Submission from the Applicant

Opposing

the Interim Decisions

not to amend the Poisons Standard in Relation to the Restricted Medical Use of MDMA and Psilocybine*

24th November 2022

Mind Medicine Australia Limited

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Melbourne VIC 3004

*For ease of understanding we have also followed the less conventional spelling of psilocybine (i.e. with an "e"at the end) which is used by the TGA in the Poisons Standard and which is followed by the Delegate in the Interim Decisions.

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A. Supporting letter from leading Australian- based neuropharmacologists Professor Arthur Christopoulos and Professor Chris Langmead from the Monash University Faculty of Pharmacy and Pharmaceutical Sciences and the Monash Neuromedicines Discovery Centre. Professor Christopoulos is Dean of the Faculty which is ranked number 1 in the World in its field.

B. Supporting Letters from World renowned neuropsychopharmacologist Professor David Nutt who is head of neuropsychopharmacology at Imperial College, London, Chairman of Drug Science and one of the World's leading researchers in psychedelic assisted therapies.

C. Letter from Mrs Bortolin to her local member, Prime Minister Anthony Albanese, about the death by suicide of her husband Franco Bortolin, his treatment resistant mental illness, his failed treatments and her belief that with psychedelic assisted therapy her husband would still be alive today.

D. Letter From Mr Graham Daniels about the immense suffering of his wife, Lianne Daniels, from treatment resistant depression, her large list of failed treatments over decades and Mr Daniels belief that psychedelic assisted therapy would give her a chance to lead a more normal life.

E. Letter From Psychiatrist Dr Stuart Saker on the desperate plight and immense suffering of the ADF Veterans that he treats, the high levels of suicide risk amongst veterans with treatment resistant mental illnesses and the need for access to psychedelic assisted therapies on compassionate grounds.

F. Submission from Dr Simon Longstaff, the Executive Director of the Ethics Centre and Australia's preeminent ethicist on the ethical dimensions of the Delegate's decision.

G. Offer from the Neuromedicines Discovery Centre at Monash University to host an independent clinical treatment registry to collate treatment information from psychiatrists and their patients if the medicines are rescheduled.

H. Goodwin et al (2022) *Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression* The New England Journal of Medicine Vol 387 No 18 pages 1637 - 1648.

I. Mitchell et al (2021) *MDMA-assisted therapy for severe PTSD; a randomised double-blind placebo-controlled phase 3 study* Nature Medicine 27:1025 -1033

J. Email from MAPS dated 14th April 2022 advising on the estimated number of patients in MDMA trials pre and post prohibition.

K. Submission from the Australia Institute and the trauma charity Fearless to the TGA on Diversion Risk dated May 2022.

1. INTRODUCTION

1.1 The Challenge of Making Decisions in the Public Interest

For the reasons given in this submission we respectfully disagree with the Delegate's Interim Decisions. We believe that there is sufficient data to justify moving the medical use of MDMA and Psilocybine to Schedule 8 of the Poisons Standard on the limited basis proposed in our rescheduling applications.

However, before we provide detailed responses to the advice received by the Delegate from the Advisory Committee on Medicines Scheduling ("ACMS") and in relation to the Delegate's own propositions in support of its Interim Decisions, we want to make some preliminary comments about the challenge of making decisions in the public interest.

We know and understand that, in making a decision about rescheduling, the Delegate (and individual members of the ACMS in providing their advice) have an onerous responsibility to examine issues associated with public health. This includes the benefits and risks associated with the medical use of these substances. We also understand that views expressed on whether the key Schedule 8 test of "established therapeutic value" has been satisfied and on what minimum research support and governance controls are appropriate are matters of careful judgement.

We see the challenges involved in forming a judgement clearly demonstrated in the present case. The Delegate (and at least a majority of the members of the ACMS) believes that the "established therapeutic value" requirement for a Schedule 8 listing have not yet been satisfied for either substance when used as part of psychotherapy. In contrast, we have leading world- renowned experts in this field (such as **Professor Arthur Christopoulos and Professor David Nutt – see letters in Appendix A and B) and almost 100% of the psychiatrists and other health professionals in their public submissions (see Section 4 below) clearly expressing their belief that the test of "established therapeutic value" has been satisfied.**

We are also conscious that the formation of views can be complex. They can be based on an analysis of complex data as well as learned experience.

However, views can also be impacted by conscious or unconscious bias and prejudice, concerns about the politics of change, vested interests in the status quo and third -party lobbying. These are issues for each decision-maker to think deeply about.

The question of whether these substances should be rescheduled when used as part of psychotherapy under controlled conditions is not just an academic question. This is because human lives will be deeply impacted by the conclusions reached by the Delegate and the advice given by individual members of the ACMS.

In considering the Final Rescheduling Decisions it's therefore critical that each individual member of the ACMS and the Delegate reflect deeply on the importance of their decisions to so many people in this country. Fortunately, this requirement to think broadly about the consequences of the rescheduling decisions is directly provided for in the governing legislation (Section 52E(1)(a) of the Therapeutic Goods Act) which specifically refers to *"the …benefit of the use of a substance"* and (f) *"any other matter that the Secretary considers necessary to protect public health".*

It is not correct to say (as the TGA has publicly said) that approvals can be obtained to clinically use these therapies under current legislation. Whilst a number of Special Access Scheme approvals have been given by the TGA to medical practitioners to use these treatments for treatment resistant "at risk" patients on compassionate grounds, approvals are not available at the State and Territory levels whilst these substances remain in Schedule 9 of the Poisons Standard. Perversely this means that a medical practitioner and their consenting patient would breach the recreational drug laws of the State or Territory recreational if they sought to utilise these medical treatments.

We therefore ask individual members of the ACMS and the Delegate to pay particular attention to the contextual matters set out in Section 1.2 below.

1.2 Contextual Matters that Should be Taken-into-Account

a. **The Inadequacy of Current Treatments for So Many People Leading to Despair, Immense Suffering and in Some Cases Suicide.**

With Depression it's estimated that about 30% of current sufferers gain no benefit from current treatments (primarily pharmaceuticals and/or psychotherapy). With post-traumatic stress disorder (PTSD) the numbers are even worse with about 70% of sufferers gaining no lasting benefit. For these people ***there is no current medical solution*.**

In some cases, treatments prescribed by psychiatrists and other health practitioners can make the patient's condition worse. **Current treatments are not riskless.**

Take the case of **Franco Bortolin** who committed suicide earlier this year leaving behind a loving wife and a young daughter. Medical attempts to help Mr Bortolin led to him being prescribed in the last 3 years of his life 19 different antidepressants and other psychiatric medications, 24 treatments with transcranial stimulation (commonly referred to as TMS) and an incredible 94 sessions with electro-convulsive therapy (ECT) where an electric current is passed through a person's brain. According to his wife, **Mrs Vanessa Bortolin**, the net result of these failed treatments was increasing despair and worsening cognitive capabilities. Suicide was Mr Bortolini's way out.

The obvious point to make here is that there are no trials supporting the extent of medication given to Mr Bortolini or the large number of ECT treatments that he was given. The psychiatrists involved were simply exercising their professional judgement.

We would urge the Delegate and members of the ACMS to directly hear from Mrs Bortolin in the following video message where she explains why she took the time to write to her local member, **Prime Minister Anthony Albanese**, about her husband's suicide – see https://youtu.be/bVpgA1z1G54. In the video **Mrs Bortolin expresses her view that had psychedelic assisted therapy been available for treatment resistant patients on compassionate grounds through our medical system her husband Franco would still be alive today, she would**

still have a loving partner and her daughter would still have a father. Mrs Bortolin's letter to the Prime Minister is also set out in **Appendix C.**

Another similar case is that of physician **Dr Kayvan Walker** who took his life through suicide earlier this year after a struggle with debilitating mental illness. In the second video link attached – see https://youtu.be/46G3tsRAhSs, Kayvan's father, medical practitioner **Dr Brian Walker**, talks about the unbearable grief associated with the suicide of his son. Like Mrs Vanessa Bortolin, Dr Walker is convinced that his son would still be alive today if psychedelic assisted therapy had been available to his son on compassionate grounds through the medical system.

Many of the submissions received by the TGA during the public submissions period (see Section 4) deal with the immense suffering of people with treatment resistant depression and treatment resistant PTSD.

In one case, attached as **Appendix D**, **Mr Graham Daniels** details the immense suffering of his wife **Leanne** from treatment resistant depression. Mr Daniels lists all of the medications and other treatments that his wife has been prescribed over a long period of time but to no avail. As you will see, prior to 2010 Leanne was prescribed 25 different psychiatric medicines. Since 2010 she has received a range of psychiatric treatments including electroconvulsive therapy and ongoing medications and consulted with many different doctors, psychiatrists, psychologists and various other specialists but to no avail.

In his letter Mr Daniels writes that "*I have researched psilocybin [assisted therapy] and it is the obvious next treatment for Leanne. There appears to be a solid foundation of evidence from highly intelligent professionals that this treatment might give Leanne the opportunity she needs to get back to life. Under supervision there appears to be ZERO downside to allowing Leanne to take this treatment. Leanne's fear is that she will never recover and will die a depressed old woman. This would just add to the tragedy of her experience….*"

The examples given above are not isolated examples. Treatment resistant "at risk" patients giving fully informed consent deserve the right, on the advice of their psychiatrist (and with the protections set out in our rescheduling applications including patient specific approvals from two levels of

government) to be able to access these therapies on a restricted basis and by doing so given the chance to heal.

b. The Terrible Mental Health Position of ADF Veterans and First Responders

Rates of treatment resistant mental illnesses are far higher amongst ADF Veterans and First Responders than the already high levels in the general population. Nearly 1 in 2 Veterans suffer from a mental disorder, suicidal ideation is nearly 10 times the general population average, co-morbidity levels are 6 times higher, substance abuse 3 times higher and more veterans are losing their lives through suicide than on the front line. First Responders have suicidal thoughts at twice the rate of the general population and a First Responder commits suicide on average every 6 weeks.

We would draw your attention specifically to the letter from psychiatrist **Dr Stuart Saker** which appeared in our rescheduling applications and is reproduced for convenience in **Appendix E**. In his letter Dr Saker advises the TGA about the very real suicide risks in the veteran community associated with treatment resistant depression and treatment resistant PTSD and his support for the limited rescheduling of these substances on the basis proposed. Dr Saker is ideally qualified to advise in this area as his practice is heavily weighted towards veterans and he himself is a veteran.

Dr Saker closes his letter by saying that *"I would ask you to act with compassion and expedite the rescheduling of these medicines so that I can commence seeking approval at the [NSW] State level as soon as possible. I have been specifically trained in the use of these therapies so I know exactly what is required."*

The current mental health system is failing so many of our ADF Veterans and First Responders because of the inadequacy of current treatments. Why shouldn't these therapies be made available to "at risk" ADF veterans and First Responders on compassionate grounds and under the watchful eyes of their psychiatrists?

c. The Pain and Suffering of Loved Ones.

Treatment resistant mental illness not only effects the lives of sufferers in the most debilitating way, but it also causes immense suffering and hardship to their families. When a sufferer takes his or her own life the pain and suffering of those left behind can last a lifetime.

d. The Adverse Side Effects and Dependence Caused by Current Medications to Treatment Resistant Patients.

Australia is now the second largest user in the World of SSRIs (commonly referred to as antidepressants). More than 1 in 8 adults Australians including 1 in 4 older people and 1 in 30 younger people were on antidepressants before the Covid lockdowns (up by an incredible 95% over 15 years!). Despite these already high figures the take up of antidepressants is much worse today because of the mental stress and despair associated with the covid pandemic (*see the analysis of OECD datasets by Servet Yanatma published in Euronews 16/11/22*)

Whilst antidepressants help some people the effect size is only small to medium, the treatment requires on-going administration, side effects can be nasty and withdrawal can be difficult. This contrasts markedly with the short course of medicine and psychotherapy, lack of dependence and much higher remission rates associated with psychedelic assisted psychotherapy.

The psychedelic assisted therapy model is very different from the current pharmaceutical business model for mental illness, which tends to be based on patients taking daily medications over long periods of time.

Patients with treatment resistant mental illnesses are often encouraged by their medical practitioners to explore a range of treatments in an attempt to alleviate their suffering. As occurred with Mr Franco Bortolin (see above), this can sometimes make their condition much worse. The fault lies not with the medical practitioners involved who are doing their best with often inadequate tools but with the lack of effective treatments for so many people and the lack

of substantive treatment innovation over decades. Outcomes for patients today are no better than they were 50 years ago.

e. The Need for Transparency.

In exercising judgment in a caring society, the human factors referred to above should always be at the forefront. We recognise that this is a heavy responsibility for the Delegate and the individual members of ACMS. One of the great myths that we so often see in the Australian health sector is that change to the status quo carries risk but that doing nothing or delaying progress involves no risk.

Unfortunately, confidence in the rescheduling outcome is made much more challenging for stakeholders in the system because of the opaqueness of the TGA's rescheduling process, the experience base of the ACMS and the TGA's practice of not publicly identifying the decision-maker (who is simply referred to as the "Delegate").

Treating "at risk" patients with treatment resistant mental illnesses and the neuropsychopharmacology involved with psychiatric medicines is a highly specialised area. Yet according to the TGA's website only the Chair of the ACMS has any experience in neuropharmacology and there is a complete absence of psychiatrists on the ACMS. The ACMS must presumably therefore rely on detailed advice from the TGA (or third parties) but that advice isn't made public. A number of the committee members are appointed by individual State and Territory governments and yet we are also not given any access to the instructions or advice that they receive from their appointing government and the basis for that advice or instruction.

The meeting of the ACMS to consider what advice it should give to the Delegate is not open to the public. No recordings of the discussion are made available and we are not told how individual members voted or formed their views.

This is all made worse by the fact that the identity of the Delegate is not made public. We therefore can't form a view on the Delegate's capacity to make a

properly considered judgment. We are also not informed about who the Delegated has consulted with and the advice that the Delegate has received from such consultations.

We also can't appeal the Delegate's decision because under the Therapeutic Goods Act the Delegate's decision is given legislative force.

We are not in any way seeking to impugn the motives of individual members of the ACMS or the Delegate. We are simply making the point that the process is opaque and the influencers on the process and the adequacy of the experience base for making the right decision is unclear. Given the enormity of this decision on the lives of so many Australians (with some treatment resistant patients becoming so desperate that they commit suicide) we don't believe this level of high level of opaqueness should be acceptable in a democratic country.

In contrast we do know the names, qualifications and experience of the recognised leading experts who have supported our rescheduling applications such as **Professor Arthur Christopoulos, Professor Chris Langmead** and **Professor David Nutt**. We also know the names and qualifications of the many psychiatrists, psychologists, researchers and other health practitioners who have overwhelmingly and publicly supported our applications because they have been prepared to identify themselves publicly in their submissions to the TGA (see Section 4 below).

f. <u>Shouldn't This be the Time?</u>

There seems to be broad recognition in the advice of the ACMS and the views of the Delegate in these Interim Decisions that Psilocybine and MDMA can be used safely in controlled medical environments and that the results to date have been promising with large effect sizes shown in a number of trials.

