have had an established therapeutic value to be given a Schedule 8 provision. The TGA was satisfied on an established therapeutic value of nabiximols by one Phase 2 successfully completed trial for Multiple Sclerosis and the **preliminary** results from one completed Phase 3 trial on Multiple Sclerosis.

MDMA has results from 76 Phase 1 and Phase 2 studies in the last 30 years (many of those in treating PTSD) and one complete (with preliminary successful results) Phase 3 study on treating PTSD. By precedence, MDMA has more evidence for therapeutic value than nabiximols did at the time of rescheduling (and still does) and the TGA were satisfied that nabiximols had an established therapeutic value. Therefore, as MDMA has significantly more evidence of a therapeutic value in comparison to nabiximols, we believe that the TGA must also see an established therapeutic value in MDMA.
It should also be noted that there are a number of Schedule 4 and Schedule 8 substances that have no 'established therapeutic value'. Some SARMS have no human studies, others have only Phase 1 and/or 2. SAMRMs are Schedule 4 and prescribed by doctors.

Ibogaine (a much longer lasting and challenging psychedelic than MDMA) is in Schedule 4 in Australia and actively prescribed in New Zealand. Ibogaine has had no human trials and has no established therapeutic value.

The TGA has granted patient access for MDMA (as well as psilocybin) under Special Access Scheme -B. According to the specifications at https://www.tga.gov.au/form/special-access scheme, the TGA only approve SAS-B applications if the relevant substance has a defined indication and treatment plan. In other words, the **TGA has already recognised a therapeutic**

value for MDMA for patients given its approvals already granted on a case-by-case basis under Special Access Scheme-B.

6.3 The Delegate's Reference to MDMA being an Illicit Drug with a high potential for misuse in the Australian Community resulting in significant harms including seizures and death

Our Response

Many medicines listed in the Poisons Standard could be described as ***illicit*** when used for recreational purposes. Examples are set out in Table 12 below.

Table 12: Comparison of substances used both medically and recreationally

Schedule 8 Controlled Drugs		**Notes**
Stimulants	Cocaine	Highly abused and misused drug in Australia, not currently used medically. Coco leaf (where cocaine comes from) is a Schedule 9 prohibited drug.
	Methamphetamine	Highly abused and misused drug in Australia, not currently used medically, its pharmacological Schedule 9 equivalent is dimethamphetamine.
	Amphetamine	Abused and misused drug in Australia, its much weaker pharmacological Schedule 9 equivalent is BZP.
Natural Cannabinoids	Cannabis	Included in Schedule 9 when not for therapeutic use.
	Nabiximols (cannabis extracts)	Included in Schedule 9 when not for therapeutic use.
	THC	Included in Schedule 9 when not for therapeutic use.
	Dronabinol (THC)	Included in Schedule 9 when not for therapeutic use
Synthetic Cannabinoids	Nabilone	Synthetic cannabinomometics are included in Schedule 9 when not for therapeutic use.
	Phenylacetylindoles (synthetic CB_1 agonists) are Schedule 9 prohibited drugs unless for therapeutic use. Phenylacetylindoles are DEA Schedule 1 – no current accepted medical use in the USA.	
Psychedelics	Ketamine	Abused and misused drug in Australia, its pharmacological Schedule 9 equivalent is PCP.

	3,4,5-Trimethoxyphenethylamine (mescaline) derivatives are Schedule 9 prohibited drugs unless for therapeutic use. Mescaline derivatives are DEA Schedule 1 – no current accepted medical use in the USA.	
Opioids	Tilidine	DEA Schedule 1 – no current accepted medical use in USA.
	Thebacon	DEA Schedule 1 – no current accepted medical use in USA.
	Bezitramide	Not FDA approved for medical use.
	Morphine (and analogues)	Abused and misused drug in Australia, its pharmacological Schedule 9 equivalent is heroine and other morphine analogues.

The reference by the Delegate to MDMA being an illicit drug in the current context is completely inappropriate given that our Rescheduling Application refers to the medicinal use of MDMA being strictly used as part of therapy in a medically controlled environment.

The reference to a high potential for misuse when used in a medically controlled environment is also wrong – see Sections 5.7 and 5.8 above.

The lack of Diversion Risk is explained in Section 5.7 above.

6.4 The Delegate's Reference to MDMA showing some evidence of causing dependence and may additionally lead to cognitive dysfunction in the medium or long term

Our Response

This broad statement could be applied to many (if not all) psychiatric medicines. The benefit of MDMA is that it was used for medical purposes in the 1960s, 1970s and first half of the 1980s in medically controlled environments without adverse medium- and long-term effects.

See Section 5.3 above which the safety of MDMA when used as part of therapy in a medically controlled environment. There is no evidence that MDMA when used in this way with only 2-3 dosed session scan cause dependence or impact upon cognitive dysfunction. See also pages 18-24 of our Rescheduling Application.

Although this statement could be true in a recreational setting where people have taken MDMA in high doses over a long period of time, it has no relevance to the medical use of MDMA in medically controlled environments where the medicine will only be used on 2-3 occasions. This statement should be in a section called Risks and adverse effects of recreational use, misuse and abuse.

We request the Delegate to focus on the following information:

i. Morbidity and mortality of MDMA use has only occurred in uncontrolled non-clinical settings (https://doi.org/10.3389/fpsyt.2019.00138);

ii. All serious adverse effects of MDMA in a clinical setting have been rare and non-life threatening (https://mapscontent.s3-us-west- 1.amazonaws.com/research-archive/mdma/MDMA-Investigator-Brochure-IB-11thEdition-MAPS-2019-07-10.pdf).
iii. Early psychotherapeutic use of MDMA was without complication (https://doi.org/10.1177%2F2050324518767442);
iv. MDMA administered therapeutically in a controlled environment does not produce dependence (addressed above);
v. Therapeutic treatment with MDMA has not been shown to increase illicit drug use (https://doi.org/10.3389/fpsyt.2019.00138).

6.5 The Delegate's Comment that "Clinical Trials will be essential to evaluation of these risks. While several Phase 11 trials have been completed, these lack appropriate sample sizes and control groups, and require vigorous follow-up in phase 111. According to the ClinicalTrials.gov database a single phase 111 trial has been registered, and completed, though its results are not yet publicly available."

Our Response

76 Phase 1 and Phase 2 trials have been complete post-prohibition (https://mapscontent.s3-us-west- 1.amazonaws.com/research- archive/MDMA+IB+12th+Edition+Final+17AUG 2020.pdf). Over 34 are posted as complete on www.clinicaltrials.gov since 2006.

There is also an established regulatory framework in Australia for the use of unregistered medicines to treat patients with treatment resistant conditions. This requires doctors to either obtain;

1) individual approvals for each patient from the TGA under the Special Access Scheme; or
2) authorised prescriber status from TGA with the requirement for data feedback

In both cases approval from the State or Territory Government in the State or Territory in which the treatment is to occur is also required.

Phase I, 2 and 3 clinical trials are an essential part of the normal pathway for a medicine that is to be registered on the Australian Therapeutic Goods Register but this pathway is not required for unregistered medicines. There just needs to be sufficient data on safety and efficacy and about the patient's treatment resistant condition to satisfy the regulator.

There is plenty of evidence on the safety and efficacy MDMA to support its use as an unregistered medicine and as part of psychotherapy for treatment resistant conditions – see Section 5.3 above and pages 9-13 and 18-27. This also accords with the Special Access Scheme approvals that have already been granted by the TGA.

A substance does not need any clinical trials (let alone Phase 3 clinical trials) to be included in Schedule 8 or Schedule 4 of the Poisons Standard. Examples include:

- Cannabis is Schedule 8 but has not passed through Phase 3 trials.
- SARMs (refer to Section 5.2 Table 10are in Schedule 4 and some have had no human studies completed. Others have only been involved in Phase 1 and/or Phase 2 trials. SARMs are still

prescribed by doctors and have unknown risks and can cause possible cancer growth in humans.

- Ibogaine is in Schedule 4 and has had no human clinical studies or trials. Ibogaine if misused can be lethal. There are two observational studies, but they were conducted years after the rescheduling of Ibogaine. The rescheduling reasons given for Ibogaine are summarized below:

In Australia, the powerful psychedelic ibogaine and its metabolite noribogaine are Schedule 4 (prescription only) medicines in Australia and in New Zealand are classified for prescription without restrictions or controls. The rescheduling of ibogaine in Australia (from Schedule 9 to Schedule 4) and New Zealand occurred in 2010 (NDPSC. Record of Reasons 58th Meeting 16-17 February 2010, 2010. TGA. https://www.tga.gov.au/sites/default/files/ndpsc- record-58).

The National Drugs and Poisons Schedule Committee (NDPSC) (the predecessor of AGMS) made the recommendation to the TGA based on the rescheduling reasons provided by the New Zealand Medicines Classification Committee (MCC) in 2009 which were:

i. The need for supervision of the substances' use in the management/treatment of addiction to limit attempts at self-treatment and prevent recreational use as a "party pill" (although noting that the documented experience is usually not pleasant);

ii. The need to control the import and supply of ibogaine, its metabolite or products containing each or both of the substances;

iii. Data suggesting that the number of deaths due to ibogaine were lower than those associated with methadone; and

iv. Opinion that although ibogaine's appeal as a recreational drug was low, there were dangers in ad hoc use as a self- medication for drug addiction following potential media interest.

This all raises the question of how the Delegate can justify the medical use of Cannabis being Schedule 8 (and Schedule 4) and Ibogaine being Schedule 4 when the proposed rescheduling of MDMA will be strictly on the basis that the substance will only ever be used in medically controlled as an adjunct to therapy and will never be taken home by the patient.

6.6 The Delegate's statement that "Given the emerging evidence base regarding safety and efficacy, I believe that down scheduling is premature."

Our Response

This statement is completely inconsistent with the fact that medical practitioners are already successfully gaining approvals for the use of MDMA under Australia's Special Access Scheme, the views of the World leading experts referred to in Section 3 above, the data set out in Section 5.2 and 5.3 above and the data set out in our Rescheduling Application.

It is also inconsistent with the safety profile of other medicines listed in Schedule 8 (see Sections 5.5 and 5.7 above).

6.7 The Delegate's reference to recent reviews in the Psychopharmacology and Progress in Neuro-Psychopharmacology and Biological Psychiatry

We have already commented on these reviews in Section 3.3 above. They do not justify the Delegate's Interim Decision not to down schedule the medical use of MDMA as part of therapy in medically controlled from Schedule 9 to Schedule 8.

6.8 The Reliance on the Clinical Memorandum on Psychedelic Therapies prepared by the Royal Australian and New Zealand College of Psychiatrist

As explained in Section 3.4, this Clinical Memorandum contains many factual errors and misleading statements and should not be relied on by the Delegate in making the Delegate's final decision.

6.9 The Delegate's reference to the fact that no comparable country has scheduled MDMA to a category equivalent to Schedule 8

We have pointed out that UN Convention signatory countries (including Australia) do take it upon themselves to move the equivalent of a Schedule 9 substance that is also in Schedule 1 of the UN Convention of Psychotropic Substances and Schedule IV of the UN Convention on Narcotic Drugs to the equivalent of our Schedule 8 of the Poisons Standard. New Zealand has already rescheduled the medical use of MDMA to the equivalent of our Schedule 8. Austalia has done this on a number of occasions (see Section 6.1). Furthermore, many other nations are providing the necessary medical exemptions for use of these treatments in medically controlled environments.

We also don't believe that this is a valid reason to deny suffering Australians with treatment resistant conditions the opportunity to access MDMA assisted therapy in safe medically controlled environments.

We should also note that each country has its own regulatory structure and in countries like the United States, Canada, Israel and Switzerland these therapies are available under either expanded access schemes or regulatory exemptions. Unfortunately, Australia's Federal system means that not rescheduling MDMA for medical use from Schedule 9 to Schedule 8 will make it impossible for doctors and patients to access these therapies because of legislative barriers that apply in most Australian States and Territories to Schedule 9 substances.

6.10 The Delegate's reference to there being no international framework for how to handle psychedelic assisted therapies

Our Response

We do not understand why people in Australia suffering from treatment resistant mental illnesses have to wait for the development of an international framework. As the Delegate will know international frameworks can take years to develop, and often do not ever eventuate due to lack of global cooperation.

The Delegate might also like to consider and explain why the medical use of cannabis was able to be rescheduled from Schedule 9 to Schedule 8 when there was no international framework in place for this substance.

6.11 The Delegate's analysis of responses and particularly the Delegates reference to "few submissions were from practicing psychiatrists"

Our Response

As set out in Section 3 above the public responses and endorsements were overwhelmingly in favor of rescheduling and a large proportion of this support came from Health Sector Experts.

The comment about "few submissions were from practicing psychiatrists" is simply wrong. As mentioned above, a total of 48 psychiatrists supported our rescheduling application and no individual psychiatrists were opposed. The supporting figure could be as high as 69 depending on the composition of the signatories of Dr Strauss' letter (see Section 3.2 above). As you will see from Section 3.2 this includes some of the most senior psychiatrists in Australia.

In addition to psychiatrists, support also came from leading psychologists, pharmacologists, researchers, addiction specialists, other medical practitioners, researchers and other scientists from both Australia and around the World. We draw your attention specifically to the World leading experts in this field detailed in Section 3 and the experts letters extracted in Section 3.

These Health Experts collectively and in many cases individually have much more experience in understanding the safety and efficacy of MDMA than the parties that the Delegate refers to on page 20 of the Interim Decision.

The quality and amount of support is directly relevant to the factors that the delegate is required to consider under Section 52E of the Therapeutic Goods Act 1989.

6.12 The Delegate's reference to points raised in public submissions from several "peak bodies" being highly pertinent

The Delegate mentions three organisations: **RANZCP,** the **AMA** and **PRISM.** Whilst RANZCP and the AMA are clearly peak bodies PRISM is ***not*** a peak body.

We comment below on each of these references by the Delegate.

1. RANZCP

The Delegate commented that "….*RANZCP advised that further research is required to assess the efficacy, safety and effectiveness of psychedelic therapies, emphasising the appropriate treatement methodologies and training protocols do not yet exist".*

Our Response

As mentioned in Section 3.2.3, the RANZCP submission draws heavily on a clinical memorandum published by RANZCP in May 2020 entitled *Clinical memorandum on the therapeutic use of psychedelic substances* which contains main factual errors and misleading statements (see Section 3.4). This clinical memorandum does not provide RANZCP with a reliable basis for opposing our Rescheduling Application. As set out in this Submission there are ample grounds that the Delegate can use to support the efficacy, safety and effectiveness of MDMA therapies in so far *and to the extent* that they are relevant to our Rescheduling Application.

We would in particular draw the delegate's attention to:

1) The terrible mental illness statistics and lack of effective treatment options for many Australians set out in Section 2;
2) The overwhelming support for rescheduling from Health Sector Experts;
3) The letter of support extracted in Section 3 from leading experts from around the World which attest to the safety and efficacy of these therapies; and
4) The relevant trial data and experience with MDMA set out in both our Rescheduling Application and this Submission.

The RANZCP comment that "*appropriate treatment methodologies and training protocols do not yet exist"* is simply wrong and ignores the fact that the methodology used in all trials to date is fairly standardised and training protocols, standard operating procedures and training manuals relevant to Australia are currently being prepared (see Section 5.8).

There are a number of other problems with the RANZCP's advice which we point out in Section 3.2.3.

We therefore respectfully submit that the reasons given by RANZCP for opposing our Rescheduling Application should **not** be relied upon by the Delegate.

2. The Australian Medical Association (AMA)

The Delegate commented that the AMA "*…advised that more high-quality research, using larger-scale studies, is required to establish the safety and efficacy of psychedelic therapies. The risk of psychosis and permanent hallucination, especially in susceptible populations, is likely to be high."*

Our Response

To suggest that studies and experience to date haven't established that MDMA can be used safely in a medically controlled environment is incorrect – see Section 5.2 and 5.3. Note also that studies to date (including the Phase 2 trials and the first stage of the Phase 3 multi-site trials) have shown extremely high rates of safety and efficacy compared to traditional treatments (see Section 5.2 and pages 25-28 of our Rescheduling Application).

The potential to develop psychosis or HPPD has never been associated with the medicinal use of MDMA and there has been no evidence to the contrary (see Section 5.3). In addition, as part of

the therapy patients are properly screened for contraindications (See Section 5.8 and pages 20-21 of our rescheduling application) and the treatment protocols only provide for 2-3 dosing sessions with MDMA in a medically controlled environment.

There are a number of other problems with the AMA's advice which we point out in Section 3.2.3.

We therefore respectfully submit that the reasons given by the AMA for opposing our Rescheduling Application should **not** be relied upon by the Delegate.

3. Psychedelic Research in Science and Medicine (PRISM)

The Delegate commented that PRISM advised that ***"…to ensure safe and ethical use, any decision to down schedule should include an extensive two-year implementation plan. Only a limited number of Australian medical professionals are currently trained to provide MDMA-assisted psychotherapy, and premature down-scheduling may put patients at increased risk of harm".***

Our Response

Contrary to the Delegate's expressed view PRISM is ***not*** a peak body. PRISM represents no members, sets no standards, has yet to complete a single trial, has no employees, does not produce audited accounts and had net expenses in the year to 30 June 2020 of only $48,015 (of which $10,000 went to Entheogenisis Australis which has a major focus on the recreational use and preservation of plant-based medicines, including psychedelics).

PRISM is a tiny research organisation seeking funds for further research.

To suggest that a 2-year implementation plan is needed before patients will be able to access MDMA therapy ignores the following facts:

(i) The safety and efficacy data already available from overseas trials (including the first stage of a Phase 3 multi -site trial– see Sections 4 and 5.2):
(ii) The views of World leading experts in the field and Health Sector Experts generally (see Section 3).
(iii) The fact that treatment methodology across all of the trials to date (and under expanded access schemes in the US, Israel and Switzerland) follows a common methodology;
(iv) The fact that training methodologies (with much learning from overseas trials and overseas courses) are well understood and are being applied in our Certificate in Psychedelic–Assisted Therapies Course and taught by a World leading teaching Faculty – see Section 5.8;
(v) The fact the treatment protocols, standard operating practices and training manuals are currently being finalised by clinical group Emyria Limited– see Section 5.8;
(vi) The fact that, even with a Schedule 8 listing, patient access to these therapies will only be on a case-by-case basis with approvals required each time from both the TGA (under Special Access Scheme – B) and the State and Territory Government where the therapy is to be conducted; and
(vii) The fact that these treatments are already available under expanded access and in a number of countries (see (iii) above) and that the TGA has already given at least 10

approvals for the use of MDMA as part of psychotherapy under Australia's Special Access Scheme.

It should be noted that in its submission PRISM acknowledges that "*As has already been established through Phase 2 and ongoing Phase 3 trials, there is good evidence that MDMA can be used safely in clinical context…. There is little evidence to suggest that three treatment days of receiving between 80 mg and 180 mg of MDMA, spread over a two-month* period*, would cause long-term harm in a patient". PRISM goes on to say that "Given that medical cannabis and cocaine are both Schedule 8 Controlled Medicines in Australia, there does not seem to be adequate evidence of the abuse potential of the drug for its classification as a Schedule 9 substance".*

Please note that Mind Medicine Australia recognises the importance of developing an established and integrated ecosystem of clinical governance and service delivery protocols in Australia and the steps outlined by us above (which have been discussed with experts in the field) are designed to achieve that.

In contrast, the proposed implementation mechanisms suggested by PRISM would ensure that it would take many years before psychiatrists and specialist addiction physicians were able to make these therapies available to people with treatment resistant conditions despite the existence of trained medical personnel, protocols and standard operating practices and despite approvals being given by the TGA under the Special Access Scheme. This is because, with the possible exception of Victoria and even with TGA approval, there are no patient access gateways in the States and Territories of Australia for medical access to MDMA as part of psychotherapy whilst the use of MDMA in this way remains a Schedule 9 substance.

This would leave patients suffering from treatment resistant PTSD or trauma related treatment resistant substance abuse with no viable medical alternatives and would encourage some of them to access these therapies through the underground. It would also put us even further behind other leading nations (such as the US, Switzerland and Israel) and inevitably lead to significant avoidable suffering and suicides.

Delaying access to these therapies for traumatised people in a controlled medical way with all the protections associated with medical treatments in this country carries substantial risks.

6.13 The Delegate's concluding comment that "Having considered the risks to consumers, the lack of training for physicians and the current state of research, I am of the view that Schedule 9 remains appropriate for MDMA"

Our Response

We deal with each of these points in turn

1) Risks to Consumers

We have already provided data and expert views confirming the safety of MDMA when used as part of psychotherapy for treatment resistant PTSD and treatment resistant Substance Abuse associated with trauma (see Sections 3.2 and 5.2 and pages 8-12 and 18-24 of our Rescheduling Application).

We note that the **Delegate has not addressed the key risks of <u>not</u> down scheduling MDMA to Schedule 8:**

1. The risks to consumers suffering from treatment-resistant conditions who are unable to access these therapies through our medical system, and who therefore choose to access these therapies underground (note that this was an essential reason given by the committee advising the Government to reschedule ibogaine from Schedule 9 to Schedule 4) – see Sections 5.8 and 6.5 above)
2. The risk to consumers with treatment-resistant PTSD and treatment resistant substance abuse of not being able to access therapies that have shown high rates of remissions to date in terms of suicide, cutting, ongoing suffering and domestic violence.
3. The risk to consumers (patients, their families and communities) of the suffering that can be caused by treatment-resistant PTSD and trauma related substance abuse which for many patients are a life sentence because there are no existing treatments that are able to get them well.

2) The Lack of Training for Physicians

This has already been dealt with in Section 5.8 above and we would welcome the opportunity to brief the Delegate and the TGA on the quality of the course, the screening process and the quality of the students and teaching faculty.

3) Current State of Research

We have already made the point in Sections 3 that the safety and efficacy of these treatments is supported by World leading experts and provided the supporting data in Sections 3.2 and 5.3 and pages 42 to 49 of our Rescheduling Application.

6.14 The Delegates comment that the rescheduling of MDMA could be reconsidered after the results of current clinical trials are known

<u>Our Response</u>

We respectfully ask the Delegate to reconsider its position in the light of all the responses and other information contained in this submission and in our original Rescheduling Application. **We believe that this firmly establishes that MDMA as part of therapy should immediately be rescheduled from Schedule 9 to Schedule 8 of the Poisons Standard.**

We also draw the Delegates attention to the considerable risks to consumers of ***not*** down scheduling (see Section 6.13).

7. A COMPARISON WITH THE CANADIAN APPROACH

7.1 A Phased Approach

Canada is taking a phased approach to rescheduling drugs like psilocybin and MDMA for medical purposes.

On August 4, 2020, Canadian Health Minister, the Honourable Patty Hajdu, granted Thomas Hartle and three other palliative Canadians exemptions to access MDMA-assisted psychotherapy under Section 56 (1) of the Controlled Drugs and Substances Act (CDSA). The legislation states that if the Minister believes the exemption is "necessary for a medical or scientific purpose or is otherwise in the public interest" (Health Canada, 2021), then an exemption should be granted. Since then, more than 30 palliative and non-palliative Canadians have received the ministerial exemptions, with hundreds of requests still under review.

On December 8, 2020, 17 healthcare professionals associated with TheraPsil, a non-profit, patient-rights advocacy group, were approved by Health Canada to possess and use psilocybin for professional training in psilocybin therapy. The approved healthcare professionals include psychologists, psychiatrists, clinical counselors, social workers, general practitioners, and nurses.

On December 11, 2020, Health Canada issued a Notice of Intent seeking public input on its decision to reverse regulatory changes made to the Food and Drug Regulations (Parts C and J) and the Narcotic Control Regulations in 2013, which prohibited access to restricted drugs – psilocybin and MDMA – through the department's Special Access Program (SAP).

Currently, access to drugs that have not yet been approved for sale in Canada can also be provided through an approved clinical trial or through the Special access Program. Practitioners treating patients with serious or life-threatening conditions can request access to drugs that have not yet been approved for sale in Canada through the Special Access Program when conventional therapies have failed, are unsuitable, or unavailable. Requests to the Special Access Program are considered on a case-by-case basis, taking into consideration the level of scientific evidence (including evidence pertaining to safety, efficacy, and quality) to support the use of the drug for the treatment of the patient's specific condition.

7.2 Health Canada's Objectives

Health Canada's **objectives** for requesting the regulatory changes are outlined in the Notice of Intent, and here is what they say:

1. Since these regulatory changes were made in 2013, "***the science pertaining to the efficacy and safety of certain restricted drugs has continued to advance. Certain restricted drugs are now demonstrating potential therapeutic uses, including in Phase II and Phase III clinical trials".***

2. ***"Based on recent scientific advancements and the potential for some restricted drugs to have therapeutic benefit, the objective of the current proposal is to restore the possibility of access to restricted drugs through Health Canada's Special Access Program, by***

reversing the remaining 2013 regulatory amendments". In practice, this would mean that practitioners could, on behalf of patients with serious or life-threatening conditions, request access to restricted drugs through the Special Access Program in instances where other therapies have failed, are unsuitable, or are not available in Canada (Canada Gazette - Notice of Intent, 2020).

7.3 Implications for Australia

Hundreds and potentially thousands of Canadians will have their lives changed because of these compassionate policy decisions made by the Canadian government in the last six months. Their decision is not based on speculative research or data. **It is based on the same compilation of science-based clinical evidence presented before the Delegate of the Secretary in our initial application to reschedule psilocybin and MDMA**.

In the midst of a global pandemic and a spiraling mental health crisis, the Government of Canada has told its citizens that psychedelic therapies used in the treatment of end-of-life distress and treatment resistant depression are necessary to help Canadians heal.

In contrast in Australia the complexity between the State and federal systems means that doctors who gain Special Access Scheme -B and Authorised Prescriber approvals from the TGA cannot actually prove the treatments in any State or territory of Australia other than perhaps Victoria. The medical use of MDMA clearly comes with the requirements for a Schedule 8 listing on the Poisons Standard and such a rescheduling will mean than Doctors can then apply for State and Territory approvals under Schedule 8 permit system that apply in those jurisdictions.

We respectfully ask the Delegate to recognise the suffering that people with treatment resistant PTSD and treatment resistant substance abuse associated with trauma and, on both scientific and humanitarian grounds, reschedule MDMA to Schedule 8 of the Poisons Standard.

8. Appendices

A. Australian Defence Force Facing Mental Health Crisis (7news article 14/2/21 referred to in Section 2).
B. Article by Professor Paul Fitzgerald on the Low Efficacy of Antidepressants (Medium article 27/5/20 referred to in Section 2).
C. Critique of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Psychedelic Therapy Clinical Memorandum (May 2020), by Chiruta et al published in January 2021 (see Sections 3.2.3 and 3.4).
D. Article in The Australian newspaper entitled *"Psychedelic Drug Memo sparks uproar"* (9/2/21 referred to in Section 3.4*).*
E. Papers referred to in Professor David Nutt's Letter set out in Table 7 (Section 3.4).
F. Findings of Safety and Tolerability Trial of MDMA-Assisted Psychotherapy for Alcohol Use Disorder (February 2021 referred to in Section 4).
G. Papers referred to in Section 5.2 Dealing with the Established Therapeutic Benefit of MDMA - Assisted Therapy.
H. Joint Submission from the Australia Institute and Fearless to the TGA explaining why Diversion Risk is Low.
I. Letter from the Academic Teaching Leaders of the Certificate in Psychedelic- Assisted Therapies to the TGA outlining the Course Approach, Teaching Program and Teaching Faculty.
J. Letter from Emyria Ltd setting out the work that they are doing in developing the Protocols, Standard Operating Procedures, Training Manuals and Data Collection Systems to support MDMA assisted psychotherapy treatments.
K. Submission by Human Rights Lawyer, Mr. Scott Leckie, on the Human Rights Issues Associated with the Delegate's Final Decision.
L. Ethical Statement by Dr Simon Longstaff, the Executive Director of the Ethics Centre, Sydney.
M. Submission from Professor Arthur Christopoulos (B.Pharm., Ph.D.) to the TGA in relation to its interim decision (Dean, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University)

MIND MEDICINE AUSTRALIA

Appendix A

Australian Defence Force Facing Mental Health Crisis

(7 News article 14/2/21 referred to in Section 2).

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

Australian Defence Force facing ‘mental health crisis’, alarming suicide figures suggest

Olivia Leeming

Published: 14/02/2021Updated: Sunday, 14 February 2021 11:10 am AEDT
https://7news.com.au/lifestyle/health-wellbeing/australian-defence-force-facing-mental-health-crisis-alarming-suicide-figures-suggest-c-2159915

Veterans warn the Defence Force is facing a “mental health crisis”, with an alarming number of suicides involving past and present members in recent months.

7NEWS has obtained new figures revealing at least 67 suspected suicides in the past 12 months, including 25 since the release of the inquiry into alleged war crimes in Afghanistan in November.

It’s understood seven individuals have taken their own life so far this year.

Heston Russell, a former major in the 2nd Commando Regiment and Voice of a Veteran founder, says some defence force members are struggling in the wake of the Brereton report and the ongoing uncertainty over whether any Australian soldiers could be charged.

“Some of the families have been involved with this inquiry since it started four years ago and still haven’t had any resolution,” he said.

Veterans warn the Defence Force is facing a “mental health crisis”, with an alarming number of suicides involving past and present members in recent months Credit: AAP

“Most of them are now completing medical discharges given they have just gone through such emotional and mental trauma so they can no longer offer effective service and still again haven’t even had any charges laid against them.”

A spokesperson for the Department of Veterans’ Affairs has told 7NEWS that suicide prevention is “one of this government’s highest priorities”.

“The sad reality is that suicide is a very complex issue and prevention is a difficult and unrelenting challenge for all Australians. Anyone who may be struggling is encouraged to reach out for help.”

Mr Russell says past and serving members must request mental health support when there should instead be a strategy to actively reach out to families who may need help.

“There are all these resources available that we keep getting told about but no one is proactively applying them … I have spoken with hundreds of veterans who will happily attest to that over the last two month period,” he said.

Any current or former serving ADF members and their families who need support are urged to contact Open Arms – a free and confidential counselling service available 24 hours a day, seven days a week.

They can be reached on 1800 011 046. If you need help in a crisis, call Lifeline on 13 11 14.

For further information about depression contact beyondblue on 1300224636 or talk to your GP, local health professional or someone you trust.

MIND MEDICINE AUSTRALIA

Appendix B

Article by Professor Paul Fitzgerald

Low Efficacy of Antidepressants

(Medium article 27/5/20 referred to in Section 2).

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

The Challenges of Depression Treatment in 2020

Paul Fitzgerald
May 27, 2020 · 5 min read

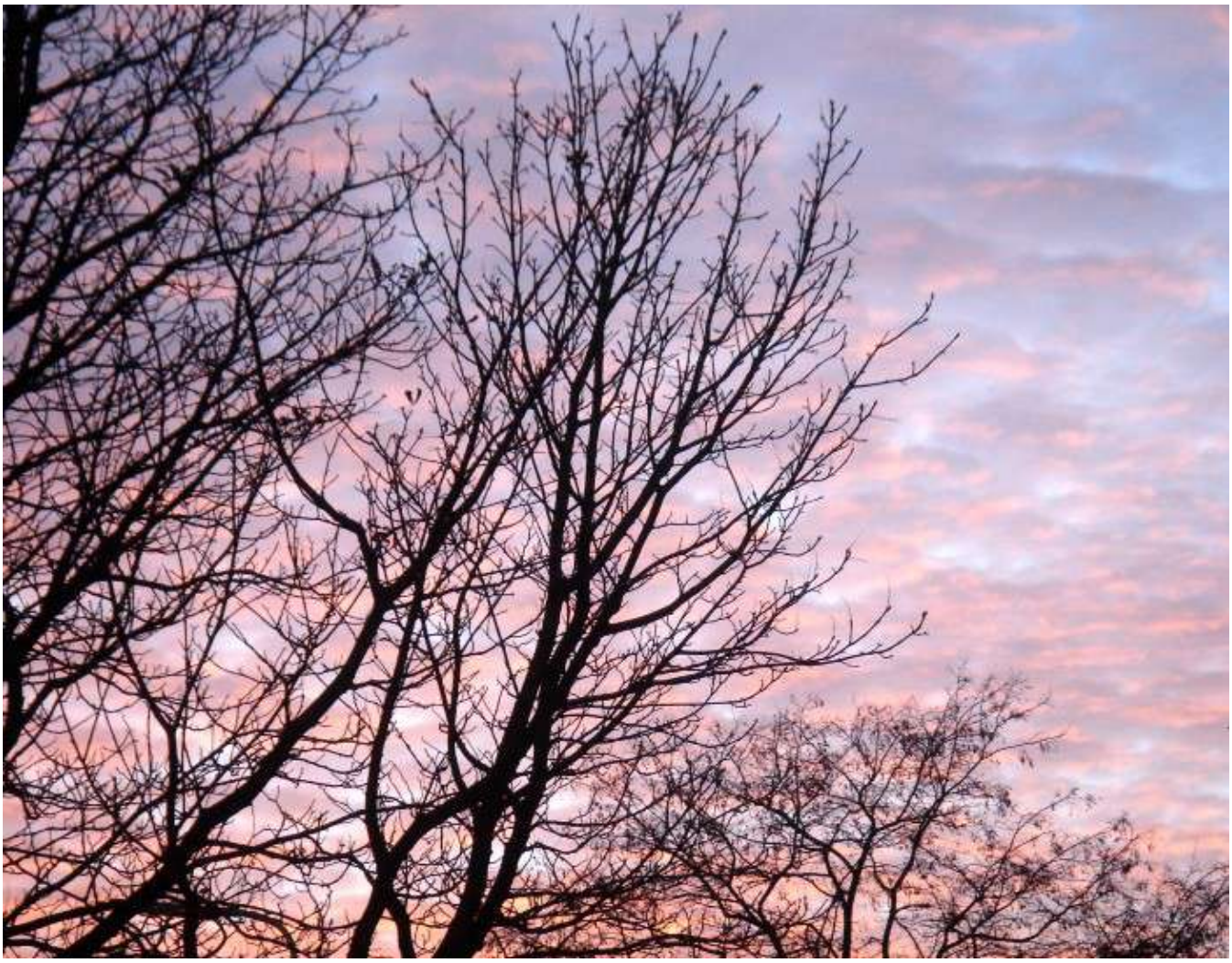


Photo by Irum Shahid from FreeImages

Over recent years there has been a laudable and impressive effort to reduce the stigma associated with mental health conditions such as depression, and to engage more people with these conditions in treatment, especially here in Australia. However, this has not been accompanied by a clear reduction in the consequences of depression, such as suicide, in our community. There are lots of possible reasons for this failing but a

completely under-recognised one concerns the limited effectiveness of the treatments we currently have available.

Whilst there are also issues with access to, and the effectiveness of, psychological treatments, I want to focus here on the limitations of existing antidepressant medication treatments. I want to make really clear up front that some patients are helped extremely well by these medications, they can change the lives of patients who respond to them, restoring their ability to function and lead fulfilling lives.

If you are taking one of these medications, what I am writing is not meant to persuade you to stop the medication, not at all, don't do this! If your medication is not working, however, talk to your doctor and make sure you actively explore what other options you have. You should set the bar high and aim to get well, to get your old life back.

The main problem with antidepressant medication I want to highlight is that they are just not effective for enough people and this limits the size of the group of people who can get the life changing benefits from them that they deserve.

The largest study that has investigated the effects of antidepressants was the sequenced treatment alternatives to relieve depression (STAR*D) study [1]. This impressive effort was funded by the National Institute of Mental Health in the US, independent of the pharmaceutical industry. It involved the sequential treatment of several thousand patients with depression who received up to 4 different steps of treatment, starting with the standard SSRI antidepressant citalopram. The study examined remission rates: the percentage of the patients who effectively got better with each stage of treatment. In the first round of treatment, ~ 37% of patients became symptom free taking citalopram, only about 30% to the second medication they tried, less than 15% to the third and only 13% to the fourth. There were also significant rates of withdrawal from treatment at each level: 21% after stage 1, 30% after stage 2 and 42% after stage 3.

Although these statistics are concerning, they don't quite paint a picture as to how bad things were as overall outcomes are determined both by whether you get better on a medication, but also how long this benefit lasts. Unfortunately relapse, a return of depression, was quite common. It was especially striking that patients who had struggled to get better initially, especially those who needed more than one medication to do so, experienced relapse at quite high rates. In fact, if a patient was in the group

who didn't respond to the first medication but then did get better, there was a greater than 50% chance that they would relapse in the next 12 months. Relapse rates were even higher if patients had required three or four courses of initial treatment.

It is possible to take these rates and to estimate the chance that a patient will respond and then remain well over a period of time: the overall value of the medication. In a paper published in 2016, Harold Sackeim did this with data from the STAR*D study [2]. His analysis found the following. The chance you would get better with the first medication, citalopram, and stay well for 12 months was about 27%. However, if a patient failed to respond to 2 initial antidepressant medication trials, the likelihood that they would respond to a subsequent medication trial and then remain well for at least 12 months fell to less than 5%. In other words, once a patient has failed to respond to 2 medications, the likelihood that they will achieve sustained benefit with the third or subsequent medication is going to be less than one in 20.

These results are really sobering and should be a siren call for attention and action. Clearly some patients do wonderfully well with treatment but many don't and once a few medications have failed, the chances of persistent response to future trials falls substantially. This has several direct and important implications.

First, we need to think more creatively in the treatment of patients who are not getting better with initial medication treatment. Consider other options, things like repetitive transcranial magnetic stimulation (rTMS) — my hobby horse and clearly an effective option in medication non responsive patients — , other forms of psychotherapy and even ECT. If medication treatment is being pursued and especially if the patient has responded, they need to be followed really closely. Everything that is possible from biological, psychological and social perspectives needs to be done, for example mindfulness based cognitive behavioural psychotherapy, to reduce their risk of relapse over time.