Given:

- **the immense pain and suffering caused by treatment resistant depression and treatment resistant PTSD which can lead to suicidality and suicide for some patients;**
- **the failure (by definition) of current treatments for these patients; and**
- **the advice received from leading experts that the Schedule 8 test of established therapeutic value has been satisfied and the clinical risks involved are minor and clearly outweighed by the public health benefits;**

shouldn't this be the time:

- **to reschedule the medicines as requested; and**
- **for the States and Territories around Australia to implement publicly disclosed policies that make the application of these therapies for "at risk" patients procedurally workable on compassionate grounds?**

Dr Simon Longstaff, the Executive Director of the Ethics Centre and Australia's preeminent ethicist summarises the position in his submission to the TGA dated 8th March 2022 in relation to our rescheduling applications (see **Appendix F**) when he says that:

"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. Or, perhaps, to sharpen the point – there is a prima facie ethical obligation to alleviate avoidable suffering. That obligation can only be set aside in the face of compelling evidence that the means available to relieve suffering would cause more harm than the suffering itself. The current evidence does not support such a conclusion when it comes to the clinical use of MDMA and psilocybin."

2. COVERAGE OF THIS SUBMISSION

As with the Delegate's interim decisions, this submission contains two independent responses in respect of the Delegate's (i) psilocybine interim decision and (ii) MDMA interim decision. Whilst we believe that combining these two decisions in one document is troublesome because each substance has generally been applied to different mental illnesses in the clinical trials to date and the evidence and proposed usage is necessarily different, we acknowledge that there are some common themes, particularly those dealing with the proposed controls.

For ease of reference, we have therefore chosen to adopt the same approach as the Delegate in the interim decisions to assist the Delegate and the members of the ACMS in considering our submission and reaching their Final Decisions.

For ease of understanding we have also followed the less conventional spelling of psilocybine (i.e. with an "e"at the end) which is used by the TGA in the Poisons Standard and which is followed by the Delegate in the Interim Decisions.

3. THE PROPOSED CONTROLS

We note that we are only seeking the rescheduling of psilocybine and MDMA from Schedule 9 to Schedule 8 of the Poisons Standard on a strictly limited basis.

Under our proposals, medical access through rescheduling would only apply where the substance;

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

Two qualified therapists (which could include the treating psychiatrist) will also be with the patient at all times during the medicine dosing sessions (of which there will only be two or three over the course of a three-month period)

Importantly the patient will never be allowed to take the medicines home (unlike many other much more dangerous psychiatric medicines).

The very tight controls and limited use that we are proposing for the rescheduling of psilocybine and MDMA contrasts markedly with the way highly addictive medicines (such as alprazolam, buprenorphine, codeine, dexamfetamine, fentanyl, flunitrazepam, ketamine, oxycodone, morphine and methadone) are prescribed by doctors (in many of the examples given, for home use) under current regulations.

Based on clinical trial protocols used to date the treatment plan will only require two to three sessions with the medicines combined with a short course of psychotherapy. All the evidence from clinical trials shows high levels of safety**. The involvement of 3 psychiatrists in the patient's diagnosis and treatment plan is far more rigorous than what we see in the clinical trial environment where usually only one psychiatrist (at best) is in these activities.**

We would respectfully also submit that the controls proposed have to be viewed in the context of MDMA and psilocybine currently being unregistered medicines. This status therefore involves two further levels of controls if the substances are rescheduled as proposed:

1. the treating psychiatrist will have to obtain the TGA's approval for the treatment on a patient specific basis under the Special Access Scheme (which only applies to treatment resistant patients); and
2. the treating psychiatrist will also have to obtain a permit from the Department of Health in the State or Territory where the treatment is planned to take place on a patient specific basis.

These are incredibly onerous requirements. The additional administrative effort required from Commonwealth, State and Territory Governments is greatly outweighed by the risks to patients (including suicide) of not rescheduling these treatments.

The benefit of rescheduling is that treatment resistant "at risk" patients will (subject to the tight controls detailed above) be able to access these therapies that have been shown to be safe and highly effective when applied as part of psychotherapy in medically controlled environments

As a caring society why would we not give treatment resistant "at risk" patients like Franco Bortolin, Kayvan Walker and Leanne Daniels, with the support of their psychiatrists, access to these therapies under the controlled conditions envisaged? It is truly ironic that a patient with a terminal disease and in physical pain can legally apply for the right to die through a medical intervention (euthanasia) but an "at risk" patient with debilitating depression or PTSD can't legally access these therapies in Australia (in contrast to a number of other western counties) under the highly restrictive conditions proposed.

The other benefit that we proposed in our applications was the use of a registry at Monash University to aggregate real time and real-world evidence of the outcomes of these therapies on a patient specific basis. This would provide all stakeholders in the system with highly relevant and timely information on the real-world application of these therapies and collect data

on any adverse effects and outcomes (including in co-morbid conditions). See the letter from the Neuromedicines Discovery Centre at Monash University attached as **Appendix G** which sets out the preparedness of Monash University to undertake this role.

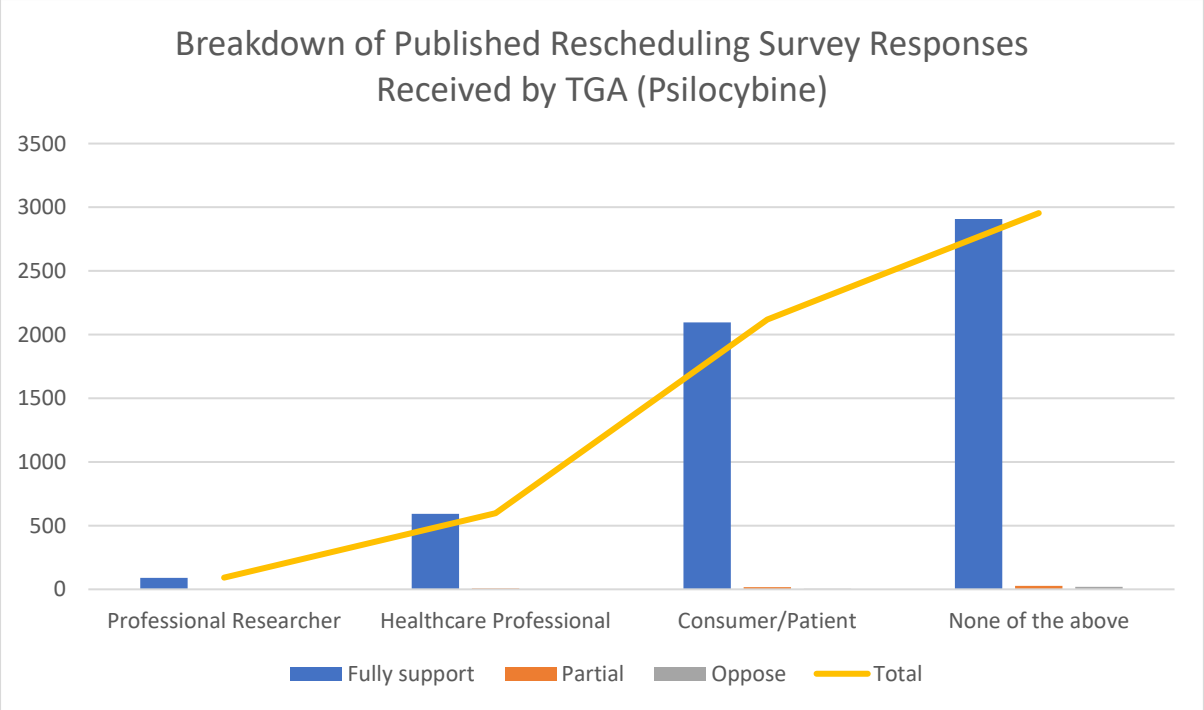
4. OVERWHELMING SUPPORT FOR THE RESCHEDULING OF MDMA AND PSILOCYBINE ON THE LIMITED BASIS PROPOSED

The public submissions responding to our Psilocybine and MDMA Rescheduling Applications (which were lodged as part of the pre- ACMS meeting public consultations) overwhelmingly supported our applications.

4.1 Psilocybine

Table 1. Breakdown of Published Rescheduling Responses Received by the TGA (Please note that according to the Interim Report there were a further 887 psilocybine submissions received by the TGA which weren't published on the TGA's website).

Position	Professional Researcher	Healthcare Professional	Consumer/Patient	None of the above	Grand Total
Fully support	89	592	2097	2907	5685
Partial	1	7	16	28	52
Oppose	2	0	5	19	26
Total	92	599	2118	2954	5763



It should be noted that:

(i) The **6,650** submissions in relation to our current psilocybine rescheduling application compared with **575** submissions lodged in relation to our first rescheduling application (lodged in July 2020). **98.65%** of the current submissions were in favour of rescheduling on the basis that we proposed whilst a further **0.9%** supported the rescheduling on a qualified basis (discussed below). This illustrates that over 99% of submissions were in support of rescheduling.

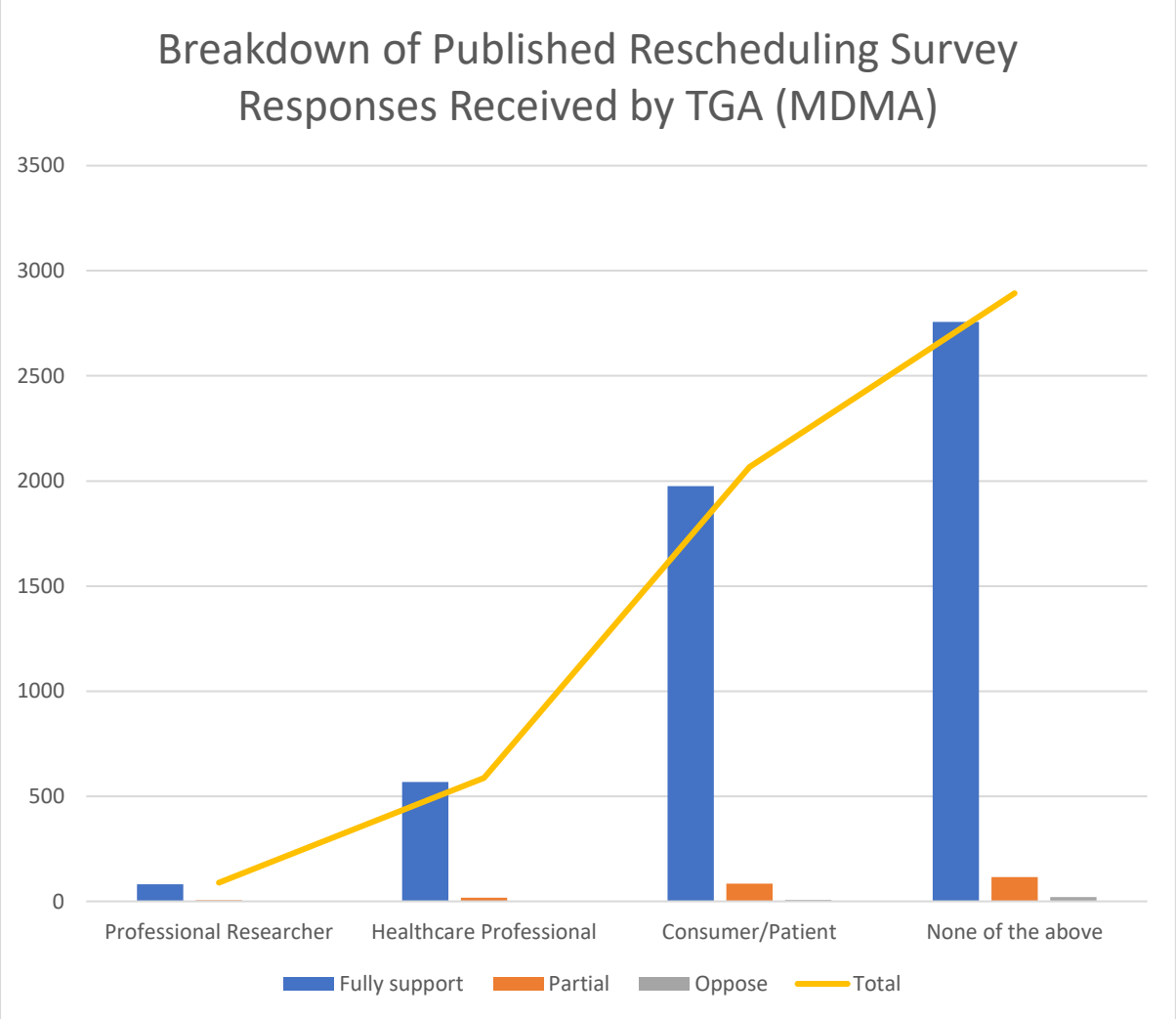
(ii) **All of the current submissions lodged by individual health practitioners** – who are at the front line dealing with patients with mental illness every day - were in favour of the proposed rescheduling.

(iii) **90** out of **92** professional researchers who lodged submissions were in favour of the proposed rescheduling. **Unlike all of these supporting researchers, the two researchers who opposed our applications were not prepared to be publicly identified.**

4.2 MDMA

Table 2. Breakdown of Published Rescheduling Responses Received by TGA. (Please note that according to the Interim Report there were a further 869 MDMA submission received by the TGA which weren't published on the TGA's website).

Position	Professional Researcher	Healthcare Professional	Consumer/Patient	None of the above	Grand Total
Fully support	81	568	1976	2757	5382
Partial	6	18	84	116	224
Oppose	2	1	7	20	30
Total	89	587	2067	2893	5636



It should be noted that:

(i) The **6,505** submissions lodged in relation to our current MDMA rescheduling application compared with **478** submissions lodged in relation to our first rescheduling application (lodged in July 2020). **95.5%** of the current submissions were in favour of rescheduling on the basis proposed with a further **4%** supporting the rescheduling on a qualified basis (discussed below) In other words over **99%** of all submissions lodged were in support of rescheduling.

(ii) **All but 1 of the 587 submissions lodged by individual health practitioners** – who are at the front line dealing with patients with mental illness every day - were in favour of the proposed rescheduling.

(iii) **81 out of 89 professional researchers** who lodged submissions supported our proposed rescheduling with **a further 6** giving qualified support **(i.e. a 98% combined support level). Unlike all of these supporting researchers who agreed to their names being public released only two researchers opposed our applications and they weren't prepared to publicly identify themselves.**

With our first rescheduling application we also listed the names of **99** (for MDMA) and **107** (for psilocybine) psychiatrists, psychologists, pharmacologists, therapists, other health practitioners and researchers who supported rescheduling and who believed that the relevant tests had been satisfied two years ago. In other words even before the Phase 3 (MDMA) and Phase 2b Compass (psilocybine) data which confirmed the results of earlier trials had been published.

We understand that rescheduling decisions are based on the Delegate's review of the factors listed in Section 52E(1) of the Therapeutic Goods Act and that the Delegate makes the final call. But there is no point having a public consultation process if the Delegate ignores the views of so many individuals lodging submissions who are overwhelmingly in favour of rescheduling and particularly those of front-line health practitioners, researchers and patients.

This failure of the consultation process is made worse when the identity and qualifications of the Delegate (particularly in neuropsychopharmacology, psychiatry and the mental health sector generally) are not disclosed, the actual detailed advice received by the Delegate from the ACMS is not disclosed, the actual advice or briefing papers given to the ACMS by the TGA or other parties are not disclosed and the communications between the Delegate or other members of the Department of Health and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) are not disclosed.

5. THE SUMMARISED VIEWS OF THE ADVISORY COMMITTEE OF MEDICINES SCHEDULING (ACMS)

5.1 Introductory Comments

The key reasoning of the ACMS in recommending against the rescheduling of MDMA and Psilocybine on the limited basis proposed is based on the Committee's view that the established therapeutic value test hasn't been satisfied for either substance.

As this is so central to the ACMS' advice and the Delegate's interim decisions we deal with "established therapeutic value" specifically in Section 6 below.

Overall, we believe that the stated reasons given by the ACMS are weak when measured (as they should be) against the enormous suffering and loss of life referred to in Section 1 above, the advice of leading experts in the field, the overwhelming public support for rescheduling and the strong safety and efficacy data available for these medicinal therapies *as unregistered medicines*.

We also note that whilst the ACMS does refer to the August 2021 Expert Report commissioned by the TGA ("*An evaluation of the therapeutic value, benefits and risks of MDMA and psilocybin for the treatment of mental behavioural disorders"*) as being part of the materials considered by the Committee, the ACMS doesn't specifically refer to the findings of that report in its advice to the Delegate. In contrast, the Delegate does specifically refer to this report so we will deal with its findings when we discuss the Delegate's arguments in Section 7 below.

However, we would point out here that the Expert Report is misleadingly referred to in the Interim Decision as being an "Independent" Expert Report. The TGA also does this on its website. Nowhere in the Experts Report do the writers claim "independence" from the TGA or other relevant parties. Indeed, in the conflict disclosures, a number of potential conflicts are raised which would normally compromise independence.

Dr Kisely is a member of the TGA's Advisory Committee on Medicines. He is also a member of one of the RANZCP committees "*that provided comments on the clinical memorandum of the therapeutic use of psychedelic substances"* which the RANZCP based its opposition to our previous rescheduling applications on.

Dr Somogyi is a co-investigator on two Commonwealth Government funded trials and at the time of writing the report was an investigator on an application for Commonwealth Government research funding.

We simply note that the TGA could have commissioned a truly independent report by including overseas experts who didn't suffer from these local conflicts.

The ACMS views on each rescheduling application and our responses are set out below.

5.2 ACMS Expressed Views in relation to our Psilocybine Rescheduling Application

a. Risks and Benefits

The ACMS accepts *"the emerging evidence of efficacy in treating depression with demonstrated low risk of adverse events with short term use in controlled settings".* This is precisely what is being proposed in our rescheduling application. **We would have no objection to the TGA limiting the application of psilocybine assisted therapy to treatment resistant depression if this is helpful.**

As stated in Section 1.8 of our application, psilocybine use is not associated with the development of psychosis in the scientific literature. For reasons of caution, patients with psychosis are specifically excluded from clinical trials and this exclusion can continue to occur under the conditions on which the TGA grants Special Access Scheme approvals and State and Territory permits are given.

The ACMS also commented that "*Trials suggest some risk of suicidal ideation although it is not clear at this stage if this is attributable to the treatment or illness".* This is presumably a reference to the results of the Compass Phase 2b trial using various dosing levels of psilocybine to support psychotherapy for patients with treatment resistant depression. The results have recently been published in the New England Journal. See the article set out in **Appendix H**. The differences in suicidality between the 25mg group and the placebo group are small and it should be noted that issues of suicidality are not uncommon with patients suffering from severe and long term mental illness.

In commenting on the Compass results, Professor David Nutt stated that:

"This study is important for several reasons. First it replicates our earlier study in treatment-resistant depression with 25mg of psilocybin [Carhart-Harris - et al lancet psychiatry 2016], thus solidifying confidence in the general principle. Second it shows a dose-response relationship with doses of 10 and 1 mg [sub-psychedelic doses] showing less efficacy than the 25 mg dose which further supports the theory that a psychedelic trip itself plays a significant role in the therapeutic outcome. Thirdly it shows the robustness of the psilocybin effect. Even though the trial was conducted in many centers in multiple countries the effects were clinically significant, suggesting that the therapy is likely to be effective in a wider role out across the world."

"Note also the adverse effects came long after drug out of body - so related to illness not psilocybin" (written advice received from Professor David Nutt).

b. <u>The purposes for which a substance is to be used and the extent of use of a substance</u>

We agree with the ACMS comments.

c. <u>Toxicity of a substance</u>

The ACMS noted that the **lethal dose** of psilocybine has been extrapolated in humans to be around 300 times the typical therapeutic dose. This provides a

huge margin of safety and can be compared to common psychiatric medicines such as Amitriptyline (10-20 times), Venlafax (50 times) and Paroxetine (30 times

d. Dosage

There is good evidence from trials on therapeutic dosage levels (confirmed further by the recent Compass Phase 2b results that show a significant dose response effect peaking at 25mg). Trials using higher doses have not recorded greater efficacy and human volunteer studies by Matthias Liechti have concluded that 25mg of psilocybine gives the best ratio of effects to adverse effects (data presented by Mathias Liechti at ICPR 2022).

The ACMS comments about lack of clarity in how the medication will be dispensed doesn't make any sense to us because these will be subject to the Schedule 8 controls and government permit systems that can deal with this (see Part 2.1 (A)2.1 of our Psilocybine Rescheduling Application dated 2nd March 2022).

e. Potential for Abuse

Low risk of addiction is noted by the ACMS (and this contrasts with the much higher addiction risks of many psychiatric medicines commonly used today including benzodiazepines, some antidepressants, and various opiate based medicines).

We agree with the ACMS comments about the risks of diversion in the clinical setting being manageable (these risks are no different to the risks associated with much more addictive and dangerous drugs used in clinical settings such a morphine, fentanyl, Alprazolam and gabapentin).

The ACMS concerns about diversion risks at other points in the distribution chain doesn't make any sense to us. We have no idea what this refers to and why it would be different for the other far more dangerous medicines that are currently in Schedule 8 of the Poisons Standard. See generally our explanation

of the supply chain controls in Part 2.1 Section (A) 2.1 of our Psilocybine Rescheduling Application.

f. Other Matters Considered by the ACMS related to Protecting Public Health

If the ACMS has concerns over the application of psilocybin assisted therapy "*beyond the conditions for which there is clinical trial evidence of therapeutic benefit"* then as mentioned above the TGA and the individual States and Territories can limit the application of the Special Access Scheme in the case of psilocybine (and therefore the application of State and Territory permit systems) to treatment resistant depression.

Of course, we understand the ACMS comment that the skill of the therapist is fundamental to properly guiding the patient through the altered state of consciousness and generating the positive results achieved to date. The same can be said of many other areas of psychiatry and psychotherapy (e.g. treating patients with suicidal ideation or patients suffering from serious substance abuse).

We are puzzled by the comment attributed to the ACMS that there are concerns *"….with using down-scheduling as a mechanism to bypass the processes for clinical trials, by inserting specific requirements (to mirror a clinical trial environment) in the entry to allow it to fit a lower schedule".*

We are not trying to bypass clinical trials. We are simply acknowledging by inserting specific requirements that we are dealing with an unregistered medicine and therefore the best evidence for appropriate requirements (as would normally be the case in these circumstances) will be derived from clinical trials. Given the failure of current treatments for treatment resistant patients and the consequential despair and loss of life (see Section 1 above) we completely fail to understand this point.

5.3 ACMS Expressed Views in relation to our MDMA Rescheduling Application

a. Risks and Benefits

There appears to be a confusion in the comments attributed to the ACMS between risks associated with recreational use (which has nothing to do with our rescheduling application) and the risks associated with medical use.

In our proposal, medical use involves only 2 -3 sessions with medical grade MDMA and takes place in a medically- controlled environment under the leadership of the treating psychiatrist, and with two therapists with the patient at all times. This is completely different from recreational use and comments such as "*in severe cases, MDMA can cause loss of consciousness and seizures"* and "*long -term use can result in sleep disturbances, difficulties with concentration, depression, heart disease, impulsivity and decreased cognitive function"* are entirely inappropriate to medical use on the basis envisaged.

Many substances used as medicine are capable of abuse if used for other purposes (witness the way that prescribed opiates can be abused).

The evidence from the trials (including the MAPS Phase 3 trial) is that MDMA assisted therapy could actually be safer than conventional therapy for patients suffering from severe treatment resistant PTSD (see Part 1 Section 2.3(2) of our MDMA Rescheduling Application).

The comment attributed to the ACMS that "*There is limited but emerging evidence that MDMA – assisted therapy may have therapeutic benefits in the treatment of PTSD"* is also at odds with the data from the six MAPS Phase 2 Trials and the first MAPS Phase 3 Trial which are showing remission rates of greater than 67 % and minimal adverse side effects (see the Nature Medicine article published in May 2021 detailing the results of the first Phase 3 trial and see out in **Appendix I**).

MDMA is not a new pharmaceutical medicine. The medicine was first synthesised by pharmaceutical company Merck in 112 (in other words over

100 years ago). Up until prohibition in the 1980s (prohibition was part of the War on Drugs and had nothing to do with medical merit) over **500,000** doses were used legally by practitioners across 20 years as part of psychotherapy – see the letter from Drug Science in the UK Chaired by Professor David in **Appendix B**.

We have also confirmed with the current sponsor of the MDMA Phase 3 trials (and the leading MDMA research house in the World), the Multidisciplinary Association for Psychedelic Studies (see the email below), that a total of 1,799 research participants have been exposed to MDMA in clinical or research studies post prohibition. See email attached in **Appendix J**. You will see in the same email there is also reference to a further 4000 people being administered MDMA with 150 therapists involved. You will also see from Professor David Nutt's letter set out in **Appendix B** that between the late 1960s and prohibition approximately 500,000 doses of MDMA across 20 years of psychotherapy were used without complications and with useful efficacy.

These are not new medicines and there is much more evidence to support their use as medicines than would be the case with many unregistered (and indeed some registered) medicines.

We should also add then when an unregistered medicines is moved to Schedule 8 (e.g. cannabis) there is not by definition the level of evidence that should be (but not always is) associated with a registered medicine. That is the nature of unregistered medicine and why the TGA has a Special Access Scheme.

We would also ask the ACMS to reflect on the evidential base on which medical cannabis was moved to Schedule 8 which was much less substantial than that currently available for MDMA.

b. <u>The purposes of which a substance is to be used and the extent of use of a substance</u>

We agree with the ACMS comments.

c. Toxicity of the Substance

The estimated lethal dose referred to (at 10-20 mg/kg bw) is many times the therapeutic dose that has been used in trials (up to 120mg with an optional half dose 1.5 to 2.5 hours into the session). This provides a large margin of safety which psychiatrists and other medical professionals are used to working with.

Also, in contrast with a range of current psychiatric medicines which are regularly prescribed and taken home by the patient, the MDMA dosing will only take place in a medically controlled environment on 2-3 occasions and the patient will never be allowed to take the medicine home.

d. The Dosage, Formulation, Labelling, Packaging and Presentation of a Substance

Optimal dosage hasn't been established for many medicines but the acceptable range is now known. MAPS is now focusing on 100mg of MDMA as the optimal dose with evidence of reduced efficacy and/or more adverse effects at lower and higher doses.

e. The Potential for Abuse

This section of advice attributed to the ACMS confuses medical use on the highly restrictive basis proposed with unrestricted recreational use. There is no evidence to suggest that the medical use on the basis proposed causes dependence (see in particular Part 2.1(A) Section 1.6 of our MDMA Rescheduling Application).

Moreover, recent expert analyses have found fundamental deficiencies in the original methodology for assessing dependence and addiction risk https://www.sciencedirect.com/science/article/abs/pii/S0028390822002799 . This criticism led the US DEA to rescind their interim decision to put several new psilocybin analogues into Schedule 1. See https://microdose.buzz/news/breaking-news-dea-reverses-decision-to-ban-5-psychedelics/

f. Other Matters Considered related to Protecting Public Health

For some reason, and despite the fact that MDMA assisted therapy is further advanced in the clinical trial and registration process than psilocybine, the ACMS raises more matters under this heading than they do in relation to psilocybine.

We deal with each of the matters raised by the ACMS in this section of their summary advice, below.

g. Psychedelic/Psychotherapy interaction and stringency of protocols

Specific protocols have been developed by MAPS and are publicly available. The treatment plan will be developed by the prescribing psychiatrist and confirmed by two other psychiatrists. Two therapists will be with patient at all times. We have proposed that reporting to a registry run by Monash University will be an integral part of these therapies and data will include outcomes, adverse events and protocols used.

h. Lack of medicines containing MDMA in the ARTG

We are not sure of the relevance of this comment and its circular. The nature of unregistered medicines is that there won't be medicines using the same molecule on the ARTG. That's the benefit of have a framework for unregistered medicines.

i. Benefits of Waiting

There is a comment attributed to the ACMS about the "*significant benefits"* of waiting for the results of more clinical trials. With almost every medicine there is a benefit in waiting for more clinical trials and that would be the case with most of the unregistered medicines already listed in Schedule 8 of the Poisons Standard and many registered medicines. But there is already a large amount of data about the safety and efficacy of MDMA in the medical environment

(see our MDMA Rescheduling Application) and that needs to be measured against the desperation and in some cases suicidal ideation (and suicide) of many patients with treatment resistant PTSD (see Section 1 above).

The current treatment paradigm is failing many people suffering from mental illness. This can cause unbearable suffering. The trials to date have shown very positive results with minimal adverse events. These medicines were extensively used before prohibition. Unbearable suffering can lead to people self-medicating or taking their own lives.

Who is the ACMS suggesting will benefit from delaying the highly restricted access to these treatments that we are proposing in our rescheduling application? How many treatment resistant "at risk" patients will suffer from such delay and how many of these patients will take their own lives?

There is now considerable evidence that MDMA assisted psychotherapy is safe and efficacious (see our Rescheduling Application**). However, if the ACMS believe that the safety and efficacy data is weaker for conditions outside of PTSD then the obvious thing to do is to cover this in the TGA Special Access Scheme approval process and the State/Territory permit systems**. We should also add that registered medicines are frequently used "off label" in Australia and the same point could be made about this practice.

j. Training

We deal with this extensively in our Rescheduling Application (see Part 2.1 Section(A)2.2) The Mind Medicine Institute has already trained 240 psychiatrists, psychologists, therapists and other relevant health practitioners in the application of psychedelic assisted therapies and the use of relevant protocols. The faculty is made up of leading international experts in this field with extensive experience in the use of these therapies (see https://cpat.mindmedicineaustralia.org/). The testimonials received from graduates of the course have been outstanding with a number describing the course as the best professional development course that they have ever done

(see https://cpat.mindmedicineaustralia.org/wp-content/uploads/CPAT-Testimonials-from-Students-26072022.pdf).

The fact that neither the Delegate, the ACMS, the TGA or the relevant peak bodies and government departments have shown any interest in understanding the high calibre of the course should not be used as an excuse for denying desperate and at times suicidal people access to these therapies.

The cases of **Franco Bortilin**, **Kayvan Walker** and **Leanne Daniels** referred to in Section 1 come to mind here in the context of protecting public health.

The assertion that we should "wait" whilst governments around Australia and relevant peak bodies do nothing or even appear to oppose action will ***not*** generate confidence in the system that the patient's interests are at the forefront of their thinking. The fact that a number of Western countries and individual States and Provinces overseas have been more proactive in this space should be noted here.

k. Diversion Risk

The ACMS fails to explain in their advice why the diversion risk for MDMA is any different than the diversion risk associated with psilocybin (where they seem to be comfortable with this in a medical environment) or with any other Schedule 8 medicine. We dealt with this alleged risk at length in our MDMA Rescheduling Application (Part 2.1 Section (A)2.1) and note that the public submission lodged by the Australia Institute specifically deals with this at length and shows that the risk is clearly low and manageable (see **Appendix K**).

l. Appropriateness of Scheduling for Establishing Clinical Governance

We don't understand this comment, particularly within the context of looking after the interests of patients and the wider Australian public. Scheduling is about therapeutic value and risks and benefits to public health. It is common

for a rescheduling to occur on a restricted or conditional basis and these can clearly relate to perceived risks. With unregistered medicines requiring approvals or permits the relevant authority will normally develop its own policy guidelines. This is exactly what the States and Territories do (or should do) as part of their Schedule 8 permit systems. Rescheduling does not take place in a vacuum.

6. THE TEST OF ESTABLISHED THERAPEUTIC

6.1 Applying the Test

The test of established therapeutic value is central to the advice of the ACMS and the decision of the Delegate.