Most critically we desperately need a broader range of new accessible and affordable therapies. This is going to take meaningful investment in experimental therapeutics, clinical trials and translational infrastructure. We need to invest in the development and testing of novel medications, but also new non invasive froms of brain stimulation such as transcranial alternating current stimulation and focused ultrasound. We also need to be open to development of other novel forms of therapy, such as psychedelic assisted psychotherapy, which is fortunately now starting to get evaluated carefully. The investment in new treatment development is critical and timely as our patients

really deserve that this be taken as seriously as the other major health problems in our community that attract widespread funding.

[1] https://www.nimh.nih.gov/funding/clinical-research/practical/stard/allmedicationlevels.shtml

[2] Sackeim H. Acute continuation and maintenance treatment of Major depressive episodes with transcranial magnetic stimulation. *Brain Stimulation* 9 (2016) 313–319

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MIND MEDICINE AUSTRALIA

Appendix C

Critique of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Psychedelic Therapy Clinical Memorandum (May 2020) published in January 2021 (see Sections 3.2.3 and 3.4).

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

Public Health eJournal
2021, Article ID 3757891, 16 pages

http://ssrn.com/abstract=3757891

Critique of the Royal Australian and New Zealand College of Psychiatrists psychedelic therapy clinical memorandum, dated May 2020

Victor Chiruta, MCMA, MPS[1, 2, *], John A. Hannan, BAPsy(Hons), MBA, PhD(c)[2, 3], Dr Nicola Santarossa, MBBS, MCoun(c)[2, 3, 4] Shana Miller, BPsySc, BClinSc[2, 5], Paulina K. Zemla, BHSc, MAut(c), NP[2, 6], Katherine Lynch, BSc(Hons)[2, 7] and Jessica Morris, BNur, RN[8]

[1]School of Health Sciences, University of South Australia, 101 Currie Street, Adelaide, SA 5001, Australia
[2]Mind Medicine Australia, 1/10 Dorcas Street, South Melbourne, VIC 3205, Australia
[3]School of Psychology, University of Queensland, Sir Fred Schonell Drive, St Lucia, QLD 4072, Australia
[3]College of Medicine and Dentistry, 349 Queen Street, James Cook University, Brisbane City, QLD 4000, Australia
[4]Faculty of Health and Behavioural Sciences, University of Queensland, St Lucia, QLD 4072, Australia
[5]School of Health and Human Sciences, Southern Cross University, Military Road, East Lismore, NSW 2480, Australia
[6]Faculty of Social Sciences, University of Wollongong, Northfields Avenue, Wollongong, NSW 2522, Australia
[7]Department of Science, University of Canterbury, 20 Kirkwood Avenue, Upper Riccarton, Christchurch 8041, New Zealand
[8]School of Nursing, Queensland University of Technology, 149 Victoria Park Road, Kelvin Grove, QLD 4059, Australia

**chivy011@mymail.unisa.edu.au*

Received 3rd January 2021 Revised 5th February 2021

Objective: The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has positioned itself against medically controlled patient access (at this current time) to 3,4-methylenedioxymethamphetamine (MDMA) and psilocybin-assisted therapies in its Therapeutic Use of Psychedelic Substances Clinical Memorandum, May 2020. The main reason given by the RANZCP for its stance is safety concerns. This critique will argue that the RANZCP's position is based on outdated, irrelevant, misinterpreted, and misinformed evidence.

Methods: Every reference in the clinical memorandum (CM) was checked against the original publications used by RANZCP to justify its position. In addition, the search engines Google Scholar, PubMed, ScienceDirect, the Multidisciplinary Association for Psychedelic Therapies (MAPS) website, the Therapeutic Goods Administration (TGA) website, relevant Australian and New Zealand legislation were searched for pertinent and up-to-date-information.

Results: There is no scientific or medical evidence from the last 70 years to suggest that either psilocybin or MDMA when administered as an adjutant to therapy in a controlled clinical setting are linked to either mental illness or negative health outcomes. On the contrary, MDMA and psilocybin have been shown to be safe, non-toxic, non-addictive, and efficacious when administered in a medically-controlled clinical environment. All associated risks are apparent in an uncontrolled setting.

Conclusion: With the recent positive media coverage of the efficacy of these medicines when used as an adjunct to therapy, there is an intrinsic risk of self-medication or underground therapy. This means, that any medical discussion must also purvey the ethical responsibilities and social duties associated with these substances. MDMA and psilocybin are easy to access either naturally (in the case of psilocybin-containing mushrooms which grow in many parts of Australia) and through the Dark Web. The RANZCP, which represents psychiatrists in Australia, is an influential organisation with a vision of improving "...the mental health of communities through high-quality psychiatric care, education, leadership and advocacy", with values that include collaboration, excellence, integrity, compassion and innovation. The RANZCP should therefore, as a matter of urgency, review and update its CM and its conclusions, keeping with the factual position in relation to the medical use of these substances.

Keywords: psychedelic medicine, MDMA, psilocybin, TGA, psychedelic therapy, psychotherapy, RANZCP

Public Health eJournal
2021, Article ID 3757891, 16 pages

http://ssrn.com/abstract=3757891

1. Introduction

In Australia, there are currently public submissions from the charitable organisation Mind Medicine Australia (MMA), to have the Australian medical regulatory body reschedule MDMA and psilocybin from schedule 9 (S9) prohibited substances to schedule 8 (S8) controlled medicines[1]. This rescheduling would allow for controlled patient access, restricted to medically controlled environments, for Australians suffering from treatment-resistant depression and treatment-resistant Post-Traumatic Stress Disorder (PTSD). These therapies are classified as breakthrough designated therapies by the US Food and Drug Administration (FDA). MDMA is a chemical sometimes present in ecstasy and psilocybin (in its natural form) is a compound found in a number of species of psychedelic mushrooms.

The RANZCP released a CM in May 2020, titled *Therapeutic use of psychedelic substances*. The CM concludes in its key message that psychedelic-assisted psychotherapy should remain research only, without access to patients outside of research trials. The CM summary states[2],

> *"Research into medicines containing psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee…"*

The RANZCP is of the position that Australia should not, at the present time, approve the use of medically supervised psychedelic-assisted psychotherapy in a clinical environment. This position is based on evidence provided in the CM. However, the CM contains referencing errors, misinformation, irrelevant data, and incomplete research. This review will scientifically analyse and academically evaluate the evidence provided in the CM.

2. Methods

Every reference in the CM was checked against the original publications. In addition, the search engines Google Scholar, PubMed, ScienceDirect, the MAPS website, the TGA website, and relevant Australian and New Zealand legislation were searched for pertinent and up-to-date-information. Relevant legislation included the *Poisons Standard February 2021*, *Therapeutic Goods (Permissible Ingredients) Determination (No. 4) 2020*, *Therapeutic Goods Act 1989*, and *Misuse of Drugs Act 1975*.

3. Correction on psychedelics and their regulation

In the CM, there is a statement that MDMA is not a psychedelic[2],

> *"Though technically not a psychedelic, MDMA is included as it is similar to psychedelics with regard to legal impediments to research and potential therapeutic methods."*

Further, the CM describes the current regulatory frameworks for psychedelics[2],

> *"Psychedelic substances are illicit and are not registered for any use by the Therapeutic Goods Administration (TGA) in Australia or Medsafe in New Zealand. They cannot be prescribed or administered outside of properly approved research trials."*

There is confusion in the CM about what a psychedelic actually is. There are also contradictory statements about the regulatory frameworks for the medical use of psychedelic substances in Australia and New Zealand.

The RANZCP state that the CM is educational material written for psychiatrists. Using the word 'illicit' is unscientific and uninformative for psychiatrists. This is an inappropriate caveat given that a number of substances are legal when used in medically-controlled environments with proper approvals, but illegal when used recreationally. Examples include morphine, ketamine, and fentanyl. In Australia, 'illicit' drugs from a medical perspective, would fall under schedule 10 (S10) of the *Poisons Standard February 2021*[3], which lists drugs of such danger to public health as to warrant full prohibition on sale, supply and use. As this review will illuminate, the phrase 'psychedelic substances' covers several discrete substances which are subject to different controls in Australia and New Zealand. Ranging from research only, controlled prescription, uncontrolled prescription or as unregulated substances. The only exception is the psychedelic plant *Acorus calamus*, which is prohibited in Australia for human therapeutic use under S10 of the *Poisons Standard February 2021*.

3.1. MDMA

Starting with the RANZCP's statement on MDMA. MDMA is both pharmacologically and structurally a psychedelic. In the scientific literature, MDMA's effects on the central nervous system (CNS) are described as psychedelic[4, 5]. MDMA has highly complex pharmacodynamics, although a target is the serotonin subtype-2A receptor (5-HT_{2A})[6]. 5-HT_{2A} is the classic serotonergic psychedelic receptor[7, 8]. Another target of MDMA is the dopamine type-2 receptor (D_2)[6]. D_2 is one of the main targets of the classic psychedelic lysergic acid diethylamide (LSD)[9, 10] and the very potent natural psychedelic salvinorin A[9]. MDMA is further described in the scientific literature as a psychedelic phenylethylamine substituted amphetamine[11, 12]. In the literature, many phenylethylamines with a substituted amphetamine are classified as psychedelics, eg. 3,4-methylenedioxyamphetamine (MDA)[13], 2,5-dimethoxy-4-methylamphetamine (DOM)[14], and 2,5-dimethoxy-4-bromophenylamine (2C-B)[15].

MDMA has been classified as a B1 controlled drug in New Zealand by Medsafe since 2005[16]. B1 is the category of controlled medicines, which includes substances such as morphine, methadone, medicinal cannabis, and amphetamine[17]. This means that with the approval of the regulator, MDMA is available for prescription in New Zealand by doctors[18]. In Australia, MDMA is federally classified as a S9 substance[3]. This means that MDMA can be legally made available for use in research and doctors can only access this medicine for patients with an appropriate approval under the TGA's Special Access Scheme-B (SAS-B) or its Authorised Prescriber Scheme[19]. Even though MDMA is federally scheduled as a prohibited substance, several patients with otherwise treatment-resistant conditions, have been approved to receive MDMA therapeutically under SAS-B[20]. The complication in Australia comes at the State level. Victoria provides for access through a permit system whilst NSW prohibits the medical use of MDMA (even with TGA approval) through provisions that were designed to prohibit the recreational use of this substance.

3.2. Ketamine

The next medicine to evaluate is ketamine. The RANZCP note in its *Psychedelic Therapy* CM, that ketamine has its own RANZCP clinical memorandum[2]. Ketamine is described in multiple scientific literature as a psychedelic[21-24]. Between the years 1985 and 1995, ketamine was studied successfully in over 1,000 participants for its use in psychedelic-assisted psychotherapy[21]. Ketamine has recently gained application once again for use in psychedelic-assisted psychotherapy[22]. The TGA has approved the psychedelic ketamine (ingredient ID: 70736) and its enantiomer esketamine (ingredient ID: 114417) for use in medicine in Australia[25]. There are currently 13 approved medicines listed on the Australian Register of Therapeutic Goods (ARTG) containing ketamine[26].

3.3. Ibotenic acid and muscimol

Another interesting group of psychedelic compounds are the GABAergic isoxazoles from the psychedelic variants of the *Amanita spp.* The psychedelic mushroom *Amanita muscaria* has rich historical entheogenic use in traditional and indigenous cultures all over the world[27-30]. The *Amanita spp.* are federally not scheduled in Australia[3] nor New Zealand[17]. However, *Amanita spp.* are prohibited for use in food in both countries[31]. The primary psychedelic compounds in the mushroom are ibotenic acid and muscimol[31]. Ibotenic acid is a prodrug for muscimol. Ibotenic acid is not scheduled in Australia[3] nor New Zealand[17]. In Australia, ibotenic acid (ingredient ID: 105657) has been approved for use in medicine by the TGA[25]. Muscimol is classified as a S9 substance in Australia[3], but unscheduled in New Zealand[17].

3.4. Harmala (Ayahuasca) alkaloids

Harmala alkaloids have become renowned for their application in the South American Ayahuasca tea[32]. Harmala alkaloids are the compounds in the Ayahuasca vine (*Banisteriopsis caapi*) that activate the N,N-dimethyltryptamine (DMT) in the Ayahuasca tea. Harmala alkaloids are federally S9 substances, but unscheduled if used in herbs or preparations for therapeutic use containing 0.1% or less of harmala alkaloids or in divided preparations containing 2mg or less of harmala alkaloids per recommended daily dose[3]. A protocol for the therapeutic use of harmala alkaloids is prescribed by the TGA. Further to this, the psychedelic plant *Peganum harmala* (ingredient ID: 83330) has been approved by the TGA for use in medicine[25]. *Peganum harmala* is used as a substitute for *Banisteriopsis caapi* in the Ayahuasca tea[33]. *Peganum harmala* has a rich history of entheogenic and spiritual use[34, 35].

3.5. DMT

In regards to DMT, DMT is federally a S9 substance in Australia[3] and a class A controlled drug in New Zealand[17]. However, the TGA have approved a handful of DMT-containing plants for use in medicine.

The ARTG lists one medicine containing *Acacia longifolia* (ARTG ID: 176056)[26]. The medicine is listed for wellbeing and contains equivalent of 500mg of *Acacia longifolia* per mL. According to Lim 2014, there would be 1-1.5mg of DMT per mL[36].

Table 1. DMT-containing plants approved for use in medicines by TGA.

Plant	ID[25]	Psychedelic	Amount
Acacia longifolia	86827	DMT	0.2-0.3%[36]
Phalaris arundinacea	87004	DMT NMT 5-MeO-DMT 5-MeO-NMT β-Carbolines	0.2-0.7%[37, 38]
Mucuna pruriens	83253	DMT Bufotenine	Unspecified[39]

NMT	N-Methyltryptamine
5-MeO-DMT	5-Methoxy-N,N-dimethyltryptamine
5-MeO-NMT	5-Methoxy-N-methyltryptamine
β-Carbolines	Harmala alkaloid family
Bufotenine	5-Hydroxy-dimethyltryptamine (5-OH-DMT)

3.6. Ibogaine

In Australia, the powerful psychedelic ibogaine and its metabolite noribogaine are schedule 4 (S4; prescription only) medicines in Australia[3] and in New Zealand are classified for prescription without restrictions or controls[40]. The rescheduling of ibogaine in Australia (from S9 to S4) and New Zealand occurred in 2010[41]. The National Drugs and Poisons Schedule Committee (NDPSC) made the recommendation to the TGA based on the rescheduling reasons provided by the New Zealand Medicines Classification Committee (MCC) in 2009:

i. The need for supervision of the substances' use in the management/treatment of addiction to limit attempts at self treatment and prevent recreational use as a "party pill" (although noting that the documented experience is usually not pleasant);
ii. The need to control the import and supply of ibogaine, its metabolite or products containing each or both of the substances;
iii. Data suggesting that the number of deaths due to ibogaine were lower than those associated with methadone; and
iv. Opinion that although ibogaine's appeal as a recreational drug was low, there were dangers in *ad hoc* use as a self medication for drug addiction following potential media interest.

4. Reason for rescheduling MDMA and psilocybin

The RANZCP's position on the use of psychedelics in therapy is in direct contradiction with the reasons the NDPSC, TGA, and MCC had for scheduling ibogaine. If the above committee points are taken into consideration for the current psychedelics in MMA's submissions (for MDMA and psilocybin) the proposed rescheduling is likely to be approved.

5. Psychedelic patterns of use in medically-controlled environments

There is increasing media interest in the use of MDMA and psilocybin as an adjunct to therapy for the treatment of the common mental health conditions listed in Table 3, such as depression, PTSD, General Anxiety Disorder (GAD), Social Anxiety Disorder (SAD), and addiction. MDMA and psilocybin have gained much attention as potential 'cures' for these disorders on mainstream Australian media (ABC[42], 7NEWS[43], The Sydney Morning Herald[44], and 60 minutes[45, 46]), particularly in the last two years. The FDA have granted both MDMA and psilocybin-assisted therapies 'breakthrough therapy' status in the US[47, 48], the FDA have opened an 'expanded access scheme' for treating PTSD with MDMA[49], the Israeli Ministry of Health has embraced the treatment of PTSD with MDMA under 'compassionate use'[50], and compassionate MDMA therapy has been conducted in Switzerland[51]. The state of Oregon in the US has legalised psilocybin therapy[52] whilst Canada has approved for patients to use psilocybin-assisted psychotherapy for depression and end-of-life anxiety[53, 54].

The Honourable Canadian Health Minister has granted patients suffering with anxiety associated with terminal illness lawful access to psilocybin therapeutically under section 56(1) of the *Controlled Drugs and Substances Act*[55]. Psychedelic-assisted psychotherapy clinics have opened up in Toronto[56], New York City, Los Angeles, Chicago, with a psilocybin microdose dispensary for therapeutic use opened in Canada[57]. This list is by no means exhaustive for MDMA and psilocybin (let alone other psychedelics). A lengthy paper on the international regulatory coverage of different psychedelic patterns of use in medically-controlled environments could be written.

According to the NDPSC, TGA, and MCC, given the increasing public awareness of uses around the world of the psychedelic substance ibogaine, there is increased risk of self-medication if there is not an accessible route through the medical system[41].

The RANZCP has not only expressed the simplistic opinion in its CM that psychedelics are 'illicit' in Australia and New Zealand, but the CM also states that[2],

"Currently psychedelic therapy is not regulated for use in any country…"

The above statement is misleading because, whilst there is no psychedelic-specific indications for the medical use of psychedelic substances, MDMA and psilocybin are accessible by doctors for their patients under expanded access schemes and regulatory provisions in a number of jurisdictions. In the case of ibogaine, it is available in Australia and New Zealand through prescription, also through clinics in Canada[58-60], Mexico[61, 62], Gabon[63], South Africa[64], Costa Rica[65] and the Bahamas[66]. Ayahuasca is also being medically administered as part of therapy for the rehabilitation of violent and sexual offenders in Brazilian jails[67, 68].

6. Safety profile of medicinal MDMA and psilocybin

6.1. Medicinal MDMA

Dangers of self-medication is a critical part of the discourse on uncontrolled unsupervised use verses controlled and medically-supervised treatments. With MDMA use, morbidity and mortality has only occurred in uncontrolled non-clinical settings[51]. All serious adverse effects in a clinical setting have been rare and non-life threatening[69].

The risks of self-medication (because of barriers for use in the medical system) was one of the key arguments behind the rescheduling of ibogaine in Australia and New Zealand. RANZCP state in its CM in relation to MDMA that[2],

> *"Clinical trials have demonstrated safety profile, for example 760 individuals have participated in the MAPS' MDMA trials with only one serious adverse event reported [17] relating to tachycardia and increased blood pressure."*

The above statement is in reference to what appears to be a very dated MAPS MDMA poster[70]. The CM states in its referencing that the poster was published in 2019 (reference [17])[2]. However, the poster has no publication date. A small referencing error has been made by RANZCP. The poster states, *'over 780 human subjects'*, not *'760 individuals'*[70]. On page 54 of a 2013 Investigator's Brochure publication, MAPS state, *'as of November 2012, 811 participants have received MDMA in trials'*[71]. This coincides with the poster publication of the number of MDMA trial participants. Although the poster does not show on its face when it was published, the American Counselling Association (ACA) make reference to an archived version of the poster in 2018[72]. It is logical to assume the release date of the poster is older than the archived version of the poster that the ACA cite.

A public poster is not scientific evidence that should be used when arguing against the profound social, medical, and economic impact of the medical rescheduling of MDMA. The poster does not cite the original source. The RANZCP clearly did not fact check the poster against the original scientific data and is incorrectly representing that this data is recent. Relevant scientific publication should be cited when discussing the regulation and medical impact of drugs and medicines. The RANZCP is of the opinion 760 individuals have participated in MDMA studies. However MAPS, which is sponsoring the current Phase 3 trials has reported much larger numbers.

MAPS report since 2001, 3,347 people have participated in MDMA studies around the world (Table 2). This is in comparison to the 760 participants reported by the RANZCP. With only one serious adverse event reported in the last 20 years of trials, the significance falls from 0.13% to less than 0.03%.

Table 2. MAPS reported trial participants who have received MDMA.

Year	# of participants	Source
Pre-1987	> 500,000	Investigator's Brochure 2020, p. 56[73]
2000-2012	811	Investigator's Brochure 2013, p. 54[71]
as of 2015	1,180	Investigator's Brochure 2016, p. 92[74]
as of 2016	1,280	Investigator's Brochure 2017, p. 133[75]
as of 2018	> 1,500	Investigator's Brochure 2018, p. 127[76]
as of 2019	(MAPS) 1,837	Investigator's Brochure 2019, p. 63[69]
as of 2020	(non-MAPS) 1,431	Investigator's Brochure 2020, p. 14[73]
in 2020	79	Safety Update Report 2020, p. 29[77]

Several sources have published that thousands of participants undertook MDMA-assisted psychotherapy until prohibition in 1987[69, 71, 73-76, 78], with MAPS publishing there were an estimated 500,000 participants in these early psychotherapy sessions[73]. An evaluation of pre-prohibition studies published in the *Drug Science, Policy and Law* journal states that, early psychotherapeutic use of MDMA was without complication[78]. It would appear that the RANZCP are basing its position on 2013 rather than 2020 data (and have excluded all pre-prohibition data about safety). RANZCP's substantive understatement of data is further evidenced by its statement in the CM that[2],

"Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics in various non-psychotic psychiatric disorders."

Since 2009, 34 completed trials for MDMA alone have been published on www.clinicaltrials.gov, with over 50 completed psychedelic-medicine trials in total. MAPS report there are 76 recent MDMA trials completed[73]. The trials are reported in Table 3. As there are so many completed psychedelic drugs studied in trials since 2006, Table 3 only collates data from 2009 (Table 3 is by no means exhaustive, excluding the hundreds of completed clinical ketamine studies and completed psychedelic clinical studies pre-prohibition).

The RANZCP position of restrictive stance on using MDMA as part of therapy is based on incomplete analysis and misinterpreted information. Furthermore, the above reference to 'several' completed psychedelic trials is clearly misleading, when there have been over 50 completed trials since 2009 and many others before that.

As previously discussed, MDMA trials have over 3,000 recent participants and approximately 500,000 pre-prohibition participants, with over 40 years worth of data. MDMA was first synthesised in 1912 by Merck[79] and has thorough toxicology studies and safety data (both short-term and long-term).

MDMA, as part of the recreational drug ecstasy, has a reputation for being associated with overdoses and deaths at dance parties[80]. In assessing the safety of MDMA, important distinctions need to be made between medicinal MDMA and the street-drug ecstasy[20]:

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

Medicinal MDMA is administered in a medically-controlled clinical setting. It is pharmaceutical grade, dosage is known, patients are properly screened, the use of the medicine is regulated, the medicine is administered only by trained health professionals, and patients receive ongoing psychological support. Understanding the distinction between the two types of substances (recreational ecstasy and medical grade MDMA) is fundamental when examining the safety evidence for MDMA.

The lethal dose of MDMA in humans is 10-20mg/kg[81]. The largest dose used in clinical studies is 1-2mg/kg[82]. The maximum therapeutic dose for MDMA is a safety factor of 5-20 when compared with the lethal dose. Paracetamol is described in the scientific literature as having a safety factor of 10 from the lethal dose when compared to its maximum therapeutic dose[83].

According to the *International Journal of Drug Policy*, in Australia between the years 2000 to 2018, 243 deaths in recreational environments involved drug toxicity where MDMA was present[84]. However, only 14 deaths between 2000 and 2018 occurred solely due to MDMA toxicity (ie. multiple drugs weren't detected).

In its CM under the heading *Risks and side effects* the RANZCP make the following observation[2],

"Frequent high dose MDMA can be neurotoxic (damaging to the nervous system) [16]…"

Although this statement is true in a recreational setting, it has no relevance to the medical use of MDMA in controlled environments. More appropriately, this statement should be in a section called *Risks and adverse effects of recreational use, misuse and abuse*. The RANZCP have omitted the following information:

i. Morbidity and mortality of MDMA use has only occurred in uncontrolled non-clinical settings[51];
ii. All serious adverse effects of MDMA in a clinical setting have been rare and non-life threatening[69];
iii. Early psychotherapeutic use of MDMA was without complication[78];
iv. MDMA administered therapeutically in a controlled environment does not produce dependence[85];
v. Therapeutic treatment with MDMA has not been shown to increase illicit drug use[51].

6.2. Psilocybin

Psilocybin is of concurrent importance with MDMA in the ethos of psychedelic-medicines as a way of changing the current mental health treatment paradigm in Australia. The RANZCP have published in the *Australian and New Zealand Journal of Psychiatry*, that many Australians with key mental illnesses are not getting well[86]. Moreover, some mental health medicines (such as antidepressants) can have serious and debilitating side-effects[87].

The RANZCP state in its CM, that it is not satisfied with the safety profile of psychedelics in psychiatric use. But psychedelics range over hundreds of different compounds and plants. The CM makes no mention of the toxicology or safety data of medicinal psilocybin. Under *Risks and side effects* in the CM, RANZCP make the following statement[2],

*"Psychedelics **when misused** can cause psychosis (hallucinogen induced psychotic disorder) as well as Hallucinogen Persisting Perception Disorder (HPPD). [18, 19] This is a potential long- term risk factor following psychedelic therapy, though this has not been investigated in research trials."*

The key terminology here is 'when misused'. Again, this statement should be in a section called *Risks and adverse effects of recreational use, misuse and abuse*. This should not cloud any potential risks associated with the medical controlled use.

When the references used by RANZCP in the CM for HPPD and psychosis (in the CM [18, 19]) are evaluated, the authors in both articles do not state that psilocybin or MDMA are associated with HPPD or psychosis[88, 89]. In [18], the authors stipulate that cannabis, cannabis co-administered with MDMA, LSD, cannabis co-administered with LSD, phencyclidine (PCP), and risperidone are associated with HPPD[88]. In [19], the authors conclude that the most common cause of drug-induced psychosis is from alcohol[89]. From the meta-analysis' study inclusions, out of 40,783 individuals with psychosis, only 208 cases were associated with hallucinogens used in a recreational setting. Although the authors included psilocybin and MDMA amongst many other hallucinogens in the keyword search, they do not specify what type of hallucinogens are associated with psychosis. 208 out of 40,783 equates to 0.5%. The other 95.5% of psychosis cases in the meta-analysis were associated with alcohol, cannabis, amphetamines, opioids, sedatives, a mix of drugs, or an unknown cause. It is of particular significance that everyone of the 0.5% of cases of hallucinogen-induced psychosis in the meta-analysis occurred in an uncontrolled setting.

A population study published in the *Journal of Psychopharmacology* was conducted across a cohort of 135,000 individuals. The study found no link between psychedelic use and psychosis[90]. The researchers concluded, individuals who had taken psychedelics were not at increased risk of developing mental health problems, including schizophrenia, psychosis, depression, anxiety disorders, and suicide attempts. However, a self-reporting study at Johns Hopkins University involved 1,993 individuals completing an online survey about their single most psychologically difficult or challenging experience after consuming psilocybin-containing mushrooms. In an uncontrolled setting, the survey revealed that 0.15% of participants reported a suicide attempt and 0.15% self-reported enduring psychosis[91].

Nevertheless, if used within a controlled setting, psilocybin has been shown to have little to no adverse reactions[92, 93]. Early therapeutic use of the pharmaceutical psilocybin (Indocybin® developed by Sandoz) was without complication[79]. In more recent trials, there have been no significant adverse events with psilocybin administration in a controlled setting[94].

The toxicity of psilocybin and psilocybin-containing mushrooms is very low[95]. The lethal dose of psilocybin is extrapolated to 6g in humans. This is 300 times the typical therapeutic dose of 20mg. It would be quite bizarre to consume 300 cups of coffee, doses of Panadol, pints of beer, or even daily multi-vitamins. The *Japanese Journal of Legal Medicine* and the *Proceedings of the Western Pharmacology Society* have published that fatal intoxication due to ingestion of psilocybin-containing mushrooms is extremely rare[96, 97]. A review on the harm potential of psilocybin-containing mushrooms published in the scientific journal *Regulatory Toxicology and Pharmacology*, found only two deaths due to direct overdosing internationally since 1960[98]. For comparison, the ABS reported 276 deaths from antidepressants and 663 deaths from anti-anxiety medication during 2016 just within Australia[99]. The lethal toxicity of fresh psilocybin-containing mushrooms in humans is 17kg[98]. It would be highly unusual and very challenging to consume 17kg of mushrooms in one sitting.

6.3. Risk of self-medication

As previously discussed, there is a huge international surge of interest in MDMA and psilocybin use in therapy. According to the NDPSC, TGA, and MCC, this media interest will be intrinsically linked to an increased risk of self-medication[41]. Considering the extremely low toxicity of psilocybin-containing mushroom and the ease of access to ecstasy pills, attempts at self-medication of psilocybin and MDMA in an uncontrolled setting is where dangers and risks can transpire. Just like with ibogaine, there is an urgent need to regulate the use of these medicines in medically controlled environments to help prevent the hazard's of self-medication from occurring.

7. How MDMA and psilocybin work in the brain

An interesting statement from the RANZCP appears in the CM[2],

"Much about the neuroscience of psychedelics remains unknown, although there are theories that they heighten emotional responses and encourage people to confront their disorder actively, which can prompt enduring shifts in mind-set."

The neuroscience of psilocybin and MDMA has been heavily researched. This topic is beyond the scope of this review and is a lengthy and complex topic. This paper will briefly point out some key studies behind the neuroscience of psilocybin and MDMA for the RANZCP to further investigate.

For psilocybin, see the following references[100-105]. There are brain imaging fMRI data to explain the therapeutic actions of psilocybin through changes of brain network dynamics in Functional Connectivity and the Default Mode Network[103].

The neuropharmacology of MDMA is very well documented throughout the academic literature. The following references study the neuroscientific relationship between MDMA-assisted psychotherapy and treating PTSD[106-111].

What is unknown is the way and why the 'mystical experience' associated with positive therapeutic outcomes is created in the brain[112, 113]. A topic bordering on the nature of human consciousness, which we are barely at the beginning of understanding.

8. The need for further research

The RANZCP note in its CM that[2],

"Further research is required to assess the efficacy, safety and effectiveness of psychedelic therapies to inform future potential use in psychiatric practices. Research into the clinical use of psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee and careful monitoring and reporting of efficacy and safety outcomes."

Trials to date suggest remission rates for treatment-resistant-depression and treatment-resistant PTSD of between 60-80%, for both psilocybin and MDMA when used as an adjunct to therapy[77, 114]. As previously mentioned, both therapies have been awarded 'breakthrough therapy' status by the FDA[47, 48] with the first MDMA Phase 3 trials successfully complete[77]. Given the high incidence of depression and PTSD in Australia[115] and associated high levels of suicide[99, 116], there needs to be substantiated reasons for insisting that these therapies should not be made available on a case-by-case basis for patients through experienced medical practitioners. The incomplete and outdated safety and efficacy data in the RANZCP CM does not support withholding these therapies.

It is a truism to state that, a particular medicine associated with a treatment for a particular mental illness would benefit from further research. However, a lack of understanding of mechanisms of action has not stopped other medicines from being used. There are many commonly prescribed pharmaceuticals with unknown therapeutic mechanism of action, such as paracetamol[117], lithium[118], general anaesthetic[119, 120], and modafinil[121]. For example, the exact way in which lithium helps stabilise mood is unknown[122-125], however its use is not questioned. Further, toxicity is a known long-term consequence of lithium, yet it continues to be prescribed[118].

There is significant data on the safety, efficacy and effectiveness of psilocybin and MDMA-assisted therapies to support the use by medical specialists as part of therapy with case specific regulatory approvals. The RANZCP further says that[2],

"The treatments can be expensive and the short timeframes of application (1-2 sessions) suggested by early research puts limits on the potential profitability of psychedelic therapies; as a result, there are few pharmaceutical companies supporting research."

For the reasons given in this paper, the above reference to 'early research' is misleading. In addition, the cost of treatment is relative. A lifetime of taking antidepressants can be far more costly for an individual than a short treatment that generates remission.

9. Discussion

The RANZCP suggest there are many unknown factors, short and long-term side-effects of using psychedelics in medically controlled environments as an aid in psychotherapy[2]. They further state, that there is only some evidence that psychedelics may have therapeutic potential.

Thousands of patients had received MDMA in psychotherapy from the 1960s until prohibition in 1986[78]. The first clinical study for MDMA in psychotherapy occurred in 1984[126]. The FDA began approving clinical trials for treating PTSD with MDMA in 2000[127]. With the first post-prohibition clinical trial complete in 2001 and the first MDMA phase 3 trial successfully completed in 2020[77]. We have 20 years of recent data and over 20 years of pre-prohibition data to assess the efficacy and safety of MDMA. Psilocybin has received regulatory approval for therapeutic use in the state of Oregon, US[52] and is being administered medically to patients in Canada[53-55]. Furthermore, reviews of all the studies indicate that both MDMA and psilocybin are safe, non-toxic, and non-addictive when used in a medically-controlled environment.

In a non-medical environment in Australia and the UK, controlled medicines buprenorphine, methadone, fentanyl, cannabis, ketamine, amphetamines, prescription medicines anabolic steroids, benzodiazepines; and unscheduled drugs

Table 3. Completed psychedelic studies since 2009.

#	Year complete	Psychedelic substance	Condition or illness	Reference
1	2020	MDMA	PTSD	https://clinicaltrials.gov/ct2/show/NCT03537014
2	2020		PTSD	https://clinicaltrials.gov/ct2/show/NCT03485287
3	2020		GAD	https://clinicaltrials.gov/ct2/show/NCT02427568
4	2019		SAD in Autistic Adults	https://clinicaltrials.gov/ct2/show/NCT02008396
6	2019		PTSD	https://clinicaltrials.gov/ct2/show/NCT02876172
6	2019		Substance-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT01148342
7	2019		Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
8	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01689740
9	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01793610
10	2018		Effects on Emotional and Social Memories	https://clinicaltrials.gov/ct2/show/NCT03050541
11	2018		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01270672
12	2018		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01386177
13	2018		PTSD	https://clinicaltrials.gov/ct2/show/NCT01211405
14	2018		GAD	https://clinicaltrials.gov/ct2/show/NCT02954562
15	2018		Emotion Processing	https://clinicaltrials.gov/ct2/show/NCT03019822
16	2018		Social Cognition	https://clinicaltrials.gov/ct2/show/NCT01616407
17	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT00353938
18	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT01958593
19	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT02102802
20	2017		PTSD	https://clinicaltrials.gov/ct2/show/NCT01458327
21	2016		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01951508
22	2016		Emotional Effects	https://clinicaltrials.gov/ct2/show/NCT01465685
23	2016		Substance-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT01771874
24	2015		PTSD	https://clinicaltrials.gov/ct2/show/NCT00090064
25	2014		Drug Addiction	https://clinicaltrials.gov/ct2/show/NCT01849419
26	2014		Amphetamine-Related Disorders	https://clinicaltrials.gov/ct2/show/NCT02232789
27	2013		MDMA Discontinuation Syndrome	https://clinicaltrials.gov/ct2/show/NCT01053403
28	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT01136278
29	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00990067
30	2013		Mechanism of Action	https://clinicaltrials.gov/ct2/show/NCT00838305
31	2013		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00886886
32	2011		Pharmacokinetics	https://clinicaltrials.gov/ct2/show/NCT01447472
33	2011		Hangover	https://clinicaltrials.gov/ct2/show/NCT01400204
34	2009		Substance-related and Mood Disorders	https://clinicaltrials.gov/ct2/show/NCT00895804
35	2020	Psilocybin	Distress, Depression, Grief	https://clinicaltrials.gov/ct2/show/NCT02950467
36	2020		Healthy	https://clinicaltrials.gov/ct2/show/NCT02163707
37	2019		Persisting Effects	https://clinicaltrials.gov/ct2/show/NCT02971605
38	2019		Healthy	https://clinicaltrials.gov/ct2/show/NCT02145091
7	2019		Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
39	2018		Depression, GAD, Cancer	https://clinicaltrials.gov/ct2/show/NCT00465595
40	2016		Healthy	https://clinicaltrials.gov/ct2/show/NCT00802282
41	2014		Pharmacology, Therapeutic Uses	https://clinicaltrials.gov/ct2/show/NCT01988311
42	2013		GAD	https://clinicaltrials.gov/ct2/show/NCT00302744
43	2019	Ayahuasca	Treatment-Resistant Depression	https://doi.org/10.1017/S0033291718001356
44	2019		Major Depression Disorder (MDD)	https://doi.org/10.3389/fpsyg.2019.0123
45	2017		MDD	https://clinicaltrials.gov/ct2/show/NCT02914769
46	2020	LSD	Microdose	https://clinicaltrials.gov/ct2/show/NCT04421105
16	2018		Emotion Processing	https://clinicaltrials.gov/ct2/show/NCT03019822
47	2019		Healthy	https://clinicaltrials.gov/ct2/show/NCT03321136
8	2019		Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
48	2016		Healthy	https://clinicaltrials.gov/ct2/show/NCT01878942
49	2016		Personal Meaning	https://clinicaltrials.gov/ct2/show/NCT02451072
50	2015		Healthy	https://clinicaltrials.gov/ct2/show/NCT02308969
51	2014		GAD	https://clinicaltrials.gov/ct2/show/NCT00920387
8	2019	Mescaline	Mood, Performance	https://clinicaltrials.gov/ct2/show/NCT02033707
52	2013	MDA	Healthy	https://clinicaltrials.gov/ct2/show/NCT00823407

tobacco and alcohol cause significantly more harm to the user and society than either MDMA or psilocybin[128, 129].

Regulating MDMA and psilocybin under strict medical guidelines and supervision will further mitigate associated risks with self-medication.