In the Interim Decision the Delegate states that "*I agree with the applicant that therapeutic value of a substance may be 'established' for the purposes of the SPF, despite there being insufficient efficacy evidence to support the inclusion of a product containing that substance in the Australian Register of Therapeutic Goods (ARTG). However, I am of the view that for the therapeutic value to be 'established' the evidence must, contrary to the applicant's arguments, go beyond the mere existence of completed clinical trials and an apprehension of therapeutic value based on a small number of promising trial results."*

In our view it would be open to the Delegate to conclude that these substances have an established therapeutic value. **There is certainly much more evidence of established therapeutic value for these substances than there ever was for medical cannabis when it was moved from Schedule 9 to Schedule 8 in 2016.**

Coming to a positive view that the test of established therapeutic value has been met would equate with the views of leading experts in this field such as **Professor David Nutt** and **Professor Arthur Christopoulos** (see Section 1), the view of all of the health practitioners and nearly all of the researchers that took the time to lodge public submissions (see Section 4) or gave permission to be named in our first application. But it would also recognise the desperate position of people with treatment resistant depression and treatment resistant PTSD, the failure of current treatments to help those people (see Section 1) and the extraordinarily positive results achieved in trials to date.

We would also take issue with the statement that all we have is an *"apprehension of therapeutic value based on a small number of promising trials".* This is not the view of the experts, researchers and practitioners referred to above and the trial outcomes summarised in our Rescheduling Applications.

In the case of MDMA we are currently through one of two Phase 3 trials that are seen as the gateway to FDA registration of MDMA assisted therapy. The Phase 3 trial results to date summarised in our MDMA application largely replicate the 6 MAPS Phase two results in terms of both safety and efficacy. There is a large effect size shown and adequacy of sample size was discussed in advance with the FDA. In the Phase 3 trial patients in the MDMA group had less serious adverse events than in the placebo group.

As mentioned in Section 5.3a above, we have confirmed with MAPS (the current sponsor of the MDMA Phase 3 trials) that a total of 1,799 research participants have been exposed to MDMA in clinical or research studies post prohibition. See email attached in **Appendix J**. You will see in the same email there is also reference to a further 4000 people being administered MDMA with 150 therapists involved. You will also see in Professor David Nutt's letter set out in **Appendix B** that between the late 1960s and prohibition, MDMA was administered in approximately 500,000 doses across 20 years of psychotherapy without complication and with useful efficacy. **MDMA is not a new medicine.**

In the case of psilocybine, the Compass Phase 2b trial has now been documented with the results published in the prestigious New England Journal of Medicine (**see Appendix H**). The Delegate acknowledged that this trial did indicate *"significant improvement in outcomes for patients with treatment resistant depression who were administered a dosage of 25mg".* The Delegate also acknowledged a further study which has a 12 month follow up which showed *"large and stable antidepressant effects throughout a 12 month follow up period".*

We would again refer you to Professor David Nutt's statement about these trial results reproduced in Section 5 above.

We would also refer you to Professor David Nutt's letter set out in Appendix B. In his letter Professor Nutt details the widespread use of psilocybine in trials (with 14 long term follow up studies) and in a number of overseas countries where psilocybine can legally be used as a medicine. **These are not new**

medicines and the evidence clearly shows that psilocybine can be used safely and with positive efficacy.

6.2 Reliance on the Expert Report

The Delegate (and presumably the ACMS) "*attached significant weight to"* to the Expert Report commissioned by the TGA *on an evaluation of the therapeutic value, benefits and risks of MDMA and psilocybin for the treatment of mental, behavioural or development disorders (***the Expert Report**). However, the writers of this report didn't express a view on whether these substances when used as part of psychotherapy had an established therapeutic value. **The experts didn't make any findings on this issue**. For the reasons given in Section 5.1 above we should also note that the report did not meet the test of being an "independent" report.

The Expert's Report only covered a limited number of the psilocybin and MDMA clinical trials conducted to date. They focused only on 8 studies in the MMA group and 6 in the psilocybine group that met their self- imposed test of being "*randomised control trials …. with either inactive or active placebos"*.

This focus on randomised control trials does not mean that all of the other trials were of "low quality" as the Delegate suggests nor that valid data can't be drawn from those trials to build up the case for meeting the "established therapeutic value test". Sir Michael Rawlins, the former head of the MHRA and NICE, pointed out in 2008 that randomised control trials are not the apex of treatment trials:

"Randomised controlled trials, long regarded at the 'gold standard' of evidence, have been put on an undeserved pedestal. Their appearance at the top of 'hierarchies' of evidence is inappropriate; and hierarchies, themselves, are illusory tools for assessing evidence. They should be replaced by a diversity of approaches that involve analysing the totality of the evidence base."

Ref = Rawlins, M. Cited in: The Royal College of Physicians: Sir Michael Rawlins attacks traditional ways of assessing evidence, opinion former article 16 October (2008). https://www.politics.co.uk/opinion-formers/ royal-college-of-physicians/article/royal-college-of-physicians-sir- michael-rawlins-attacks-trad [Accessed 11 Jun 2022].

In fact, the findings of the Expert's Report could easily have been used by the ACMS and the Delegate to support a conclusion that these medical therapies had met the test of "established therapeutic value". We have extracted some key comments from the report below (with bolding of text used to highlight key points made).

For MDMA when used with Psychotherapy

"Six of the eight studies were on post-traumatic stress disorder, one on anxiety due to a life-threatening disease and the other on social anxiety in adults with autism. Half of the studies on PTSD used inactive placebo as the control while the remainder used low doses of MDMA. In all studies both the intervention group and controls received supplementary intense psychotherapy.

"In general, between four and twelve weeks following administration, ***there were statistically significant differences for MDMA doses of greater than 100 mg in comparison with inactive or active controls.*** *Most information was on MDMA symptom scores compared to active controls in post-traumatic stress disorder (Standardised Mean Difference=-0.86, 95%CI=-1.23 to -0.50; k=4).* ***We consider a standardised mean difference of this magnitude to be a strong effect size.***

*"……****Effect sizes were large in all comparisons but with wide confidence intervals.***

MDMA was well tolerated in all the studies*. The main adverse effects were anxiety, restlessness, fatigue, jaw-clenching, headache and transient increases in blood pressure.* ***Serious events such as suicidal ideation were rare and occurred almost entirely in the placebo arm or were otherwise unrelated to the therapy".***

For Psilocybin when used as part of psychotherapy

"Four of the six studies were for anxiety or depression for a life-threatening disease, two on treatment-resistant depression and one on obsessive-compulsive disorder. Two used low-dose psilocybin as the control and another

two used the vasodilator niacin as it induces a mild physiological reaction (e.g. flushing) without any psychological effects.

***"One study reported statistically significant differences between psilocybin and niacin, and another between high and low dose psilocybin, for subjects with anxiety or depression due to life threatening disease. Psilocybin was also superior to remaining on a waitlist in a study of treatment resistant depression. In another study of treatment resistant depression, there was no significant difference between psilocybin and a registered antidepressant (escitalopram) in the pre-determined primary outcome, although changes in secondary outcomes almost uniquely favoured psilocybin**. In the fifth study, there were no statistically significant differences between psilocybin and controls at the two-week follow-up, although both groups showed longer-term improvements following cross-over. In the final study there was no significant effect of dose on obsessive-compulsive symptoms possibly because of low numbers and unexpectedly high response to the very low dose placebo.*

"Three studies also assessed whether participants had shown a clinically significant response or were in remission as regards depression or anxiety. ***There were statistically significant differences favouring psilocybin as opposed to both active placebo (niacin or low dose psilocybin) and the antidepressant escitalopram (for all but one measured outcome in the case of the latter).***

"Psilocybin was also well tolerated in all the studies. The main effects were anxiety, headache and transient increases in blood pressure."

6.3 The Conclusions Stated in the Expert Report

"By combining the effects of small and possibly underpowered studies, meta-analyses can help to establish the relative efficacy of interventions such as MDMA and psilocybin where large studies may be impractical. ***Although we were only able to combine results from 9 studies for either beneficial or adverse effects, we did demonstrate statistically significant differences of the two psychedelic agents between both inactive and active treatments for***

***either continuous scores or dichotomous responses**. However, it is important to note that this was in highly supportive and structured environments including intense psychotherapy sessions in many cases.*

***"Both agents were well-tolerated in supervised trials with or without additional use of psychotherapy**. However, trial quality including blinding and follow-up was variable and only a small proportion of potential participants were included in the randomised phase.*

"We conclude that MDMA and psilocybin may show promise in highly selected populations but only where these medicines are administered in closely clinically supervised settings and with intensive professional support."

In relation to psilocybine it should be noted that these comments of the Expert Panel would no doubt be even stronger today because this review occurred before the results of the Compass Phase 2b multi- site trial were announced. This is by far the largest psilocybin trial completed to date (see the published article on the Compass Phase 2b results published in the New England Journal set out in **Appendix H).**

6.4 Conclusions in Relation to the Established Therapeutic Value Test

Given the safety and efficacy results and the tightness of our proposed Schedule 8 controls we would ask the Delegate to conclude in favour of "established therapeutic value" for both psilocybine and MDMA assisted therapies. There is clear evidence to support such a conclusion and it would be consistent with the level of support that we received for our applications and the views of noted experts in the field.

Deciding in favour of "established therapeutic value" will enable a limited number of "at risk" treatment resistant patients to be given the chance to benefit from these therapies but only if:

- their psychiatrist and the reviewing psychiatrists believe that the particular therapy was appropriate to the patient's circumstances;

- the patient gave informed consent; and

- the treating psychiatrist received patient specific approvals at both the federal level (under the TGA's Special Access Scheme) and the State/Territory level.

The use of the proposed registry would then provide "real time" feedback on the success of these therapies in clinical practice. It should be noted that this is the best form of evidence of the application of a medicine in a real world clinical environment (as opposed to the normally narrow environment and patient parameters associated with clinical trials).

7. THE DELEGATE'S REASONS FOR THE INTERIM DECISIONS

For reasons of brevity, we won't repeat our comments from the previous section where the Delegate raises an issue or expresses a view already covered by our responses to the ACMS' summary advice. We will simply cross reference below to our earlier comments.

The Delegate's Interim Decisions against rescheduling are essentially based on the following 7 propositions:

- **Proposition 1**. The substances meet the Schedule 9 requirements and positioning the substances in Schedule 9 ensures appropriate controls over access.

- **Proposition 2**. The limited evidence of benefit for both substances is outweighed by the risks to patients and public health from any increased access associated with down-scheduling.

- **Proposition 3**. The views of the Delegate in the Interim Decision accord with the views of the Royal Australian and New Zealand College of Psychiatrists (RANZCP).

- **Proposition 4**. Whilst the controls proposed could theoretically ensure the benefit for treated patients is realised, they ignore the way they would operate in practice under State and Territory legislation.

- **Proposition 5**. Whilst expanded access schemes have been instituted for these medicinal therapies in countries including the United States, Israel and Switzerland under compassionate access grounds these are analogous to the current use of the Special Access Scheme in Australia which allows patient access to Schedule 9 substances.

- **Proposition 6**. There are still no approved therapeutic products containing either substance anywhere in the World.

- **Proposition 7.** The views of RANZCP and the Australian Psychological Society (APS) apparently outweigh the overwhelming number of supportive submissions lodged, the views of leading Researchers in the field such **Professor David Nutt** and **Professor Arthur Christopoulos** and from front-line Health Sector Experts (many of whom are members of these peak bodies).

Our response to each of these propositions are dealt with below.

Proposition 1. The substances meet the Schedule 9 requirements and positioning the substances in Schedule 9 ensures appropriate controls over access.

In the Interim Decision the Delegate acknowledges that the inclusion of psilocybine and MDMA in Schedule IV of the UN Convention on Psychotropic Substances 1971 is *"not a barrier to the current [rescheduling] proposals"*

This means that the Schedule 9 criteria which the Delegate is relying on must be that that the medical use of these substances has "*no currently established therapeutic value"* and that these substances are "*likely to present a high risk of dependency, misuse or illicit use".*

We have dealt specifically with the test of "established therapeutic value" in Section 6 above. We believe (for the reasons given) that it would be appropriate for the Delegate to exercise judgement in favour of this test being satisfied. It is certainly open to the Delegate to this.

This leaves the last Schedule 9 test that these substances, when used medically in the manner envisaged, are "*likely to present a high risk of dependency, misuse or illicit use".*

On the high risk of dependency limb there is absolutely no evidence from the trials conducted to date that the limited medical use of these substances (just 2 – 3 doses) in the manner followed in the trials and envisaged in the proposed rescheduling controls would lead to dependency. We would refer you to Section 5 above where we detail the considerable number of people who have

been through psilocybine or MDMA trials pre and post prohibition and who have used these medicines clinically as part of therapy. These are not small population sizes. These is very little if any evidence of dependence from either medical or recreational use.

The last Schedule 9 test of "*likely to present a high risk of …. misuse or illicit use"* is essentially an argument over diversion risk. Yet the Delegate acknowledges in the Interim Decisions that the risk of diversion of these substances in a controlled medical environment is low.

The Delegate does make a comment that diversion risk is higher in other parts of the distribution chain but doesn't support this statement with any evidence. The Delegate also doesn't explain why these substances differ from a risk perspective from other controlled substances that are already in Schedule 8 of the Poisons Standard, and which can be much more addictive medicines if abused (see Section 5.2(e) and 5.3(f)v above).

We should also point out that a number of current psychiatric drugs prescribed for medical purposes are far more addictive and dangerous than MDMA and Psilocybine even when MDMA and Psilocybine are used recreationally (by definition medical use in the manner that we are proposing is even safer). This is shown very clearly from the following reports

a. The Report of the Melbourne Coroner on Victorian overdose deaths, 2011-2020

   See - https://www.coronerscourt.vic.gov.au/sites/default/files/2021-07/CCOV%20-%20Overdose%20deaths%20in%20Victoria%202011-2020%20-%2029Jul2021.pdf

   Also see the extracts from the report following.

to discern whether there are any other trends, because of the low frequencies and substantial year-to-year variability in the data.

2.4. Contributing drug groups

Pharmaceutical drugs were further disaggregated into drug groups for more detailed analysis, using a slightly modified version of the US Drug Abuse Warning Network (DAWN) Drug Vocabulary level two groupings.[3]

Table 7 shows the annual frequency of Victorian overdose deaths 2011-2020 involving each of the major contributing pharmaceutical drug groups, with illegal drugs and alcohol included for context. Most overdose deaths were from combined drug toxicity, which is why the annual frequencies for each drug group in Table 7 sum to greater than the overall annual frequency.

Table 7: Annual frequency and proportion of contribution to overdose deaths, among major contributing pharmaceutical drug groups plus alcohol and illegal drugs, Victoria 2011-2020.