10. Questions to RANZCP

Given the high remission rates being achieved in overseas trials, the safety data outlined above, the inadequacy of current treatments for many Australians, and the risks associated with self-medication:

1. What is the precise research that the RANZCP believes needs to be undertaken and why?
2. How does that RANZCP envisage that this research will be funded in a timely manner?
3. What is the timeframe anticipated by RANZCP before these therapies are made available to Australians suffering from key treatment-resistant mental illnesses? Further, how can this time lag be justified?

11. Conclusion

For suffering Australians who have exhausted conventional means of treatment, there needs to be a clear regulatory avenue in Australia to have controlled medical access to MDMA and psilocybin-assisted psychotherapies. A thoroughly researched and objective clinical practice explanatory memorandum is required from RANZCP, the institutional representative of psychiatry in Australia and New Zealand.

Conflicts of interests

Victor Chiruta was the main researcher and writer for the applications to the TGA to have MDMA and psilocybin rescheduled from S9 prohibited drugs to S8 controlled medicines.

Acknowledgments

The authors would like to acknowledge Peter Hunt AM (Chair of MMA) for his suggestions in this review.

Abbreviations

2-CB	2,5-Dimethoxy-4-bromophenylamine
5-HT$_{2A}$	Serotonin subtype-2A receptor
5-MeO-DMT	5-Methoxy-N,N-dimethyltryptamine
5-MeO-NMT	5-Methoxy-N-methyltryptamine
5-OH-DMT	5-Hydroxy-N,N-dimethyltryptamine
ABS	Australian Bureau of Statistics
ACA	American Counseling Association
ARTG	Australian Register of Therapeutic Goods
CM	Clinical memorandum
CNS	Central nervous system
D_2	Dopamine type-2 receptor
DOM	2,5-Dimethoxy-4-methylamphetamine
FDA	Food and Drugs Administration
GAD	General Anxiety Disorder
HPPD	Hallucination Persistent Perception Disorder
LSD	Lysergic acid diethylamide
MAPS	Multidisciplinary Association of Psychedelic Studies
MCC	Medicines Classifications Committee
MDA	3,4-Methylenedioxyamphetamine
MDD	Major Depressive Disorder
MDMA	3,4-Methylenedioxymethampehetamine
MMA	Mind Medicine Australia
NMT	N-Methyltryptamine
NDPSC	National Drugs and Poisons Schedule Committee
PCP	Phencyclidine
PTSD	Post-Traumatic Stress Disorder
RANZCP	Royal Australian College of Psychiatrists
S4	Schedule 4
S8	Schedule 8
S9	Schedule 9
S10	Schedule 10
SAS-B	Special Access Scheme-B
SAD	Social Anxiety Disorder
TGA	Therapeutic Goods Administration

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Appendix D

Article in The Australian newspaper entitled

“Psychedelic Drug Memo sparks uproar” (9/2/21) (see Section 3.4).

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THE AUSTRALIAN

Psychedelic drug memo sparks uproar

EXCLUSIVE

By **MAX MADDISON**, EXCLUSIVE

10:44AM FEBRUARY 9, 2021 • 39 COMMENTS

The peak body for psychiatrists has been savaged by its own members for a "pitiful" clinical memorandum, including a "childish misrepresentation" of data, which lay behind the health regulator's preliminary decision not to reclassify psychedelic medicines.

The Royal Australian and New Zealand College of Psychiatrists has come under fire for the five-page document, with members of the college saying expert advice was ignored and the memorandum was released for political reasons, rather than scientific fact.

Malvern Private Hospital medical director Eli Kotler said he was "disappointed" by its release and "sadly not surprised" by the Therapeutic Goods Administration's interim decision.

"Both (the RANZCP and TGA) statements appear to unfortunately perpetuate the stigma around these treatments by conflating illicit substances with medicines. They also appear to have been selective with the data used for their respective conclusions," RANZCP member Dr Kotler told The Australian.

"One could be led to believe that the peak mental-health body in this country lacks an appreciation of the significance of trauma underlying many of the illnesses we treat."

In the clinical memorandum, the RANZCP said there "remained many unknown factors and side effects, including long-term side effects, including the risk of inducing psychosis in vulnerable populations."

However, Newcastle-based psychiatrist and RANZCP member Chris Bench questioned the transparency of the process, saying the college's own specialist body on psychedelic therapy hadn't been consulted before the memorandum was released, and he remained mystified as to who had

written the document. “One of the questions I was asking is, who has actually drawn up this memorandum, what was their expertise? I think part of it has been done for political reasons,” Dr Bench said.

The weight of the memorandum was made apparent in the TGA’s interim decision, which ruled against rescheduling psilocybin (the active ingredient in magic mushrooms) and MDMA (ecstasy) on Wednesday, and referenced the RANZCP’s document in it’s reasoning.

“I also note the findings of a recent clinical memorandum on psychedelic therapies ... which found that evidence of safety and efficacy is limited but emerging,” the TGA’s ruling said. “I believe that these findings support my conclusion that current use of psilocybin should be limited to carefully monitored research trials.”

There are also considerable doubts regarding the veracity of research contained within the document, according to Toronto Private Health psychiatrist Stuart Saker.

“There’s a lot of objections to what they’ve written. And it’s not a good reflection of the literature. There’s some misrepresentation around numbers of people, some almost clownish, childish misrepresentation around numbers of people who’ve been in clinical trials,” Dr Saker said.

“And they’ve substantially misrepresented that to the TGA. I don’t even know who’s produced the memorandum because it’s pitiful, really.”

RANZCP President John Allan said the memorandum would be reviewed in “due course”, adding: “The evidence for psychedelics just isn’t quite there yet, which was reinforced by the interim decision of the TGA.”

MAX MADDISON, JOURNALIST

Max Maddison is a reporter at The Australian. He graduated from a Bachelor of Politics, Economics and Social Sciences (Hons I) at the University of Sydney. He began working for the paper in 2015 as an Editorial... Read more

Appendix E

Papers referred to in Professor David Nutt's Letter set out in Table 7 (see Section 3.4)

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Australia

VIEWPOINT

The Current Status of Psychedelics in Psychiatry

David Nutt, MD, PhD
Imperial College London, London, United Kingdom.

Robin Carhart-Harris, PhD
Imperial College London, London, United Kingdom.

In the 1950s, the Swiss pharmaceutical company Sandoz, which employed the chemist Albert Hofmann, who discovered lysergic acid diethylamide (LSD) and the similar serotonergic psychedelic psilocybin, made these drugs available to the psychiatric research community as the products Delysid and Indocybin, respectively. By the 1960s, these drugs had caused a revolution in brain science and psychiatry because of their widespread use by researchers and clinicians in many Western countries, especially the US. Before LSD was banned, the US National Institutes of Health funded more than 130 studies exploring its clinical utility, with positive results in a range of disorders but particularly anxiety, depression, and alcoholism. However, the displacement of LSD into recreational use and eventual association with the anti-Vietnam war movement led to all psychedelics being banned in the US. This ban became ratified globally under the 1971 UN Convention on narcotics. Since then, research funding, drug production, and the study of psychedelics as clinical agents has been virtually stopped. Until very recently, no companies would manufacture medical-grade psychedelics, which made getting regulatory approval for clinical research—especially clinical trials—very difficult and in some countries (eg, Germany) impossible.

The past decade has seen a resurrection in human psychedelic drug research, especially involving psilocybin. There were 2 drivers to this. The first was the discovery by Griffiths et al[1] that a single high dose (25 mg) of psilocybin, given in a psychotherapeutic setting, produced enduring positive changes in mood and well-being in people who do not have depression. The second was our series[2] of neuroimaging studies in healthy volunteers, which revealed that psilocybin produced profound and meaningful alterations in brain function, especially of the default mode network, consistent with an antidepressant effect. These findings suggested the possible utility of psilocybin for treating depression and initiated the launch of studies in the UK and US that further supported an antidepressant outcome from a single, 25-mg psilocybin dose in people with resistant depression[3] and those with anxiety and depression symptoms provoked by life-threatening cancer diagnoses.[4,5] There have also been open studies showing efficacy in both alcohol and tobacco dependence.[6]

Based on these positive findings, at least 2 companies have been set up to take psilocybin to the clinic by funding multicenter, dose-finding studies of psilocybin in depression, and a search of ClinicalTrials.gov (in April 2020) revealed that more than 30 psychedelic drug trials are registered (mostly with psilocybin, although a few are with LSD). These include studies in anorexia, obsessive-compulsive disorder, and addictions, as well as depression. At least 2 of the depression trials[7,8] (those of COMPASS Pathways and Usona Institute) are randomized clinical trials compatible with the US Food and Drug Administration and European Medicines Agency registration processes and have been given fast-track status in this field. Many of the trials in other disorders are open-label designs to gather feasibility and safety data to underpin subsequent double-blind randomized clinical trials. Once these regulatory-standard trials have been conducted, if the outcomes are positive, then it seems plausible that psilocybin will become a licensed medicine for some forms of mental illness when used in an approved treatment model.

In the depression trials, the treatment model is becoming standardized as a 4-stage process: assessment, preparation, experience, and integration. Assessment determines if the patient is suitable for psychedelic therapy, both from a mental and physical perspective. Currently, people with a personal or family history of psychosis and bipolar disorder are excluded, as are those with significant health issues (eg, hypertension) because psychedelics transiently increase blood pressure. Certain medications need to be stopped or at least reduced before the treatment, because they can block or attenuate the effect of the psychedelic. Specifically, medicines that block 5-$HT2_A$ receptors (eg, amitriptyline, olanzapine, quetiapine, risperidone, trazodone) need to be withdrawn, and serotonin reuptake inhibitors ideally stopped or, if that is not feasible, tapered down, because they produce subsensitivity of the 5-$HT2_A$ receptor.

In modern studies,[3-5] preparation sessions typically take place the day before the drug administration, the participant is prepared for the experience by at least 1 trained therapist, who are often referred to as *guides*, based on the analogy of the psychedelic experience being a psychological journey. An overview of the dynamics and nature of psychedelic experiences is explained, including how it can be challenging for many people, how any such challenges can be best confronted, and how the participant can get the most out of the experience. During the psychedelic experience, the individual is offered eyeshades and earphones to listen to a music compilation that has been prepared in advance (which they can specify) because music seems to enhance the therapeutic process. For oral psilocybin, the sessions last 4 to 5 hours. Verbal engagement with the therapists is not expected, and most patients go deep into their own visions, thoughts, and memories and do not want to be disturbed. But the guide or guides are present, and with permission, they can hold the patient's hand to reassure the person that he or she is being looked after. The next day is the integration session—during which the same guide or guides talk through the experience and help the patient make sense of it. Ideally, a small number of standard, talk-based psychotherapeutic sessions are further available for issues that emerged during the psychedelic experience to be processed,

Corresponding Author: David Nutt, MD, PhD, Imperial College London, Du Cane Road, Burlington Danes Building, London W12 ONN, United Kingdom (d.nutt@imperial.ac.uk).

insights to be further integrated, and guidance given on how best to cultivate positive cognitive and lifestyle changes.

In all of the treatment studies conducted so far, the psychedelic is given just once or twice over a few weeks with psychotherapeutic input (which, in the case of addictions, can be a standard 10-week to 20-week abstinence-based program). In this regard, psychedelic treatments are being considered as a new paradigm in psychiatric medicine—that of drug-facilitated psychotherapy.

Why might psychedelics work in such a wide range of disorders? We suggest this may be because these conditions are all internalizing disorders. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addiction, drug craving drives behavior that is specific, narrow, and rigid; individuals with addiction ruminate on the drug, including where to get it, how to pay for it, etc. In obsessive-compulsive disorder and anorexia, there is excessive rumination about threats to the person, from contamination or the effects of eating or overeating, respectively. Neuroimaging studies reveal that psychedelics probably work by disrupting brain systems and circuits that encode these repetitive thoughts and behaviors. The psychedelic experience opens a therapeutic window that disrupts entrenched thinking and allows insight, which with psychotherapeutic support can lead to a recalibration of one's spectrum of associations.[9]

So far, the published trials of psychedelic therapy have yielded promising tolerability and efficacy data. Effect sizes have generally been greater than those of current treatments,[3-5] although confirmation biases may be inflating these. Retention rates are excellent, and few adverse effects have been reported. Head-to-head comparative efficacy studies with current treatments are necessary to fully gauge how promising psilocybin therapy is in comparison with current treatments. In this vein, our research team will report the results of our psilocybin vs escitalopram comparison in major depression later this year.

Perhaps the major challenge is how to scale the treatment up. The current model is time and therapist intensive, and even though only a couple doses of medicine are required, this is currently costly because of the many regulatory challenges associated with psychedelics still being scheduled as very dangerous, illegal drugs under the UN Conventions and all Western governments' drug laws. Another issue is how to provide enough psychedelic-trained therapists and ensure good practice through structuring, manualizing, monitoring, and delivering quality training and practice. Several of the centers currently researching psychedelic therapy are offering training under the supervision of more experienced therapists; for example, Kings College in London, in the UK, has successfully piloted group training of potential therapists, some of whom also received psilocybin as part of this course (though self-experience is not required). If this form of therapy does become more widely used, more formal training of large numbers of therapists will be required.

ARTICLE INFORMATION

Published Online: July 29, 2020. doi:10.1001/jamapsychiatry.2020.2171

Conflict of Interest Disclosures: Dr Nutt reported grants and personal fees from COMPASS Pathways during the conduct of the study. Dr Carhart-Harris reported serving as a scientific advisor to COMPASS Pathways, Usona Institute, Entheon Biomedical, Synthesis, and Mindleap.

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Psychedelic Psychiatry's Brave New World

David Nutt,[1,*] David Erritzoe,[1] and Robin Carhart-Harris[1]
[1]Centre for Psychedelic Research, Department of Psychiatry, Imperial College London, London W12 0NN, UK
*Correspondence: d.nutt@imperial.ac.uk
https://doi.org/10.1016/j.cell.2020.03.020

After a legally mandated, decades-long global arrest of research on psychedelic drugs, investigation of psychedelics in the context of psychiatric disorders is yielding exciting results. Outcomes of neuroscience and clinical research into 5-Hydroxytryptamine 2A (5-HT2A) receptor agonists, such as psilocybin, show promise for addressing a range of serious disorders, including depression and addiction.

Introduction—Why the Psychedelic Revolution in Psychiatry?

Research leading to the discovery of new pharmacological treatments for psychiatric disorders has been painfully slow. With a few exceptions, including the use of orexin antagonists for insomnia, current medicines are derivatives of drugs discovered in the 1950s through serendipity and refined through pharmacological modifications. For these reasons, most major pharmaceutical companies have retreated from researching brain targets, threatening to halt a progression in research knowledge and possibly inducing the same sort of dark age that antibiotic research has found itself in.

One way out is to revisit drugs that were once used but fell out of use because of political machinations, especially the war on drugs (Nutt, 2015). Cannabis was the first to be resurrected and the glutamate receptor antagonist anesthetic ketamine has recently been shown to have antidepressant properties, leading to the enantiomer esketamine becoming licensed in the USA and Europe. Now, serotonergic psychedelics, particularly psilocybin (the active compound in "magic mushrooms") are being resurrected as potential treatments for a range of different psychiatric disorders (Rucker et al., 2018). These drugs include LSD, ayahuasca (a drink that contains dimethyltryptamine [DMT] and a monoamine oxidase inhibitor that prevents its breakdown in the gut), as well as 5-MeO-DMT (from the Sonora toad) and mescaline (from the peyote cactus). In the 1950s and 1960s, LSD was widely researched and was considered to achieve major breakthrough treatments by many psychiatrists. At the same time, psilocybin was an experimental medicine supplied by Sandoz as "Indocybin". However, once LSD became used recreationally by young people, it was banned and most other psychedelics were sucked into the legislation; research on their potential therapeutic efficacy ground to a halt. In the past decade, research on these compounds has been re-established by a few groups around the world, culminating in new centers for psychedelic research at Imperial College London and Johns Hopkins University.

Because psilocybin is a Schedule 1 controlled drug, meaning that it has been defined as having high potential for abuse with limited therapeutic utility, it took several years of battling with regulators and ethics committees to gain permission to do clinical research with it, but the struggle was worth it. Its effects on patients suffering from depression were remarkable—e.g., two experiences with psilocybin improved depression scores for weeks, and in some people, years (Carhart-Harris et al., 2018), positioning it as one of the most powerful therapeutics for treatment-resistant depression. There have also been three placebo-controlled trials of psilocybin for anxiety and depression related to end-of-life diagnoses (reviewed in Rucker et al., 2018). Based on this body of positive findings, at least two companies have been set up to take psilocybin to the clinic, funding multi-center dose-finding studies of psilocybin in depression (U.S. National Library of Medicine, 2020a; 2020b). In parallel, we will soon be completing a double-blind trial of psilocybin versus the selective serotonin reuptake inhibitor (SSRI) escitalopram in depression (U.S. National Library of Medicine, 2020c). There have also been studies showing efficacy in alcoholism and tobacco dependence (Rucker et al., 2018), and similar studies in anorexia, obsessive-compulsive disorder (OCD), chronic pain, and opioid use disorder are being developed.

This might seem a strange and disparate set of disorders for a single medicine to work in, and this speaks to the innovative nature of psychedelic therapy. In most studies, the psychedelic is given just once (though in a few studies, twice or three times over a period of weeks) as part of an ongoing psychotherapy course, in complete contrast to currently available medications, which are given at least daily, often with little therapeutic support. We suggest one way of looking at the difference between them is that current medicines suppress symptoms in a similar way that insulin suppresses hyperglycemia in diabetes. Standard antidepressants protect against the stressors that lead to and perpetuate depression, but don't directly access and remedy underlying biopsychosocial causes. In contrast, psychedelic therapy harnesses a therapeutic window opened up by the brain via the effects of the drugs to facilitate insight and emotional release and, with psychotherapeutic support, a subsequent healthy revision of outlook and lifestyle (Carhart-Harris and Nutt, 2017).

Arguably all of the conditions in which psychedelics have been shown to work share the common feature of being internalizing disorders. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addictions, the object of addiction takes on the role

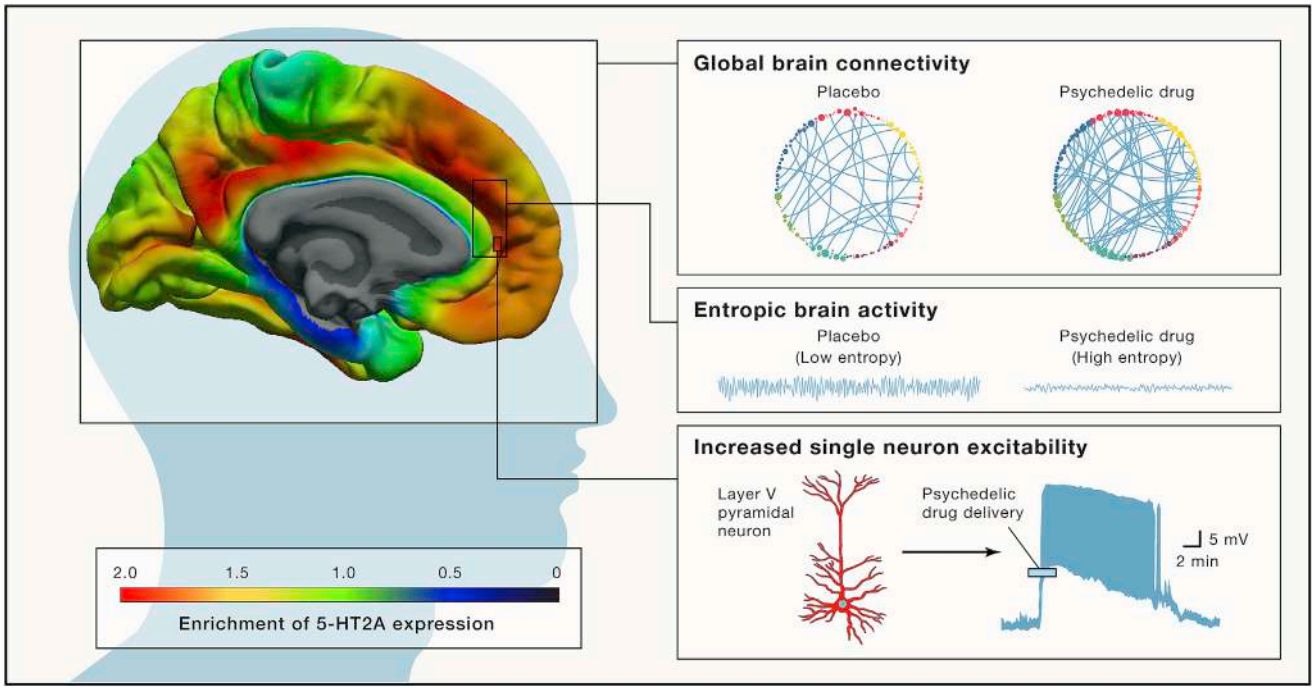

Figure 1. The Three Levels of Activity of Psilocybin

Psilocybin, along with other serotoninergic psychedelics, acts to stimulate 5-HT2A receptors in the cortex, particularly layer 5 pyramidal cells. This leads to massive depolarization and thence rapid repeated firing of these neurons (lower inset). Because these neurons are responsible for organizing cross-cortical integration, this activity results in a profound alteration of cortical signaling. Both magnetoencephalography and electroencephalography measures reveal a major loss of typical rhythmical activity, resulting in a state of extreme desynchronization or enhanced entropy (middle inset). Also, these layer 5 neurons mediate the "top down" perceptual and cognitive predictions (so called "priors"), which form the basis of normal brain processing. Thus, under psychedelics the brain "escapes" from its usual tightly constrained and predictable ways of working; this leads to a global increase in connectivity (top inset) that allows new insights into past behavior, memories, actions, feelings, and beliefs. These in turn can lead to therapeutic changes in conditions such as depression and addiction, which are driven by dysfunctional brain processing. Average density map for 5-HT2A receptor adapted from Beliveau et al. (2017).

of negative thinking in depression, driving behavior that is specific, narrow, and rigid; addicts ruminate on relief afforded by the object, how to get it, how to pay for it, etc. The rationale for using psychedelics in OCD and anorexia is consistent given that there is rumination on intrusive thoughts, e.g., about contamination or calorie mismanagement. Psychedelics likely work by dysregulating activity in systems and circuits that encode these habits of thought and behavior (Carhart-Harris and Friston, 2019), allowing them to recalibrate as the acute effects of the drugs subside. Despite this potential for efficacy across a range of disorders and the initial promising results, many questions remain.

Is 5-HT2A Stimulation the Therapeutic Mechanism of Action?

The defining action of classic serotonergic psychedelics is mediated primarily through agonism of the 5-Hydroxytryptamine 2A (5-HT2A) receptor (Figure 1). This is exemplified by recent positron emission tomography research, showing that the psychedelic effects of psilocybin in humans are predicted by the degree of occupancy of the 5-HT2A receptor revealed by displacement of the agonist tracer [11C]Cimbi-36 (Madsen et al., 2019). Moreover, 5-HT2A receptor antagonists such as ketanserin block psychedelic effects (Preller et al., 2017). The 5-HT2A receptor is maximally expressed in the cerebral cortex, and because humans have considerably more cortex than other species, they logically have the highest expression. These receptors show some regional heterogeneity in the cortex, being relatively sparse in the sensorimotor cortex, and especially dense in visual and association cortices—with high expression also noted in the claustrum *in vitro*.

5-HT2A receptors are localized on the cell bodies and apical dendrites of large pyramidal neurons concentrated in layer V of the cortex. There are also found, albeit to a lesser degree, on GABAergic interneurons that regulate pyramidal cell firing (Andrade, 2011). Activation of 5-HT2A receptors appears to increase the excitability of the host neuron, causing a spike to wave decoherence and associated dysregulation of spontaneous activity in cortical populations. This dysregulation reliably manifests as increased entropy in on-going activity recorded via local field or scalp potentials, as well as related changes in the power spectrum, e.g., marked decreases in alpha oscillations. A number of aspects of cortical functioning associated with predictive processing appear to be dysregulated under psychedelics, including the following: functioning of layer V pyramidal neurons; the strength of alpha oscillations; the strength of backward traveling waves; and the integrity, segregation, and hierarchical organization of intrinsic networks. This is consistent with our current hypothesis that the main functional effect of psychedelics is to relax the precision weighting of the predictive models encoded in the brain (Carhart-Harris and Friston,

2019). An earlier model takes a different view: that psychedelics disrupt the normal gating of sensory inputs via the thalamus (Vollenweider and Geyer, 2001), and this leads to altered perceptions. However, given a low density of 5-HT2A receptors in the thalamus, it might be that thalamic effects are driven by psychedelics disrupting cortical activity that projects to the thalamus, so the two theories might not be so different.

The therapeutic benefit we theorize is also mediated via this receptor, but as yet, this has not been established in humans—because to do this would require a trial in which a 5-HT2A receptor antagonist is given before the psychedelic to see whether this blocks its therapeutic effects.

Would Shorter-Acting Psychedelic Drugs Work?

Different psychedelics have very different durations of action. LSD and mescaline are two of the longer lasting (8–14 h), whereas the effects of DMT and 5-MeO-DMT are much shorter, with effects lasting less than 30 min from either a smoked or injected dose, although DMT consumed in ayahuasca will work for about 2–3 h. Psilocybin acts for about 4–5 h after oral ingestion. The oral route is generally considered the most appealing for therapeutic work because the resulting "trip" allows the patient to enter into the psychedelic state with plenty of time for them to explore personal material and potentially experience therapeutic breakthrough (Roseman et al., 2018b). It is theoretically possible, however, that a short trip, such as with i.v. DMT, might "shake-up" and "reset" abnormal patterns of brain activity and so could have some therapeutic benefit. It seems likely that this idea will soon be tested, and if it works, it could significantly reduce the costs of psychedelic therapy by saving on therapist time.

Are the Psychedelic Effects Necessary?

The extensive use of microdosing psychedelics to putatively improve wellbeing and creativity (Kuypers et al., 2019) raises the question of whether a full psychedelic experience is needed. Microdosing involves taking—usually on a regular basis, e.g., 3 times a week—a low dose of a psychedelic that is devoid of subjective psychoactive effects. As yet there have been no trials of microdosing for any psychiatric disorder, and it seems improbable that a single microdose of psilocybin would have as big an effect in depression as the 25 mg psilocybin "macrodose" usually used. Growing evidence suggests the best outcomes from psilocybin are in patients experiencing the most powerful psychedelic effects, variously called breakthrough, peak, or mystical experiences (Roseman et al., 2018b). Additional insight on this question might come from the COMPASS Pathways study (U.S. National Library of Medicine, 2020a), where patients are randomized to either a 1 mg (i.e., a microdose) or to a 10 mg or 25 mg dose (which do have psychedelic effects). The prediction is that the 25 mg dose will be more effective than the 10 mg dose and the 1 mg (microdose) will be ineffective, but the outcomes remain to be seen.

Why Are the Effects So Enduring?

Both the depression and tobacco smoking trials have shown that, in some people, psilocybin can produce clinical remission, in some cases persisting for years. Similar findings are described in the older psychedelic literature, where enduring positive psychological changes were commonly reported. So how does this happen? For now, this question is easier to address from the perspective of psychology, where the key might be how psychedelics relax limiting beliefs and, in parallel, promote insight and an emotional release that can motivate the revision of these beliefs. Indeed, in our depression trial, insight and emotional breakthrough were significant predictors of the longer-term changes (Roseman et al., 2018b). More work is needed to address how insight and emotional release registers in terms of altered brain functioning and anatomy, but several pre-clinical studies have shown that psychedelics promote neural plasticity in key circuits relevant to treating neuropsychiatric disorders, e.g., Ly et al. (2018).

How Much Is "Just Pharmacology"?

Currently, psilocybin therapy for psychiatric disorders is given within a structured psychotherapeutic setting with a considerable therapist input. There is always a preparatory session before drug administration. There are always one, and in some studies two, therapists present during the psychedelic session—which lasts up to 6 h. The next day, and beyond, there are further integration sessions with the same therapists to help patients talk through and thereby "ground" their experiences. This amount of therapist exposure has significant cost implications and therefore naturally leads to the question—is the psychotherapy really necessary? Would just giving the drug alone produce the same clinical benefits? To some extent, this is a false dichotomy, because any effect on the brain is, by implication, an effect on the mind and vice versa, and so the question is more whether there can be an action on the brain and long-term therapeutic effect, without a noticeable mediating subjective experience. A question like this could be addressed either via sub-perceptual microdosing or via giving the psychedelic during sleep or under anesthesia.

Although ethically challenging to implement, giving individuals a psychedelic under anesthesia and assessing its subsequent effect on a mental-health-relevant outcome might help resolve debate about the importance of the psychological components of psychedelic therapy, as well as the imperfection of current blinding procedures. Ours' and others' data do suggest that there is a positive interaction between the neuroplastic effects of 5-HT2A receptor agonism and what is done with that plasticity (Roseman et al., 2018b). Indeed, part of the core drug action seems to be to make people exceptionally sensitive to what lies beyond their (ego) boundaries, whether this be material percolating up from their inner world, e.g., in terms of emotions and memories, or coming into the brain from the outer world, e.g., in terms of the therapist(s) present and music heard.

What Are the Brain Mechanisms through Which Psychedelics Remedy Psychiatry Disorders?

There is great current interest from both neuroscience and clinical perspectives in understanding how psychedelics remedy psychiatry disorders. Knowing "the answer" would not only help reassure sceptics that psychedelics are more than just a powerful placebo but would also help maximize their therapeutic benefit—particularly in directing interventional processes to maintain wellness.

Table 1. A Brief Summary of the Many Factors that Together Make the Case for Psychedelic Research in Psychiatry

Supporting points	Supporting references
Massive mental health burden, Limited breakthrough treatments, Industry pull-out from psychiatry	Carhart-Harris and Friston (2019) Carhart-Harris and Nutt (2017) Rucker et al. (2018)
Growing evidence of safety & efficacy for psychedelics	Carhart-Harris et al. (2018) Carhart-Harris and Nutt (2017) Rucker et al. (2018)
Limited abuse potential (e.g. not addictive)	Nutt (2015)
Novel action	Carhart-Harris and Friston (2019) Carhart-Harris and Nutt (2017)
Rapid action. Enduring action. Transdiagnostic action	Carhart-Harris et al. (2018) Rucker et al. (2018)
New, plausible multi-level models of action	Andrade (2011) Barrett et al. (2020) Carhart-Harris and Friston (2019) Roseman et al. (2018a) Vollenweider and Geyer (2001)
Bridges psychotherapy and pharmacology	Carhart-Harris et al. (2018)
New level of institutional support (new research centres)	Imperial College London and John Hopkins
Area attracting venture investment	COMPASS Pathways, Usona
Long heritage of medicinal use (unlike modern medicines)	Nutt (2015) Rucker et al. (2018)

This is the prime need right now because, despite the impressive immediate effects of psilocybin on depression, about half of patients relapse within 6 months. Why this is is presently unknown, but it supports the idea that, in some people, depression can become a persistent, intractable, problem that might influence thinking processes forever. In others, it might be a defense against a traumatic event or loss that psychedelics uncover and help the patient process and move on from. More work is needed to test our assumption that the most severe presentations might require more than just a single-dose treatment.

As described above, the 5-HT2A receptor is likely the key molecular mediator of cases of major psychological change. This receptor seems to have a low level of basal activity in normal brain states because its complete blockade with 5-HT2A antagonists has almost no effect on daytime mind and brain functioning. Interestingly 5-HT2A antagonists do enhance deep (stages 3–4) sleep (Idzikowski et al., 1987), a state of heightened brain synchronicity, the exact opposite of the entropic brain state seen with psychedelics (Carhart-Harris and Friston, 2019). We suggest that in states of extreme stress, when novel behavioral responses are vital, the 5-HT2A system might be activated to provide solutions to the crisis and also help lay down new, more adaptive behavioral and cognitive patterns (Carhart-Harris and Nutt, 2017). The "resetting" of normal functioning in intrinsic brain networks, like the default-mode network, might be related to this adaptive mechanism (Carhart-Harris et al., 2017).

When thinking in terms of brain regions and circuits underpinning clinical responses, a lot of work in recent years has focused on the role of the amygdala in unconscious threat processing, as well as prefrontal control of this. Amygdala response to threat cues (e.g., a fearful face) measured with fMRI is significantly increased in depressed people. A range of different drug treatments for depression have been shown to suppress this hyperresponsivity and this has become a prime theory for how these medicines work. Recently, psilocybin has been shown to do something similar in healthy volunteers 1 week after psilocybin (Barrett et al., 2020), but an opposite effect was seen in treatment-resistant patients (TRDs) 1 day after psilocybin therapy (Roseman et al., 2018a), which potentially implies a complex, non-linear process of change. We also found evidence of decreased "resting-state" blood flow in the temporal cortex, which contains the amygdala, 1 day after psilocybin for TRDs that was predictive of positive outcomes (Carhart-Harris et al., 2017). Our current trial of psilocybin versus the SSRIs escitalopram in major depressive disorder (U.S. National Library of Medicine, 2020c) aims to more comprehensively address this matter after a standard treatment with each.

Protecting Research

Major hurdles facing research with psychedelics include the burden that their Schedule 1 status incurs and a lack of mainstream funding, and we suspect these things are related. The Schedule 1 status of psychedelics led to vastly increased regulations on research, associated costs, and damaging stigma that likely deterred governmental agencies, other reputable funding bodies, and companies from backing the relevant research. Before LSD was banned, the US NIH funded over 130 studies exploring its clinical utility; however, since the ban, it has funded none and until a few years ago, no company was committed to manufacturing medical grade psychedelics and thus procurement of the required drugs for clinical trials was almost impossible (Nutt, 2015).

Nowadays, both COMPASS Pathways and Usona are making psilocybin at scale with others starting. Natural plant-based products such as ayahuasca, peyote, and magic mushrooms are now legal in some South American countries and are becoming decriminalized in a few US cities. Moreover, magic mushrooms could be legalized in the US state of Oregon later this year. Magic truffles, which contain the same active compound, are legal in the Netherlands, and this loophole, combined with a growing interest in the therapeutic potential of psilocybin, has led to fast-growing industry in Dutch truffle retreats. Some finance journalists have begun predicting a "shroom boom" to rival the "green rush" seen with medicinal cannabis (Raphael, 2018). This escalating recreational use presents an opportunity to collect "Big Data" for educational and harm-reduction purposes, and we have set-up an online

platform for doing this, called psychedelicsurvey.com.

It is possible to make new 5-HT2A receptor agonist ligands that would, at the time of synthesis, be outside national or UN Conventions. However, based on recent examples, the risk of them becoming restricted would be very high. In the UK, the ultra-restrictive 2016 Psychoactive Substances Act makes all novel psychoactive compounds illegal, and some of the newer 5-HT2A receptor agonists (e.g., the NBOMeS) have been found to be more toxic than the older ones, a situation similar to that seen with the growth of legal but more harmful synthetic cannabinoids.

Overall, it seems the best way forward to fostering research and therapeutic application is to press for a rescheduling of psychedelics with proven therapeutic utility, especially psilocybin. That psilocybin was made Schedule 1 (i.e., having no medical value) on the shirt-tails of politically motivated banning of LSD has had an immense negative effect on treatment and research (Nutt, 2015). A campaign to re-schedule psilocybin is now underway in the UK, led by the charity DrugScience.org.uk and has international, scientific support.

Summary

The resurrection of research into the neuroscience and therapeutic application of psychedelics represents one of the most important initiatives in psychiatry and brain science in recent decades. It rectifies decades of global research paralysis that emerged as collateral damage from the war on drugs and that has become one of the worst examples of censorship of human research in the history of science. The past ten years have seen the first green shoots of recovery with a number of teams across several continents beginning human neuroimaging and clinical trials that have delivered remarkable insights into brain function and instigated an exciting new approach to the treatment of a range of psychiatric disorders (Table 1). What is now needed is a combined, multi-level, multidisciplinary program of research into the mechanisms underpinning these findings.

ACKNOWLEDGMENTS

The first psilocybin depression trial was funded by the UK Medical Research Council. The Beckley Foundation and the Alexander Mosley Charitable Trust have supported much of our imaging and clinical work, respectively.

David Nutt is a scientific advisor to COMPASS Pathways. Robin Carhart-Harris is a scientific advisor to COMPASS Pathways, Usona Institute, Synthesis Institute, and Entheon Biomedical.

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Original Paper

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder

Journal of Psychopharmacology
1–9

DOI: 10.1177/0269881121991792
journals.sagepub.com/home/jop
SAGE

Ben Sessa[1], Laurie Higbed[1], Steve O'Brien[1], Claire Durant[1], Chloe Sakal[2], Daniel Titheradge[3], Tim M Williams[4], Anna Rose-Morris[4], Elsa Brew-Girard[4], Sam Burrows[4], Chantelle Wiseman[5], Sue Wilson[1], James Rickard[6] and David J Nutt[1,2]

Abstract

Background: 3,4-methylenedioxymethamphetamine (MDMA) therapy has qualities that make it potentially well suited for patients with addictions, but this has never been explored in a research study. We present data from the Bristol Imperial MDMA in Alcoholism (BIMA) study. This is the first MDMA addiction study, an open-label safety and tolerability proof-of-concept study investigating the potential role for MDMA therapy in treating patients with alcohol use disorder (AUD).

Aims: This study aimed to assess if MDMA-assisted psychotherapy can be delivered safely and can be tolerated by patients with AUD post detoxification. Outcomes regarding drinking behaviour, quality of life and psychosocial functioning were evaluated.

Methods: Fourteen patients with AUD completed a community alcohol detoxification and received an eight-week course of recovery-based therapy. Participants received two sessions with MDMA (187.5 mg each session). Psychological support was provided before, during and after each session. Safety and tolerability were assessed alongside psychological and physiological outcome measures. Alcohol use behaviour, mental well-being and functioning data were collected for nine months after alcohol detoxification.