Drug type	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Frequency	**362**	**365**	**381**	**387**	**454**	**494**	**523**	**543**	**516**	**526**
Benzodiazepines	180	199	213	215	238	263	303	304	285	281
Illegal drugs	146	126	157	160	223	264	267	260	274	270
Pharmaceutical opioids	165	188	176	182	185	183	198	207	207	189
Antidepressants	101	141	135	144	161	165	196	196	170	179
Alcohol	89	80	96	94	106	124	151	161	145	154
Antipsychotics	65	78	76	81	91	107	136	109	103	113
Anticonvulsants	13	10	37	45	51	54	75	87	85	92
Non-benzo anxiolytics	33	38	56	48	60	40	56	47	54	51
Non-opioid analgesics	30	44	39	49	46	35	38	40	50	38
Proportion	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**
Benzodiazepines	49.7	54.5	55.9	55.6	52.4	53.2	57.9	56.0	55.2	53.4
Illegal drugs	40.3	34.5	41.2	41.3	49.1	53.4	51.1	47.9	53.1	51.3
Pharmaceutical opioids	45.6	51.5	46.2	47.0	40.7	37.0	37.9	38.1	40.1	35.9
Antidepressants	27.9	38.6	35.4	37.2	35.5	33.4	37.5	36.1	32.9	34.0
Alcohol	24.6	21.9	25.2	24.3	23.3	25.1	28.9	29.7	28.1	29.3
Antipsychotics	18.0	21.4	19.9	20.9	20.0	21.7	26.0	20.1	20.0	21.5
Anticonvulsants	3.6	2.7	9.7	11.6	11.2	10.9	14.3	16.0	16.5	17.5
Non-benzo anxiolytics	9.1	10.4	14.7	12.4	13.2	8.1	10.7	8.7	10.5	9.7
Non-opioid analgesics	8.3	12.1	10.2	12.7	10.1	7.1	7.3	7.4	9.7	7.2

Benzodiazepines were the most frequent contributing pharmaceutical drug group, playing a role in an average 54.5% of overdose deaths annually across the period. The next most frequent pharmaceutical drug groups were opioids (an average 41.3% of overdose deaths each year), antidepressants (annual average 34.9%) and antipsychotics (annual average 21.1%).

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3 The main modifications were that the DAWN 'anxiolytics' group was divided into benzodiazepine and non-benzodiazepine anxiolytics, and the DAWN 'analgesics' group was divided into pharmaceutical opioids and non-opioid analgesics.

One notable trend in the data was the rise in anticonvulsant involvement over time. As shown in Table 8, this trend was primarily driven by rising pregabalin involvement in Victorian overdose deaths; this is discussed further below. There was also a gradual increase over time in antidepressant involvement, which may potentially be explained by the increase over time in antidepressant prescribing in Australia.[4]

2.5. Individual contributing drugs

Table 8 shows the annual frequency of overdose deaths, Victoria 2011-2020, involving the most frequent contributing individual drugs. The individual drugs are tabulated by the major drug groups to which they belong.

Table 8: Annual frequency and proportion of contribution to overdose deaths, among most prevalent individual contributing drugs, Victoria 2011-2020.

Drug type	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Benzodiazepines	**180**	**199**	**213**	**215**	**238**	**263**	**303**	**304**	**285**	**281**
Diazepam	124	133	165	169	192	204	242	235	232	217
Alprazolam	43	57	45	28	23	23	27	31	28	29
Clonazepam	14	18	19	25	33	31	48	40	35	43
Oxazepam	44	40	17	19	34	27	23	35	28	18
Temazepam	48	34	22	20	25	26	32	29	20	16
Nitrazepam	11	24	26	13	17	22	11	16	13	14
Illegal drugs	**146**	**126**	**157**	**160**	**223**	**264**	**267**	**260**	**274**	**270**
Heroin	125	107	128	136	171	190	220	203	212	187
Methamphetamine	29	34	51	53	72	120	93	96	111	111
Cocaine	2	3	5	7	15	11	10	17	20	27
NPS	0	0	3	0	2	8	2	8	17	33
MDMA	1	1	3	4	5	12	7	4	13	17
GHB	3	1	0	1	0	4	6	5	7	18
Pharma opioids	**165**	**188**	**176**	**182**	**185**	**183**	**198**	**207**	**207**	**189**
Methadone	72	75	70	67	67	72	71	72	74	65
Oxycodone	46	46	61	46	58	54	66	62	59	61
Codeine	38	55	46	47	48	46	37	34	42	39
Tramadol	15	18	24	23	32	26	32	35	37	28
Morphine	12	13	9	12	9	13	18	19	18	10
Fentanyl	5	17	11	11	23	13	14	18	5	5
Buprenorphine	14	4	3	7	4	2	8	20	11	16

(Table continued over page)

4 See for example Whitely D and Raven M, "1 in 8 (over 3 million) Australians are on antidepressants - Why is the Lucky Country so miserable?", *PsychWatch Australia*, 25 August 2019, <https://www.psychwatchaustralia.com/post/1-in-8-over-3-million-australians-are-on-antidepressants-why-is-the-lucky-country-so-miserable>, accessed 23 July 2021.

(Table continued from previous page)

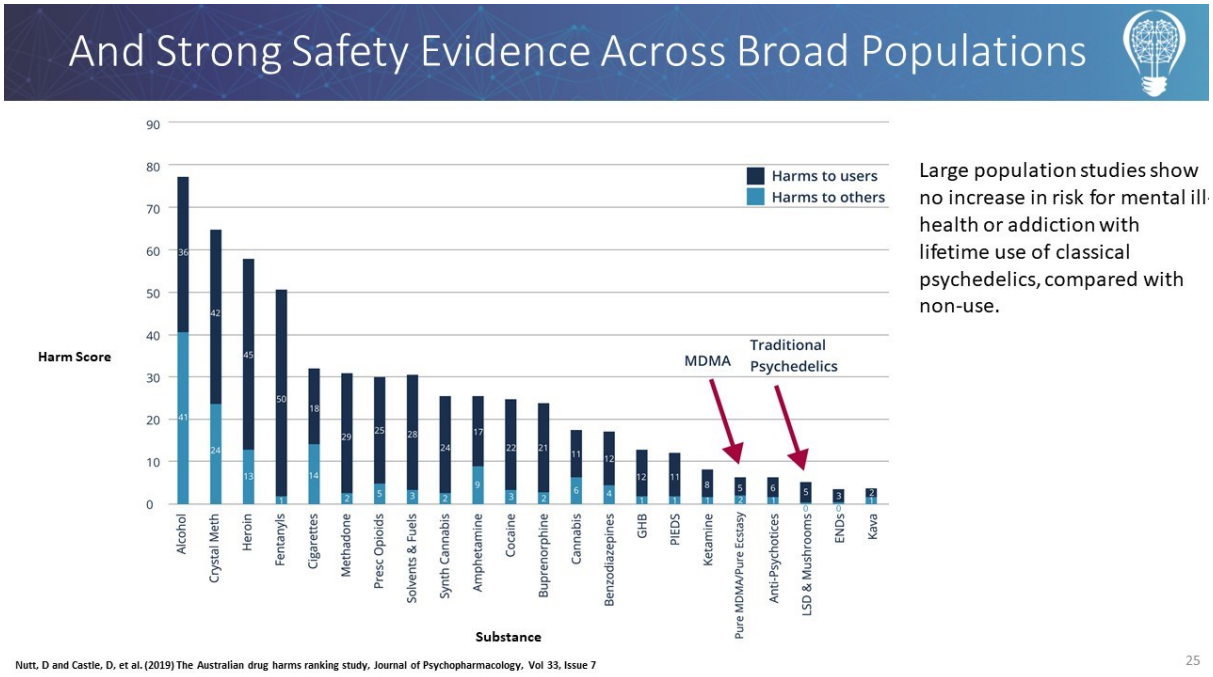
Drug type	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Antidepressants	**101**	**141**	**135**	**144**	**161**	**165**	**196**	**196**	**170**	**179**
Mirtazapine	23	26	30	29	50	25	42	59	45	54
Amitriptyline	22	32	25	41	28	34	47	40	41	32
Citalopram	21	25	25	25	26	28	35	26	26	34
Venlafaxine	16	15	20	19	10	22	27	18	20	18
Duloxetine	7	14	11	12	12	15	12	19	20	17
Sertraline	4	12	13	9	12	11	18	19	20	13
Desvenlafaxine	3	6	8	11	15	19	15	18	12	15
Fluoxetine	8	13	10	7	12	16	10	12	12	10
Alcohol	**89**	**80**	**96**	**94**	**106**	**124**	**151**	**161**	**145**	**154**
Antipsychotics	**65**	**78**	**76**	**81**	**91**	**107**	**136**	**109**	**103**	**113**
Quetiapine	34	41	41	48	49	57	74	53	50	53
Olanzapine	17	22	16	21	30	36	41	42	33	44
Risperidone	11	8	10	7	9	14	9	13	10	4
Zuclopenthixol	4	6	3	3	5	4	14	4	7	8
Chlorpromazine	4	10	6	3	5	5	5	4	5	4
Clozapine	0	4	6	2	4	5	3	3	3	6
Anticonvulsants	**13**	**10**	**37**	**45**	**51**	**54**	**75**	**87**	**85**	**92**
Pregabalin	0	0	17	27	34	34	52	69	66	69
Valproic Acid	5	6	13	9	9	6	7	5	7	7
Lamotrigine	1	2	2	2	2	3	6	10	7	8
Non-benzo anxiolytics	**33**	**38**	**56**	**48**	**60**	**40**	**56**	**47**	**54**	**51**
Doxylamine	11	21	23	13	14	13	18	18	16	10
Zopiclone	6	13	14	11	17	13	17	13	22	18
Pentobarbitone	11	1	8	15	18	9	10	6	9	4
Zolpidem	5	5	4	6	11	6	8	6	8	8
Diphenhydramine	4	2	7	5	5	4	6	6	7	10
Non-opioid analgesics	**30**	**44**	**39**	**49**	**46**	**35**	**38**	**40**	**50**	**38**
Paracetamol	24	42	37	37	42	30	32	32	47	34
Ibuprofen	4	5	2	7	5	4	1	7	4	2

Some notable findings from inspection of Table 8 are presented in the next section of this data summary.

b. The Pennington Institute –Australia's Annual Overdose Report 2022

See https://www.penington.org.au/wp-content/uploads/2022/09/Penington-Institute-AAOR-2022.pdf#msdynttrid=PSFVQjTZk714eksOdrr10sAYheN-5XRiVor6LQgZTH8

c. The Australian drug harms ranking study - Contribution of harm to user and harm to others. [GET RID OF BANNER BELOW and MAKE EASIER TO READ]



For the reasons given above the risks associated with the medical use of these substances doesn't even rise to the level of risk assumed by the Schedule 8 requirements.

In the interests of public accountability, we would ask the Delegate to explain why the current system of Schedule 8 controls that governs the management of far more dangerous and addictive medicines can't be used to govern the limited use of psilocybine and MDMA as part of therapy in controlled medical environments. This is particularly important given that we are dealing with

patients at risk suffering from treatment resistant mental illnesses and the fact that current treatments have, by definition, failed this patient population.

We deal with the way current Schedule 8 controls work and why they are suitable for these substances in detail in our Rescheduling Applications (see Part 2.1 Section(A)2.1 of our MDMA application and Part 2.1 Section A2.1 of our Psilocybine Application).

Proposition 2. The limited evidence of benefit for both substances is outweighed by the risks to patients and public health from any increased access associated with down-scheduling.

We have dealt with established therapeutic value and supporting evidence in Section 6 above and at length in our rescheduling applications. The Delegate's comment that this is outweighed by the risks to patients and public health from any increased access is essentially about translation risk. We commented on our view that translation risk is manageable in detail in Part 2.1 Section (A)2.2 of our MDMA Application and Part 2.1 Section(A)2.2 of our Psilocybin Application.

Our solution to the specific concerns raised by the Delegate in the interim decisions in relation to each substance are set out below:

1. **Concern**: *"the broadness of the indication (treatment resistant mental illness) included in the current psilocybine proposal, as this appears to be much broader than the indications for which there is emerging evidence (such as treatment resistant depression).*
   Our Response. This can be easily dealt with by restricting the application of the rescheduling in relation to psilocybine to treatment resistant depression or by covering this in the TGA Special Access Scheme patient approval process and/or State and Territory permit systems.

2. **Concern. "***the broadness of the indication (treatment resistant mental illness) included in the current MDMA proposal"*

Our Response. This can easily be dealt with by restricting the application of the rescheduling in relation to MDMA to treatment resistant PTSD or by covering this in the TGA Special Access Scheme patient approval process and/or State and Territory permit systems.

3. **Concern.** The lack of Phase 3 trials.
   Our Response. This is not unusual with the rescheduling of unregistered medicines. **The obvious example is medicinal cannabis at the time of its rescheduling**. We have already commented above on the large effect size of the first MDMA Phase 3 trial and that it reflects the findings of the six Phase 2 trials.

4. **Concern.** The problems associated with the translation from a clinical trial setting to clinical practice.
   Our Response. We dealt with the management of translation risk at length in our Applications (see Part 2.1(A)2.2 of the Psilocybine Application and Part 2.1(A)2.2 of the MDMA Application). Indeed, we have been told by State public servants operating in this area that it is perfectly normal for the pharmaceutical units of State Governments to develop policies in relation to Schedule 8 medicines to support their permit systems when the medicines have been rescheduled.

5. **Concern.** Not dispensing the substances from a pharmacy due to lack of registered products would bypass the nationally implemented real-time prescription monitoring system, hence limiting oversight and governance
   Our Response. The obvious response to this concern is to make it a condition of TGA Special Access Scheme patient approval that the substances must be dispensed by a pharmacy and part of this nationally implemented real-time system. Benefit would also be obtained from the proposed registry. In contrast to what is essentially a process issue, the benefits of rescheduling to patients with treatment resistant conditions is obvious. Provided that the diagnostic and review conditions are met and approvals received these treatment resistant patients get the

opportunity of receiving a therapy that has achieved remarkable results in trials to date.

Proposition 3. The views of the Delegate in the Interim Decision accord with the views of the Royal Australian and New Zealand College of Psychiatry (RANZCP).

The Delegate placed significant emphasis in its Interim Decisions on the views of RANZCP despite RANZCP's reputation for being slow to adopt new treatment options. This is demonstrated in its position on the use of medicinal cannabis and its slowness to adopt Trans Cranial Stimulation (commonly referred to as TMS) as a viable treatment option.

RANZCP is a unique membership organisation because it controls the awarding of the entry qualifications in this country of psychiatrists and these psychiatrists have to be members of RANZCP in order to practice their profession.

Importantly RANZCP *does not* represent the interests of patients suffering from mental illness and all peak bodies have vested interests.

One of the problems with clinical memoranda produced by RANZCP from an external readers perspective is that no information is given about the knowledge base and experience of the writers or of members of the committees that vet the drafts or of the conflicts that any person involved in the process may have.

In our responses to the interim decisions in relation to our first rescheduling applications lodged in July 2020 we noted that RANZCP's then clinical memorandum contained a significant number of errors and we sought to engage with RANZCP on these issues but without success.

We note that there is a circularity in RANZCP's latest clinical memorandum dated July 2022 because it cross refers to the TGA's Expert's Report referred to above to support its case (see our comments above on the Expert's Report).

One area of particular concern is that RANZCP fails to distinguish between the requirements for unregistered medicine and the more onerous requirements for registered medicine. As previously mentioned, we have applied for the rescheduling of MDMA and psilocybin as unregistered medicines for limited purposes. Much of what RANZCP says in in its clinical memorandum properly relates to the more onerous tests for registered medicines.

It's also noteworthy that RANZCP doesn't appear to trust its own members to prescribe these therapies even with the tight controls envisaged in our applications. Yet at the same time, as we saw in the case of **Franco Bortolin in Section 1,** polypharma and ECTs can be extensively used even though there is no trial evidence to support this practice**. Please note that we are not being critical of these practices because psychiatrists have to make difficult judgement calls in real situations in relation to very ill patients but it does feel to us like double standards**.

Having given this background we note that RANZCP does make a number of positive statements relevant to our rescheduling discussion:

- RANZCP acknowledges the "*large amount of research into psychedelic assisted therapies in the treatment of mental illness were done in the 1950s and 1960s"* with renewed interest from the late 1990s and that results of trials to date have shown minimal side effects.
- RANZCP endorses the positive statements highlighted in Section 6.2 above taken from the TGA's Expert Report including the statement that *"to date in controlled trials, with psychedelic substances at therapeutic doses …demonstrate an initial high safety ratio and low risk profile with limited psychological concerns".* We should add that there has been no indication of any deterioration in safety and risk in the long term follow ups.
- RANZCP confirm that MDMA and psilocybine are well tolerated in all studies.
- RANZCP also confirm that practical steps are used to minimise risks in patient selection (we have adopted the same approach in our rescheduling applications and training program).

- RANZCP confirm that there is minimal risk of prolonged psychotic disorders with appropriate screening.
- Whilst RANZCP refers to the risk of "bad trips" this description is a misinterpretation of the clinical experiences where the "trip" process is emotionally challenging yet leads to positive outcomes. In that sense psychedelic therapy is no different from other forms of psychotherapy where patients are exposed to events, memories or phobias that induce great stress and trauma in order to overcome them. A challenging experience (or bad trip) in psychiatric treatment is no different to pain from cutting the body in surgery. It can be necessary for optimal remediation of the underlying disorder.
- Whilst RANZCP express concern about unknown factors and side effects they fail to draw from the evidence of the widespread use of these substances for recreational purposes and from the long- term follow up studies that been done. It's therefore hard to understand why the writers of the clinical memorandum believe that these factors wouldn't be known.

RANZCP goes on to say that

> "*Some countries (including Israel, Switzerland and Canada) have expanded access to allow for MDMA and psilocybin to be used under expanded access schemes or other regulatory provisions, often on 'compassionate use' grounds for example in use in end-of-life depression and anxiety. The emerging evidence of the therapeutic potential of MDMA and psilocybin is reflected in the breakthrough designation by the Food and Drug Administration (FDA) in the USA of MDMA for PTSD and psilocybin for treatment-resistant depression. This designation indicates that the FDA believes the therapy may offer substantial advantages over current therapies and is designed to expedite a treatment's transition to a prescribed medicine subject to adequate trial results"*

This quote taken from the clinical memorandum ***does not go on*** to explain why Australians should be denied the rights that people in countries like Israel,

Switzerland and Canada have to access these medicines on compassionate grounds.

It may be that RANZCP has not been briefed on the dysfunctional nature of Australia's own Commonwealth- based expanded access scheme (the TGA's Special Access Scheme) when applied to the use of these medicines which is caused by the failure of all States and Territories around Australia to provide permit processes for the medical use of these medicines as part of therapy. RANZCP's confusion on this issue is demonstrated by the following quote:

"*In Australia, outside of clinical trials, it is possible to seek approval to supply psychedelic substances under the TGA's Special Access Scheme (Category B) or the Authorised Prescriber Scheme although, as schedule 9 substances, additional state or territory permissions may be required."*

The reality is that additional State and Territory permissions are required (to avoid breaching recreational drug laws) but are not legally available due to a lack of applicable Schedule 9 State and Territory permit systems.

RANZCP also recognises the commercial challenges with pharmaceutical companies in its 2022 clinical memorandum which highlights the need for transparency when it says that:

"*It is acknowledged that research into the therapeutic potential of psychedelic substances has been limited by legal restrictions and practical difficulties. Due to the illegal nature of the substances and the fear of harm, research trials often involve lengthy ethics approvals and complicated access pathways, which may act as barriers to research. The treatments can be expensive, and the short timeframes of application (1-2 sessions) puts limits on the potential profitability of psychedelic therapies; as a result, there are few pharmaceutical companies supporting research. Accordingly, much of the research is funded by privately funded research and educational organisations that promote the therapeutic uses of psychedelics."*

This view (which we agree with) highlights the benefits of our rescheduling proposal where these therapies can be available on a highly conditional basis

to “at risk” treatment resistant patients on compassionate grounds and data can be collected through the proposed registry.

To summarise. Of course more research is needed. That same statement would apply for most psychiatric medicines. But the need for further research shouldn’t stop patients on compassionate grounds accessing these therapies with appropriate approvals. This is exactly why we have unregistered medicines and a Special Access Scheme.

The question that we believe should be answered by RANZCP (and the Delegate) is this.

If you were sitting across the table from Mrs Bortolin’s husband, Franco, before he committed suicide and were properly briefed on his condition and on all of the failed treatments that he had experienced, would you still deny Franco access to these therapies on compassionate grounds given the terrible consequences that you know would occur with such a denial?

<u>Proposition 4. Whilst the controls proposed could theoretically ensure the benefit for treatment resistant patients is realised, they ignore the way they would operate in practice under State and Territory legislation.</u>

We found this to be a particularly troubling proposition. The current system of medical treatment has, by definition, failed a significant number of patients. These patients are glibly referred to by the system as “treatment resistant”. But this nomenclature completely ignores the suffering of these people and the fact that, for some, the suffering will become so bad that suicide is seen as a way out.

In these circumstances we respectfully submit that it defies the principle of good government and the need for compassion that appropriate policies can’t be developed by State and Territory Health Departments. If “*States and Territories do not have established mechanisms to give effect to the controls in the current psilocybine and MDMA proposals relating to training, including accreditation by an appropriate body or to oversee the requirements for review by two additional psychiatrists”* then frankly (when people are suffering

terribly because of system failure and some of these people are committing suicide) the States and Territories should develop those mechanisms.

Our frustration with these statements is highlighted by the fact that this is exactly what the Province of Alberta in Canada and the State of Oregon (and now potentially Colorado) in the United States is doing. Holland is also a first world country and these types of issues have not been a barrier to patient access.

Proposition 5. Whilst expanded access schemes have been instituted in countries including the United States, Israel and Switzerland under compassionate access grounds these are analogous to the current use of the Special Access Scheme in Australia which allows patient access to Schedule 9 substances

With respect, this is absolute nonsense. Yes, it has been possible for psychiatrists in Australia to apply for and receive Special Access Scheme approvals from the TGA to treat a treatment resistant "at risk" patient with these therapies. However, there are no permit systems currently available in any State or Territory of Australia that would enable a psychiatrist to legally use these therapies, despite this TGA approval. At the moment, we have a dysfunctional federal system in relation to the use of these substances whilst they remain in Schedule 9 and as a result "at risk" treatment resistant patients are paying the price for this, some with their lives.

Proposition 6. There are still no approved therapeutic products containing either substance anywhere in the World

We are not sure what the relevance of this is. Registration of a medicine is not a prerequisite for rescheduling and as discussed above these substances are being made available to treatment resistant "at risk" patients in a number of overseas countries without any adverse reports.

Proposition 7. The views of RANZCP and the Australian Psychological Society (APS) apparently outweigh the overwhelming number of supportive submissions lodged, the views of leading Researchers in the field such Professor David Nutt and Professor Arthur Christopoulos and from front-line Health Sector Experts (many of whom are members of these peak bodies).

We have already discussed the position of RANZCP under Proposition 3 above but we note again that RANZCP is not an organisation that has been set up to represent the interests of patients. We believe that in the interests of transparency discussions that have taken place between RANZCP and representatives of the TGA or more broadly the Commonwealth Department of Health should be fully disclosed.

Governments are increasingly on record as saying that the views of patients with lived experience are important and need to be properly considered. This is at odds with the Delegate's reliance on RANZCP and APS.

As far as the Australian Psychological Society (APS) is concerned we should also note that APS is a member- based organisation representing the interests of only about 20% of psychologists in this country. APS does not exist to protect the interests of patients although it recognises and promotes the principle of beneficence.

However, the APS submission makes it clear that its comments relate to "the widespread adoption of psychedelic assisted therapy" which is associated with the registration of a medicine on the Australian Therapeutic Good Register. But rescheduling of an unregistered medicine is not by definition about widespread use given the constraints of the TGA's Special Access Scheme

This difference between the widespread usage of a registered medicine and narrow usage of an unregistered medicine on compassionate grounds perhaps explains why APS ticked the "no comment" box when lodging its submission rather than one of the "for" or "Against" boxes.

The APS makes no mention in its submission about the appropriateness of rescheduling these substances as ***unregistered medicines*** so that they would be available to patients "at risk" who satisfied the treatment criteria under the

TGA's Special Access Scheme on a case-by-case basis with supporting Schedule 8 State/Territory permits.

Perhaps the Delegate should ask the APS the same question that I suggested the Delegate should ask RANZCP:

If you were sitting across the table from Mrs Bortolin's husband, Franco, before he committed suicide and were properly briefed on his condition and on all of the failed treatments that he had experienced, would you still deny Franco access to these therapies on compassionate grounds given the terrible consequences that you know will occur with such a denial?

8. CONCLUSIONS

We believe that there is more than sufficient evidence to justify a decision by the Delegate to reschedule the restricted use of psilocybine and MDMA as part of therapy for treatment resistant mental illnesses (and specifically treatment resistant depression and treatment resistant PTSD if the Delegate wishes to restrict the rescheduling in this way).

We believe, based on the evidence and the weight of opinion available to the Delegate, that it is in order for the Delegate to form a judgement that the Schedule 8 tests for rescheduling have been satisfied. Medicines always benefit from more trials (and this is true even for registered medicines) but there comes a point when there is enough data available and compassion requires affirmative action.

Rescheduling doesn't mean widespread access. As these are currently unregistered medicines, approvals will be required by the treating psychiatrists from both the TGA (under the Special Access Scheme) and the State or Territory government where the treatment is proposed to occur ***on a patient specific basis***. There are plenty of checks and balances.

It's simply not good enough for members of the ACMS representing State and Territory Governments to argue about process when people with treatment resistant depression and/or treatment resistant PTSD are literally committing suicide because of the unbearable suffering associated with their conditions and the failure of current treatments. All these governments need to do is to develop appropriate policy controls, something that they have done for all of the other medicines that are currently listed in Schedule 8.

APPENDICES

A. Supporting letter from leading Australian- based neuropharmacologists Professor Arthur Christopoulos and Professor Chris Langmead from the Monash University Faculty of Pharmacy and Pharmaceutical Sciences and the Monash Neuromedicines Discovery Centre. Professor Christopoulos is Dean of the Faculty which is ranked number 1 in the World in its field.

B. Supporting Letters from World renowned neuropsychopharmacologist Professor David Nutt who is head of neuropsychopharmacology at Imperial College, London, Chairman of Drug Science and one of the World's leading researchers in psychedelic assisted therapies.

C. Letter from Mrs Bortolin to her local member, Prime Minister Anthony Albanese, about the death by suicide of her husband Franco Bortolin, his treatment resistant mental illness, his failed treatments and her belief that with psychedelic assisted therapy her husband would still be alive today.

D. Letter From Mr Graham Daniels about the immense suffering of his wife, Lianne Daniels, from treatment resistant depression, her large list of failed treatments over decades and Mr Daniels belief that psychedelic assisted therapy would give her a chance to lead a more normal life.

E. Letter From Psychiatrist Dr Stuart Saker on the desperate plight and immense suffering of the ADF Veterans that he treats, the high levels of suicide risk amongst veterans with treatment resistant mental illnesses and the need for access to psychedelic assisted therapies on compassionate grounds.

F. Submission from Dr Simon Longstaff, the Executive Director of the Ethics Centre and Australia's preeminent ethicist.

G. Offer from the Neuromedicines Discovery Centre at Monash University to host an independent clinical treatment registry to collate treatment information from psychiatrists and their patients if the medicines are rescheduled.

H. Goodwin et al (2022) Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. The New England Journal of Medicine Vol 387 No 18 pages 1637 - 1648.

I. Mitchell et al (2021) MDMA-assisted therapy for severe PTSD; a randomised double-blind placebo-controlled phase 3 study. Nature Medicine 27:1025 -1033

J. Email from MAPS dated 14th April 2022 advising on the estimated number of patients in MDMA trials pre and post prohibition.

K. Submission from the Australia Institute and the trauma charity Fearless to the TGA on Diversion Risk dated May 2022.

MIND MEDICINE
AUSTRALIA

Appendix A

Supporting letter from leading Australian- based neuropharmacologists Professor Arthur Christopoulos and Professor Chris Langmead from the Monash University Faculty of Pharmacy and Pharmaceutical Sciences and the Monash Neuromedicines Discovery Centre. Professor Christopoulos is Dean of the Faculty which is ranked number 1 in the World in its field.

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1st March 2022

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Yours sincerely,

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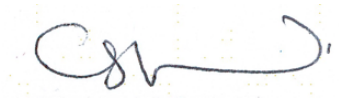

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References

1. https://www.pc.gov.au/inquiries/completed/mental-health/report
2. Whitaker, R. (2011) Anatomy Of An Epidemic. Crown Publishers, NY. ISBN: 9780307452429.
3. Mithoefer et al. (2019) MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacol*. 236: 2735.
4. Jerome et al. (2020) Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacol*. 237: 2485.
5. Bahji et al., (2020) Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. *Prog. Neuropsychopharmacol*. *Biol. Psych.* 96: 109735.
6. Mitchell et al. (2021) MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat. Med.* 27:1025–1033
7. Rothman and Baumann (2002) Therapeutic and adverse actions of serotonin transporter substrates. *Pharmacol. Ther*. 95: 73.
8. Shellenberg et al. (2020) An update on the clinical pharmacology of methylphenidate: therapeutic efficacy, abuse potential and future considerations. *Exp. Rev. Clin. Pharmacol.* 13: 825.
9. Hysek et al. (2014) Pharmacokinetic and pharmacodynamic effects of methylphenidate and MDMA administered alone or in combination. *Int. J. Neuropsychopharmacol*. 17: 371.
10. Shoblock et al. (2003) Neurochemical and behavioral differences between d-methamphetamine and d-amphetamine in rats. *Psychopharmacol.* 165: 359.
11. Bonomo et al. (2019) The Australian drug harms ranking study. *J. Psychopharmacol.* 33*:* 759*.*

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12. Mithoefer et al. (2011) The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J. Psychopharmacol.* 25: 439.
13. https://maps.org/research/mdma/ptsd/phase3.
14. Nutt et al. (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nature Rev. Neurosci.* 14: 577.

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MIND MEDICINE
AUSTRALIA

Appendix B

Supporting Letters from World renowned neuropsychopharmacologist Professor David Nutt who is head of neuropsychopharmacology at Imperial College, London, Chairman of Drug Science and one of the World's leading researchers in psychedelic assisted therapies.

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Drug Science

The Secretary

Medicines Scheduling Unit

Therapeutic Goods Administration

Canberra, ACT.

London, 23/02/2022

Dear Sir/Madam,

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

We note that the rescheduling proposed by Mind Medicine Australia in its application is very restrictive;

SCHEDULE 9 – Proposed Amended Entry

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

SCHEDULE 8 – Proposed New Entry

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

a) used as part of psychotherapy in medically controlled environments; and
b) under the authorisation of a treating psychiatrist who has received specific training in the use of this substance as part of therapy; and

c) where the patient's diagnosis and the proposed treatment plan has been confirmed by at least two independent reviewing psychiatrists ; and
d) where the substance has been manufactured in accordance with the *Narcotic Drugs Act 1967and/ or* ;
e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or
f) in therapeutic goods supplied in accordance with the *Therapeutic Goods Act 1989*.

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

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

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

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

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

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

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

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

Key Findings of the Compass Pathways Phase 2b Trial

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

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

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

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

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

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

The adverse events were manageable and consisted of:

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

Treatment-emergent adverse event (TEAE) incidence:

83.5% (66 patients) in 25mg group

74.7% (56 patients) in 10 mg group

72.2% (57 patients) in 1 mg group

Drug Science

Treatment-emergency serious adverse event (TESAE) incidence:

6.3% (5 patients) in 25mg group

8.0% (6 patients) in 10 mg group

1.3% (1 patient) in 1mg group

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

Table 2. Primary and Secondary Outcomes.*

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

Adverse events were also low and easily manageable.