Results: MDMA treatment was well tolerated by all participants. No unexpected adverse events were observed. Psychosocial functioning improved across the cohort. Regarding alcohol use, at nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox. This compares favourably to a previous observational study (the 'Outcomes' study) by the same team with a similar population of people with AUD.

Conclusions: This study provides preliminary support for the safety and tolerability of a novel intervention for AUD post detox. Further trials to examine better the therapeutic potential of this approach are now indicated.

Keywords
MDMA, alcohol use disorder, psychotherapy, alcoholism, psychedelics

Introduction

Alcohol use disorder

Drinking is a socially acceptable behaviour. The majority of people consume alcohol without significant problems, but a growing number drink in a harmful manner. Alcohol use disorder (AUD; (American Psychiatric Association (APA), 2013) encompasses a broad spectrum of clinical presentations related to harm associated with alcohol use. Approximately 24% of the adult population of England consume alcohol harmfully, with about 6% of men and 2% of women meeting the criteria for alcohol physical dependence. AUD is characterised by often serious withdrawal symptoms on the cessation of alcohol, drinking to avoid withdrawal symptoms, tolerance, the persistent desire to drink and continuing drinking despite negative consequences (NICE, 2011). The impact of alcohol misuse is widespread, encompassing alcohol-related illness and injuries, as well as significant social impact on family, friends and the wider community. Patients with AUD frequently have a past history of psychological trauma and commonly

[1]Imperial College London, Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, London, UK
[2]Drug Science, London, UK
[3]School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
[4]Avon and Wiltshire NHS Foundation Trust, Bath, UK
[5]Centre for Academic Mental Health, School of Medicine, University of Bristol, Bristol, UK
[6]Biotherapy Services, London, UK

Corresponding author:
Ben Sessa, Division of Brain Sciences, Faculty of Medicine, Imperial College London, Centre for Neuropsychopharmacology, Dorothy Hodgkin Building, Whitson Street, London, SW7 2AZ, UK.
Emails: bensessa@gmail.com; b.sessa@imperial.ac.uk

present with high levels of depression, social anxiety and social exclusion, having become dependent upon alcohol as a form of self-medication (Castillo-Carniglia et al., 2019). Furthermore, in the context of the current coronavirus disease 2019 pandemic, attention to the issue of the best management of AUD has become even more pertinent (Clay and Parker, 2020).

Traditional treatments for AUD include medical and psychosocial interventions. Pharmacological options include acamprosate, naltrexone, nalmefene and disulfiram, which reduce cravings and deter relapse respectively (Krampe et al., 2006; Paille and Martini, 2014; Rösner et al., 2010; Soyka and Rösner, 2008). Benzodiazepines are commonly prescribed as part of alcohol detoxification programmes (Lingford-Hughes et al., 2012). Large-scale studies of psychosocial interventions have emphasised the importance of psychotherapies and non-pharmacological supports (Anton et al., 2006; Miller and Wilbourne, 2002; Project MATCH Research Group, 1998; UK Alcohol Treatment Trial (UKATT) Research Team, 2005). In recent years, mindfulness techniques have been increasingly explored as a potential approach to assist recovery through interrupting the tendency to respond to stress with alcohol use and not to react automatically to cravings (Marcus and Zgierska, 2009).

3,4-methylenedioxymethamphetamine

3,4-methylenedioxymethamphetamine (MDMA) is a phenethylamine that raises levels of monoamine neurotransmitters in the brain. MDMA elevates mood, increases sociability and feelings of closeness to others, and can facilitate imagination and memory (Sessa et al., 2019). Evidence from neuroimaging studies shows a decrease in amygdala/hippocampus activity (Carhart-Harris et al. (2014) and an association between reduced amygdala activity and improved ability to process negative memories (Carhart-Harris et al., 2013). Together with changes in social cognition, interpersonal closeness and communication, these data support the proposition that MDMA could be of benefit as an adjunctive psychotherapeutic treatment for alcohol addiction and co-morbid psychological disorders (Sessa, 2018). The use of MDMA-assisted psychotherapy to manage post-traumatic stress disorder (PTSD) has been explored since the 1980s (Greer and Tolbert, 1998). More recently, long-term follow-up data from the first completed trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD has found statistically and clinically significant gains in symptom relief, with no subjects reporting harm from participation in the study (Mithoefer et al., 2010, 2013). The US-based research group, the Multidisciplinary Association for Psychedelic Studies (MAPS), has published favourable results of its Phase II studies (Mithoefer et al., 2019). MAPS is now in the Phase III stage of medicine development, with anticipated licensing and Food and Drug Administration approval in the USA expected by late 2022 to early 2023. European approval by the European Medicines Agency is anticipated by 2023.

Potential risks associated with MDMA as an adjunct to psychotherapy

Rarely, users of clinical MDMA experience an increase in anxiety associated with derealisation-type experiences (Mithoefer et al., 2010). Acute neurocognitive effects include a transient reduction in verbal and visual memory, which tend to resolve after the drug has worn off (Kuypers and Ramaekers, 2007). MDMA misuse potential needs to be borne in mind when proposing giving the drug to a population with pre-existing addiction issues. However, in studies where MDMA has been administered clinically in a therapeutic setting to healthy volunteers without any previous experience with ecstasy, subjects did not express a wish to use it outside of the clinical setting (Mithoefer et al., 2013). Taken together, these findings suggest that clinically administered MDMA is not likely to result in problematic use (Jerome et al., 2013). In order to monitor the risk of patients using MDMA outside of the study, we monitored their use or desire to use illicit ecstasy with specific questions pertaining to this issue asked in the final (session 10) therapy session.

Clinical MDMA increases blood pressure, heart rate and body temperature (Harris et al., 2002) and causes jaw tightness, bruxism, reduced appetite, poor concentration and impaired balance (Mithoefer et al., 2010). Despite historical reports of neurocognitive deficits in recreational ecstasy users, contemporary studies have failed to demonstrate any significant long-term neurotoxicity associated with recreational ecstasy when use of other recreational drugs is controlled for (Hanson and Luciana, 2010; Selvaraj et al., 2009). There have been no reports of long-term neurotoxicity or neurocognitive impairments when pure MDMA has been administered in a controlled clinical setting (Mithoefer et al., 2013).

Methods

Approvals and drug source

This trial, sponsored and approved by Imperial College London, received a favourable opinion from the Central Bristol Research Ethics Committee of the National Research Ethics Service and from the Medicines and Healthcare products Regulatory Agency (MHRA). A Home Office licence for the storage and dispensing of Schedule 1 drugs was obtained. GMP MDMA was obtained from Sterling Pharmaceuticals (Newcastle) and formulated into the investigational medicinal product (62.5 mg MDMA in gelatine capsules) by the Pharmacy Manufacturing Unit at Guy's and St Thomas' NHS Foundation Trust (London, UK).

Study design

This was an open-label, within-subjects, safety and tolerability feasibility study in 14 patients aged 18–65 years with AUD who had recently undergone detoxification. All patients received MDMA-assisted therapy. The main outcome measures were the number of patients completing the eight-week psychotherapy course, the number accepting the second booster dose of MDMA on drug-assisted days and adverse events. Secondary outcome measures included changes in drinking behaviour (measured by units per week consumed at three, six and nine months since completion of detoxification), measures of mental well-being, psychosocial functioning, quality of life and concomitant drug use.

Patients with a primary diagnosis of AUD who were seeking detoxification – with or without medical assistance – were recruited from the North Somerset Substance Misuse Service (Addaction). Patients received an eight-week course of recovery-based therapy

comprising 10 psychotherapy sessions. On two of these (sessions 3 and 7), patients were dosed with open-label MDMA during a six- to eight-hour assisted therapy session. On each dosing session, participants received an initial oral dose of 125 mg MDMA, followed two hours later by a booster dose of 62.5 mg MDMA. The booster dose served to prolong the experience, allowing for greater time for psychotherapy under the influence of the drug.

Other sessions (sessions 1, 2, 4, 5, 6 and 8–10) comprised one-hour psychotherapy sessions, employing aspects of motivational interviewing and 'third-wave' cognitive–behavioural approaches. Patients remained in the study for approximately 10 months.

Inclusion criteria

The inclusion criteria were as follows:

- Informed consent.
- Primary diagnosis (as defined by DSM-IV) of AUD.
- Successful alcohol detoxification (no longer consuming any alcoholic substances).
- Between 18 and 65 years old.
- Able to identify in advance a supportive significant other(s) who could accompany them to study visits if required and be contacted by the study team in the event that the patient could not be contacted.
- Proficient in speaking and reading English.
- Agree to comply with requirements of protocol.

Exclusion criteria

The inclusion criteria were as follows:

- Lacking capacity.
- History of, or a current, primary psychotic disorder, bipolar affective disorder type 1 or personality disorder.
- A serious suicide risk as determined by the Columbia-Suicide Severity Risk Scale (C-SSRS).
- Relevant abnormal clinical findings at screening visit judged by the investigator to render the subject unsuitable for study, including but not limited to a history of cardiac disease, hypertension and stroke, severe liver disease, a history of epilepsy or a history of malignant hyperthermia (central core disease).
- Regular user of ecstasy (material represented as containing MDMA), for example more than five times in the last five years or at least twice in the six months prior to the start of the study.
- Currently taking or unwilling/unable to stop any medications likely to interact with MDMA in the opinion of the investigators during the eight-week MDMA-assisted therapy.
- Regular use of/dependence on other drugs such as benzodiazepines, synthetic cannabinoids, cocaine and heroin.
- Female participants of childbearing age/potential must use an effective form of birth control for at least six days after administration of MDMA, and must not be pregnant and/or breast-feeding until the end of the treatment phase.
- For males with partners of childbearing age/potential, participants must themselves confirm use of an effective form of birth control for at least six days after administration of MDMA and confirm their partner will also.
- Taken part in a study involving an investigational product in the last three months.
- Patients who might face additional risks from immunosuppression (e.g. patients with immunological diseases or patients with active infection or history of infections within four weeks of MDMA administration).

AUD was identified using the DSM-IV SCID interview. Screening comprised of written informed consent, an evaluation of the patient's physical and mental health background, a psychiatric interview (MINI) and assessments of depression and anxiety severity using the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder Assessment (GAD-7) questionnaires. Severity of AUD was established using the Severity of Alcohol Questionnaire (SADQ) and the Short Inventory of Problems for Alcohol (SIP) questionnaire. Patients received a thorough physical health check comprising an electrocardiogram, routine blood tests, blood pressure, heart rate and physical examination. Following screening, eligible patients underwent the process of detoxification either by gradually cutting down alcohol consumption over many weeks or with a medically assisted detoxification regime. The majority of participants were also taking medications for anxiety and/or depressive symptoms (e.g. selective serotonin reuptake inhibitors). According to the inclusion/exclusion criteria, associated medications known to attenuate the effects of MDMA were subsequently gradually reduced and stopped under medical supervision ahead of the first MDMA session. A further 'baseline' visit clarified successful detoxification using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) questionnaire before eligible participants entered the eight-week course of psychotherapy. This entailed weekly 60-minute outpatient non-drug psychotherapy sessions delivered by two clinicians (B.S. and L.H.) trained in delivering MDMA-assisted psychotherapy by the USA-based organisation MAPS.

Dosing with MDMA occurred twice during the eight-week course on weeks 3 and 6. Physiological changes, observer and subject ratings of distress (Subjective Units of Distress (SUDS)) and the intensity of MDMA's acute psychoactive effects were measured throughout the drug-assisted session. Acute anxiety was managed primarily psychologically, but sedative medication (oral lorazepam) was available. Participants remained overnight in the treatment centre after each drug-assisted session, overseen by medically trained 'night sitters' who were on hand to support participants as required but instructed to avoid delivering any psychotherapeutic interventions.

Participants were seen the morning after each drug-assisted session for an integration psychotherapy session, and then telephoned daily for six days to assess changes to mood, suicidal risk factors (using the C-SSRS) and quality of sleep (using the Leeds Sleep Evaluation Questionnaire). Following the end of the eight-week therapeutic course, participants carried out additional follow-up questionnaires. They were then seen again at three, six and nine months (since baseline) for longer-term follow-up data collection.

Data analysis

All data were recorded on paper case report forms and then digitized into MS Excel spreadsheets. Analysis and graphing were

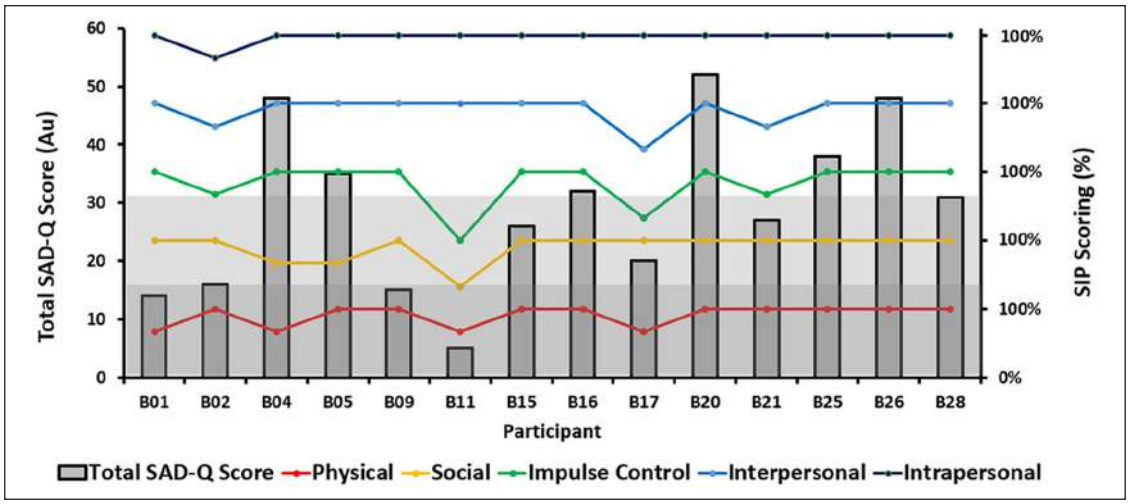

Figure 1. Severity of Alcohol Questionnaire (SADQ) measures alcohol dependency (Au = arbitrary units). Short Inventory of Problems for Alcohol (SIP) is a 15-question measure of self-noted consequences of drinking. Both were observed at screening. SIP categories are separated each between 0% and 100% on the second *y*-axis. A score of 31 or higher indicates severe alcohol use disorder (AUD) severity. A score of 16–30 indicates moderate AUD severity (light-grey area). A score lower than 16 indicates mild AUD severity (dark-grey area). Four SADQ questions were unanswered, in which case, mean substitution was applied using the average row value for the relevant time period and participant. B05, B16, B20 and B21 had one question missing each.

performed using GraphPad Prism Prism version 8.4.3 (GraphPad Software LLC, La Jolla, CA) or MS Excel. As this was a non-randomised, controlled, open-label study, no hypothesis testing was performed. When calculating timeline follow-back results, alcohol consumption levels at last observation were used in the case of drop-outs or when participants had undertaken a second detoxification (Hamer and Simpson, 2009).

Results

Demographics

Thirty-six participants attended face-to-face screening visits, and 14 were enrolled (8 males and 6 females; $M_{age} = 48$ years). All were white British. Four were employed, nine were unemployed and one was retired. The average age of first alcohol use was 13 years old. The average age when alcohol became problematic was 34 years old. Nearly two-thirds (64%) of participants reported a history of alcohol-related blackouts, 14% had experienced alcohol withdrawal–induced seizures, 86% of participants reported having experienced risky or vulnerable incidences due to alcohol and 75% of participants had had forensic/offending behaviour secondary to their alcohol use.

Severity of AUD criteria at screening and baseline

As per the inclusion criteria, all eligible patients scored above the diagnostic threshold on the DSM-5 SCID questionnaire for AUD. We also measured AUD severity using the SIP questionnaire and the SADQ questionnaire (Figure 1), with most eligible participants in the moderate to severe range. At the baseline visit (within one week of detox completion), 100% of eligible participants had successfully completed detoxification, which was assessed using the CIWA scale.

Physiological and tolerability effects during MDMA sessions

Of the 14 participants, 12 received both sessions of MDMA-assisted psychotherapy. So, in total, 26 drug-assisted psychotherapy sessions with MDMA were administered during the trial. Temperature, blood pressure and heart rate were measured at $t = 0$, before taking the medicine, then half-hourly up to $t = 2$ hours, then hourly thereafter for a minimum of six hours from the time of dosing (Figure 2).

Except for one participant, all of these physiological parameters remained within normal limits for all these sessions. As expected, we saw a mild transient rise in blood pressure, temperature and heart rate over the course of the MDMA session. No patients experienced sustained abnormal physiological disturbance, symptomatic experiences of raised blood pressure, heart rate or temperature or any other adverse events during MDMA sessions. No medical interventions were required in respect of these or any other physiological events during MDMA sessions. One participant experienced a transient abnormal rise in blood pressure after taking the initial dose of 125 mg MDMA, reaching 183/118 mmHg at two hours after dosing, attributed to the participant forgetting to take her regular antihypertensive medication on the morning of dosing. Although she was asymptomatic and no medical intervention was required, it was decided to withhold the two-hour supplemental dose. Her blood pressure subsequently spontaneously returned to normal in the following two hours, and she agreed with the study team to omit the booster dose of MDMA on that day. She did, however, receive her second MDMA session three weeks later (after taking her antihypertensive medication in advance appropriately), which was uneventful in terms of blood pressure. Another participant only received her first MDMA session. She subsequently relapsed back to heavy drinking in the context of personal psychosocial issues unconnected with the study, and therefore she chose not to have her second MDMA session.

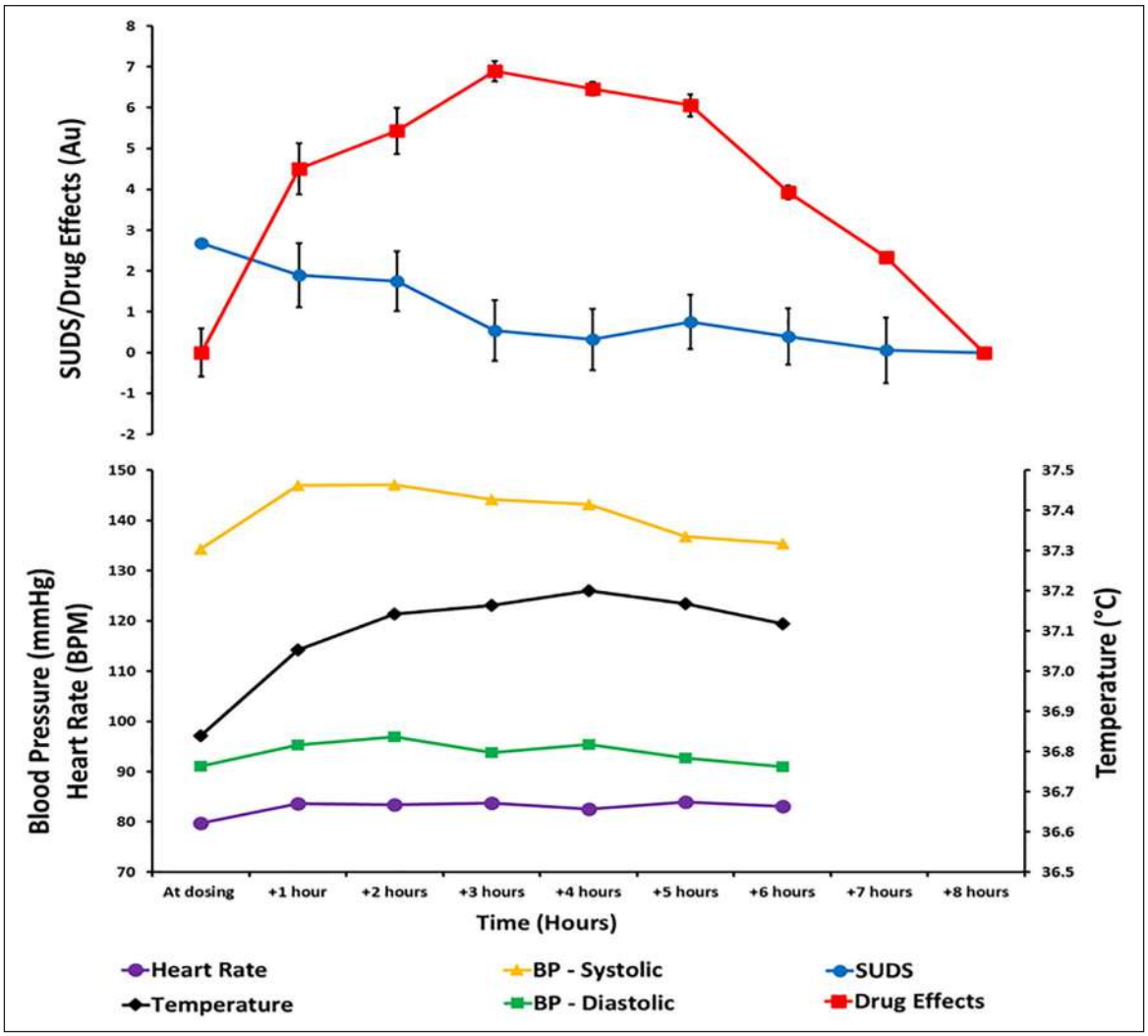

Figure 2. Pooled data of blood pressure, temperature, heart rate, observed drug effects and Subjective Units of Distress (SUDS) observed over the duration of the MDMA sessions. SUDS and drug effects observed over eight hours; physiological data observed over six hours following dosing. Mean data for each session are used, except in the case of missing data, where available session data are applied. Error bars (where applied) indicate ±standard error of the mean (SEM).

Subjective Units of Distress (SUDS) and participant report of drug effects were also measured hourly throughout the MDMA sessions (Figure 3). Most subjects predictably reported mildly raised SUDS scores at the beginning of the sessions before taking MDMA – consistent with expected anxiety ahead of dosing – which subsequently reduced during the course of the session as the positive effects of MDMA emerged. Participants gave their own subjective score (0–10) of whether they felt drug effects, and the therapists also recorded their own objective score of how 'altered' the participant appeared. There was no significant difference between observers' and participants' drug effects scores. Drug effects rose expectedly over the first two hours, with a notable further increase after the booster dose was given at $t=2$ hours, and a subsequent plateau and then decline over the following six hours. By the end of the MDMA session day, all drug effects had returned to baseline. No participants reported any significant neurocognitive impairments associated with receiving MDMA in the weeks and months following participation in the study.

Changes in drinking behaviour

Whilst changes in drinking behaviour were not a primary outcome measure, we nevertheless collected data in respect of units of alcohol consumed per week in the month before participants' detoxification, immediately after detox ('baseline'), throughout the eight-week MDMA therapy course and for up to nine months after detox. Of the 14 eligible participants who underwent the course of MDMA-assisted psychotherapy, at the nine-month follow-up end point, 11 participants were drinking fewer than 14 units of alcohol per week (including nine who were totally abstinent from alcohol), and three participants had relapsed to drinking more than 14 units of alcohol per week. On average, participants were drinking 130.6 units of alcohol per week in the month before detoxification, and no units at the point of detox. After nine months, the average amount of consumed alcohol had risen back to 18.7 units per week (Figure 3).

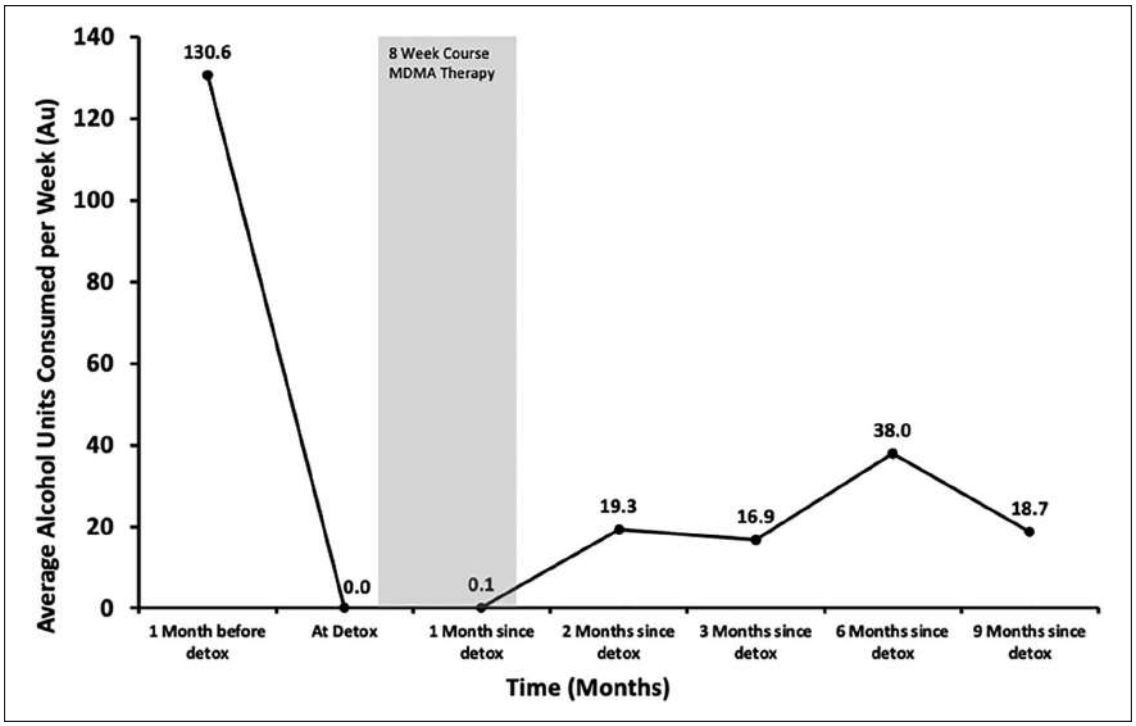

Figure 3. Timeline follow back (TLFB) assesses drinking behaviour prior to and following the study. Data are collected daily by self-reporting and reviewed at one month prior to detox, immediately following detox and at one, three, six and nine months follow-up. A full data set was not available for three of the participants. One participant dropped out of the study at three months, and two patients failed to provide data at the nine-month follow-up. Two participants had a second detox since starting the study. For these participants, TLFB drinking behaviour data were carried forward from the point of drinking levels before the second detox.

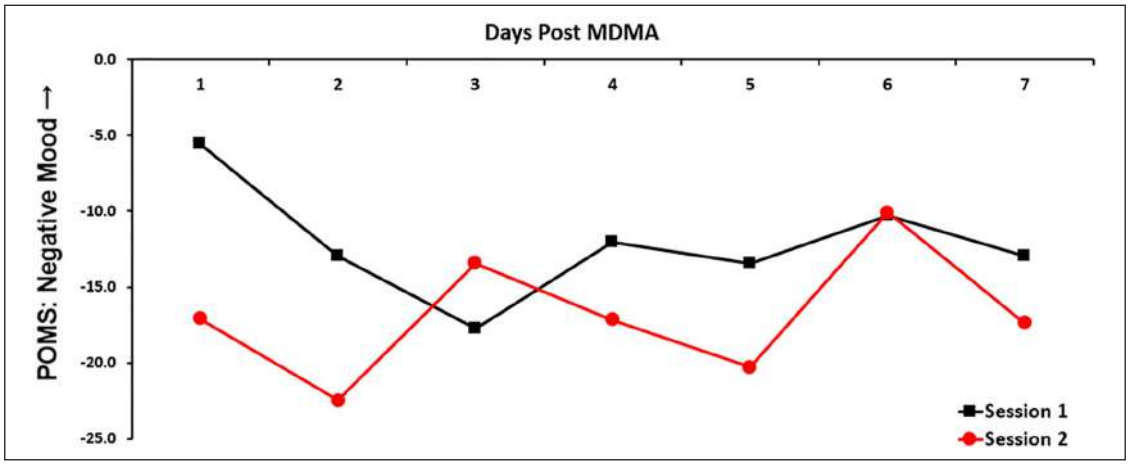

Figure 4. Profile Of Mood States (POMS). Individual composite scores of mood disturbance observed daily over a week following dosing. Mean data shown for both MDMA sessions. In the case of absent data for either session, the available data for the remaining session are used.

Seven-day follow-up after MDMA sessions

Considerable medical literature and the popular press report the anecdotal observation of ecstasy users experiencing an acute 'come-down' effect and a drop in mood in the days after using the drug recreationally. In order to measure this prospectively with clinical MDMA, we measured participants' mood states by daily Profile Of Mood States measurements for seven days after each MDMA session (Figure 4). Positive scores represent depressed affect, zero represents no change in mood/affect and results below zero represent a positively felt mood. Average scores across both MDMA sessions for all 14 participants (26 MDMA sessions) revealed no evidence of any mood disturbance during the week after taking each session of clinical MDMA. Indeed, participants sustained a positive mood for seven days. This result contrasts with anecdotal reports from recreational ecstasy users.

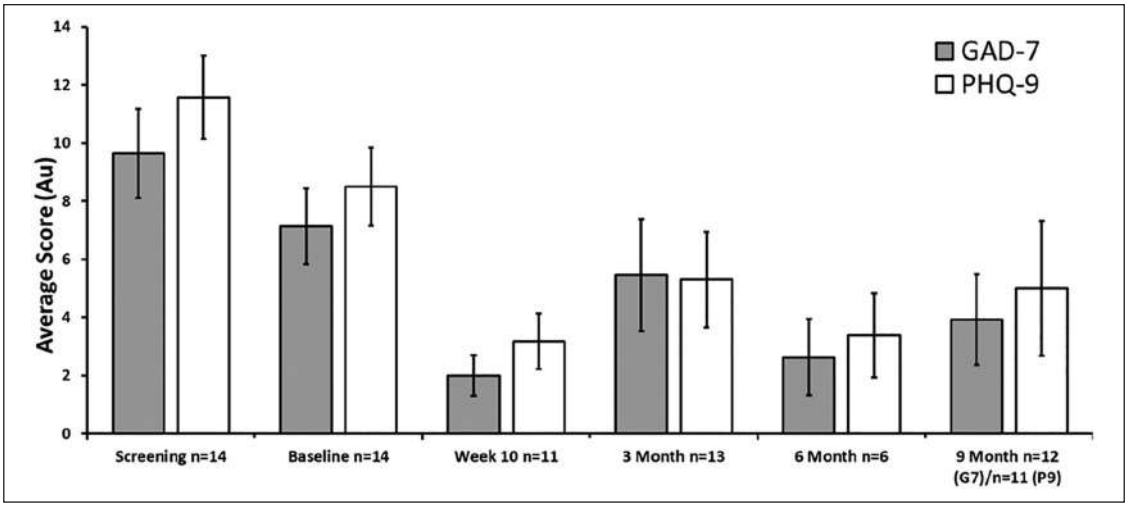

Figure 5. General Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9). Self-report scales for anxiety and depression, respectively. Recorded at screening, baseline and week 10, and then at three, six and nine months of follow-up. Greater scores report indication of heightened anxiety/depression. Error bars indicate ±SEM.

Other mental health measures and quality of life measures

Brief assessments of mood and anxiety were made at screening, baseline, after the eight-week MDMA therapy course and at the three-, six- and nine-month follow-ups using the PHQ-9 and GAD-7 rating scales, respectively (Figure 5). Scores demonstrated a reduction in both anxiety and depression after screening and baseline time points, followed by a transient rise in anxiety and depression scores three months after baseline, a further reduction at six months and a moderate rise again at nine months post detox.

Suicidality

Participants underwent the C-SSRS at screening, baseline, throughout the eight-week therapy course, in the week after each MDMA session and at the three-, six- and nine-month follow-up visits. No participants reported current suicidal ideation, intent or plans or self-harm behaviour during the course of the study

Adverse events

The acute effects of MDMA-assisted psychotherapy were well tolerated by participants. No unexpected adverse events occurred. No participants reported any desire to use illicit ecstasy/illicit MDMA following receiving clinical MDMA as part of this trial. No psychotic symptoms were observed in any of the patients.

A variety of further data were collected, including changes to the quality of sleep, quality of life measures and changes to compassion and empathy scales, which will be published in forthcoming papers.

Discussion

In this first safety and tolerability study, we demonstrate that MDMA-assisted psychotherapy could be useful in treating AUD, probably through its capacity to enhance the psychotherapeutic process or indirectly through augmenting the treatment of comorbid psychological conditions commonly associated with AUD (Jerome et al., 2013).

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of harmful use of alcohol. Recreational MDMA users have reported improved intrapersonal attitudes and prosocial attitudes towards the self, which could be a mechanism by which the drug enhances psychotherapy, especially for patients with pre-existing histories of trauma (Stolaroff, 2004). Similarly, Mithoefer et al. (2010) described MDMA's capacity to 'make yourself present in the moment' – a core concept of mindfulness. Drug-assisted psychotherapies with the 'classic' psychedelic compounds LSD and psilocybin utilise the induced subjective mystical/spiritual effects of the psychedelic experience and have found the depth of this experience is strongly associated with maintained recovery from harmful substance use (Sessa and Johnson, 2015). However, not all patients are able or willing to tolerate the classic psychedelic experience, and compliance is a critical aspect of addiction therapy. Whilst there is also an, albeit minimal, subjective spiritual/mystical experience associated with MDMA (Sumnall et al., 2006), it is generally better tolerated than the classic psychedelics, with fewer perceptually disturbing effects compared to LSD and psilocybin. Therefore, MDMA offers an alternative opportunity for enhanced psychotherapy in patients with AUD.

Prior to carrying out the BIMA study, the same study team carried out a non-interventional observational study, following 14 participants through their treatment-as-usual post-alcohol detox (the 'Outcomes Study'; Sessa et al., 2020). The eligibility criteria and questionnaires used in the Outcomes Study were similar to the BIMA study in respect of assessment of AUD, severity of AUD, success of detoxification and follow-up of outcomes in respect of mental health issues and drinking behaviours – measured at three, six and nine months post detox but without the additional eight-week therapeutic course with MDMA-assisted psychotherapy,

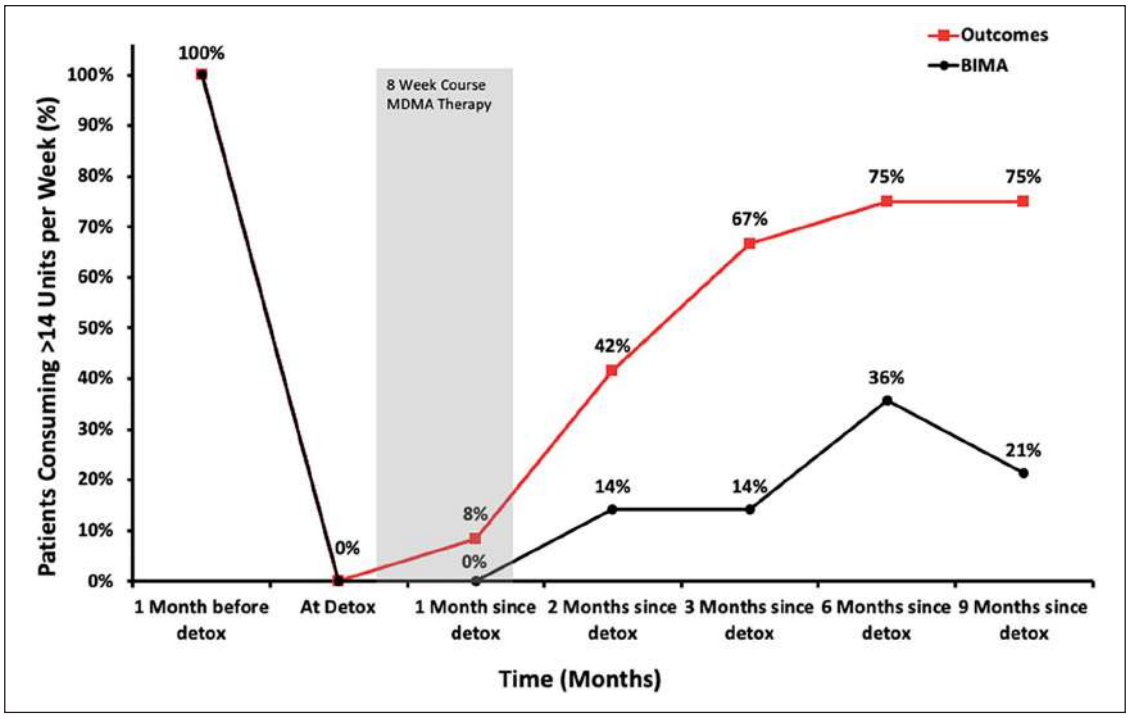

Figure 6. TLFB showing % of patients consuming more than the 14 recommended daily units of alcohol (Sessa et al., 2020).

which occurred post detox. Whilst it is not appropriate to compare these two studies statistically, as patients were not randomised into the studies, Figure 6 demonstrates the success of BIMA participants in terms of alcohol consumption over nine months compared to current best treatments available locally. Only 21% of participants who had undergone MDMA-assisted psychotherapy were drinking in excess of 14 units of alcohol a week in comparison with the 75% observed in the Outcomes Study.

Limitations

The BIMA study had a relatively small sample size. As directed by the MHRA, given that the study was exploring a first-time drug intervention in a previously unexplored clinical population, it was an open-label, non-placebo-controlled study. Therefore, all patients knew they would be getting MDMA. Whilst efforts were made to test objectively for alcohol use using regular breath alcohol analysis, review participants' medical notes throughout the study and carry out Gamma-GT blood tests post course, all data represented above were nonetheless reliant primarily on retrospective self-report. The study team considered other techniques to assess alcohol use objectively, such as worn alcohol sweat meters, but given that efficacy (drinking outcome) was not a primary outcome measure, this was concluded to be overly intrusive for this type of study.