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

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

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

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

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

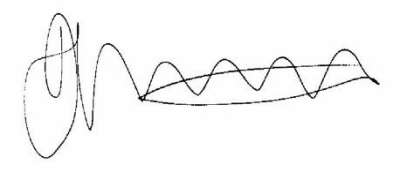
[2] Gukasyan N, Davis AK, Barrett FS, et al. (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of Psychopharmacology* 36(2). SAGE Publications Ltd STM: 151–158. DOI: 10.1177/02698811211073759.

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

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

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

Yours sincerely



Prof David Nutt and the Drug Science Scientific Committee

Prof Jo Neill

Dr David Erritzoe

Drug Science is the leading independent scientific body on drugs in the UK. We work to provide clear, evidence-based information without political or commercial interference.

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

Drug Science

The Secretary

Medicines Scheduling Unit

Therapeutic Goods Administration

Canberra, ACT.

London, 23/02/2022

Dear Sir/Madam,

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

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

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

The Mind Medicine Australia Proposal

SCHEDULE 9 – Proposed Amended Entry

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

SCHEDULE 8 – Proposed New Entry

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

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

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

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

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

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

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

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

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

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

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

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

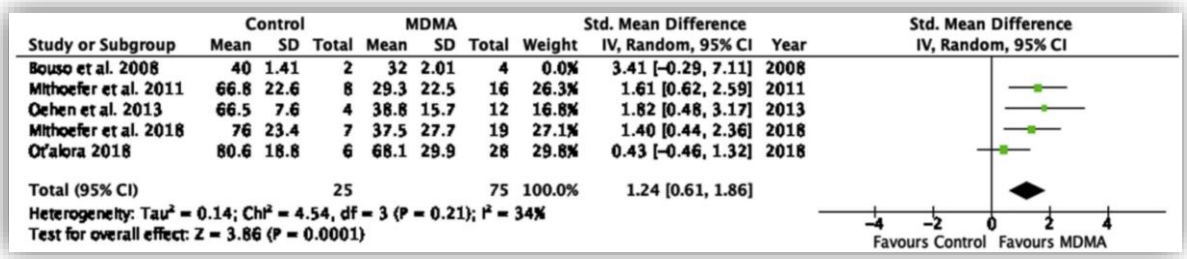
- Significant media and online anecdotal evidence from people who have taken MDMA-therapy outside of the legal medical system.

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

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

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

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



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

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

Through a series of worldwide trials, MAPS has finalised a Phase 3 trial and multiple Phase 2 trials for the use of MDMA-assisted psychotherapy in the treatment of PTSD. Participants underwent two or three 90-minute preparatory psychotherapy sessions which were followed by two to three supervised MDMA (or placebo) sessions. The data across Phase 3 and Phase 2 trials showed that MDMA assisted psychotherapy had a 54.2% remission rate for treatment resistant PTSD sufferers, compared to 23% in the placebo group. Across these Phase 2 and Phase 3 trials the dropout rate was also low which illustrates MDMA's tolerability and strong patient adherence.

The MAPS Phase 2 trials were conducted between 2004-2017 with a total of 103 participants. In the follow ups of two of these studies, it was also found that following treatment with MDMA assisted psychotherapy, patients continued to improve in their mental wellbeing.

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

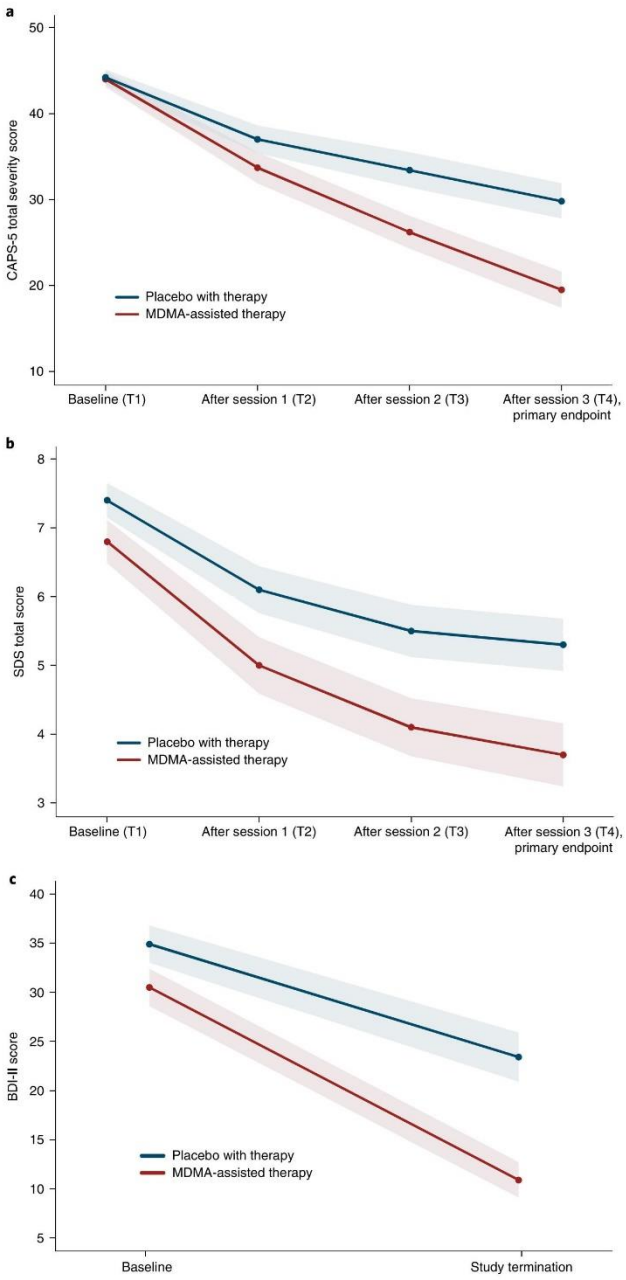


Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an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

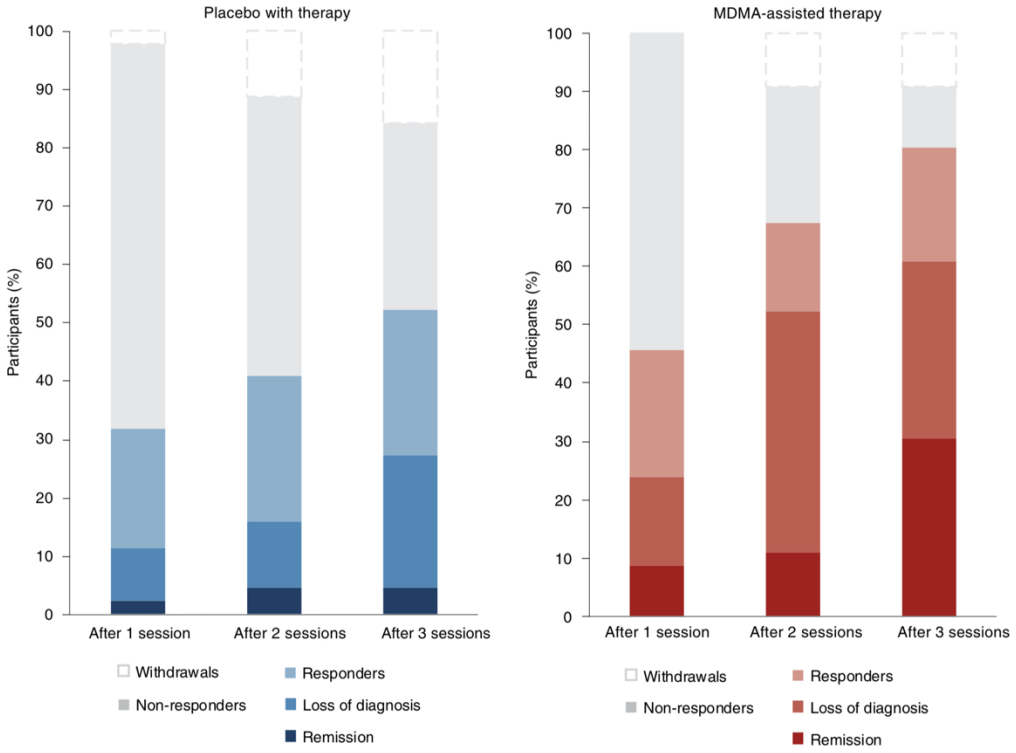


Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure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

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

Table 2 | Participants with treatment-emergent SAEs and AESIs

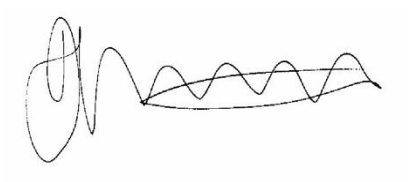
	MDMA ($n=46$), n (%)	Placebo ($n=44$), n (%)
SAEs	–	2 (4.5)
Suicide attempts	–	1 (2.3)
Suicidal ideation resulting in self-hospitalization	–	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	–
Suicidal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

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

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

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

Yours sincerely



Prof David Nutt and the Drug Science Scientific Committee

Prof Jo Neill

Dr David Erritzoe

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MIND MEDICINE AUSTRALIA

Appendix C

Letter from Mrs Bortolin to her local member, Prime Minister Anthony Albanese, about the death by suicide of her husband Franco Bortolin, his treatment resistant mental illness, his failed treatments and her belief that with psychedelic assisted therapy her husband would still be alive today.

hello@mindmedicineaustralia.org
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Level 1/10 Dorcas St
Southbank Vic 3006
Australia

A Letter to Anthony Albanese

7th of November 2022

4TH November 2022

To my local member, Anthony Albanese,

Please read and re-read my letter. I have lived in your electorate for 37 years and have delivered pamphlets for your initial campaign.

I'll never forget the morning I woke up contemplating whether to help my husband - and father of our young daughter - take his own life.

He had been suffering so deeply, for so long, until we had finally reached the point of exhausting every option Australia's medical system had to offer.

And whilst to people like my husband, suicide presents itself as an accessible option, in this country, seeking psychedelic assisted psychotherapy under the close supervision of a psychiatrist, is not.

Anthony, if this doesn't highlight the absurd cruelty of the TGA's current stance on psychedelic medicines, then frankly, I don't know what will.

In what world is it fair to deny treatment-resistant Australians access to these potentially life-saving medicines under the guise of "keeping them safe"?

Born and bred in the inner west of Sydney, my husband Franco was a successful businessman who loved his family. We were married for 30 wonderful years and spent the 11 of them raising our beautiful daughter Zara.

On the 5th of April 2018, Franco - who had rarely ever been ill - wakes up to tell me he needs to see a doctor urgently. Upon his first session, Franco was diagnosed with a severe form of clinical depression, prescribed an antidepressant, and referred to both a psychiatrist and a psychologist.

Four weeks later my husband is admitted into a private hospital where his medication is changed for the first time, but not for the last.

Only four weeks after admission, the doctors started Franco on a course of ECT, Electric Convulsive Therapy - a process whereby electricity is passed through your brain to induce a seizure to treat mental illness.

Two doses of ECT later, he is transferred to Concord Hospital where under the supervision of the tribunal, he is hospitalised for another 3 months and administered a further 22 ECTs.

After four months in the hospital, my husband comes home.

What follows over the coming three years is a further seven hospitalisations, totalling in nineteen months in hospital, where he was administered a staggering 96 ECTs, 24 Transcranial Magnetic Stimulations (TMS) and prescribed 19 different antidepressants and antipsychotic drugs. You can read more about all of Franco's doctors, hospitals, treatments on the attached Appendix.

All of this at the cost of tens of thousands of dollars and endless heartache for Franco, myself and our family.

Worse still, the side effects from Franco's treatment were so severe that he could no longer remember the route to his own daughter's school, let alone his mother's house just around the corner. It was devastating for me to witness the man I love, a man who had always been so highly functional, no longer remember how to get to his own mother's house barely down the road.

This was Franco's reality, and this remains the reality for the thousands of Australians suffering from treatment-resistant mental illnesses today.

Franco was one of the strangest men I've ever known, but after years of futile attempts at getting better, he began to lose hope, as did I.

That was until I saw the 60 Minutes program on Psychedelic Medicines, prompting me to reach out to Australian journalists for more information. From there, I was then referred onto Mind Medicine Australia, a charity advocating for the clinical use of Psychedelic-Assisted Therapies. After years of seeking help to no avail, it was a relief for our family's suffering to finally be heard, but more so, to see a progressive change on the horizon for Australia's treatment of mental illness.

I began to feel reassured when I heard of the remarkable overseas progress of psychedelic therapies within treatment-resistant populations. Even more promising was that these positive results were occurring after just two to three medicinal sessions alongside a short course of psychotherapy.

All up, Franco spent over a year and half of his life in hospital, was administered shock therapy almost a hundred times and trialled every class of anti-depressant available to him.

To hear of these clinically trialled medicines that helped patients make meaningful progress in just two to three sessions, reinvigorated me with hope. I felt this was our only solution, we had tried everything else and seen the leading experts in NSW. To me, Psychedelic-Assisted Therapies seemed like the only way I could keep my husband alive.

But, on October 21ST 2022 the TGA once again denied access to Psychedelic Medicines, citing insufficient evidence to warrant their rescheduling for therapeutic use. This is despite over 13,000 submissions to the TGA. Over 98% of those were in favour of rescheduling both Psilocybin and MDMA as Controlled Medicines for use in clinical environments for people who are suffering unbearable pain, like my husband.

Yet, mounting evidence from over 200 peer-reviewed studies around the globe has continually demonstrated the safe and effective use of these medicines in clinical settings.

Just recently, a trial at Imperial College London showed that remission rates for depression were twice as high for those who underwent just two treatments of psilocybin with a short course of psychotherapy, versus patients who were administered a daily dose of a leading anti-depressant in combination with psychotherapy.

Even Franco's key psychiatrist was in support of Psychedelic-Assisted Therapy, with the crucial caveat being, that it must be administered and closely monitored under the supervision of a qualified therapist.

Anthony, this is all that we wanted.

Our request was, and still is a simple one. It is fair and reasonable in its logic.

Whilst Australia drags its feet, these therapies are being administered right now, in places like Canada, USA, Switzerland, Israel and other more progressive nations.

Anthony, why should Australians have to break the law or travel overseas to access these safe and effective treatments when all else has failed?

I was so desperate to help my husband that I even considered going to an "underground" therapist, but my family urged me not to, because under current Australian law, that would make me a criminal. I couldn't risk that. And I couldn't risk taking him overseas to a country where these treatments are legal due to his suicidal ideation. I couldn't do that to our daughter.

It was an impossible choice.

Then the day came that I had to make the heartbreaking decision to hospitalise my husband once again. Every day I listened as he told me that he wanted to die, begging me to help him. I'm his wife, we share a child together, and I'm left to make this excruciating decision because

there's nowhere else to turn, nothing else I can give him, there's nothing more I can do.

I also became terrified for our daughter, and the impact this would have on her for the rest of her life.

And this is why, one morning I woke up contemplating helping the man I love to kill himself.

Anthony, you tell me, if your partner was suffering unbearably and wanted to end her life, what would you do? Have you personally experienced someone close to you suffering such severe depression that they are trying desperately and repeatedly to end their life?

For me this isn't some hypothetical plucked from an ethics case study.

This is my lived experience.

This is my reality.

Sadly, my family will never get a chance to find out if Psychedelic-Assisted Therapies could have saved my dear husband's life.

My daughter and I will never know.

Because... two weeks after being released from hospital, Franco took his own life.