Conclusion

In summary, this study demonstrates that MDMA-assisted psychotherapy can be safely delivered, is well tolerated and has the potential to enhance and intensify the psychotherapeutic processes in the treatment of patients with AUD. MDMA, given in a psychotherapeutic context, may reduce avoidance of emotionally distressing thoughts, images or memories of alcohol misuse while increasing empathy for the self and others. It may also address symptoms of other conditions that are frequently co-morbid with harmful use of substances, particularly those symptoms associated with a history of psychological trauma.

A logical next step would be to carry out a placebo-controlled randomised controlled trial in which the level of therapist contact is consistent between conditions. This would enable any between-group differences in clinical outcomes to be attributed to MDMA rather than to the psychological support provided.

Acknowledgements

We also wish to express thanks to Minirigs – the Bristol-based electronics company that provided the stereo equipment for the experimental sessions. We are grateful to Dr Mendel Kaelen, who provided the playlists for the MDMA therapy sessions. Thank you to all the staff at the Clinical Research and Imaging Centre (particularly Jade, Cathy and Hannah). Enormous gratitude to the local staff and the research and development team at Addaction, without whose support this project would never have happened. In particular, we thank our expert user, Mr Kevin Speller. The staff at MAPS – especially Rick Doblin, Michael Mithoefer and Ilsa Jerome – provided essential support and guidance throughout the project – including provision of the IB and ongoing advice regarding MDMA pharmacology and therapeutic issues. We are grateful to Dr James Rickard, Chief Scientific Officer at Biotherapy Services, for providing pharmacy support, to Dr Tim White (at Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit, London, UK) for production of the IMP and to Dr Liz McCullough at BRI pharmacy for storing and dispensing the study medication. And finally, we are extremely grateful to the pool of local junior doctors who gave their time to act as post-MDMA night sitters after each of the participants drug-assisted sessions, including Sakal, C., (night sitters lead), Titheradge, D., Rose-Morris, A., Brew-Girard, E., Alderton, K.,

Burrows, S., Secker, A., Loysen, S., Hall, K., Lilford, P., Flowers, J., Wright, L., Roberts, R., Lawton, S., Meyer, A., Salter, E., Guy, J., Brown, R. and Rifkin-Zybutz, R. Most importantly, we extend enormous gratitude to the patients who participated in this study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The authors are grateful to the Alexander Mosley Charitable Trust for the entire funding of the study.

ORCID iDs

Ben Sessa https://orcid.org/0000-0002-1212-6060
Chantelle Wiseman https://orcid.org/0000-0002-0146-3969

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MIND MEDICINE AUSTRALIA

Appendix F

Findings of Safety and Tolerability Trial of MDMA-Assisted Psychotherapy for Alcohol Use Disorder (February 2021 referred to in Section 4).

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

Original Paper

First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder

Journal of Psychopharmacology
1–9

DOI: 10.1177/0269881121991792
journals.sagepub.com/home/jop
SAGE

Ben Sessa[1], Laurie Higbed[1], Steve O'Brien[1], Claire Durant[1], Chloe Sakal[2], Daniel Titheradge[3], Tim M Williams[4], Anna Rose-Morris[4], Elsa Brew-Girard[4], Sam Burrows[4], Chantelle Wiseman[5], Sue Wilson[1], James Rickard[6] and David J Nutt[1,2]

Abstract

Background: 3,4-methylenedioxymethamphetamine (MDMA) therapy has qualities that make it potentially well suited for patients with addictions, but this has never been explored in a research study. We present data from the Bristol Imperial MDMA in Alcoholism (BIMA) study. This is the first MDMA addiction study, an open-label safety and tolerability proof-of-concept study investigating the potential role for MDMA therapy in treating patients with alcohol use disorder (AUD).

Aims: This study aimed to assess if MDMA-assisted psychotherapy can be delivered safely and can be tolerated by patients with AUD post detoxification. Outcomes regarding drinking behaviour, quality of life and psychosocial functioning were evaluated.

Methods: Fourteen patients with AUD completed a community alcohol detoxification and received an eight-week course of recovery-based therapy. Participants received two sessions with MDMA (187.5 mg each session). Psychological support was provided before, during and after each session. Safety and tolerability were assessed alongside psychological and physiological outcome measures. Alcohol use behaviour, mental well-being and functioning data were collected for nine months after alcohol detoxification.

Results: MDMA treatment was well tolerated by all participants. No unexpected adverse events were observed. Psychosocial functioning improved across the cohort. Regarding alcohol use, at nine months post detox, the average units of alcohol consumption by participants was 18.7 units per week compared to 130.6 units per week before the detox. This compares favourably to a previous observational study (the 'Outcomes' study) by the same team with a similar population of people with AUD.

Conclusions: This study provides preliminary support for the safety and tolerability of a novel intervention for AUD post detox. Further trials to examine better the therapeutic potential of this approach are now indicated.

Keywords
MDMA, alcohol use disorder, psychotherapy, alcoholism, psychedelics

Introduction

Alcohol use disorder

Drinking is a socially acceptable behaviour. The majority of people consume alcohol without significant problems, but a growing number drink in a harmful manner. Alcohol use disorder (AUD; (American Psychiatric Association (APA), 2013) encompasses a broad spectrum of clinical presentations related to harm associated with alcohol use. Approximately 24% of the adult population of England consume alcohol harmfully, with about 6% of men and 2% of women meeting the criteria for alcohol physical dependence. AUD is characterised by often serious withdrawal symptoms on the cessation of alcohol, drinking to avoid withdrawal symptoms, tolerance, the persistent desire to drink and continuing drinking despite negative consequences (NICE, 2011). The impact of alcohol misuse is widespread, encompassing alcohol-related illness and injuries, as well as significant social impact on family, friends and the wider community. Patients with AUD frequently have a past history of psychological trauma and commonly

[1]Imperial College London, Centre for Neuropsychopharmacology, Division of Brain Sciences, Faculty of Medicine, London, UK
[2]Drug Science, London, UK
[3]School of Physiology, Pharmacology and Neuroscience, University of Bristol, Bristol, UK
[4]Avon and Wiltshire NHS Foundation Trust, Bath, UK
[5]Centre for Academic Mental Health, School of Medicine, University of Bristol, Bristol, UK
[6]Biotherapy Services, London, UK

Corresponding author:
Ben Sessa, Division of Brain Sciences, Faculty of Medicine, Imperial College London, Centre for Neuropsychopharmacology, Dorothy Hodgkin Building, Whitson Street, London, SW7 2AZ, UK.
Emails: bensessa@gmail.com; b.sessa@imperial.ac.uk

present with high levels of depression, social anxiety and social exclusion, having become dependent upon alcohol as a form of self-medication (Castillo-Carniglia et al., 2019). Furthermore, in the context of the current coronavirus disease 2019 pandemic, attention to the issue of the best management of AUD has become even more pertinent (Clay and Parker, 2020).

Traditional treatments for AUD include medical and psychosocial interventions. Pharmacological options include acamprosate, naltrexone, nalmefene and disulfiram, which reduce cravings and deter relapse respectively (Krampe et al., 2006; Paille and Martini, 2014; Rösner et al., 2010; Soyka and Rösner, 2008). Benzodiazepines are commonly prescribed as part of alcohol detoxification programmes (Lingford-Hughes et al., 2012). Large-scale studies of psychosocial interventions have emphasised the importance of psychotherapies and non-pharmacological supports (Anton et al., 2006; Miller and Wilbourne, 2002; Project MATCH Research Group, 1998; UK Alcohol Treatment Trial (UKATT) Research Team, 2005). In recent years, mindfulness techniques have been increasingly explored as a potential approach to assist recovery through interrupting the tendency to respond to stress with alcohol use and not to react automatically to cravings (Marcus and Zgierska, 2009).

3,4-methylenedioxymethamphetamine

3,4-methylenedioxymethamphetamine (MDMA) is a phenethylamine that raises levels of monoamine neurotransmitters in the brain. MDMA elevates mood, increases sociability and feelings of closeness to others, and can facilitate imagination and memory (Sessa et al., 2019). Evidence from neuroimaging studies shows a decrease in amygdala/hippocampus activity (Carhart-Harris et al. (2014) and an association between reduced amygdala activity and improved ability to process negative memories (Carhart-Harris et al., 2013). Together with changes in social cognition, interpersonal closeness and communication, these data support the proposition that MDMA could be of benefit as an adjunctive psychotherapeutic treatment for alcohol addiction and co-morbid psychological disorders (Sessa, 2018). The use of MDMA-assisted psychotherapy to manage post-traumatic stress disorder (PTSD) has been explored since the 1980s (Greer and Tolbert, 1998). More recently, long-term follow-up data from the first completed trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD has found statistically and clinically significant gains in symptom relief, with no subjects reporting harm from participation in the study (Mithoefer et al., 2010, 2013). The US-based research group, the Multidisciplinary Association for Psychedelic Studies (MAPS), has published favourable results of its Phase II studies (Mithoefer et al., 2019). MAPS is now in the Phase III stage of medicine development, with anticipated licensing and Food and Drug Administration approval in the USA expected by late 2022 to early 2023. European approval by the European Medicines Agency is anticipated by 2023.

Potential risks associated with MDMA as an adjunct to psychotherapy

Rarely, users of clinical MDMA experience an increase in anxiety associated with derealisation-type experiences (Mithoefer et al., 2010). Acute neurocognitive effects include a transient reduction in verbal and visual memory, which tend to resolve after the drug has worn off (Kuypers and Ramaekers, 2007). MDMA misuse potential needs to be borne in mind when proposing giving the drug to a population with pre-existing addiction issues. However, in studies where MDMA has been administered clinically in a therapeutic setting to healthy volunteers without any previous experience with ecstasy, subjects did not express a wish to use it outside of the clinical setting (Mithoefer et al., 2013). Taken together, these findings suggest that clinically administered MDMA is not likely to result in problematic use (Jerome et al., 2013). In order to monitor the risk of patients using MDMA outside of the study, we monitored their use or desire to use illicit ecstasy with specific questions pertaining to this issue asked in the final (session 10) therapy session.

Clinical MDMA increases blood pressure, heart rate and body temperature (Harris et al., 2002) and causes jaw tightness, bruxism, reduced appetite, poor concentration and impaired balance (Mithoefer et al., 2010). Despite historical reports of neurocognitive deficits in recreational ecstasy users, contemporary studies have failed to demonstrate any significant long-term neurotoxicity associated with recreational ecstasy when use of other recreational drugs is controlled for (Hanson and Luciana, 2010; Selvaraj et al., 2009). There have been no reports of long-term neurotoxicity or neurocognitive impairments when pure MDMA has been administered in a controlled clinical setting (Mithoefer et al., 2013).

Methods

Approvals and drug source

This trial, sponsored and approved by Imperial College London, received a favourable opinion from the Central Bristol Research Ethics Committee of the National Research Ethics Service and from the Medicines and Healthcare products Regulatory Agency (MHRA). A Home Office licence for the storage and dispensing of Schedule 1 drugs was obtained. GMP MDMA was obtained from Sterling Pharmaceuticals (Newcastle) and formulated into the investigational medicinal product (62.5 mg MDMA in gelatine capsules) by the Pharmacy Manufacturing Unit at Guy's and St Thomas' NHS Foundation Trust (London, UK).

Study design

This was an open-label, within-subjects, safety and tolerability feasibility study in 14 patients aged 18–65 years with AUD who had recently undergone detoxification. All patients received MDMA-assisted therapy. The main outcome measures were the number of patients completing the eight-week psychotherapy course, the number accepting the second booster dose of MDMA on drug-assisted days and adverse events. Secondary outcome measures included changes in drinking behaviour (measured by units per week consumed at three, six and nine months since completion of detoxification), measures of mental well-being, psychosocial functioning, quality of life and concomitant drug use.

Patients with a primary diagnosis of AUD who were seeking detoxification – with or without medical assistance – were recruited from the North Somerset Substance Misuse Service (Addaction). Patients received an eight-week course of recovery-based therapy

comprising 10 psychotherapy sessions. On two of these (sessions 3 and 7), patients were dosed with open-label MDMA during a six- to eight-hour assisted therapy session. On each dosing session, participants received an initial oral dose of 125 mg MDMA, followed two hours later by a booster dose of 62.5 mg MDMA. The booster dose served to prolong the experience, allowing for greater time for psychotherapy under the influence of the drug.

Other sessions (sessions 1, 2, 4, 5, 6 and 8–10) comprised one-hour psychotherapy sessions, employing aspects of motivational interviewing and 'third-wave' cognitive–behavioural approaches. Patients remained in the study for approximately 10 months.

Inclusion criteria

The inclusion criteria were as follows:

- Informed consent.
- Primary diagnosis (as defined by DSM-IV) of AUD.
- Successful alcohol detoxification (no longer consuming any alcoholic substances).
- Between 18 and 65 years old.
- Able to identify in advance a supportive significant other(s) who could accompany them to study visits if required and be contacted by the study team in the event that the patient could not be contacted.
- Proficient in speaking and reading English.
- Agree to comply with requirements of protocol.

Exclusion criteria

The inclusion criteria were as follows:

- Lacking capacity.
- History of, or a current, primary psychotic disorder, bipolar affective disorder type 1 or personality disorder.
- A serious suicide risk as determined by the Columbia-Suicide Severity Risk Scale (C-SSRS).
- Relevant abnormal clinical findings at screening visit judged by the investigator to render the subject unsuitable for study, including but not limited to a history of cardiac disease, hypertension and stroke, severe liver disease, a history of epilepsy or a history of malignant hyperthermia (central core disease).
- Regular user of ecstasy (material represented as containing MDMA), for example more than five times in the last five years or at least twice in the six months prior to the start of the study.
- Currently taking or unwilling/unable to stop any medications likely to interact with MDMA in the opinion of the investigators during the eight-week MDMA-assisted therapy.
- Regular use of/dependence on other drugs such as benzodiazepines, synthetic cannabinoids, cocaine and heroin.
- Female participants of childbearing age/potential must use an effective form of birth control for at least six days after administration of MDMA, and must not be pregnant and/or breast-feeding until the end of the treatment phase.
- For males with partners of childbearing age/potential, participants must themselves confirm use of an effective form of birth control for at least six days after administration of MDMA and confirm their partner will also.
- Taken part in a study involving an investigational product in the last three months.
- Patients who might face additional risks from immunosuppression (e.g. patients with immunological diseases or patients with active infection or history of infections within four weeks of MDMA administration).

AUD was identified using the DSM-IV SCID interview. Screening comprised of written informed consent, an evaluation of the patient's physical and mental health background, a psychiatric interview (MINI) and assessments of depression and anxiety severity using the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder Assessment (GAD-7) questionnaires. Severity of AUD was established using the Severity of Alcohol Questionnaire (SADQ) and the Short Inventory of Problems for Alcohol (SIP) questionnaire. Patients received a thorough physical health check comprising an electrocardiogram, routine blood tests, blood pressure, heart rate and physical examination. Following screening, eligible patients underwent the process of detoxification either by gradually cutting down alcohol consumption over many weeks or with a medically assisted detoxification regime. The majority of participants were also taking medications for anxiety and/or depressive symptoms (e.g. selective serotonin reuptake inhibitors). According to the inclusion/exclusion criteria, associated medications known to attenuate the effects of MDMA were subsequently gradually reduced and stopped under medical supervision ahead of the first MDMA session. A further 'baseline' visit clarified successful detoxification using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) questionnaire before eligible participants entered the eight-week course of psychotherapy. This entailed weekly 60-minute outpatient non-drug psychotherapy sessions delivered by two clinicians (B.S. and L.H.) trained in delivering MDMA-assisted psychotherapy by the USA-based organisation MAPS.

Dosing with MDMA occurred twice during the eight-week course on weeks 3 and 6. Physiological changes, observer and subject ratings of distress (Subjective Units of Distress (SUDS)) and the intensity of MDMA's acute psychoactive effects were measured throughout the drug-assisted session. Acute anxiety was managed primarily psychologically, but sedative medication (oral lorazepam) was available. Participants remained overnight in the treatment centre after each drug-assisted session, overseen by medically trained 'night sitters' who were on hand to support participants as required but instructed to avoid delivering any psychotherapeutic interventions.

Participants were seen the morning after each drug-assisted session for an integration psychotherapy session, and then telephoned daily for six days to assess changes to mood, suicidal risk factors (using the C-SSRS) and quality of sleep (using the Leeds Sleep Evaluation Questionnaire). Following the end of the eight-week therapeutic course, participants carried out additional follow-up questionnaires. They were then seen again at three, six and nine months (since baseline) for longer-term follow-up data collection.

Data analysis

All data were recorded on paper case report forms and then digitized into MS Excel spreadsheets. Analysis and graphing were

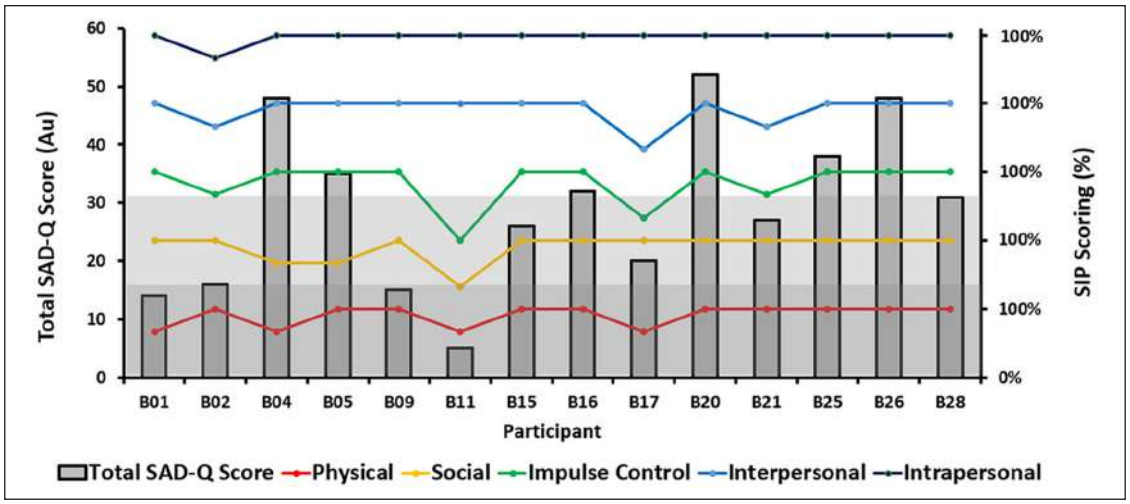

Figure 1. Severity of Alcohol Questionnaire (SADQ) measures alcohol dependency (Au = arbitrary units). Short Inventory of Problems for Alcohol (SIP) is a 15-question measure of self-noted consequences of drinking. Both were observed at screening. SIP categories are separated each between 0% and 100% on the second *y*-axis. A score of 31 or higher indicates severe alcohol use disorder (AUD) severity. A score of 16–30 indicates moderate AUD severity (light-grey area). A score lower than 16 indicates mild AUD severity (dark-grey area). Four SADQ questions were unanswered, in which case, mean substitution was applied using the average row value for the relevant time period and participant. B05, B16, B20 and B21 had one question missing each.

performed using GraphPad Prism Prism version 8.4.3 (GraphPad Software LLC, La Jolla, CA) or MS Excel. As this was a non-randomised, controlled, open-label study, no hypothesis testing was performed. When calculating timeline follow-back results, alcohol consumption levels at last observation were used in the case of drop-outs or when participants had undertaken a second detoxification (Hamer and Simpson, 2009).

Results

Demographics

Thirty-six participants attended face-to-face screening visits, and 14 were enrolled (8 males and 6 females; $M_{age} = 48$ years). All were white British. Four were employed, nine were unemployed and one was retired. The average age of first alcohol use was 13 years old. The average age when alcohol became problematic was 34 years old. Nearly two-thirds (64%) of participants reported a history of alcohol-related blackouts, 14% had experienced alcohol withdrawal–induced seizures, 86% of participants reported having experienced risky or vulnerable incidences due to alcohol and 75% of participants had had forensic/offending behaviour secondary to their alcohol use.

Severity of AUD criteria at screening and baseline

As per the inclusion criteria, all eligible patients scored above the diagnostic threshold on the DSM-5 SCID questionnaire for AUD. We also measured AUD severity using the SIP questionnaire and the SADQ questionnaire (Figure 1), with most eligible participants in the moderate to severe range. At the baseline visit (within one week of detox completion), 100% of eligible participants had successfully completed detoxification, which was assessed using the CIWA scale.

Physiological and tolerability effects during MDMA sessions

Of the 14 participants, 12 received both sessions of MDMA-assisted psychotherapy. So, in total, 26 drug-assisted psychotherapy sessions with MDMA were administered during the trial. Temperature, blood pressure and heart rate were measured at $t = 0$, before taking the medicine, then half-hourly up to $t = 2$ hours, then hourly thereafter for a minimum of six hours from the time of dosing (Figure 2).

Except for one participant, all of these physiological parameters remained within normal limits for all these sessions. As expected, we saw a mild transient rise in blood pressure, temperature and heart rate over the course of the MDMA session. No patients experienced sustained abnormal physiological disturbance, symptomatic experiences of raised blood pressure, heart rate or temperature or any other adverse events during MDMA sessions. No medical interventions were required in respect of these or any other physiological events during MDMA sessions. One participant experienced a transient abnormal rise in blood pressure after taking the initial dose of 125 mg MDMA, reaching 183/118 mmHg at two hours after dosing, attributed to the participant forgetting to take her regular antihypertensive medication on the morning of dosing. Although she was asymptomatic and no medical intervention was required, it was decided to withhold the two-hour supplemental dose. Her blood pressure subsequently spontaneously returned to normal in the following two hours, and she agreed with the study team to omit the booster dose of MDMA on that day. She did, however, receive her second MDMA session three weeks later (after taking her antihypertensive medication in advance appropriately), which was uneventful in terms of blood pressure. Another participant only received her first MDMA session. She subsequently relapsed back to heavy drinking in the context of personal psychosocial issues unconnected with the study, and therefore she chose not to have her second MDMA session.

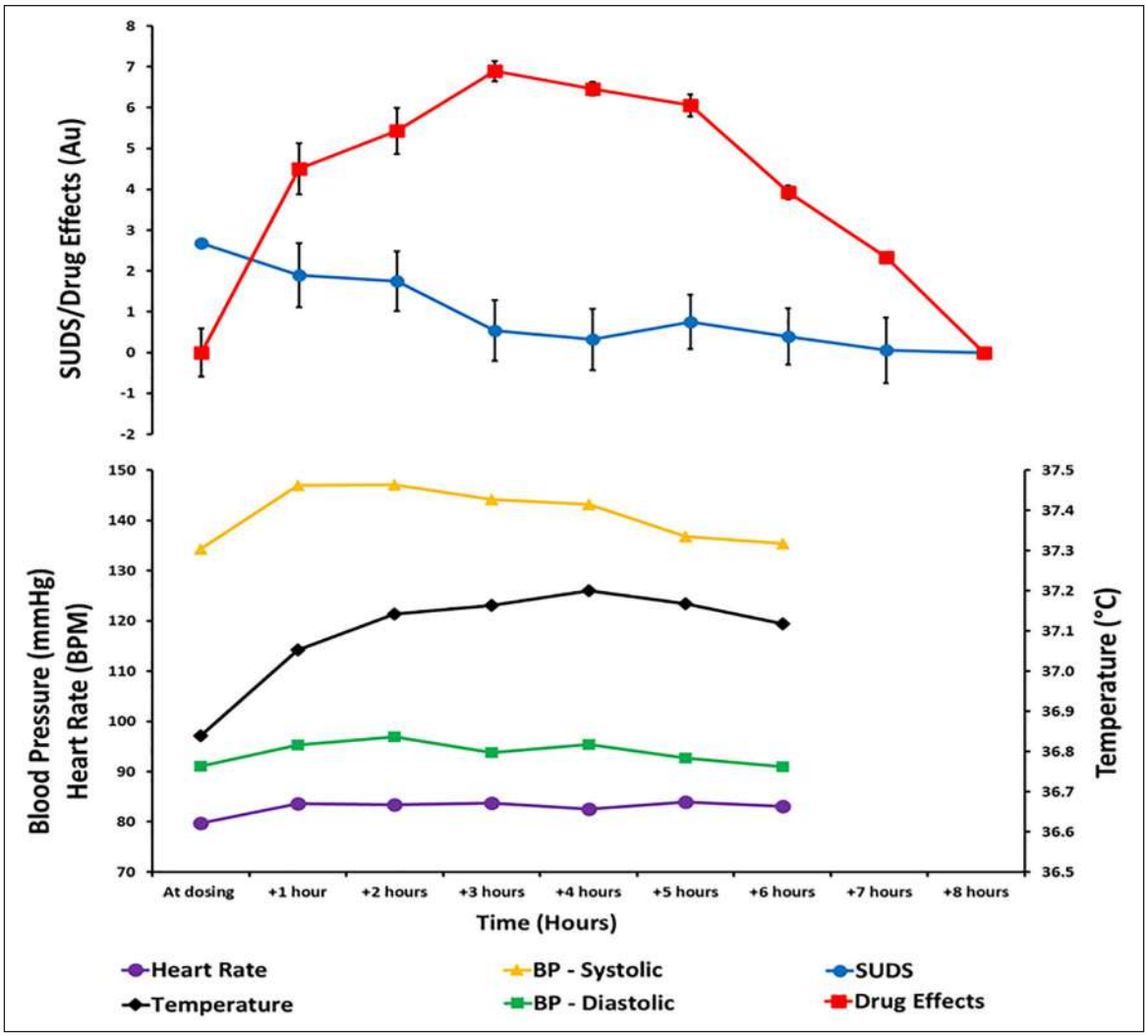

Figure 2. Pooled data of blood pressure, temperature, heart rate, observed drug effects and Subjective Units of Distress (SUDS) observed over the duration of the MDMA sessions. SUDS and drug effects observed over eight hours; physiological data observed over six hours following dosing. Mean data for each session are used, except in the case of missing data, where available session data are applied. Error bars (where applied) indicate ±standard error of the mean (SEM).

Subjective Units of Distress (SUDS) and participant report of drug effects were also measured hourly throughout the MDMA sessions (Figure 3). Most subjects predictably reported mildly raised SUDS scores at the beginning of the sessions before taking MDMA – consistent with expected anxiety ahead of dosing – which subsequently reduced during the course of the session as the positive effects of MDMA emerged. Participants gave their own subjective score (0–10) of whether they felt drug effects, and the therapists also recorded their own objective score of how 'altered' the participant appeared. There was no significant difference between observers' and participants' drug effects scores. Drug effects rose expectedly over the first two hours, with a notable further increase after the booster dose was given at $t=2$ hours, and a subsequent plateau and then decline over the following six hours. By the end of the MDMA session day, all drug effects had returned to baseline. No participants reported any significant neurocognitive impairments associated with receiving MDMA in the weeks and months following participation in the study.

Changes in drinking behaviour

Whilst changes in drinking behaviour were not a primary outcome measure, we nevertheless collected data in respect of units of alcohol consumed per week in the month before participants' detoxification, immediately after detox ('baseline'), throughout the eight-week MDMA therapy course and for up to nine months after detox. Of the 14 eligible participants who underwent the course of MDMA-assisted psychotherapy, at the nine-month follow-up end point, 11 participants were drinking fewer than 14 units of alcohol per week (including nine who were totally abstinent from alcohol), and three participants had relapsed to drinking more than 14 units of alcohol per week. On average, participants were drinking 130.6 units of alcohol per week in the month before detoxification, and no units at the point of detox. After nine months, the average amount of consumed alcohol had risen back to 18.7 units per week (Figure 3).

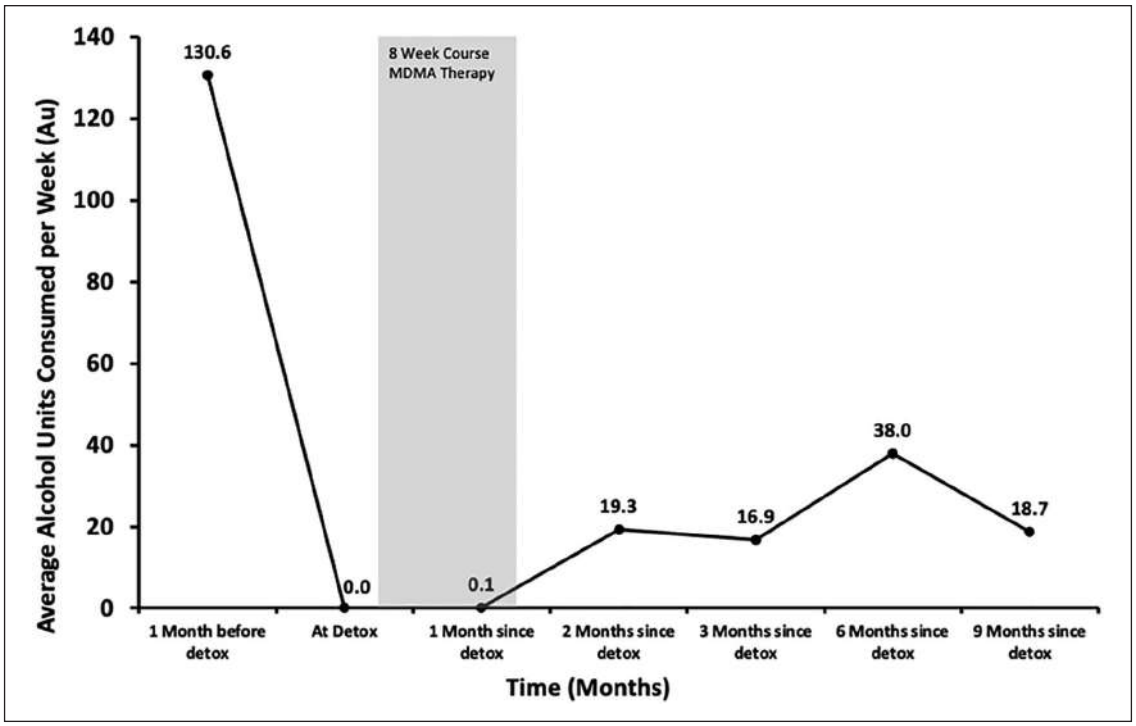

Figure 3. Timeline follow back (TLFB) assesses drinking behaviour prior to and following the study. Data are collected daily by self-reporting and reviewed at one month prior to detox, immediately following detox and at one, three, six and nine months follow-up. A full data set was not available for three of the participants. One participant dropped out of the study at three months, and two patients failed to provide data at the nine-month follow-up. Two participants had a second detox since starting the study. For these participants, TLFB drinking behaviour data were carried forward from the point of drinking levels before the second detox.

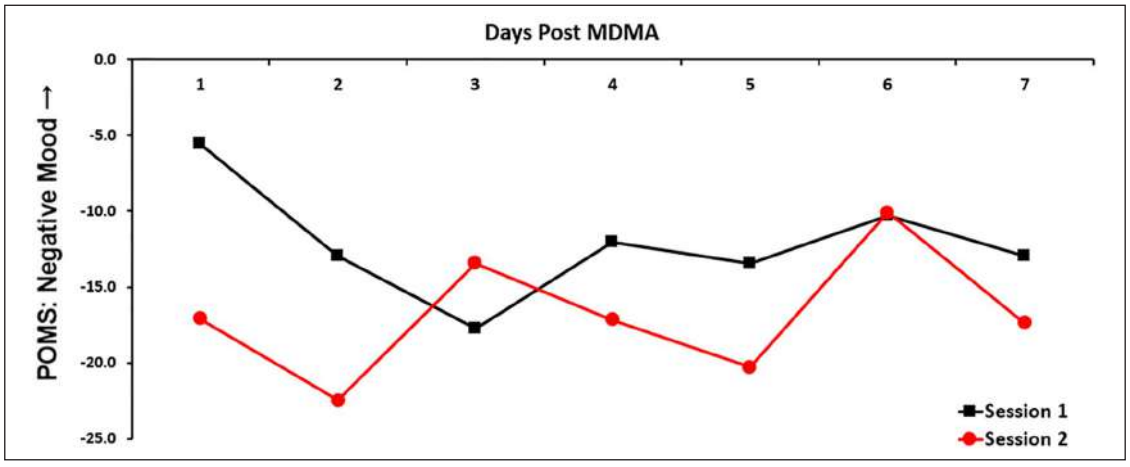

Figure 4. Profile Of Mood States (POMS). Individual composite scores of mood disturbance observed daily over a week following dosing. Mean data shown for both MDMA sessions. In the case of absent data for either session, the available data for the remaining session are used.

Seven-day follow-up after MDMA sessions

Considerable medical literature and the popular press report the anecdotal observation of ecstasy users experiencing an acute 'come-down' effect and a drop in mood in the days after using the drug recreationally. In order to measure this prospectively with clinical MDMA, we measured participants' mood states by daily Profile Of Mood States measurements for seven days after each MDMA session (Figure 4). Positive scores represent depressed affect, zero represents no change in mood/affect and results below zero represent a positively felt mood. Average scores across both MDMA sessions for all 14 participants (26 MDMA sessions) revealed no evidence of any mood disturbance during the week after taking each session of clinical MDMA. Indeed, participants sustained a positive mood for seven days. This result contrasts with anecdotal reports from recreational ecstasy users.

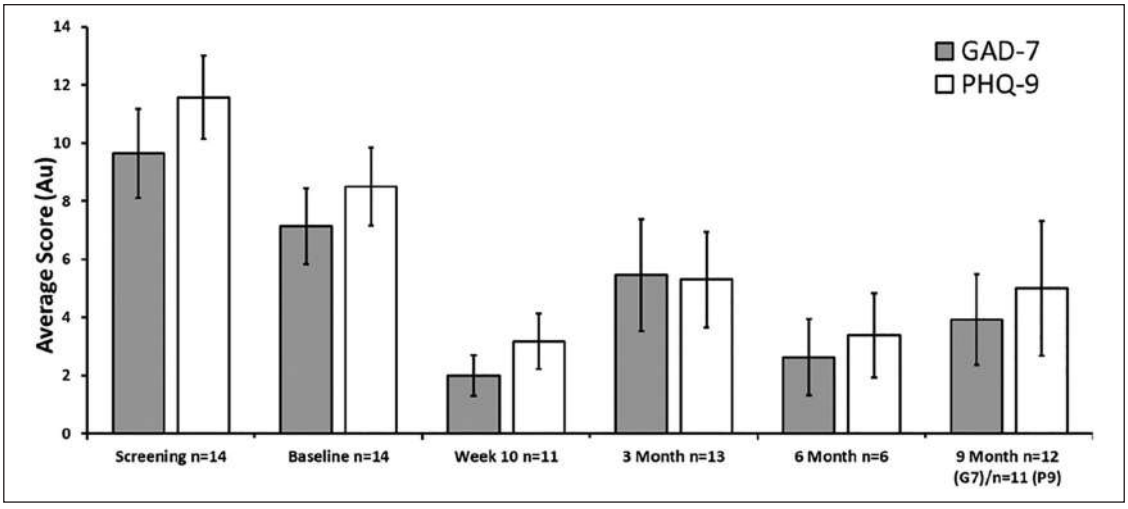

Figure 5. General Anxiety Disorder 7 (GAD-7) and Patient Health Questionnaire 9 (PHQ-9). Self-report scales for anxiety and depression, respectively. Recorded at screening, baseline and week 10, and then at three, six and nine months of follow-up. Greater scores report indication of heightened anxiety/depression. Error bars indicate ±SEM.

Other mental health measures and quality of life measures

Brief assessments of mood and anxiety were made at screening, baseline, after the eight-week MDMA therapy course and at the three-, six- and nine-month follow-ups using the PHQ-9 and GAD-7 rating scales, respectively (Figure 5). Scores demonstrated a reduction in both anxiety and depression after screening and baseline time points, followed by a transient rise in anxiety and depression scores three months after baseline, a further reduction at six months and a moderate rise again at nine months post detox.

Suicidality

Participants underwent the C-SSRS at screening, baseline, throughout the eight-week therapy course, in the week after each MDMA session and at the three-, six- and nine-month follow-up visits. No participants reported current suicidal ideation, intent or plans or self-harm behaviour during the course of the study

Adverse events

The acute effects of MDMA-assisted psychotherapy were well tolerated by participants. No unexpected adverse events occurred. No participants reported any desire to use illicit ecstasy/illicit MDMA following receiving clinical MDMA as part of this trial. No psychotic symptoms were observed in any of the patients.

A variety of further data were collected, including changes to the quality of sleep, quality of life measures and changes to compassion and empathy scales, which will be published in forthcoming papers.

Discussion

In this first safety and tolerability study, we demonstrate that MDMA-assisted psychotherapy could be useful in treating AUD, probably through its capacity to enhance the psychotherapeutic process or indirectly through augmenting the treatment of comorbid psychological conditions commonly associated with AUD (Jerome et al., 2013).

The capacity for MDMA to increase feelings of empathy and compassion for the self and others may contribute to improved self-awareness and subsequently reduce the denial of harmful use of alcohol. Recreational MDMA users have reported improved intrapersonal attitudes and prosocial attitudes towards the self, which could be a mechanism by which the drug enhances psychotherapy, especially for patients with pre-existing histories of trauma (Stolaroff, 2004). Similarly, Mithoefer et al. (2010) described MDMA's capacity to 'make yourself present in the moment' – a core concept of mindfulness. Drug-assisted psychotherapies with the 'classic' psychedelic compounds LSD and psilocybin utilise the induced subjective mystical/spiritual effects of the psychedelic experience and have found the depth of this experience is strongly associated with maintained recovery from harmful substance use (Sessa and Johnson, 2015). However, not all patients are able or willing to tolerate the classic psychedelic experience, and compliance is a critical aspect of addiction therapy. Whilst there is also an, albeit minimal, subjective spiritual/mystical experience associated with MDMA (Sumnall et al., 2006), it is generally better tolerated than the classic psychedelics, with fewer perceptually disturbing effects compared to LSD and psilocybin. Therefore, MDMA offers an alternative opportunity for enhanced psychotherapy in patients with AUD.

Prior to carrying out the BIMA study, the same study team carried out a non-interventional observational study, following 14 participants through their treatment-as-usual post-alcohol detox (the 'Outcomes Study'; Sessa et al., 2020). The eligibility criteria and questionnaires used in the Outcomes Study were similar to the BIMA study in respect of assessment of AUD, severity of AUD, success of detoxification and follow-up of outcomes in respect of mental health issues and drinking behaviours – measured at three, six and nine months post detox but without the additional eight-week therapeutic course with MDMA-assisted psychotherapy,

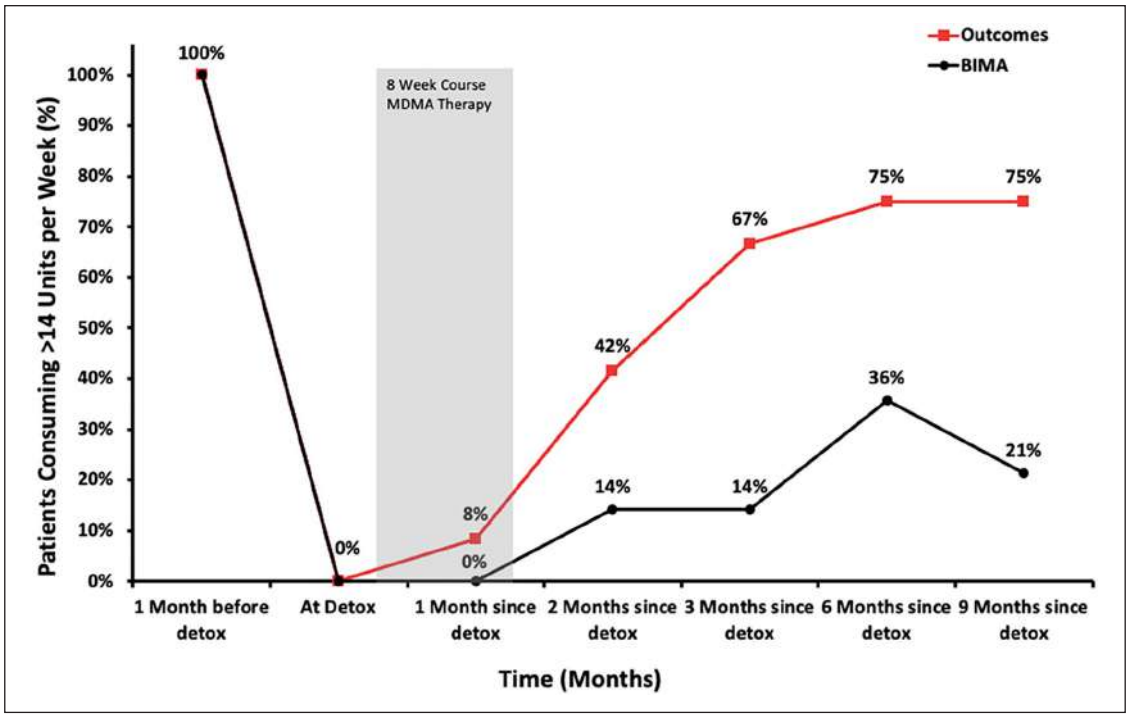

Figure 6. TLFB showing % of patients consuming more than the 14 recommended daily units of alcohol (Sessa et al., 2020).

which occurred post detox. Whilst it is not appropriate to compare these two studies statistically, as patients were not randomised into the studies, Figure 6 demonstrates the success of BIMA participants in terms of alcohol consumption over nine months compared to current best treatments available locally. Only 21% of participants who had undergone MDMA-assisted psychotherapy were drinking in excess of 14 units of alcohol a week in comparison with the 75% observed in the Outcomes Study.

Limitations

The BIMA study had a relatively small sample size. As directed by the MHRA, given that the study was exploring a first-time drug intervention in a previously unexplored clinical population, it was an open-label, non-placebo-controlled study. Therefore, all patients knew they would be getting MDMA. Whilst efforts were made to test objectively for alcohol use using regular breath alcohol analysis, review participants' medical notes throughout the study and carry out Gamma-GT blood tests post course, all data represented above were nonetheless reliant primarily on retrospective self-report. The study team considered other techniques to assess alcohol use objectively, such as worn alcohol sweat meters, but given that efficacy (drinking outcome) was not a primary outcome measure, this was concluded to be overly intrusive for this type of study.

Conclusion

In summary, this study demonstrates that MDMA-assisted psychotherapy can be safely delivered, is well tolerated and has the potential to enhance and intensify the psychotherapeutic processes in the treatment of patients with AUD. MDMA, given in a psychotherapeutic context, may reduce avoidance of emotionally distressing thoughts, images or memories of alcohol misuse while increasing empathy for the self and others. It may also address symptoms of other conditions that are frequently co-morbid with harmful use of substances, particularly those symptoms associated with a history of psychological trauma.

A logical next step would be to carry out a placebo-controlled randomised controlled trial in which the level of therapist contact is consistent between conditions. This would enable any between-group differences in clinical outcomes to be attributed to MDMA rather than to the psychological support provided.

Acknowledgements

We also wish to express thanks to Minirigs – the Bristol-based electronics company that provided the stereo equipment for the experimental sessions. We are grateful to Dr Mendel Kaelen, who provided the playlists for the MDMA therapy sessions. Thank you to all the staff at the Clinical Research and Imaging Centre (particularly Jade, Cathy and Hannah). Enormous gratitude to the local staff and the research and development team at Addaction, without whose support this project would never have happened. In particular, we thank our expert user, Mr Kevin Speller. The staff at MAPS – especially Rick Doblin, Michael Mithoefer and Ilsa Jerome – provided essential support and guidance throughout the project – including provision of the IB and ongoing advice regarding MDMA pharmacology and therapeutic issues. We are grateful to Dr James Rickard, Chief Scientific Officer at Biotherapy Services, for providing pharmacy support, to Dr Tim White (at Guy's and St Thomas' NHS Foundation Trust Pharmacy Manufacturing Unit, London, UK) for production of the IMP and to Dr Liz McCullough at BRI pharmacy for storing and dispensing the study medication. And finally, we are extremely grateful to the pool of local junior doctors who gave their time to act as post-MDMA night sitters after each of the participants drug-assisted sessions, including Sakal, C., (night sitters lead), Titheradge, D., Rose-Morris, A., Brew-Girard, E., Alderton, K.,

Burrows, S., Secker, A., Loysen, S., Hall, K., Lilford, P., Flowers, J., Wright, L., Roberts, R., Lawton, S., Meyer, A., Salter, E., Guy, J., Brown, R. and Rifkin-Zybutz, R. Most importantly, we extend enormous gratitude to the patients who participated in this study.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: The authors are grateful to the Alexander Mosley Charitable Trust for the entire funding of the study.

ORCID iDs

Ben Sessa https://orcid.org/0000-0002-1212-6060
Chantelle Wiseman https://orcid.org/0000-0002-0146-3969

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MIND MEDICINE AUSTRALIA

Appendix G

Sources Referred in Sections 5.2
In order of reference

(Source papers provided separately on USB to the TGA)

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MIND MEDICINE AUSTRALIA

Appendix H

Joint Submission from the Australia Institute and Fearless to the TGA explaining why Diversion Risk is Low

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FEARLESS
RESTORING CONTROL TO VICTIMS OF TRAUMATIC STRESS

The Australia Institute
Research that matters.

Proposed amendments to the Poisons Standard

Joint submission

The proposed rescheduling of psilocybin and MDMA from Schedule 9 to Schedule 8 of the Poisons Standard offers large potential benefits and minimal costs or risks.

September 2020

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The Australia Institute is an independent public policy think tank based in Canberra. It is funded by donations from philanthropic trusts and individuals and commissioned research. We barrack for ideas, not political parties or candidates. Since its launch in 1994, the Institute has carried out highly influential research on a broad range of economic, social and environmental issues.

FearLess

FearLess is a charity that works with people living with the consequences of post traumatic stress (often referred to as PTSD). We also help family members in any way affected by it. Our members come from all walks of life including those living with PTSD and their families or people who want to do their bit to make the lives of people living with post traumatic stress more enjoyable and fulfilling. Our work complements the activities of other community-based organisations and government agencies that provide services to people with post traumatic stress.

More details at: fearless.org.au

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SUMMARY

The Australia Institute and FearLess support the rescheduling of psilocybin and MDMA from Schedule 9 to Schedule 8 of the Poisons Standard. The potential risks from this change are small while the benefits are potentially large. Academic studies recognise the low level of harm caused by these substances. Despite researchers finding "easy to very easy" access to these substances, in 2019 just 3.0% of the population used MDMA and 1.6% used any hallucinogens (which includes LSD as well as psilocybin), demonstrating their non-addictive nature. As Schedule 8 is still a rigorous regime it seems unlikely that rescheduling would affect illicit use.

INTRODUCTION

The Australia Institute and FearLess welcome the opportunity to make a submission on proposed amendments to the Poisons Standard. The Institute is a Canberra-based think tank conducting research on a broad range of economic and social issues, including mental health. FearLess is a charity that works with people living with the consequences of post traumatic stress (often referred to as PTSD). While we have limited expertise in the chemical, biological or pharmacological aspects of psilocybin and MDMA, from a public policy and economic perspective, the proposal to change their classification and facilitate their therapeutic use appears to offer large potential benefit for minimal cost or risk.

POTENTIAL BENEFITS

The costs of poor mental health are substantial to say the least. While dollar terms are far from an ideal way to measure such a personal problem, the cost to the Australian economy of mental ill health is estimated by the Productivity Commission at $130 billion per year relating to diminished health and life expectancy for those living with mental ill-health and a further $43-51 billion per year, relating to healthcare provided by governments, family and friends.[1] As such, even a small improvement in mental health treatment would provide large economic benefit.

Such an improvement could be assisted by this rescheduling, as it would, in our understanding, facilitate development of new treatments for a range of mental health problems. Existing treatments for depression and PTSD have low success rates and can be

[1] Productivity Commission (2019), *Mental Health: Draft Report* https://www.pc.gov.au/inquiries/completed/mental-health/draft

costly. They often require long term pharmaceutical usage or long term therapy, neither of which have high success rates. Side effects from common medications can be significant. [2]

In contrast, trials of psilocybin therapy for depression and MDMA therapy for PTSD suggest they can achieve:

- Lower remission rates.
- Assistance after only a few sessions, reducing the need for long term pharmaceutical usage and/or long term therapy.
- Fewer side effects.

Overseas trials suggest that in a clinical environment these treatments are safe and non-addictive. The clinical environment is important as these trials emphasise the role of mindset and environment ('set' and 'setting') to the outcomes from psychedelic therapy. Set and setting are significantly more controlled in a clinical setting than when these substances are used recreationally.

The potential for better outcomes with lower costs and risks indicated in trials is recognised by the US FDA granting breakthrough status to psilocybin and MDMA for treatment of depression and PTSD respectively.[3] Early access schemes for psilocybin-assisted psychotherapy have been approved in Canada and Switzerland, while early access schemes for MDMA-assisted psychotherapy have been approved in Israel, Switzerland and Australia.

Though not at the same stage as the trials of psilocybin therapy for depression and MDMA for PTSD, we note the success of trials using psychedelic therapy to treat addiction. If this success is repeated in further trials, rescheduling will facilitate the use of this therapy to treat addiction.

OTHER DRUGS IN SCHEDULE 8

We note that psilocybin and MDMA are considered to cause less harm to users or society compared to several drugs already on Schedule 8 (buprenorphine, methadone, cannabis, ketamine, amphetamine) and Schedule 4 (anabolic steroids, benzodiazepines).[4] Figure 1

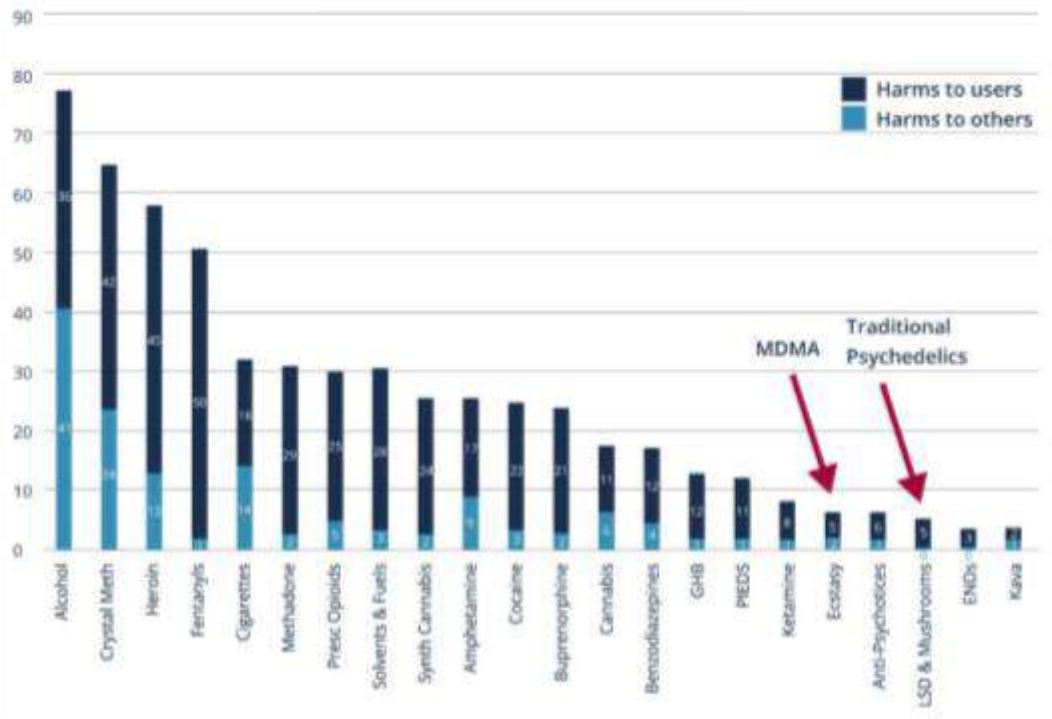
[2] Detailed references for these points can be found in the submissions by Mind Medicine Australia (2020) to the TGA for rescheduling https://mindmedicineaustralia.org/important-resources/

[3] Saplakoglu (2019) *FDA Calls Psychedelic Psilocybin a 'Breakthrough Therapy' for Severe Depression*, https://www.livescience.com/psilocybin-depression-breakthrough-therapy.html

[4] Bonomo et al (2019) *The Australian drug harms ranking study,* https://journals.sagepub.com/doi/abs/10.1177/0269881119841569

below shows that MDMA and psychedelics are among the least harmful substances analysed by the *Australian drug harms ranking study*:

Figure 1: Relative harm to users and harm others



Source: Bonomo et al (2019)

This ranking is based on a facilitated workshop with 25 Australian drug research experts. Note that legal substances such as alcohol, cigarettes and solvents rank far higher than MDMA or psychedelics.

RESCHEDULING UNLIKELY TO LEAD TO INCREASED USAGE

The risk that the rescheduling of these substances contributes to illicit use seems low.

MDMA in the form of ecstasy tablets is already considered "easy or very easy to obtain" by some 83% of ecstasy users and tablets sell for a low price. Nationally, the price for a single MDMA tablet/capsule ranged between $15 and $45 in 2017–18.[5]

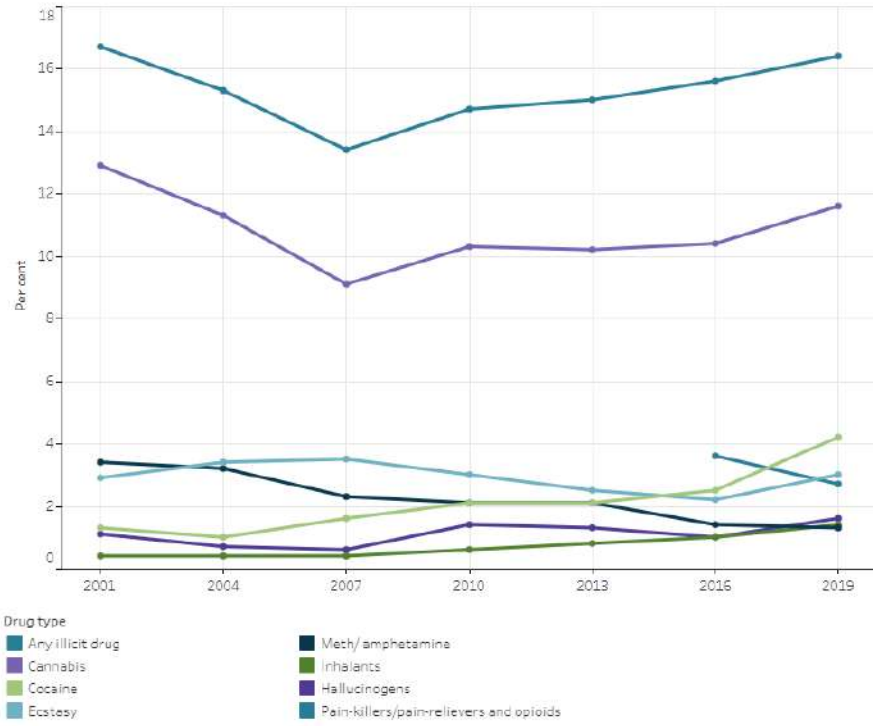
Data on the ease of obtaining psilocybin and its price is quite limited, likely reflecting its low harm and low priority for drugs enforcement efforts. The *Illicit Drug Data Report 2017–18* does not contain any information on the ease of obtaining psilocybin. The report does note

[5] Australian Criminal Intelligence Commission (2019) *Illicit Drug Data Report 2017–18,* p35, p37, https://www.acic.gov.au/sites/default/files/illicit_drug_data_report_2017-18.pdf?v=1564727746

that there are some twenty species of psilocybin that grow naturally in Australia, suggesting easy seasonal access for people with some knowledge of mycology (and potential risks for those that lack such expertise). South Australia was the only state to report a price for one gram of psilocybin in 2017–18, which ranged between $10 and $15.[6]

Despite their easy availability and low price, usage of ecstasy and psilocybin is low across the population. In 2019 just 3.0% of the population had used ecstasy in the last 12 months, only 1.6% of the population had used hallucinogens (which includes LSD as well as psilocybin),[7] as shown in Figure 2 below:

Figure 2: Use of illicit drugs in the last 12 months



Source: AIHW (2020) *Illicit drug use*. Percentage of population aged over 14.

The fact that ecstasy and psilocybin are cheap and easy to obtain in part reflects their non-addictive nature which reduces demand. This is particularly shown in the case of hallucinogens, which 10.4% of the Australian population had used in their lifetime but only 1.6% had used in the last 12 months.[8] It also reflects that they are considered a low priority for low enforcement efforts (reflecting the low harm they cause compared to other illegal

[6] Australian Criminal Intelligence Commission (2019), p93.

[7] Australian Institute of Health and Welfare (2020) *Illicit Drug use,* https://www.aihw.gov.au/reports/australias-health/illicit-drug-use

[8] AIHW (2019) *National Drug Strategy Household Survey 2019 - Illicit use of drugs,* p2 https://www.aihw.gov.au/getmedia/9569b88d-3326-46e2-8df8-bf88a93e2d22/aihw-phe-270-Chapter4-Illicit-drugs.pdf.aspx

drugs). Given that Schedule 8 is still a rigorous regime it seems unlikely that rescheduling would affect use and availability.

CONCLUSION

A reclassification of psilocybin and MDMA from Schedule 9 to Schedule 8 offers potentially large benefits and seemingly minimal costs and risks. There appear to be no parties that would be harmed by reclassification, with the possible eventual exception of anti-depressant manufacturers. However such a change would take place slowly, and represents the basic market process of improvements in treatment.

MIND MEDICINE
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Appendix I

Letter from the Academic Teaching Leaders of the Certificate in Psychedelic- Assisted Therapies (CPAT) to the TGA outlining the Course Approach, Teaching Program and Teaching Faculty

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Level 1/10 Dorcas St
Southbank Vic 3006
Australia

Attention: Secretary, Department of Health, Australian Government, Canberra.

Subject: Submission relating to Notice of Interim Decisions to Amend (or Not Amend) the Current Poisons Standard, dated 3 February 2021, in relation to Psilocybin and MDMA.

Dear Secretary,

The following letter addresses two reasons articulated in the Notice of Interim Decisions to Amend (or Not Amend) the Current Poisons Standard, dated 3 February 2021. For ease, the points raised are below.

For Psilocybin

> *"It will take years to develop a curriculum and accredited training process for psychiatrists. To protect public health and prevent misuse, psilocybin should not be down-scheduled until all necessary safeguards have been established and implemented." Pg 15*

And

For MDMA

> *"It will take time to develop a curriculum and accredited training process for psychiatrists. To protect public health and prevent inappropriate uses, MDMA should not be down-scheduled until all necessary safeguards have been established and implemented." Pg 19.*

We, external members of the Academic Team, responsible for the development and implementation of the Certificate in Psychedelic Assisted Therapies will address the above reasons by making a number of pertinent points outlined below. The **Certificate in Psychedelic Assisted Therapies (CPAT)** has been developed specifically with the objective of providing the clinical training necessary for existing qualified Psychiatrists, Psychologists, Psychotherapists, GPs, physicians, mental health nurses, social workers, drug and addiction specialists to work with patients utilising psilocybin and MDMA therapeutically if these medicines become rescheduled to Schedule 8. Although there is ongoing research and clinical guidelines are being refined, the course both builds upon extensive existing knowledge and will continue to be developed iteratively as further best practice evidence is published. This is a relatively common practice in mental health training and treatment.

A) The professionals directly involved in developing CPAT have extensive experience in either or both the treatment of complex mental health issues and the development of Accredited education programs. The Academic Team have a cumulative 80+ years in education and mental health treatment. The members are:

- Brad Seaman BSc (Hons) – External Project Manager
  20 years in Education including professional development of Medical Practitioners, TAFE Lecturer, educating youth in schools, professional development of teachers, social workers and business professionals. The most recent 11 years were spent as CEO of a private VET and Higher Education provider accrediting and delivering

qualifications in mental health treatment. Brad has been involved in the accreditation of more than eight specialist tertiary qualifications.

- Dr. Tra-ill Dowie PhD – Lead External Academic
  Head of the Faculty of Psychotherapy at Ikon Institute Australia. Dr Dowie is the Chair of the Australian Counselling Association (ACA) Panel for Trauma Standards & Practice. Dr Dowie is a practising psychotherapist, supervisor and public speaker. He holds dual PhDs, receiving a PhD in Psychiatry from Monash University and a PhD in Philosophy from the University of Melbourne.
- Nigel Denning MA, MPsych – Lead External Academic
  Nigel is a Counselling Psychologist, AHPRA registered supervisor and Managing Director of Integrative Psychology, a Psychology/Psychiatry practice in East Melbourne. He is a former Family Violence Co-ordinator for Relationships Australia and is currently the Deputy President of the In Good Faith Foundation, an organisation that supports Institutional Abuse and cult survivors. Nigel is also a registered Neuro-psychotherapy supervisor with IAAN. Nigel has been involved in Transpersonal Psychology and consciousness studies for over thirty years. He has studied extensively under Stanislav Grof MD and worked closely with Tav Sparks and Grof Transpersonal Training to develop training approaches to Holotropic breathwork and therapy influenced by this modality. Nigel also conducted one of the few peer reviewed research studies on Holotropic breathwork and accredited a Graduate Certificate in Depth Psychology.
- Dr. Alana Roy PhD – Lead Internal Academic
  Dr Alana Roy is a psychologist, social worker and therapist and has spent the last 14 years working in mental health, suicide prevention, trauma, sexual abuse and family violence and the disability sector. Alana has worked with borderline personality and dissociative identity disorder in various roles in the community. Alana works at several universities as a Research Fellow and Supervisor of students on placement. Alana also provides integration and harm minimisation services to clients in the communities who are travelling overseas or using these medicines in Australia.
- Melissa Warner BSc. – Internal Academic
  As an advocate for innovative solutions for mental health, Melissa is co-founder of the Australian Psychedelic Society. After graduating in Neuroscience from the University of Melbourne, Melissa travelled to leading international centres of psychedelic research, investigating mental health treatments. Melissa is currently a post-graduate student in Psychology at the University of Melbourne.

B) Complementing the domestic academic team engaged by Mind Medicine Australia a broad range of experts from Australia and overseas are involved in the delivery of the CPAT program. These professionals represent the absolute leaders in the fields of neuropharmacology, neuroscience, psychiatry and clinical treatment utilising psychedelic medicines. The esteem of these academics should not be underestimated, with academic roles at institutions including Yale, Harvard, Stanford, Johns Hopkins, British Colombia, Imperial College London, North Carolina, Bristol University, Warwick and Melbourne. Together they have authored much of the leading research in the field. In addition to the core Academic Team there are a further 19 International Academics involved in teaching the CPAT course. This expert Faculty can be found at https://cpat.mindmedicineaustralia.org and Attachment 1

C) The CPAT program has been developed with future tertiary accreditation in mind. Utilising their experience in Accreditation and Higher Education the Academic Team developed the CPAT program to be the equivalent volume of two Masters level subjects. Proposed developments include recognition of the course as professional development by the RANZCP, RACGP (and other relevant bodies) and formal Accreditation of the subjects in a University Graduate Qualification or stand-alone Graduate Certificate of Psychedelic-Assisted Therapy.

Having reviewed other psychiatric and psychological qualifications such as the University of Melbourne Masters of Psychiatry, we have constructed a course that would currently be equivalent to 50 credit points in accordance with contemporary higher education standards in the field.

The existing training course has a set of Course Objectives, detailed below. Each of the Course Objectives has a set of learning objectives which are achieved throughout the delivery of the training and assessed before any participant is eligible for addition to the Interim Register of Psychedelic Practitioners. Attachment 2 contains the Subject Outlines developed to guide the development of the course.

Course objectives	Learning Objectives
a) Develop a sound understanding of the CPAT rationale of psychedelic assisted Psychotherapy.	a) Develop a clear knowledge of the psycho-biological model of consciousness. b) Develop a clear understanding of the role of state and stage as pertaining to organisation of mind. c) Articulate ethno-medicine contributions to healing practice through the use of psychoactive substances. d) Develop a meta-perspective on the role of perceptual disruption and redefinitions of personal ontologies and epistemologies in psychedelic experiences.
b) Develop clear knowledge pertaining to the history and context of psychedelic psychotherapy.	a) Develop a clear understanding of the role of psychedelics in human evolution. b) Develop a clear historical contextualisation of early psychedelic psychotherapy begin with the work of Hoffman and proceeding through to the works Grof, Metzner, Leary, Ram Das, Huxley, Fradiman, Shulgin. c) Critically conceptualise the political and cultural landscape leading to the rise and fall of psychedelics. d) Contextualise the re-emergence of psychedelic assisted psychotherapy through the development of MAPS in the united states and the development of mind medicine Australia.
c) Develop a strong working knowledge of key factors in clinical application of psychedelic psychotherapy including: Assessment, formulation and treatment planning with a key focus on contraindications and risk.	a) Develop a clear conceptual knowledge of psychedelic psychotherapy specific to substance selection and treatment presentations. b) Appraise current approaches to the interface between neuroscience and the drugs utilised in psychedelic assisted psychotherapy. c) Apply psychedelic assisted psychotherapy knowledge and skills into existing clinical frameworks. d) Develop the ability to present a coherent psychedelic psychotherapy case formulation which articulates the rationale for psychedelic use. e) Develop clear knowledge of treatment resistant presentations and their relevance to psychedelic assisted psychotherapy.
d) Develop a clear working knowledge of current scheduling pertaining to drugs utilised in	a) Develop a clear understanding of the legal status of MDMA. b) Develop a clear understanding of the legal status of Psilocybin. c) Develop a clear understanding of the legal status of Ketamine. d) Develop a clear understanding of the legal status of ibogaine.

psychedelic assisted psychotherapy within the Australian legal framework.	e) Develop a clear understanding of the legal status of Iboga. f) Develop a clear understanding of the legal status of Ayahuasca. g) Develop a clear understanding of the legal status of DMT. h) Develop a clear understanding of the legal status of Bufotenin. i) Develop a clear understanding of the legal status of LSD. j) Develop a clear understanding of the legal status of Peyote.
e) Appraise current research methodologies and their application to clinical practice.	a) Explore the status of current meta studies investigating outcome research pertaining psychedelic assisted treatment. b) Explore the status of Clinical studies and trials pertaining psychedelic assisted treatment. c) Critical evaluate methodological design in the area of psychedelic assisted treatment.
f) Develop a comprehensive understanding of risk as outlined in the current ethics of state change research.	a) Develop an understanding of the role of screening and exclusion criteria in psychedelic assisted treatment. b) Develop a clear articulation of therapist attributes pertaining to psychedelic assisted treatment: Personal experience of psychedelic experience, sensitivity to non-ordinary experience. c) Develop a clear sense of the role and function of time as pertaining to psychedelic assisted treatment. d) Develop a clear understanding of the ethical issues surrounding suggestion and influence pertaining to psychedelic assisted treatment. e) Develop a clear understanding of the role and ethical boundaries of touch within psychedelic assisted treatment.
g) Apply and develop the CPAT clinical model in a variety of clinical settings	a) Develop a working understanding of the interpersonal neurobiology and theory of mind. b) Develop an effective understanding of the phenomenology of non-ordinary states. c) Display an understanding of pre-cognition, metacognition, mentalisation and organisation of mind as applied to non-ordinary states. d) Display competent basic counselling skills. e) Effectively conduct intake, pre-assessment and screening processes. f) Effectively conduct first and second assessment sessions. g) Competently prepare for the psychedelic treatment. h) Competently conduct the psychedelic treatment session. i) Effectively conduct integration, follow-up and concluding sessions. j) Effectively identify and manage risks, psychological and medical issues that may present before, during or after the treatment.
k) Develop strong clinical approaches to integrating psychedelic experiences with reference to state and stage process and development.	a) Develop an understanding of state as a transitory process containing potential resources for ordinary waking states. b) Develop an understanding of stage as the process of stabilisation of states within the developmental potential of human beings. c) Develop a clear conceptual understanding of the process of integration as the regulation and stablisation of mind. d) Develop a clear set of clinical tools for facilitating integration: artwork, non-directed narrative, somatic work.
l) Develop Increased metacognitive ability as a clinician within the psychedelic assisted psychotherapy context.	a) Employ strong reflective practices of oneself as a clinician in psychedelic assisted treatment. b) Understand the role of supervision in psychedelic assisted treatment. c) Explore and understand individual counter transferential vulnerabilities in psychedelic assisted treatment. d) Understand transferential contents directed towards clinicians as well substances in psychedelic assisted treatment.

D) The volume of learning involved in the CPAT program is significant and in-line with Higher Education standards. The program contains over 113 hours of face-to-face learning, 115 prescribed readings and 37 recommended readings. The prescribed readings alone equate to approximately 230 hours of additional study. This is in line

with, or higher than, most higher education programs. Again, drawing the comparison to the University of Melbourne Masters, which has approximately 52 face to face contact hours.

E) As part of the construction of the CPAT course, a Clinical Guidelines Handbook has been generated. This is a significant piece of the foundation necessary for the training of clinicians involved in the future delivery of psychedelic-assisted therapy. This document will go through an extensive process of improvement and external peer review by the leading experts in the field before publishing. All clinical members of the Mind Medicine Board (https://mindmedicineaustralia.org.au/board/) and members of the Advisory Board will review the clinical guidelines (https://mindmedicineaustralia.org.au/advisory-board/). This constitutes more than 48 external clinicians and academics.

F) Mind Medicine Australia and its Academic team have been developing gold standard protocols based on the existing and emerging research on the best clinical best practice internationally and the Australian professional landscape. These clinical protocols are an essential part of the training program and are an extension of well documented clinical approaches, for example those developed by MAPS in the U.S., which have produced sound clinical evidence for the efficacy of these substances.

   Mind Medicine Australia has worked closely with the Emyria clinical network around the development of clinical protocols for the treatment of treatment resistant PTSD, Anxiety and Depression. Emyria's clinical expertise has informed and will continue to inform the clinical practices and training protocols used in the CPAT program.

G) The accreditation process in Australia is rigorous and sometimes lengthy. MMA has developed the CPAT program with movement towards accreditation in mind. The pilot course, currently being delivered, will form the academic foundation of an application for accreditation.

   - Phase 1 will involve an application for recognition as professional development with the RANZCP, RACGP and other relevant peak bodies. This will be submitted in the second half of 2021.
   - Phase 2 will involve accreditation of the subjects within CPAT through partnership with an Australian University. Discussions have already commenced. Recognition is anticipated to be completed for University-partnered delivery in 2022.
   - Phase 3 will involve the likely formal accreditation of a Graduate Certificate of Psychedelic-Assisted Therapy. The likely timeframe for this is 2022-2023.

   These accreditation timeframes and trajectory will be influenced by the Scheduling processes currently in consideration.

H) The CPAT course has a rigorous entrance criteria and process. All applicants must have a minimum Bachelors level qualification and minimum three years of clinical experience. Applicants are then interviewed before being offered a position in the course. It is important to note that the current international clinical protocols suggest that a psychiatrist prescribes the medicines and that two clinicians are involved in the

therapeutic treatment process. Therefore, non-psychiatrists have been able to engage in the learning process, as they will be the "clinician". The current and enrolled student population in the pilot program all meet these inclusion criteria and are roughly in the following groups: 15 Psychiatrists, 28 Psychologists, 15 GP's, 28 Social Workers and other Mental Health Clinicians.

I) An Interim Register of Psychedelic-Assisted Therapists will be convened and moderated by the Mind Medicine Australia Board until such time that it can be administered by an appropriate third-party organisation. It is anticipated that this Register will be transitioned to an independent body. Members of this independent body may come from a variety of organisations, such as the RACGP, AMA, APS, PACFA, AASW, APA, and the fields of public health, addictions, mental health, psychopharmacology, neuropharmacology and law. This body may be modelled on the Oregon Psilocybin Advisory Board (https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/Pages/psilocybin-services-act.aspx) and would ensure unbiased, non-political, clinically driven rigour. This independent body has yet to be formed and its membership will be informed by independent consultation.

   To be a member of this Register professionals will have an appropriate clinical qualification, be a member of a professional body, be a successful graduate from the CPAT qualification, have a minimum of three years of supervised clinical practice, maintain 20 hours of annual continuing professional development, engage in 6 hours of annual supervision, and meet the code of conduct. Further, CPAT students will be required to complete 3 pro-bono supervised psychedelic assisted psychotherapy sessions to ensure clinical skills and facilitate cost-effective sessions for patients. Registrants will have different designations based on whether they are able to prescribe (when legal), lead or support the therapeutic treatment. The Board will review the Register bi-annually and exclude registrants that do not meet or maintain the standards.

   Though not directly part of the CPAT course, but closely related, MMA has developed a suite of Psychological Support Services which provides professional supervision, academic study groups, psychedelic education, integration and mental health assessment and therapeutic support via Medicare and NDIS services. This service has been designed to meet the enormous demand of patients and professionals seeking clinical support and academic leadership in this field.

When considering the field of psychedelic-assisted therapies and the possible rescheduling of psilocybin and MDMA it is important to note the following points. These are outside the remit of the CPAT training detailed above, but nonetheless are realities of the current Australian landscape.

- Psychedelics are already being used illegally. Rescheduling to Schedule 8 neither changes their illicit nature in a recreational setting nor is there any evidence that medical use will increase their illicit use or abuse. Rescheduling of Cannabis has not increased its illicit use to the knowledge of these authors.

- Psychiatrists, doctors, psychologists, psychotherapists and other mental health professionals are already providing treatment services to members of the Australian public that have illegally consumed these drugs. This treatment is commonly referred to as 'integration' treatment and in no way supports the illicit use of these drugs, but it does already require clinicians to demonstrate their clinical ability to respond to the effects of these drugs in a clinical setting.

  Many Australian Psychiatrists, Doctors and Psychologists have a formative understanding of the clinical protocols necessary for psychedelic treatment because these protocols are already well established in other countries, such as the United States. The CPAT training course provides Australian clinicians specific and relevant local training in line with Australian professional ethical and legal standards. Although people share relatively similar physiologies internationally, it is still necessary for effective practice in Australia.

If Australian mental health professionals do not try to develop new and innovative clinical approaches to treating mental health, the Australian population is going to continue to get the disappointing results we are already getting, and the majority of patients will not get well.

Unless we focus on developing effective and safe treatments that can lead to remissions in the majority of patients, we will inevitably experience a worsening health and wellbeing landscape and the enormous associated social and economic costs. This will result in increasing reliance on long-term use of anxiolytics, antidepressants and antipsychotics that lead to significant side effects, irreversible brain changes and enormous suffering. It is our responsibility to responsibly and carefully, with due diligence, expand the repertoire of treatment options available to our frontline mental health professionals before many more lives are lost.

Sincerely on behalf the CPAT Academic Team

Dr. Alana Roy

Brad Seaman ……

Melissa Warner

Nigel Denning

Dr. Tra-ill Dowie

26th of February 2021.

Attachment 1: Certificate in Psychedelic-Assisted Therapies Faculty

Dr Gabby Agin-Liebes (USA)

PhD

Gabby Agin-Liebes, PhD is a clinical psychologist with 10 years of experience working as a therapist and investigator on academic trials with psilocybin-assisted therapy at New York University, Yale and UC San Francisco (UCSF). Her research has applied quantitative and qualitative methodologies within psilocybin-assisted and mindful self-compassion-based interventions to treat substance use and trauma-based disorders. She is currently a National Institutes of Health-funded research fellow at UCSF studying novel interventions for treating opioid addiction and chronic pain that target dysregulated emotion regulation and attentional bias processes. She is the lead author on a paper published earlier this year, and featured in several news outlets, which found that psilocybin-therapy led to sustained clinical remission from depression and anxiety in individuals with cancer up to 4.5 years later.

Dr Wade Davis CM (Canada)

PhD

Wade Davis is a writer and photographer whose work has taken him from the Amazon to Tibet, Africa to Australia, Polynesia to the Arctic. Explorer-in-Residence at the National Geographic Society from 2000 to 2013, he is currently Professor of Anthropology and the BC Leadership Chair in Cultures and Ecosystems at Risk at the University of British Columbia.

Wade has authored 22 books, including *One River, The Wayfinders* and *Into the Silence*, he holds degrees in anthropology and biology and received his Ph.D. in ethnobotany, all from Harvard University. In 2016, he was made a Member of the Order of Canada. In 2018 he became an Honorary Citizen of Colombia.

Dr Rick Doblin (USA)

BSc, PhD

Rick Doblin, Ph.D., is the founder and executive director of the Multidisciplinary Association for Psychedelic Studies (MAPS). He received his doctorate in Public Policy from Harvard's Kennedy School of Government, where he wrote his dissertation on the regulation of the medical uses of psychedelics and marijuana and his Master's thesis on a survey of oncologists about smoked marijuana vs. the oral THC pill in nausea control for cancer patients. His undergraduate thesis at New College of Florida was a 25-year follow-up to the classic Good Friday Experiment, which evaluated the potential of psychedelic drugs to catalyze religious experiences. He also conducted a thirty-four year follow-up study to Timothy Leary's Concord Prison Experiment.

Rick studied with Dr Stanislav Grof and was among the first to be certified as a Holotropic Breathwork practitioner. His professional goal is to help develop legal contexts for the beneficial uses of

psychedelics and marijuana, primarily as prescription medicines but also for personal growth for otherwise healthy people, and eventually to become a legally licensed psychedelic therapist. He founded MAPS in 1986, and currently resides in Boston with his wife and empty rooms from three children who are all in college or recently graduated.

Dr James Fadiman (USA
BA, PhD

James Fadiman B.A. (Harvard) M.A., Ph.D. (Stanford) began his personal psychedelic research a few weeks before starting his graduate work at Stanford where he did his dissertation on the effectiveness of LSD-assisted therapy. During the research lull of 40 years, he has held a variety of teaching (San Francisco State, Brandeis, and Stanford) consulting, training, counseling and editorial positions. He has taught in psychology departments, design engineering, and for three decades, at the Institute of Transpersonal Psychology (now Sofia University) that he co-founded.

He has published textbooks, professional books, a self-help book, a novel, and a series of videos, *Drugs: the children are choosing* for National Public Television. His books have been published in 8 languages. He has been the subject of a one-hour documentary released by Page3 Films, featured in a National Geographic documentary and had three solo shows of his nature photography.

He had his own consulting firm and sat on two non-profit boards as well as having been the president of several small natural resource companies. He has been involved in researching psychedelic for spiritual, therapeutic and creative uses and is known for his pioneering work on microdosing. He has published *The Psychedelic Explorer's Guide: Safe, Therapeutic, and Sacred Journeys*, and most recently, *Your Symphony of Selves: Discover and Understand More of Who You Are.*

Dr Albert Garcia-Romeu (USA)
PhD

Albert Garcia-Romeu, Ph.D. is a member of the Psychiatry and Behavioral Sciences faculty at the Johns Hopkins University School of Medicine and a Guest Researcher at the National Institute on Drug Abuse Intramural Research Program. His research examines the effects of psychedelics in humans, with a focus on psilocybin as an aid in the treatment of addiction. He received his doctorate in Psychology in 2012 from the Institute of Transpersonal Psychology in Palo Alto, CA, where he studied self-transcendence and meditation, and their relationship to mental health. His current research interests include clinical applications of psychedelics, mindfulness, and altered states of consciousness and their underlying psychological mechanisms. He additionally studies real-world drug use patterns and impacts on public health, and the role of spirituality in mental health and addiction. He is a founding member of the Johns Hopkins Center for Psychedelic and Consciousness Research and the International Society for Research on Psychedelics.

Dr Ingmar Gorman (USA)
PhD

Dr Ingmar Gorman is the co-founder of Fluence, a psychedelic education company training mental health providers in psychedelic treatments. He is a psychologist specializing in helping people who use psychedelics and other psychoactive compounds. He received his clinical training at the New School for Social Research, Mount Sinai Beth Israel Hospital, Columbia University, and Bellevue Hospital. He completed his NIH postdoctoral fellowship at New York University in 2017. Dr Gorman was formerly the Director of the Psychedelic Education and Continuing Care Program, formerly site co-principal investigator and current active therapist on a Phase 3 clinical trial of MDMA-assisted Psychotherapy for Post-Traumatic Stress Disorder and active therapist on a Phase 2 clinical trial of Psilocybin-assisted Psychotherapy for Treatment Resistant Depression.

Dr Mendel Kaelen (UK)
PhD

Mendel Kaelen is the founder and CEO of Wavepaths. Prior to this, he worked as a PhD and postdoctoral neuroscientist at Imperial College London for 7 years, where his research was the first to demonstrate music's central role in psychedelic therapies. He developed methods and protocols for the use of music to enhance therapy outcomes and out of this, the vision for Wavepaths. He is a thought leader on the therapeutic use of music and publishes and speaks frequently on this topic. He has been featured in Nature News, San Francisco Chronicles, Vice Motherboard, Rolling Stone and TEDx. Mendel's work is driven heavily by his personal work with psychedelic medicines and psychotherapies that started 15 years ago. He lives and works in London (UK), and in his spare time likes to get into nature, and to get out of his mind with his Shakuhachi and modular synthesiser.

Dr Gabor Maté CM (Canada)
BA, MD, Doctor of Laws (honoris causa)

Gabor Maté is a retired physician who, after 20 years of family practice and palliative care experience, worked for over a decade in Vancouver's Downtown East Side with patients challenged by drug addiction and mental illness. The bestselling author of four books published in twenty-five languages, Gabor is an internationally renowned speaker highly sought after for his expertise on addiction, trauma, childhood development, and the relationship of stress and illness.

His book on addiction received the Hubert Evans Prize for literary non-fiction. For his ground-breaking medical work and writing he has been awarded the Order of Canada, his country's highest civilian distinction, and the Civic Merit Award from his hometown, Vancouver. His books include *In the Realm of Hungry Ghosts: Close Encounters With Addiction; When the Body Says No; The Cost of Hidden Stress;*

Scattered Minds: The Origins and Healing of Attention Deficit Disorder; and (with Gordon Neufeld) *Hold on to Your Kids: Why Parents Need to Matter More Than Peers.* www.drgabormate.com.

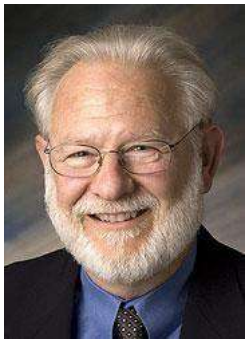
Friederike Meckel (Switzerland)

MD

Friederike Meckel trained as a medical doctor and a medical psychotherapist in Germany. From 1989-1991 she trained as a Holotropic Breathwork© facilitator with Prof. Stanislav Grof in the US. Friederike began to realize the additional therapeutical benefits of psychoactive substances through her own experiences. She happened to have the extraordinary good fortune to join a psychotherapeutic training group which instructed therapists in the use of psycholytic psychotherapy with MDMA and LSD in the early nineties in Switzerland. She also trained as a couple's therapist, a family therapist and a family-constellation-worker. In 1994, she started working in her own private psychotherapeutic practice providing non-drug psychotherapy, Holotropic Breathwork©-groups and systemic-family-constellation work. Over a couple of years, she started developing her specific way of psychotherapy with the use of psychedelics, working underground, in groups, with specifically chosen clients. She speaks about her work in conferences and interviews.

Dr David E. Nichols (USA)

BSc, PhD



David E. Nichols PhD is an Adjunct Professor of Chemical Biology and Medicinal Chemistry at the University of North Carolina, Chapel Hill. Previously he held the Robert C. and Charlotte P. Anderson Distinguished Chair in Pharmacology and was a Distinguished Professor of Medicinal Chemistry and Molecular Pharmacology at the Purdue University College of Pharmacy. He received his B.S. degree in chemistry from the University of Cincinnati in 1969, and the PhD in Medicinal Chemistry from the University of Iowa in 1973, following which he did postdoctoral work in pharmacology at the University of Iowa, College of Medicine. In 2004 he was named the Irwin H. Page Lecturer by the International Society for Serotonin Research and in 2006 he received the first Provost's Outstanding Graduate Mentor award from Purdue University. He has published more than 300 scientific articles, most of which deal with the relationship between molecular structure and biological action.

Professor David Nutt (UK)

BA, MB BChir, MRCP, MA, DM, MRC Psych, FRCPsych, FMedSci, FRCP, FSB

Renowned researcher, policy advisor and author, Professor David Nutt, is currently Head of Neuropsychopharmacology at Imperial College London. Under the leadership of Professor Nutt, the Psychedelic Research Group at Imperial College is one of the world's foremost psychedelic research laboratories, publishing landmark research on psychedelic therapies and neuroimaging studies of the psychedelic state.

Professor Nutt has also held many leadership positions in both UK and European academic, scientific and clinical organisations, including presidencies of: the European Brain Council, the British Neuroscience Association, the British Association of Psychopharmacology, the European College of Neuropsychopharmacology.

He was previously Chair of the UK Advisory Council on the Misuse of Drugs.

Dr Nikola Ognyenovits

M.D., FRACGP, FACRRM, FACHAM (RACP)

Dr Nikola Ognyenovits is a Hungarian born Australian Addiction Medicine Specialist Physician living in Brisbane, Australia. He works in public alcohol and drug services and in private practice. After graduating as M.D. in 1987, he trained and worked in psychiatry, rural general practice, emergency medicine and aero-medical retrievals.

He was introduced to non-ordinary states of consciousness through Holotropic Breathwork and had the privilege of learning from Stanislav Grof and Tav Sparks. Dr Nikola has co-facilitated numerous breathwork sessions, trained with the Foundation of Shamanic Studies and participated in shamanic healing traditions globally.

After training in Ketamine Assisted Psychotherapy with The Ketamine Training Center, he has incorporated ketamine treatment into his private practice. He sees great potential in the application of ibogaine for addictions and has supported clients pre and post treatment. Dr Nikola is an advocate of the ethical and controlled use of psychedelic-assisted psychotherapies in the treatment of addictions and associated mental health conditions.

Dr William (Bill) Richards (USA)

PhD

William A. Richards (Bill), a psychologist in the Center for Psychedelic and Consciousness Research at the Johns Hopkins School of Medicine, has been implementing research studies with psilocybin since 1999.

His graduate degrees include M.Div. (Yale), S.T.M. (Andover-Newton) and Ph.D. (Catholic University). He also studied with Abraham Maslow at Brandeis University and with Hanscarl Leuner at Georg-August University in Göttingen, Germany, where his involvement with psilocybin research originated in 1963. From 1967 to 1977, he implemented projects of psychotherapy research with LSD, DPT, MDA and psilocybin at the Maryland Psychiatric Research Center, including protocols designed to investigate the promise of psychedelics in the treatment of alcoholism, depression, narcotic addiction and the psychological distress associated with terminal cancer, and also their use in the training of religious and mental-health professionals. His book, Sacred Knowledge: Psychedelics and Religious Experiences has been released by Columbia University Press.

Dr Arne Rubinstein

MBBS, FRACGP

Dr Arne Rubinstein is an internationally recognised expert on Rites of Passage. His trainings and programs have been attended by over 200,000 people in more than 20 countries around the world and are now a part of over 50 schools around Australia. Dr Arne is a medical doctor and specialised first in Family Medicine and then spent 15 years in Emergency Medicine until he moved full time creating Rites of Passage globally.

He is the author of the best-seller *The Making of Men* and has won multiple awards for his work including being nominated in 2008 for Australian of the Year for his groundbreaking work. He has worked in Europe, The USA, Bhutan, Israel, Indonesia and supported the re-introduction of Rites of Passage for the Butchulla Aboriginal mob in Queensland. He is passionate about Rites of Passage becoming mainstream once again. Dr Arne is the proud father of two wonderful young men and a mentor to many others.

Dr Ben Sessa (UK)

MBBS, B.SC, MRC PSYCH

Ben Sessa is a consultant child and adolescent psychiatrist who has worked with young people and adults in the field of addictions and trauma-related psychiatry for over 20 years. For the last 15 years Ben has been at the forefront of psychedelic research in the UK through his affiliations with Bristol University and Imperial College London, under the auspices of Professor David Nutt. He has taken part as a study doctor and as a healthy subject both receiving and / or administering MDMA, psilocybin, LSD, DMT and ketamine in multiple UK research studies. He runs one of the first UK-based medical cannabis prescribing clinics.

Ben is the Chief Medical Officer at AWAKN Life Sciences, a new start-up company opening Europe's first psychedelic medical clinic, which will be providing psychedelic therapies, therapist training courses and conducting independent research. Ben is the co-founder and former president of Europe's largest psychedelic conference, Breaking Convention.

With a background in digital art, programming and performance art, Melissa brings a creative and future-focused outlook to her pursuits. Melissa is currently a post-graduate student at The University of Melbourne on the path towards clinical psychology and is creating therapeutic virtual reality programs to support psychedelic-assisted therapy and enhanced wellbeing.

Dr Jeremy Weate (Canada)

PhD

Jeremy Weate has a PhD in Philosophy from the University of Warwick. He has over 17 years strategic advisory experience, focused on minister-level guidance on the mining sector across over 50 projects in over 30 countries in Europe, Africa, Central Asia and the South Pacific. Jeremy also has a decade-long interest in the medicalization of ibogaine. In 2018, he helped set up Tabula Rasa Retreat in Portugal, now of the leading ibogaine treatment facilities globally. He has organised ibogaine conferences in Vienna, Porto and London. He is CEO of the Vancouver-based Universal Ibogaine, which will IPO on the Toronto Stock Exchange later this year. Universal Ibogaine will take ibogaine through clinical trials in Canada, with a view to multi-country phase 3 trials in Canada, Australia, New Zealand and Israel. The company will launch holistically minded psychedelic-assisted therapy clinics in North America and subsequently globally this decade under the ClearSky Recovery brand.

Dr John Webber

MBBS, DPM, FRANZCP

Raised and educated in Melbourne, Australia, Dr John Webber completed his medical degree at Melbourne University and his intern years at the Royal Melbourne Hospital. Initially drawn to a surgical path, he was eventually drawn by his heart and life circumstances to a career in psychiatry. His first years of psychiatric training were at the Royal Melbourne Hospital psychiatry department, and his training later included a year at the Melbourne Neuropsychiatry Centre. Dr Webber completed his specialist qualification through the Royal Australia and New Zealand College of Psychiatrists and has since worked in a successful private practice for over 30 years. His areas of interest include bipolar disorder, depressive disorders, hypnosis, and anxiety disorders, as well as mentoring young psychiatrists.

Attachment 2a: Subject Outline (Draft)

Foundations of Psychedelic Assisted Therapy

Core Subject, Level 100
Subject Code

Introduction

This subject sets out the historical and intellectual foundations of psychedelic assisted therapy. This subject seeks to take an inter-disciplinary stance for conceptualising psychedelic psychotherapy. In addition, this subject will outline issue's pertaining to legal and political factors that are central to psychedelic assisted therapy. Critically this subject outlines the mind medicine Australia's clinical model which will be foundational for subsequent course material and clinical applications.

Administrative Details

Award Course:	Master of Counselling and Psychotherapy
Level:	Level 100
Type:	Core Subject
Subject Code:	
Weighting:	6 Credit Points
Duration:	One trimester
Pre-Requisites:	
Co-Requisites:	

Unit Contacts

Role	Staff	Name	Contact Details
Unit Coordination	Head of Faculty		
	Education Support		
Lecturers	Adelaide Campus		
	Melbourne Campus		
	Sydney Campus		

Student Workload

Timetabled Hours:	3	hours per week
Notional Personal Hours:	9	hours per week
Total Workload Hours:	12	hours per week

Delivery Mode

- ☑ face to face onsite
- ☑ blended learning
- ☐ work integrated learning
- ☐ full-time
- ☐ part-time

Academic Details

Student Learning Outcomes

At the successful completion of this subject, students will be able to:

a) Develop clear knowledge pertaining to the history and context of psychedelic psychotherapy

b) Develop a sound understanding of the CPAT rationale of psychedelic assisted Psychotherapy.

c) Develop a clear working knowledge of current scheduling pertaining to drugs utilised in psychedelic assisted psychotherapy within the Australian legal framework .

d) Develop Increased metacognitive ability as a clinician within the psychedelic assisted psychotherapy context.

Assessment Tasks

A description of each assessment task for this subject is provided in the table below. Students should refer to the assessment briefs for more details on task requirements and the assessment (marking) criteria.

To pass this subject, students must attempt all assessment tasks and achieve an overall pass of 50% or more.

Assessment Task	Assessed	Weighting	Learning Outcomes
Assessment 1 **Presentation** Work in small groups to produce a 30 min podcast presentation on the clinical use of a psychedelic substance these should be assigned in week one of the course through discussion with lecturer. Students to follow Ikon podcast process and procedures working in small groups to produce their presentation presentations are delivered from week 4 til 12. Each group is required to facilitate a 20 min conversation in class on the their presentation the week after it was been published.	Weeks 4-12	20%	a,c, d

Grading is allocated as 10% for presentation and 10% for student lead discussion. Non presenting students involvement and engagement is reflected in class participation and class participation grade at the end of semester. Students will be advised of the date of presentation during Week 1.			
Assessment 2 **Annotated Bibliography** Students are required to engage with 10-20 academic resources that they will use for their written essay. Students must write a summary of each reference critically evaluating the source, validity and the argumentation of the piece. This should then finish with a brief evaluation of the utility of the piece for the major essay. References should follow APA 7 style guide. Each entry should be between 150-300 words not including the reference. Length: 3000 words.	Week 7	20%	a, b, c, d,

Assessment Task	Assessed	Weighting	Learning Outcomes
Assessment 3 **Written Assessment** Essay questions: "What are the dangers of applying a psychedelic assisted therapy model? Discuss with reference to the history and current research pertaining to psychedelic therapy". "Psychedelics are not mind altering substances rather they are value altering. Discuss in relation to psychedelic assisted therapy" "Different states mean different worlds. Discuss in relation to psychedelic assisted therapy" "Hypothesize a treatment approach for a dis-identified patient who you believe would be well suited to psychedelic assisted therapy. Include a full formulation and case history. Pay particular attention to matters of risk and safety".	Week 12	50%	a, b, c, d,

Assessment 4 **Journal** 15 minutes of class time will be provided each lesson for the writing of reflective journal. The lecturer may provide set questions to reflect on, or you will be asked to consider and reflect upon what you have learned in the class. Students and expected to demonstrate active engagement with weekly content through discussion and reflective journaling. The journaling may follow lecturer provided questions or be student lead. Students are expected to reflect on podcast presentations, lecture content and class discussion as well as readings and personal experience. Students are required to write approximately 500 words per week in their journal, students will not be punished for making longer entries. A journal summary should be the last entry reflecting on the subject and the learning process as a whole.	Week 12	10%	a, b, c, d,

Subject Structure & Lecture Plan

Session	Topic	Assessment Activity
1	**Origins of Psychedelic Assisted Therapy: Pre history and History** a) Develop a clear understanding of the role of psychedelics in human evolution b) Develop a clear historical contextualisation of early psychedelic psychotherapy begin with the work of Hoffman and proceeding through to the works Grof, Metzner, Leary, Ram Das, Huxley, Fradiman, Shulgin c) Contextualise the re-emergence of psychedelic assisted psychotherapy through the development of MAPS in the united states and the development of mind medicine Australia ***Prescribed Reading:*** Sean J. Belouin and Jack E. Henningfield (2018) Psychedelics: Where are we now, why we got here, what we must do. Neuropharacology. 142 7-19 Carhart-Harris, R. L., & Goodwin, G. M. (2017). The therapeutic potential of psychedelic drugs: past, present, and future. *Neuropsychopharmacology*, *42*(11), 2105-2113. ***Recommended Reading:*** Stevens, J. (1987). *Storming heaven: LSD and the American dream*. Grove Press.	

2	**Conceptual Foundations of Psychedelic Therapy** a) Develop a clear understanding of the role of state and stage as pertaining to organisation of mind. b) Develop a clear knowledge of the psycho-biological model of consciousness c) Develop a meta-perspective on the role of perceptual disruption and redefinitions of personal ontologies and epistemologies in psychedelic experiences. ***Prescribed Reading:*** Locke, R. G., & Kelly, E. F. (1985). A preliminary model for the cross-cultural analysis of altered states of consciousness. *Ethos*, *13*(1), 3-55. Gellhorn, E., & Kiely, W. F. (1972). Mystical states of consciousness: neurophysiological and clinical aspects. *Journal of nervous and mental disease*. Swanson, L. R. (2018). Unifying theories of psychedelic drug effects. *Frontiers in pharmacology*, *9*, 172. Hofstadter, D. (2007). *I Am a Strange Loop*. Basic Books. Chapter 1. Doblin, R., & Burge, B. (Eds.). (2014). *Manifesting minds: A review of psychedelics in science, medicine, sex, and spirituality*. North Atlantic Books. ***Recommended Reading:*** James, W. (1892). The stream of consciousness. *Psychology*.	

Session	Topic	Assessment Activity
3	**Politics of State Based Knowledge** a) Critically conceptualise the political and cultural landscape leading to the rise and fall of psychedelics. b) Critically explore psychedelics as value altering substances and therefore inherently political c) Critically explore the professional implications of therapeutic treatment in the context of the politicisation states and psychedelics ***Prescribed Reading:***	

	Noorani, T. (2020). Making psychedelics into medicines: The politics and paradoxes of medicalization. *Journal of Psychedelic Studies*, *4*(1), 34-39. Byock, I. (2018). Taking psychedelics seriously. *Journal of palliative medicine*, *21*(4), 417-421. Shortall, S. (2014). Psychedelic drugs and the problem of experience. *Past & Present*, *222*(suppl_9), 187-206. ***Recommended Reading:*** Leary, T. (2009). *Turn on, tune in, drop out*. Ronin Publishing.	
4	**Shamans, Healings, Journeys and Modern Practice** a) Develop a meta-perspective on shamanism as a template for state dependent treatment b) Articulate ethno-medicine contributions to healing practice through the use of psychoactive substances. c) Explore traditional concepts of rites of passage and initiation for their contributions for PAT. ***Prescribed Reading:*** Evgenia Fotiou (2019) The role of Indigenous knowledges in psychedelic science. Journal of Psychedelic Studies 4(1) 16, 23 Roberts, T. B., & Winkelman, M. J. (2013). Experiences, Therapies, and Their Implications for Transpersonal Psychology. *The Wiley-Blackwell handbook of transpersonal psychology*, 459. Metzner, R. (1998). Hallucinogenic drugs and plants in psychotherapy and shamanism. *Journal of psychoactive drugs*, *30*(4), 333-341. Levi-Strauss, C. (1965). Structural Anthropology. London: Chapter X:'The effectiveness of symbols' Bell, Catherine, (1997). Ritual: Perspectives and Dimensions.Oxford, UK: OUP Chapters 1-3 Campbell, Joseph. Myths to Live By.Chapters X and XI Feinsten, D., and Krippner, S. (1988). Personal Mythology: The Psychology of Your Evolving Self. Los Angeles: Tarcher. Chapters 1 and 2 ***Recommended Reading:*** . Hillman, James. 1997. Suicide and the Soul.NY: Harper and Row. Chapter VIII	

5	**Psychedelic Assisted Therapy and the Law** a) Develop a clear understanding of the legal status of MDMA b) Develop a clear understanding of the legal status of Psilocybin. c) Develop a clear understanding of the legal status of Ketamine. d) Develop a clear understanding of the legal status of ibogaine e) Develop a clear understanding of the legal status of Iboga. f) Develop a clear understanding of the legal status of ayahuasca g) Develop a clear understanding of the legal status of DMT h) Develop a clear understanding of the legal status of Bufotenin. i) Develop a clear understanding of the legal status of LSD. j) Develop a clear understanding of the legal status of Peyote ***Prescribed Reading:*** Marks, M. (2018). Psychedelic Medicine for Mental Illness and Substance Use Disorders: Overcoming Social and Legal Obstacles. *NYUJ Legis. & Pub. Pol'y*, *21*, 69. Haden, M., Emerson, B., & Tupper, K. W. (2016). A public-health-based vision for the management and regulation of psychedelics. *Journal of Psychoactive Drugs*, *48*(4), 243-252. Bright, S., & Williams, M. (2018). Should Australian psychology consider enhancing psychotherapeutic interventions with psychedelic drugs? A call for research. *Australian Psychologist*, *53*(6), 467-476. Aday JS, Bloesch EK, Davoli CC. 2019: A year of expansion in psychedelic research, industry, and deregulation. *Drug Science, Policy and Law*. January 2020. Wallis, N. (2017). Submission to the Victorian inquiry into drug law reform. Mind medicine Psychedelic Medicine Scheduling document. ***Recommended Reading:*** Mind medicine Psychedelic Medicine Scheduling document.	

Session	Topic	Assessment Activity
6	**Mind medicine Australia's Psychedelic Assisted Therapy Clinical Model of Practice.**	

	a) Critically review the Grofian approach to psychedelic assisted therapy b) Critically Review MAPS protocols for psychedelic assisted therapy c) Develop an integrated understanding of the MMA clinical model ***Prescribed Reading:*** Sessa, B. (2014). Why psychiatry needs psychedelics and psychedelics need psychiatry. *Journal of psychoactive drugs*, *46*(1), 57-62. Franz X. Vollenwelder and Katrin H. Preller (2020) Psychedelic Drugs: neurobiology and potential for treatment of psychiatric disorders. Nature David E. Nichols (2016) Psychedelics. Pharmacological Review 68 264-355 ***Recommended Reading:*** Michael Winkelman and Ben Sessa (eds) (2018) Advances in Psychedelic Medicine: State of the Art Therapeutic Applications. Greenwood. Santa Barbara, California.	
7	**Understanding Pharmacology in Psychedelic assisted therapy** a) Critically explore the pharmacokinetics of MDMA and Psilocybin. b) Critically explore the pharmacodynamics of MDMA and Psilocybin. c) Critically explore issue of dosage and usage of MDMA, and Psilocybin. d) Critically explore Risks and Safety of MDMA and Psilocybin. e) Critically explore Potential Role in Medicine of MDMA, and Psilocybin. ***Prescribed Reading:*** Nichols, D. E., Johnson, M. W., & Nichols, C. D. (2017). Psychedelics as medicines: an emerging new paradigm. *Clinical Pharmacology & Therapeutics*, *101*(2), 209-219. dos Santos, R. G., & Hallak, J. E. C. (2020). Therapeutic use of serotoninergic hallucinogens: A review of the evidence and of the biological and psychological mechanisms. *Neuroscience & Biobehavioral Reviews*, *108*, 423-434. Papaseit, E., Torrens, M., Pérez-Mañá, C., Muga, R., & Farré, M. (2018). Key interindividual determinants in MDMA pharmacodynamics. *Expert Opinion on Drug Metabolism & Toxicology*, *14*(2), 183-195.	

	Passie, T., Seifert, J., Schneider, U., & Emrich, H. M. (2002). The pharmacology of psilocybin. *Addiction biology*, *7*(4), 357-364. Tylš, F., Páleníček, T., & Horáček, J. (2014). Psilocybin–summary of knowledge and new perspectives. *European Neuropsychopharmacology*, *24*(3), 342-356. ***Recommended Reading:*** Spinella, M. (2001). *The psychopharmacology of herbal medicine: plant drugs that alter mind, brain, and behavior*. MIT Press. chapter 9	
8	**Understanding Pharmacology in Psychedelic assisted therapy** a) Critically explore the pharmacokinetics of Ketamine, ibogaine, b) Critically explore the pharmacodynamics of Ketamine, ibogaine c) Critically explore issue of dosage and usage of Ketamine, ibogaine. d) Critically explore Risks and Safety of Ketamine, ibogaine, e) Critically explore Potential Role in Medicine of Ketamine, ibogaine f) Critically explore Potential Role in Medicine Ketamine, ibogaine. ***Prescribed Reading:*** Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., ... & Wolfson, P. (2019). Ketamine assisted psychotherapy (KAP): Patient demographics, clinical data and outcomes in three large practices administering ketamine with psychotherapy. *Journal of psychoactive drugs*, *51*(2), 189-198. Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., ... & Gould, T. D. (2018). Ketamine and ketamine metabolite pharmacology: insights into therapeutic mechanisms. *Pharmacological Reviews*, *70*(3), 621-660. Shapiro, B. (2018). Ibogaine: History, Pharmacology, Spirituality, & Clinical Data. *Integrative Addiction and Recovery*, 447. ***Recommended Reading:*** Brown, T. K., Noller, G. E., & Denenberg, J. O. (2019). Ibogaine and Subjective Experience: Transformative States and Psychopharmacotherapy in the Treatment of Opioid Use Disorder. *Journal of psychoactive drugs*, *51*(2), 155-165.	

Session	Topic	Assessment Activity
9	**Understanding Pharmacology in Psychedelic Assisted therapy** a) Critically explore the pharmacokinetics of ayahuasca, DMT, Bufotenin, LSD, Peyote b) Critically explore the pharmacodynamics of ayahuasca, DMT, Bufotenin, LSD, Peyote c) Critically explore issue of dosage and usage of ayahuasca, DMT, Bufotenin, LSD, Peyote d) Critically explore Risks and Safety of ayahuasca, DMT, Bufotenin, LSD, Peyote e) Critically explore Potential Role in Medicine of ayahuasca, DMT, Bufotenin, LSD, Peyote ***Prescribed Reading:*** Liechti, M. E. (2017). Modern clinical research on LSD. *Neuropsychopharmacology*, *42*(11), 2114-2127. Hamill, J., Hallak, J., Dursun, S. M., & Baker, G. (2019). Ayahuasca: psychological and physiologic effects, pharmacology and potential uses in addiction and mental illness. *Current neuropharmacology*, *17*(2), 108-128. Barker, S. A. (2018). N, N-Dimethyltryptamine (DMT), an endogenous hallucinogen: Past, present, and future research to determine its role and function. *Frontiers in neuroscience*, *12*, 536. ***Recommended Reading:*** Dinis-Oliveira, R. J., Pereira, C. L., & da Silva, D. D. (2019). Pharmacokinetic and pharmacodynamic aspects of peyote and mescaline: clinical and forensic repercussions. *Current molecular pharmacology*, *12*(3), 184-194.	
10	**Oraganised and Optimised Minds** a) Context state dependant knowledge b) Explore topics such flow states, peak experiences, mediative states, metacognition, STER with case examples. c) Explore how the Brain effects optimised minds. d) Explore how motility and embodiment connects to organisation of mind e) What do optimised minds reveal about the concept of organisation or coherence of mind.	

	Prescribed Reading: Chapter two in Steven Kotler, Jamie Wheal - Stealing Fire_ How Silicon Valley, the Navy SEALs, and Maverick Scientists Are Revolutionizing the Way We Live and Work-Dey Street Books (2017) Swann, C., Keegan, R. J., Piggott, D., & Crust, L. (2012). A systematic review of the experience, occurrence, and controllability of flow states in elite sport. *Psychology of Sport and Exercise*, *13*(6), 807-819. Sinnett, S., Jäger, J., Singer, S. M., & Philippe, R. A. (2020). Flow States and Associated Changes in Spatial and Temporal Processing. *Frontiers in Psychology*, *11*. Lambert, J., & Csikszentmihalyi, M. (2020). Facilitating or foiling flow: the role of momentary perceptions of feedback. *The Journal of Positive Psychology*, *15*(2), 208-219. Daniel P. Brown (author), Robert A.F. Thurman (foreword) - Pointing Out the Great Way_ The Stages of Meditation in the Mahāmudrā Tradition-Wisdom Publications (2006) Chapter 15 Mihaly Csikszentmihalyi (auth.) - Flow and the Foundations of Positive Psychology_ The Collected Works of Mihaly Csikszentmihalyi-Springer Netherlands (2014) chapter 14 Mihaly Csikszentmihalyi (auth.) - Flow and the Foundations of Positive Psychology_ The Collected Works of Mihaly Csikszentmihalyi-Springer Netherlands (2014) Joëlle Proust - The Philosophy of Metacognition_ Mental Agency and Self-Awareness-Oxford University Press (2014) Michael J. Beran, Johannes Brandl, Josef Perner, Joelle Proust - Foundations of Metacognition-Oxford University Press (2012) vol_16_no_1_churchill_and_murray_integrating_adult_developmental_and_metacognitive_theory ***Recommended Reading:*** Csikszentmihalyi, M. (2020). *Finding flow: The psychology of engagement with everyday life*. Hachette UK.	
11	**Integration and Metacognition** a) Understand the role of metacognition in psychedelic assisted treatment b) Identify and explore personal experiences that require integration	

	c) Apply clinical skills to facilitate the integration of disintegrated experiences d) Explore and develop skills required for integration and metacognitive improvement. e) Develop a sound grasp of how current metacognitive focused approaches to treatment relevant to psychedelic assisted therapy ***Prescribed Reading:*** Chapter 1 in Dimaggio, G., Montano, A., Popolo, R., & Salvatore, G. (2015). *Metacognitive Interpersonal Therapy for Personality Disorders: A treatment manual* (1st edition). Routledge. Carcione , A. , Semerari , A. , Nicolò , G. , Pedone , R. , Popolo , R. , Conti , L. , Fiore , D. , Procacci , M. and Dimaggio , G. (2011) 'Metacognitive mastery dysfunctions in personality disorder psychotherapy' , Psychiatry Research , 190 : 60 – 71 . ***Recommended Reading:*** Bateman, A., & Fonagy, P. (2013). Mentalization-based treatment. *Psychoanalytic inquiry*, *33*(6), 595-613.	
12	**The Phenomenology of other worlds** a) Demonstrate a strong grasp of non inference based approaches to state based experience. b) Explore key coded descriptions of qualities associated with state change and psychedelic experiences: 1.Grof peri natal matrices 2.Grof spiritual emergency 3.John Weir Perry c) Explore key phenomenological qualities of state based experience: 1.meaning 2.integration 3.Boundry states 4.Psychic flexibility 5.Agency 6. Life world formation I. Spatiality and Motility II. Vectors of experience III. Time IV. organisational Rationalities V. Ontologies	

	VI. Transcendence ***Prescribed Reading:*** Perry, J. W. (1953). The self in psychotic process; its symbolization in schizophrenia. Grof, C., & Grof, S. (2017). Spiritual emergency: The understanding and treatment of transpersonal crises. *International Journal of Transpersonal Studies*, *36*(2), 5. Grof, S. (2003). Implications of modern consciousness research for psychology: Holotropic experiences and their healing and heuristic potential. *The Humanistic Psychologist*, *31*(2-3), 50-85. Szabo, A., Horvath, L., & Szummer, C. (2014). Phenomenology and altered states of consciousness: A new framework for analysis. *Psychologia Hungarica Caroliensis*, *2*(2), 7-29. ***Recommended Reading:*** Masters, R. E., & Houston, J. (1966). *The varieties of psychedelic experience* (Vol. 9289). New York: Holt, Rinehart and Winston.	

Attachment 2b: Subject Outline (Draft)

Psychedelic Assisted Therapy in Practice

Core Subject, Level 100
Subject Code

Introduction
This subject explores the key clinical skills required for working in psychedelic assisted therapy. This subject draws together key factors such as pre substance sessions, substance sessions and post substance sessions and integration. This subject explores best practice standards for psychedelic assisted therapy. This subject further integrates these standards with applications for traumatic, non-responsive, addictions and end of life presentations.

Administrative Details

Award Course:	Master of Counselling and Psychotherapy
Level:	Level 100
Type:	Core Subject
Subject Code:	
Weighting:	6 Credit Points
Duration:	One trimester
Pre-Requisites:	
Co-Requisites:	

Unit Contacts

Role	Staff	Name	Contact Details
Unit Coordination	Head of Faculty		
	Education Support		
Lecturers			

Student Workload

Timetabled Hours:	3	hours per week
Notional Personal Hours:	9	hours per week
Total Workload Hours:	12	hours per week

Delivery Mode

- ☑ face to face onsite
- ☑ blended learning
- ☐ work integrated learning
- ☐ full-time
- ☐ part-time

Academic Details

Student Learning Outcomes

At the successful completion of this subject, students will be able to:

e) Develop a strong working knowledge of key factors in clinical application of psychedelic psychotherapy including: Assessment, formulation and treatment planning with a key focus on contraindications and risk.

f) Appraise current research methodologies and their application to clinical practice.

g) Develop a comprehensive understanding of risk as outlined in the current ethics of state change research.

h) Apply and develop the CPAT clinical model in a variety of clinical settings

i) Develop strong clinical approaches to integrating psychedelic experiences with reference to state and stage process and development.

j) Develop Increased metacognitive ability as a clinician within the psychedelic assisted psychotherapy context.

Assessment Tasks

A description of each assessment task for this subject is provided in the table below. Students should refer to the assessment briefs for more details on task requirements and the assessment (marking) criteria.

To pass this subject, students must attempt all assessment tasks and achieve an overall pass of 50% or more.

Assessment Task	Assessed	Weighting	Learning Outcomes
Assessment 1 **Altered States Experience** Under take an altered states session as part of the certificate of psychedelic assisted therapy.	Weeks 4-12	20%	a, c, d, e, f

Assessment 2 **Personal Reflection** Part A Write up a first personal reflection on the experiences of the session. Part B Reflect on the clinical insights gained from the first person experience and how these insight may effect your clinical work conducting psychedelic assisted therapy Length: 3000 words.	Week 7	20%	a, b, c, d, e

Assessment Task	**Assessed**	**Weighting**	**Learning Outcomes**
Assessment 3 **Written Assessment** Develop a clinical practice model document based on the mind Medicine Australia Clinical model which is adopted for your unique clinical setting. Word length: 5,000 words	Week 12	50%	a, b, c, d, e, f
Assessment 4 **Journal** 15 minutes of class time will be provided each lesson for the writing of reflective journal. The lecturer may provide set questions to reflect on, or you will be asked to consider and reflect upon what you have learned in the class. Students and expected to demonstrate active engagement with weekly content through discussion and reflective journaling. The journaling may follow lecturer provided questions or be student lead. Students are expected to reflect on podcast presentations, lecture content and class discussion as well as readings and personal experience. Students are required to write approximately 500 words per week in their journal, students will not be punished for making longer entries. A journal summary should be the last entry reflecting on the subject and the learning process as a whole.	Week 12	10%	a, b, c, d,e,f

Subject Structure & Lecture Plan

Session	**Topic**	**Assessment Activity**

1	**Clinical Applications of Psychedelic Therapy: Introduction** d) Develop a clear understanding of the Mind Medicine Australia's clinical treatment model. e) Demonstrate the ability to conceptualise and formulate clearly following the MMA treatment model f) Develop a clear articulation of therapist attributes pertaining psychedelic assisted treatment g) Demonstrate the ability to develop a therapeutic alliance in the context of psychedelic assisted therapy. h) Contextualise related clinical models of practice such as sensory motor processing, somatic experiencing and holotrophic breath work ***Prescribed Reading:*** Nutt, D., Erritzoe, D., & Carhart-Harris, R. (2020). Psychedelic Psychiatry's Brave New World. *Cell*, *181*(1), 24-28. Tingying Chi, Jessica A. Gold. (2020). A review of emerging therapeutic potential of psychedelic drugs in the treatment of psychiatric illness. Journal of the Neurological Sciences 411 116715 Jason B. Luoma, Christina Chwyl, Geoff J. Bathje, Alan K. Davis & Rafaele Lancelotta. (2020) Meta-Analysis of Placebo Controlled Trials of Psychedelic Assisted Therapy. Journal of Psychoactive Drugs, 52:4, 289-299, DOI: 10.1080/02791072.2020.1769878 Susan W. Wheeler and Natalie L. Dyer (2020) A Systematic Review od Psychedelic-Assisted Psychotherapy for Mental Health: An Evaluation of the Current Wave of Research and Suggestions for the Future. Psychology of Consciousness: Theory, Research and Practice. 7:3 pp 279-315 ***Recommended Reading:*** Michael Polan How to Change Your Mind: What te New Science of Psychedelcs Teaches Us About Consciousness, Dying, Addiction, Depression and Transcendence Albert Hoffman LSD: My Problem Child	
2	**Risk and Assessment** a) Problematise the issue of risk and risk assessment in psychedelic assisted therapy. b) Develop an understanding of the role of screening, assessment and exclusion criteria in psychedelic assisted treatment. c) Explore critical incidence and emergency in psychedelic assisted therapy d) Assess Prerequisites and Contraindications for conducting	

	psychedelic assisted therapy ***Prescribed Reading:*** Mw Johnson 1, Wa Richards, Rr Griffiths (2008) Human hallucinogen research: guidelines for safety. Journal of Psychopharmacology Aug; 22(6):603-20. doi: 10.1177/0269881108093587. Epub 2008 Jul 1. Romeu et al., Clinical Applications of hallucinogens: a review. Exp Clin Psychopharmacology, 2016; 24(4): 229=268 Peter Gasser, et al. (2014). Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. Journal of Nervous and Mental Disease. 2014 Jul; 202(7): 513–520. PMCID: PMC4086777, PMID: 24594678 Vizeli,P., & Liechti, M.E. (2017). Safety Pharmacology of acute MDMA administration in healthy subjects. Journal of Psychopharmacology, 31(5), 576-588 Smith, E. D. (1988). Evolving ethics in psychedelic drug taking. *Journal of Drug Issues*, *18*(2), 201-214. ***Recommended Reading:*** Halpern, J & Pope, H. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug and Alcohol Dependence, 2003; 69(2): 109-119	

Session	Topic	Assessment Activity
3	**The Set & Setting:** a) Develop a clear understanding of the critical factors effecting mind set in psychedelic therapy. b) Develop a clear understanding of the physical setting requirements for psychedelic psychotherapy: space, bedding, music etc. c) Develop a clear understanding of the physical safety requirements in the administration of psychedelic assisted therapy (ie. Cardiac support services) d) Demonstrate the ability to conduct preparatory sessions for psychedelic assisted therapy ***Prescribed Reading:***	

	Janis Phelps (2017) Developing Guidelines and Competencies for the Training of Psychedelic Therapists. Journal of Humanistic Psychology. 1-38 Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D., Watts, R., Branchi, I., & Kaelen, M. (2018). Psychedelics and the essential importance of context. *Journal of Psychopharmacology*, *32*(7), 725-731. Hartogsohn, I. (2017). Constructing drug effects: A history of set and setting. *Drug Science, Policy and Law*, *3*, 2050324516683325. ***Recommended Reading:*** Eisner, B. (1997). Set, setting, and matrix. *Journal of Psychoactive Drugs*, *29*(2), 213-216.	
4	**Supporting Transpersonal Experience** a) Develop a clear articulation of the variety of transpersonal experiences that are prevalent in psychedelic assisted therapy session. b) Demonstrate the ability to exercise skills in stabilisation and regulation as required within a psychedelic assisted therapy session c) Develop the clinical skills required for the non-specific qualities of non-interference and presence. d) Develop the ability to articulate personal and parallel experiences as a clinician as they may occur in psychedelic assisted therapy sessions ***Prescribed Reading:*** Albert Garcia-Romeu, Roland Griffiths and Matthew W. Johnson (2014) Psilocybin-Occasioned Mystical Experiences in the Treatment of Tobacco Addiction. Current Drug Abuse Reviews, 7, 157-164 Roland R. Griffiths et al. (2018) Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive change in psychological functioning and in trait measures of prosocial attitudes and behaviours. Journal of Psychopharmacology 32(1) 49-69 Sessa, Ben, Laurie Higbed, and David Nutt. A review of 3,4-methylenedioxymethamphetamine (MDMA0-assisted psychotherapy. Frontiers in Psychiatry 10 (2019): 138 ***Recommended Reading:*** . James, W. (1985). *The varieties of religious experience* (Vol. 15). Harvard University Press.	

5	**Experience and Altered States: Preparing for Psychedelic Assisted Therapy** a) Demonstrate the ability to run pre-substance sessions b) Develop a clear understanding of the role and function of teams in a clinical setting when conducting psychedelic assisted therapy c) Develop a clear understanding of the therapist's role in psychedelic assisted psychotherapy d) Understand the role and use of touch in accordance patient collaboration e) Understand the role of music in PAT f) Understand the effects of substance ingestion with regard to timing and clinical practice. g) Facilitate affect, sensate and memory processing in an active psychedelic assisted therapy session ***Prescribed Reading:*** Phelps, J. (2017). Developing guidelines and competencies for the training of psychedelic therapists. *Journal of Humanistic Psychology*, *57*(5), 450-487. Danforth, A. (2009). Focusing-oriented psychotherapy as a supplement to preparation for psychedelic therapy. Journal of Transpersonal Psychology, 41, 151-160. Cooper, K. (2014). Guide manual for pharmacokinetics of psilocybin in healthy adult volunteers study (Unpublished manuscript). University of Wisconsin, Madison. Frederick S. Barrett et al. (2017) Qualitative and Quantitative Features of Music Reported to Support Peak Mystical Experiences during Psychedelic Therapy Sessions. Frontiers in Psychology 25 July 2017 Bonny, H. L., Pahnke, W. N. (1972). The use of music in psychedelic (LSD) psychotherapy. Journal of Music Therapy, 9, 64-87 ***Recommended Reading:*** Mendel Kaelen et al. (2017) The hidden therapist: evidence for a central role for music in psychedelic therapy. Pschopharmacology	
Session	**Topic**	**Assessment Activity**

6	**Experience and Altered States: Conducting Psychedelic Assisted Therapy** a) Demonstrate the ability to recognize and attend to both underlying psychological processes and the experience produced by the medicine. b) Demonstrate the ability to respond to obstructions and blockages in the psychedelic assisted therapy session c) Demonstrate the ability to conclude a psychedelic assisted therapy session in a safe and appropriate manner d) Demonstrate the ability to work with post session experiences such as Dreams, STUG's or other such process's. e) Demonstrate the ability to assess safety post session f) Demonstrate the ability to conduct integration focused sessions and developed integration focused homework **Prescribed Reading:** Blewett, D. B., & Chwelos, N. (2002). *Handbook for the therapeutic use of lysergic acid diethylamide-25: individual and group procedures*. Multidisciplinary Association for Psychedelic Studies. Dahlberg, C. C. (1967). LSD facilitation of psychoanalytic treatment: A case study in depth. In Abramson, H. (Ed.), The use of LSD in psychotherapy and alcoholism (pp. 237-257). Indianapolis, IN: Bobbs-Merrill. Fadiman, J. (2011). The psychedelic explorer's guide: Safe, therapeutic and sacred journeys. Rochester, VT: Park Street Press. ***Recommended Reading:*** Bravo, G., & Grob, C. (1989). Shamans, sacraments, and psychiatrists. *Journal of psychoactive drugs*, *21*(1), 123-128.	
7	**Experience and Altered States: Integrating Psychedelic Assisted Therapy** a) Demonstrate the ability to sit in a non-interfering manner with an active altered state experience. b) Demonstrate the ability to debrief and apply supervision to psychedelic assisted therapy c) Develop a clear grasp of the role of art therapy and other expressive therapies in psychedelic assisted therapy. d) Demonstrate the ability to integrate other treatment approaches with psychedelic assisted therapy	

	e) Demonstrate the use of mentalisation skills in post psychedelic integration sessions ***Prescribed Reading:*** Chapter 19 Fadiman, J. (2011). The psychedelic explorer's guide: Safe, therapeutic and sacred journeys. Rochester, VT: Park Street Press. Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., Brenneisen, R. (2014). Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. Journal of Nervous and Mental Disease, 202, 513-520 Greer, G., Tolbert, R. (1998). A method of conducting therapeutic sessions with MDMA. Journal of Psychoactive Drugs, 30, 371-379. Metzner, R. (2015). Allies for awakening: Guidelines for productive and safe experiences with entheogens. Berkeley, CA: Regent Press. ***Recommended Reading:*** Rogers, C. (1961). On becoming a person. Boston, MA: Houghton Mifflin.	
8	**Trauma and Psychedelic Assisted Therapy** a) Critically analyse and integrate into practice psychedelic assisted therapy for treating trauma. b) Assess presentations of trauma using a phasic model of trauma treatment. c) Develop a clear understanding how trauma affects procedural memory and the body as this factors pertain to psychedelic assisted therapy. d) Consolidate and synthesise theoretical concepts of psychedelic assisted therapy in order to respond in a safe and sensitive manner to a range trauma experiences. e) Analyse and evaluate the ethical and professional development issues relevant to clinical practice with trauma in psychedelic assisted therapy. ***Prescribed Reading:*** Anees Bahji et al. (2020) Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. Progress in Neuropharmacology & Biological Psychiatry. 96 109735	

	Sascha B. Thal and Miriam J.J. Lommen (2018) Current perspectives on MDMA-assisted Psychotherapy for Posttraumatic Stress Disorder. Journal of Contemporary Psychotherapy (2018) 48 99-108 Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Doblin, R. (2013). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. Journal of Psychopharmacology, 27, 28-39 ***Recommended Reading:*** Van der Kolk, B. A. (1994). The body keeps the score: Memory and the evolving psychobiology of posttraumatic stress. *Harvard review of psychiatry*, *1*(5), 253-265.	

Session	Topic	Assessment Activity
9	**Addiction, Substance Abuse and Psychedelic Assisted Therapy** a) Critically review current approaches to PAT for AOD treatment b) Understand the requirements for safety when conducting PAT for AOD c) Review formulation and rationale for PAT with AOD including transtheoretical and states of change processes d) Have a clear understanding of the intake, induction, treatment and integration for PAT for AOD ***Prescribed Reading:*** Michael P. Bogenshutz and Jessica M. Pommy (2012) Therapeutic mechanisms of classic hallucinogens in the treatment of addictions: from indirect evidence to testable hypotheses. Drug Testing and Analysis. Wiley, July 2012 Teri S. Krebs and Pal-Orjan Johansen (2012) Lycergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomised control trials. Journal of Psychopharmacology. 26, 994 Albert Garcia-Romeu et al. (2019) Cessation and Reduction in alcohol consumption and misuse after psychedelic use. Journal of Psychpharmacology 1-14 Johnson M., et al. Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug and Alcohol Abuse. 2017; 43(1):55-60 ***Recommended Reading:***	

	Maté, G. (2010). In the realm of the hungry ghosts. Berkeley, CA: North Atlantic.	
10	**End of Life and Psychedelic Assisted therapy** a) Understand the unique position of end of life (EOL) processes in PAT b) Explore existential issues that may present at end of life as part of case formaulation and treatment planning c) Understand treatment process and rationale in EOL d) Establishing safety in EOL treatment e) Therapist care in EOL work ***Prescribed Reading:*** Clinical Memorandum Therapeutic use of psychedelic substances May 2020 RANZP Griffiths, R., et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomised double-blind trial. Journal of Psychopharmacology 2016; 30; 1181-1197 Gasser, P., et al., LSD-assisted psychotherapy for anxiety associated with a life threatening disease: a qualitative study of acute and sustained subjective effects. Journal of Psychopharmacology. 2015; 29(1); 57-68 ***Recommended Reading:*** Bossis, A. (2014). Psilocybin and mystical experience: Implications for the alleviation of existential and psycho-spiritual distress at end of life. In Ellens, J. H. (Ed.), Seeking the sacred with psychoactive substances (Vol. 2, pp. 251-284).	
11	**Treating Other Conditions with PAT** a) Critically review other treatment programs currently researched for treating conditions such as depression, anxiety, OCD b) Critically analyse the conceptualisation process involved in assessing treatment for presenting problems c) Critically demonstrate the factors addressing safety in using PAT for alternate clinical presentations d) Demonstrate the clinical application of the themes of Integration and organisation of mind for state change in PAT setting interventions in clinical presentation in PAT	

	e) Articulate the limitations in working with PAT ***Prescribed Reading:*** D.E.Nichols, M.W.Johnson and C.D.Nichols. (2017) Psychedelics as Medicines: An Emergng New Paradigm. Clinical Pharmacology and Therapeutics Volume 1, Number 2 R.L.Carhart-Harris et al. (2017) Psilocybin with psychological support for treatment-resistant depression: six month follow up. Psychopharamacology (2018) 235 399-408 Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Schmidt, B. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. Journal of Psychopharmacology, 30, 1165-1180 ***Recommended Reading:*** Zarate, C., Singh, J., Carlson, P., Brutsche, N., Ameli, R., Luckenbaugh, D., Manji, H. (2006). A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Archives of General Psychiatry, 63, 856-864	
12	**Case Conceptualisation and Treatment Planning in PAT** a) Analyse and evaluate the implementation of a comprehensive case conceptualisation framework as applied to PAT b) Consolidate, synthesise and engage appropriate theoretical and practice paradigms, relative to specific clinical issues in PAT c) Demonstrate the ability to present a clinical case using an integrated PAT case formulation ***Prescribed Reading:*** Smith, G. C. (2014). Revisiting formulation: Part 1. The tasks of formulation: Their rationale and philosophic basis. *Australasian Psychiatry*, *22*(1), 23-27. Smith, G. C. (2014). Revisiting formulation: part 2. The task of addressing the concept of the unique individual. Remediating problems with formulation. *Australasian Psychiatry*, *22*(1), 28-31. Greenway, K. T., Garel, N., Jerome, L., & Feduccia, A. A. (2020). Integrating psychotherapy and psychopharmacology: psychedelic-assisted psychotherapy and other combined treatments. *Expert Review of Clinical Pharmacology*, 1-15.	

	Recommended Reading: Sim, K., Gwee, K. P., & Bateman, A. (2005). Case formulation in psychotherapy: Revitalizing its usefulness as a clinical tool. *Academic Psychiatry*, *29*(3), 289-292.	

MIND MEDICINE
AUSTRALIA

Appendix J

Letter from Emyria Ltd setting out the work that they are doing in developing the Protocols, Standard Operating Procedures, Training Manuals and Data Collection Systems to support MDMA assisted psychotherapy treatments.

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

February 2021

Dear Sir/Madam,

Emyria supports the TGA's requirement for a high level of clinical evidence to maintain patient safety. However, having observed the intense global research led on MDMA and psilocybin assisted therapies by highly-respected institutions like Imperial College, Mount Sinai, Johns Hopkins, Yale and other key universities in North America and Europe, we believe that there is sufficient safety data and enough promising efficacy data to allow for the listing of these substances on Schedule 8 of the Poisons Standard for use as part of therapy in medically controlled environments.

Emyria's clinical services subsidiary, Emerald Clinics, deals with patients with complex diseases – a large portion of which also have unmet mental health challenges, irrespective of their primary diagnosis. We therefore recognise firsthand the need for alternative mental health treatment options for these patients and others like them. We've also demonstrated through our intensive, evidence-generating clinical model, that we can provide these patients with safe access to novel treatments while also generating robust and ethically-sourced Real World Data (RWD) that can be used as Real World Evidence (RWE) to improve the development of these treatments.

RWD are the data relating to patient health status and/or the delivery of health care routinely collected from electronic health records (EHRs), claims and billing activities, product and disease registries, patient-generated data and data gathered from other sources e.g. mobile devices. RWE is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWE can be generated by different study designs or analyses, including but not limited to, randomised trials, including large simple trials, pragmatic trials, and observational studies. [1] RWE can help address some shortcomings with traditional clinical trials as it can improve care, is more generalisable to "real patients", and can ultimately accelerate both drug registration and care model evaluation. It's for these reasons and more that RWE is becoming increasingly interesting to regulators – so much so that 2020 saw 75 percent of FDA-approved NDAs and BLAs include an RWE study, up from 49 percent in 2019. [2]

Since late 2018, Emerald Clinics, has cared for over 3,500 patients receiving pharmaceutical-grade cannabinoid-based medicines (CBMs) for a wide range of medical indications where standard-of-care was either not effective or not suitable. All CBMs are prescribed via the TGA's Special Access Scheme Part B (SAS-B) or by an Authorised Prescriber. During care, each consenting patient is monitored carefully using validated clinical assessments and patient-reported outcome measures, and all data is captured into clinical-trial grade data management systems. We are currently analysing this RWE and using it to inform drug development programs with the goal of obtaining registration, thereby dramatically accelerating traditional clinical drug development timelines.

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[1] Real-World Evidence, US Food & Drug Administration, 30/11/2020.
[2] The role of real-world evidence in FDA approvals, Aetion, 2020

emyria

We present our Emerald Clinics model of evidence-generating care as an exemplar for how unregistered treatments can be made available to patients with unmet medical needs, safely and under appropriate clinical supervision, while simultaneously contributing knowledge to support our understanding of what new treatments work best, for whom, and when. Our ultimate goal is still to support formal drug registration with the TGA, however the model has allowed us to provide benefit to patients outside of rigid, exclusive and expensive clinical trial apparatus.

Recently, we've been working with Mind Medicine Australia to develop such an evidence-generating care model for MDMA and psilocybin. The model comprises:

- Controlled documents:
    - An observational study protocol modelled off active Phase 3 and Phase 2b clinical trials and incorporating an evidence-based schedule of assessments
    - Detailed schedule of licensed and validated assessments covering clinical and patient-reported outcomes as well as health economic outcomes
    - Training manuals and Standard Operating Procedures covering all clinical interventions
    - Data governance framework to provide a structured approach to reducing risk associated with handling personal health information, and to ensure compliance with all laws and regulations with respect to data.
- Appropriately credentialled clinicians to ensure patient safety at all times, including:
    - Clinical specialists including psychiatrists and GPs to assist with patient screening, review and safety, as well as protocol input as required
    - GCP-trained clinicians to maintain data integrity
    - CPAT-trained therapists including licensed psychologists and social workers to ensure a standardised, consistent experience and help maintain duty of care.
- Additional aspects:
    - Clinical-trial grade data management system and processes
    - Fit-for-purpose facility with close proximity to psychologists, psychiatrists and physicians.

By following the principles of a learning health system – that is, a cyclical process where data is analysed and learnings fed back into the system to expedite the transfer of new knowledge from discovery into practice – we believe that we can accelerate the evaluation and registration of these treatments.

Yours sincerely,

DocuSigned by:
Michael Winlo
Signer Name: Michael Winlo
Signing Reason: I approve this document
Signing Time: 18-Feb-2021 | 22:44 PST
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Dr Michael Winlo
Managing Director, Emyria Ltd

MIND MEDICINE
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Appendix K

Submission by Human Rights Lawyer, Mr. Scott Leckie, on the Human Rights Issues Associated with the Delegate's Decision.

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

DISPLACEMENT SOLUTIONS

Rue des Cordiers 14, Geneva 1207, Switzerland
8 Dickinson Grove, Mount Martha VIC 3934, Australia
displacementsolutions.org

1 March 2021

Dear Delegate,

I am writing today to encourage you to re-consider your recent interim decision to not reschedule either psilocybin (item 2.4) or MDMA (item 2.5). I am writing on behalf of an international human rights organisation I founded and direct, Displacement Solutions. I am an international human rights lawyer who has worked in more than 80 countries throughout my career and who has taught at several of Australia's leading law schools including the Australian National University, the University of Melbourne and Monash. I have advised and continue to advise numerous United Nations agencies and have written more than 300 books, articles, and major reports.

Among other things relevant to this submission, I have worked extensively in war zones, disaster zones and in many post-conflict settings and met with thousands upon thousands of soldiers and military officers, UN officials and peacekeeping troops and ordinary citizens who have sustained serious post-traumatic stress disorders from their experiences in what can be described as nothing short of horrendous circumstances whether in Bosnia & Herzegovina, Kosovo, Sri Lanka, Timor Leste, the Republic of Georgia, Myanmar and so many other places I have worked and which have all seen and endured so much hardship.

Similarly, through my decades of global travel and work I have met with additional thousands of people on all continents (with the exception of Antarctica) who have directly experienced both the effects of psilocybin and/or MDMA, quite literally none of whom that I have spoken with has ever expressed anything other than the utterly profound nature of these experiences, which for many of these people fundamentally changed their lives for the better.

I have very carefully reviewed your interim decisions and while appreciating your arguments and the important responsibilities you have in making your various determinations, believe that another outcome is possible; one that *does* reschedule the substances outlined in items 2.4 and 2.5 from Schedule 9 to Schedule 8 of the Poisons Standard.

If we first focus exclusively on the issue of PTSD combined with the severe growth in mental health disorders, anxiety and other psychological imbalances (which, of course, have gotten far worse since the advent of COVID-19), the evidence is abundant, convincing and crystal clear that the overwhelming majority of those with PTSD - no matter what the cause - can and do benefit in phenomenal ways from the professionally-guided therapeutic use of the two substances we are discussing. This is particularly true given the fact that the currently prescribed medicines for these conditions often do not have the intended or hoped for results, and matched head-to-head with 'alternative' therapies such as psilocybin and/or MDMA in the tests undertaken to date, generally end up second best in this regard. You state in your

interim decision that 'psilocybin, when misused, can cause psychosis', which is a sentiment that could be applied to countless other substances if they too are misused. Given that human beings have been eating mushrooms containing psilocybin for hundreds of human generations - albeit not in controlled therapeutic settings - with little or no evidence of the emergence of psychosis, I would respectfully ask you re-consider this line of argumentation.

Moreover, in section (e) of your interim decision, you state that there is a 'high risk of diversion for misuse'. While there may be some distinction between psilocybin and MDMA in this respect, given that MDMA is manufactured in laboratories and that psilocybin appears ubiquitously in nature all around the world, again I would respectfully ask you re-consider this view given that rescheduling from Schedule 9 to Schedule 8 would have absolutely no impact upon reducing or increasing public access to psilocybin. I believe the same reasoning can be applied to MDMA when considering the highly trained professionals who would be involved in administering these new treatments. The training and protocols associated with the therapeutic use of these substances would go a long way to preventing your concerns of diversion for misuse.

Please recall that current protocols for many medicines used in hospitals, as strict as they are, do not in practice prevent the diversion of these drugs and as a result, highly restricted medicines are freely available for patients in every hospital in the country. Having just spent two of the past five months in hospital, I have witnessed first-hand just how easily drugs with no therapeutic value, but which may dull the pain - especially opiates - are doled out like candy to anyone who is or who claims to be in anguish, with all too scant regard for the possibility of severe addiction and serious health problems as a result of over-use of these very strong drugs. Needless to say, the financial, social, health and other costs of legalising alcohol are, as you know, immense and growing. This drug - alcohol - that is promoted so widely in this country in advertising, through sponsorships of sporting teams and companies and is viewed so widely as an acceptable social lubricant, has little or no therapeutic uses associated with it, and yet it is freely available to anyone with enough money to pay for it.

As a country which can be extremely proud of its public health care system and the access this ensures for everyone, to allow the widespread promotion of the use of alcohol, to hand out opiates in hospitals almost as if they were lollies and then to continue to ban the therapeutic use of both psilocybin or MDMA, both of which have proven track records of curing serious PTSD and other mental problems affecting quite literally millions of Australians simply does not make sense.

To prohibit the guided use of psilocybin and/or MDMA, but particularly psilocybin that grows naturally without human assistance or intervention just about everywhere, has only the net result of effectively denying Australians an important part of their human right to the highest attainable level of health, as articulated in countless international treaties that have been ratified by the Commonwealth. To cite but one example, the International Covenant on Economic, Social and Cultural Rights, which Australia ratified in 1975, in Article 12 provides for rights to "the enjoyment of the highest attainable standard of physical and mental health". These and other international legal norms, which are binding on Australia, cannot be simply ignored or wished away by sole reference to the UN Convention on Psychotropic Substances to which you refer in your interim decisions.

In effect, therefore, denying access to controlled use in therapeutic settings by trained professionals for patients suffering from PTSD and other mental diseases, when these therapies are known to have an exceptionally high and risk-free success rate, undermines any effort to ensure that all Australians are able to enjoy the *highest attainable standard* of physical and mental health. To deny these substances in these settings to anyone, but in particular the brave men and women in our armed forces who could benefit so greatly from them, is unnecessarily cruel when anyone who looks knows that PTSD can virtually always be helped by the professionally guided usage of them. Heroic soldiers and everyone else in this country with PTSD or other mental health challenges should have access to any and all medicines that exist and are proven to work on whatever disorder or illness they have, including both psilocybin and MDMA.

As you surely know, a growing group of countries and jurisdictions within countries have de-criminalised and/or legalised the use of psilocybin, including for use in therapeutic settings, most recently the state of Oregon in the United States. Even a quick glance at a Wikipedia site on the legal status of psilocybin[1] shows clearly that were you to allow the rescheduling from Schedule 9 to 8, the country would be far from alone in this regard. Rescheduling would place Australia in a category of nations that took the view that if the medicine to assist is there, we will allow access to it.

Given your important responsibilities, in the interests of giving relief to countless millions of people who could potentially benefit from the therapeutic and guided use of both psilocybin and MDMA, I very much trust you will reconsider your initial interim findings.

Australia will be a better country if everyone throughout the country were truly able to achieve the highest attainable level of physical and mental health through the regulated access to therapies with a proven ability to assist where other treatments have not.

Thank you very much for considering my submission and the hundreds of others that have been presented supporting rescheduling. It is difficult to imagine how much unnecessary human suffering can be prevented or resolved through ensuring access to forms of medicine that clearly work but which are now unavailable to people, in particular members of the armed forces, and who could benefit so much from them.

Sincerely yours,

Scott Leckie
Director and Founder

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[1] https://en.wikipedia.org/wiki/Legal_status_of_psilocybin_mushrooms

MIND MEDICINE AUSTRALIA

Appendix L

Ethical Statement by Dr Simon Longstaff, the Executive Director of the Ethics Centre, Sydney.

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

THE ETHICS CENTRE

THE SECRETARIAT **02.03.20**
MEDICINES RESCHEDULING UNIT
THERAPEUTIC GOODS ADMINISTRATION
CANBERRA ACT 2600

TO WHOM IT MAY CONCERN

In making this submission, I should note that I am a Director of Mind Medicine Australia. As such, I acknowledge that I am not a disinterested advocate. That said, I would ask that the arguments made below be judged on their own merit – rather than by reference to their proponent.

It is a commonplace statement of government that it has no higher duty than to keep the people safe. Governments and their agents cite this duty as the justification for all manner of legislative, regulatory and policy initiatives in areas ranging from national security and policing to food safety and of particular relevance here, the control of medicines. Coupled with a concern to oversee the stewardship of public resources and to avoid burdening the public with futile remedies, the TGA is charged with ensuring that all regulated medicines are both safe and efficacious.

While this framework is reasonable and to a large degree justifiable, it is not complete. For example, it would seem perverse for any government to keep its people safe and secure while being indifferent to their welfare, more generally. Indeed, it could be argued that any government that permits otherwise preventable suffering is potentially complicit in the perpetuation of a considerable evil. To suffer in safety – is yet to suffer.

Modern societies are finally coming to understand the extent to which people suffer due to mental illness - such as depression and Post Traumatic Stress Disorder (PTSD). This suffering persists in the significant number of cases where currently available treatments have limited effectiveness. Even when effective, conventional pharmaceuticals risk creating their own forms of ‘practical dependency’ (in that, even where they offer relief, one becomes ‘yoked’ to the prescribed drugs as the cost of maintaining improved health).

The suffering caused by mental illness is especially debilitating because it attacks the underlying self - an illness so profound as to have caused fear and stigma over centuries. It is easy enough for this fear and stigma to transfer to substances that touch these parts of the self - especially if those substances are historically associated with practices that were deemed irrational and superstitious by those who laid the foundations for the European Enlightenment - marked as it is by principles of calculative rationality and the ascendancy of science, mathematics and the like.

LVL 2 LEGION HOUSE
161 CASTLEREAGH ST SYDNEY NSW 2000
SIMON.LONGSTAFF@ETHICS.ORG.AU
T +61 2 8267 5734
WWW.ETHICS.ORG.AU

However, the fact that substances, like psilocybin, might once have been employed in pre-scientific practices (such as shamanism) should not taint our judgement about what can be known of them from the standpoint of modern science and medicine. It might be argued that the scientific evidence for the safety and efficacy of these old/new medicines is not complete. However, when indexed against the suffering that might be relieved, is it sufficient? That is, is there evidence enough to err on the side of compassion - albeit conditioned by prudence.

At least some jurisdictions are answering this question in the affirmative. For example, the Food and Drug Administration (FDA) has recognised that the prospect of alleviating the suffering caused by Post Traumatic Stress Disorder is a sufficient good to mediate concerns about some aspects of the medicinal use of MDMA.

I would submit that this bears the hallmark of wise regulation – where proportionate access to means that, on balance seem likely to reduce suffering without causing undue harm is balanced with a regime of prudent oversight and controls.

The submissions before you do not request that psilocybin and MDMA be made available without restrictions. The request is far more modest; simply that properly trained and qualified clinicians be able to prescribe and administer pharmaceutical grade medicines, in controlled doses, as part of an integrated suite of therapies. The TGA is not being asked that these medicines be unregulated. The request is simply that they lawfully be available for use when clinically indicated.

The unregulated use of opiates can be dangerous. However, we do not ban the clinical use of morphine simply because some people are addicted to heroin. Likewise, that fact that some people take risks with psilocybin and MDMA, outside of a clinical setting, should not prevent the use of these substances within a regulated, clinical setting.

Given all of the above, I would request that you approve the application for re-scheduling, adding whatever qualifications and recommendations you think appropriate. Let the available science be the guide. The possibility of some harm should not count for more than the absolute certainty of deep suffering amongst those denied even the possibility of relief offered by these medicines.

In summary: the alleviation of human suffering cannot always await the attainment of perfect knowledge. The greater the suffering, the greater the requirement to apply a test of sufficiency.

Yours sincerely,

DR SIMON LONGSTAFF AO
EXECUTIVE DIRECTOR

MIND MEDICINE AUSTRALIA

Appendix M

Submission from Professor Arthur Christopoulos (B.Pharm., Ph.D.) to the TGA in relation to its interim decision (Dean, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University)

hello@mindmedicineaustralia.org
www.mindmedicineaustralia.org

Level 1/10 Dorcas St
Southbank Vic 3006
Australia

MONASH University
Pharmacy and Pharmaceutical Sciences

March 3rd, 2021

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear colleagues,

I am a pharmacist, Professor of Analytical Pharmacology and Dean of the Faculty of Pharmacy and Pharmaceutical Sciences, Monash University. Prior to my current appointment, I was a Senior Principal Research Fellow of the National Health and Medical Research Council of Australia. I have nearly 30 years' experience as an international authority in the study of medicinal drug targets, with particular expertise in neuropharmacology and psychiatric drugs. I write with regards to the TGA Delegate's interim decision (dated 3rd Feb, 2021) not to amend the current Poisons Standard for MDMA from Schedule 9 to Schedule 8.

As I indicated in my initial submission, I am supportive of the down-scheduling of MDMA on the basis of a significant body of accumulated, peer-reviewed, literature over many decades – but particularly since the turn of the millennium – indicating that, when used in a *clinical environment* under direct monitoring by a trained clinician, MDMA is safe, non-addictive with a well-established adverse effect profile that can be appropriately managed as part of the clinical context under which the substance would be administered.

In reviewing the reasons given by the Delegate for their interim decision, it is my view that many of the issues raised by the Delegate for denying down-scheduling of MDMA are what one would expect if the application was for the approval of MDMA as a medicine on the Australian Register of Therapeutic Goods (ARTG), but overly stringent if one considers the pharmacology of MDMA in the context of a Schedule 8 substance.

According to the Scheduling Policy Framework relating to Schedule 9 substances, one of the key criteria for this category is that the 'substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use'; in the interim decision, the Delegate agreed that this is the case for MDMA. However, as clearly summarised in Table 1 of the Appendix of the Multidisciplinary Association for Psychedelic Substances (MAPS) Investigator's Brochure (12th edition, 17th August 2020), *there have already been over 70 clinical trials conducted assessing the potential therapeutic efficacy of MDMA* (https://maps.org/research/mdma/mdma-research-timeline/104-other-mdma-resources/5400-mdma-investigator-s-brochure-and-fda-annual-report&Itemid=485), with the majority of these trials finding positive results. Indeed, the two key reviews highlighted by the Delegate in the interim decision, namely Illingworth et al. (2021) and Bahji et al. (2020), also note in their analysis of recent clinical trials that the use of MDMA in conjunction with psychotherapy is associated with a high treatment response rate in PTSD. I agree with the Delegate that the vast majority of the clinical trials to date have been limited in patient number, and there remain a dearth of large, appropriately controlled Phase 2 and 3 trials. Although this indicates that more such trials are required in the context of eventual consideration of MDMA for inclusion on the ARTG as a registered medicine, I respectfully contend that the existing clinical trial and peer-reviewed studies more than satisfy the criterion of 'established therapeutic value' in relation to a listing on the Poisons Standard.

A second major issue that I would like to address relates to the Delegate's concerns about MDMA adverse effects. From my interpretation of the interim decision, there has been a potential blurring

381 Royal Parade, Parkville, VIC 3052, Australia
Phone +61 3 9903 9067; Email arthur.christopoulos@monash.edu
www.monash.edu/pharm/research/areas/drug-discovery/labs/analytical-neuropharmacology/home
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of the expected adverse effects of medicinal MDMA in a clinically supervised setting relative to unsupervised and/or chronic MDMA use. Certainly, the statement that "adverse effects are unknown in the context of psychotherapy" is surprising. As I indicated above, the MAPS Investigator's Brochure summarises the trials conducted to date, and the expected adverse effects are well-known from these trials and other studies. The most common expected adverse effects include acute elevation in blood pressure and heart rate, anxiety and dilated pupils (Mas et al., 1999, J. *Pharmacol. Exp. Ther.*, 290: 136; Cami et al., 2000, *J. Clin. Psychopharmacol.*, 20: 455; Liechti et al., 2001, *Psychopharmacol.*, 154: 161; Harris et al., 2002, *Psychopharmacol.*, 162: 396). The meta-analysis by Bahji et al. (2020, *Prog. Neuropsychopharmacol. Biol. Psych.,* 96: 109735), cited by the Delegate, also found that there were no serious adverse events in four of the five clinical studies they investigated; in the fifth trial where some serious adverse events were identified, it was concluded that the majority of these events were actually not due to MDMA. The severe adverse effects listed by the Delegate, specifically loss of consciousness and seizures, have never been reported (to my knowledge) in a clinical setting; rather, they are associated with the unsupervised, recreational use of MDMA.

Finally, I cannot envisage how medicinal MDMA is likely to present a high risk of misuse or illicit use in the context of clinical administration – which would involve only one, two or three appropriately spaced administrations under the direct supervision of a trained clinician. As highlighted in the important Australian drug harm ranking study by Bonomo et al. (2019, *J. Psychopharmacol.* 33*:* 759), which involved addiction specialists, MDMA is significantly safer than alcohol, opiates (and prescription opioids), cannabis and benzodiazepines (to name a few).

As I alluded to above, it is my opinion that the majority of concerns raised by the Delegate are appropriate in the context of whether there is sufficient data to support MDMA approval as a medicine listed on the ARTG, but the large body of data on the pharmacology of this substance are overwhelmingly consistent with the criteria for a Schedule 8 classification in the Poisons Standard.

Sincerely,

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

381 Royal Parade, Parkville, VIC 3052, Australia
Phone +61 3 9903 9067; Email arthur.christopoulos@monash.edu
www.monash.edu/pharm/research/areas/drug-discovery/labs/analytical-neuropharmacology/home
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