He couldn't hold on any longer.

What breaks my heart is that this is a shared reality for so many Australian families, people who are on the brink of society struggling silently, waiting for access to these medicines. Waiting for an anonymous bureaucrat (the Delegate) with a stroke of their pen, to give Australians access to the same therapies that Canada, USA, Germany, Switzerland, Portugal, Israel, the Netherlands and other nations already have.

And whilst there isn't a day that goes by that I don't miss Franco, he is not the one that I blame.

I blame the regulator so disconnected from the suffering of the people it claims to serve. I blame the Government that would rather let innocent people suffer and die than legalise innovative therapies that are continually proven to be both safe and effective.

The saddest part is, that I know that this truth will eventually be revealed.

But Anthony, every day that we wait, people die.

We are better than this.

Anthony, you were elected on a mandate of compassion. It is time for change. Access to safe and effective medical treatment is a basic human right.

Anthony, you can help put a stop to the immense suffering in this nation.

Please reschedule these substances for therapeutic use.

Please don't let another child lose a parent to suicide.

In light of this, I request a personal meeting with you – my local representative – to express my concerns directly so that together, we can find a way forward for all those suffering.

Sincerely,

Vanessa

Appendix – Medications, Procedures & Detailed Summary

Medication taken since start of illness 6th April 2018

Prescribed by	Name of drug	dosage	start	finish	side effects	Type
Main Antidepressant						
GP	Escitalopram	10mg	06-Apr-18	27-Apr-18	3rd day very bad & lost sleep etc	SSRi
Dr Paisley	Venlafaxine	300mg	28-Apr-18	13-Jul-18	constipation	SNRI
Concord	Sertraline	??	13-Jul-18	25-Jul-18	suicidal thoughts increased	SSRI
Concord	Nortriptyline	200mg	25-Jul-18	08-Dec-18	headaches, fatigue, blurred vision	Tricyclic
Dr Paisley	Parnate	60mg	10-Dec-18	17-Feb-19	Diarrhea, weak, tripping over, low BP	MAOI
Dr Paisley	Dothiepin	200-225mg	08-Mar-19	01-Apr-19	worse headaches (migraine)	Tricyclic
Dr Paisley	Cymbalta	120mg	27-Jun-19	15-Apr-20	ok (brain zapping when withdrawing)	SNRI
Dr Paisley	Brintellix	20mg	16-Apr-20	04-Jun-20	ok	SSRI
Prof Phillip Mitchell	Bupropion (Zyban)	150mg/150mg	05-Jun-20	08-Jul-20	ok but not great. Became worse when increasing dose (brain zapping when withdrawing)	NDRI
Prof Phillip Mitchell	Clomipramine	150mg	01-Sep-20	09-Oct-20	very confused, increase loss of memory, blurry vision, very high agitation	Tricyclic
Dr Paisley	Desvenlafaxine	400mg	18-Dec-20		ok	SNRI
Dr Caetano	Amitriptyline/Bupropion					
Additional antidepressants, Antipsychotics etc added to main Antidepressants						
Dr Paisley	Olanzapine	5mg-10mg	20-Apr-18	13-Sep-19	used various times	Atypical antipsychotic
Concord	Quetiapine IR	200mg	30-May-18	29-Aug-18	akathisia	Atypical antipsychotic
Concord	Mirtazapine	30mg	30-May-18	25-Jul-18		antidepressant
Concord	Lithium	1250mg	01-Aug-18	02-May-19	fatique	Bi-polar drug
Dr Paisley	Agomelatine	25mg	17-Oct-18	03-Jan-19	increase fatique	Atypical antidepressant
Dr Paisley	Lurasidone (Latuda)	40-80mg	21-Nov-19	15-Jan-19	Parkinsonian, weak,	Atypical antipsychotic

Dr Paisley	Aripiprazole (Abilify)	10mg	21-Sep-19	Cont'd	Goes to bed early very sleepy. Pacing, Tik with lips blowing bubbles. Coming off it insomnia (needed lorazapam). Few days thinking of death	Atypical antipsychotic
Other Drugs taken						
Dr Paisley	Tertroxin	40mg	17-Feb-19	26-Mar-19		Thyroid
Dr Paisley	Lorazapam	2.5-7.5mg	27-Apr-18		Best medication	Benzo
prof Parker	Alprazolam	2mg twice day	03-Jun-19		not as effective at Lorazapam	Benzo
Concord	Promethazine	25mg	30-May-18			Sleeping
Dr Paisley	Neurofolin	1 satchel	21-Nov-18	08-Feb-19	didn't help	
Dr Paisley	Ritalin		15-Feb-19	various times	didn't help	
Prof Phillip Mitchell	Lithium	250/250	27-Jun-20	various times	very weak and slow. Sleep efected	

Procedures done

ECT	St John of God	21-May-18	23-May-18	2	Unlateral
	Concord hospital (involuntary)	30-May-18	06-Jun-18	4	Unilateral
	Concord hospital (involuntary)	08-Jun-18	03-Aug-18	20	Bilateral
				26	
	St John of God	01-Jul-19	21-Aug-19	23	Bilateral
	St John of God (outpatient)	26-Aug-19	07-Oct-19	6	Bilateral
				29	
	Northside	09-Jul-20	11-Aug-20	12	bi frontal with ketamine
	Northside	13-Aug-20	01-Sep-20	7	bi-temporal without ketamine
	Northside-increased to level 8	03-Sep-20	03-Sep-20	1	bi-temporal (HIGH)with ketamine
	Royal North Shore (involuntary)	11-Sep-20	26-Oct-20	15	bi-temporal(HIGH) with ketamine
	St John of God (outpatient)	30-Oct-20	16-Nov-20	6	bi-temporal(HIGH) NO ketamine
				41	
	TOTAL ECT to date			96	

TMS	St John of God (outpatient)	29-Oct-18	30-Nov-18	25	No improvement

Detailed Summary

Date:	Prescribed by:	Drug (brand name)	dosage	Start	end	Other drugs taken	side effects
05-Apr-18	**NOTE:**	**Woke up and he couldn't work out what was wrong. He asked to see doctor straight away - 5th April 2018**					
05-Apr-18	GP	**NEW** Escitalopram (lexapro)	10mg	6/4/2018	27/4/2018		Suicidal 3 days into taking drug, sleepless, loss of appetite
	NOTE:	3 days in to taking drug his condition deteriorated. Sleepless, loss of appetite, agitated, restless					
	NOTE:	Week into illness friend asked him about funeral he attended a week before illness and he could not remember anything. Asked him about other events over a 4 month period prior to illness and nothing. ie annual work conference for a week in blue moutains, moving into new house late Dec 2017, conversations had with various friends					
	NOTE:	Tried 2 clinical psychologist. Father in law living with us tried helping with meditation, going for walks, talking. Nothing was working. Everyday his condition worsened. Requested appt to see a psychiatrist					
20-Apr-18	consulting psychiatrist					**ADD 20/04/18** Olanzapine 5mg	Sleep got worse
	NOTE:	2 days after taking Olanzapine he stopped sleepingl. 4 days later he was referred to hospital					
27-Apr-18	**HOSPITAL**	**Admission 27th April 2018 - St John of God (Burwood) - Treating Psychiatrist Dr Shannon Paisley**					
	NOTE:	Diagnosed with Melacholic Depression upon admission - had all symptoms - highly agitated and couldn't sit still. Of course the idea of coming into hospital played role in his state of mind upon entering					
	Psychiatrist Paisley	**NEW** Venlafaxine 300mg (efexor)	37.5mg increased to 300mg	28/4/2018		Olanzapine 5mg. **ADD 28/04/18** Lorazapam 2.5mg PRN	Lorazapam was a life saver
	NOTE:	2 weeks after admission Doctor talked about ECT if his condition did not improve with the meds at end of week 3. Lorazapam helped with his agitation and various sleep tablets meant he could sleep a little. He would always say he was never fully asleep when they checked on him. Unable to interact with others. No feeling. Always restless. Could not sit down. Cried a lot "begging for help". Lorazapam always helped him					
21-May-18	**PROCEDURE**	**ECT (2 x unilateral) commenced Monday 21 May 2018 - refused 3rd ECT**					
	NOTE:	First night of ECT and he started to tell me his penis was getting smaller which meant he could not urinate at all. Sleep was effected. NO bowel movements					
	NOTE:	Became delussional the night after 2nd ECT - refused 3rd ECT and did not want to eat. Penis not functional and part of brain disappeared. Couldnt sleep or go to the toilet. Treating Psychiatrist came to see him to try and work it out but unfortunately nursing staff felt he was at risk therefore transferred to Concord					

25-May-18	**HOSPITAL**	**Involuntary transfer 25 May 2018 - Concord Hospital**					
30-May-18	**PROCEDURE**	**Involuntary ECT (24 sessions) commenced Monday 30 May 2018 - finished 3rd August 2018**					
		(4 x unilateral) and (20 x bilateral). Tribunal approved 2 lots of 12 ECT sessions 29th May and 26th June					
	Concord Hosp (1st psych)	Venlafaxine (efexor)	300mg		13/7/2018	Olanzapine 5mg. Lorazapam 2.5mg PRN. **ADD 30/05/18:** Mirtazapine 30mg, Promethazine 25mg and quetiapine IR 200mg	ok
02-Jun-18	**NOTE:**	**day after 2nd ECT and he started saying he wanted to die. The pain he was feeling was too hard to bear**					
23-Jun-18	**NOTE:**	**Weekend leave started. He was able to sleep through night and shower himself but still pacing**					
13-Jul-18	Concord Hosp (1st psych)	**NEW** Sertraline (Zoloft)	???	13/7/2018	25/7/2018	Mirtazapine 30mg. Quetiapine IR 200mg Olanzapine 5mg. Lorazapam 2.5mg PRN.	suicidal thoughts increased
14-Jul-18	**NOTE:**	**Extended Weekend leave as they thought he might be able to leave soon. Over weekend he was very BAD and wanted to die. Returned to hospital**					
17-Jul-18	**NOTE:**	**2 good days in hospital after I had told him that I couldn't come to hospital anymore if he didn't stop talking about dying. Seemed to shock him into thinking I was leaving him and he told the nurses he needed to get better. His mood improved and he interacted with other patients.**					
20-Jul-18	**NOTE:**	**SUICIDAL: Social outing with other patients on bus. Franco tried to open van door and jump out when crossing Birkenhead Pt**					
23-Jul-18	**NOTE:**	**SUICIDAL: Day out with Zara and I at park and he started to say he couldn't go on and was saying goodbye to us. Headed to parramatta road and I had to get daughter to run after him and stop him. WORSE DAY**					
24-Jul-18	**NOTE:**	**Hospital requested extension of involuntary time in hospital after previous day incident and new Psychiatrist Dr Chowdrey was assigned. Psychiatrist on panel had been very concerned as to how hospital had been managing Franco and whether so much ECT was necessary etc**					
25-Jul-18	Concord Hosp (2nd psych Dr Chowdrey)	**NEW** Nortriptyline	75mg increase to 125mg night	25/7/2018		**ADD 01/08/18** lithium 750mg (250mg/500mg). Quetiapine XR 200mg Olanzapine 7.5mg	headaches, little fatigue

02-Aug-18	**NOTE:**	**Franco able to start communicating with others. Shower himself. Participate in group activities. Sleep better. Wasn't crying anymore and didn't feel helpless. Started going on daily group walks around hospital**					
19-Aug-18	**NOTE:**	**Franco was still not his old self. He couldn't understand why hopsital was discharging him. He had constant headache and was fatigued. He was however SAFE**					
20-Aug-18		**Released from Concord 20th August 2018**					
29-Aug-18	Psychiatrist Paisley	Nortriptyline	125mg			**INCREASE 29/08/18** lithium 1000mg (500mg/500 mg). **INCREASE** Olanzapine 10mg. **CEASED** Quetiapine (30/05/18 to 29/08/18)	headaches, little fatigue. Quetiapine ceased due to Akathisia
12-Sep-18	Psychiatrist Paisley	Nortriptyline	**INCREASE 12/9/18**150mg (50mg/100mgmorn/ night)			Lithium 1000mg, Olanzapine 10mg	Headaches & Fatique (dragging legs). Low stamina
17-Oct-18	**NOTE:**	**Agitated as mood not improving. TMS was suggested to see if that would help. Sleep good**					
17-Oct-18	Psychiatrist Paisley	Nortriptyline	150mg (50mg/100mgmorn/ night)			**INCREASE 17/10/18** Lithium 1250mg (500mg/750 mg). **REDUCE** Olanzapine 5mg **ADD** Agomelatine 25mg night	"as above"
29-Oct-18	**PROCEDURE**	**Commenced TMS at St John of God Burwood as an OUTPATIENT (25 sessions) 29th October to 30 November 2018**					
31-Oct-19	Psychiatrist Paisley	Nortriptyline	150mg (50mg/100mgmorn/ night)			Lithium 1250mg, Agomelatine 25mg **31/10/19 REDUCE** Olanza 2.5mg	"as above"

01-Nov-18	Psychiatrist Paisley	Nortriptyline	**INCREASE 01/11/18** 200mg (100/100mg morn/night)			Lithium 1250mg (500mg/750 mg), Agomelatine 25mg, olanzapine 2.5mg	Headaches & Fatique (dragging legs). Low stamina
08-Nov-18	**NOTE:**	**Not a good day. Feeling very down and hopeless**					
21-Nov-18	Psychiatrist Paisley	Nortriptyline	200mg (100/100mg morn/night)			Lithium 1250mg (500mg/750 mg), Agomelatine 25mg. **ADD** Latuda 40mg **REDUCE** olanzapine NIL. **ADD** Neurofolin satchel 1 daily	Latuda clumsy and weak. Continued headaches
26-Nov-18	**NOTE:**	**Very bad day. Started to talk about dying. Agitated etc. Needed to get him into hospital**					
29-Nov-18	**HOSPITAL**	**Admission to St John of God (Burwood) 29 November 2018 - Psychiatrist Dr Shannon Paisley**					
01-Dec-18	Psychiatrist Paisley	**REMOVE** Nortriptyline	Reduce to NIL over 8 days		8/12/2018	Lithium 1250mg (500mg/750 mg), Agomelatine 25mg. **INCREASE 03/12** Latuda 80mg. Neurofolin satchel 1 daily **ADD** PRN olanzapine 2.5mg	Latuda clumsy and weak. Continued headaches
10-Dec-18	Psychiatrist Paisley	**NEW** Parnate	10mg increase to 40mg (morn/mid)	###### ##		Lithium 1250mg (500mg/750 mg), Agomelatine 25mg. Latuda 80mg. Neurofolin satchel 1 daily **ADD** PRN Lorazapan 1mg. **ADD** Vitamin D	Diarrhea,weak,low BP, parkinsonian. Numbness in mouth
18-Dec-18		**Released from SJOG Burwood 18th December 2018**					

18-Dec-18	**NOTE:**	**Not suicidal. Good communicate and not agitated. Was however very unbalanced, Diarrhea. Not able to drive. Cognitively impaired. Could not make decisions. NO more headaches**					
03-Jan-19	Psychiatrist Paisley	Parnate	**INCREASE 03/01/19** 60mg (30mg/30mg) (morn/mid)			Lithium 1250mg (500mg/750 mg), Latuda 80mg. Neurofolin satchel 1 daily. Vitamin D and B6, Evening Primrose **CEASE** Agomelatine (17/10/18 to 01/01/19).	Diarrhea,weak,low BP, parkinsonian.
15-Jan-19	Psychiatrist Paisley	Parnate	60mg (30mg/30mg) (morn/mid)			Lithium 1250mg (500mg/750 mg), Neurofolin satchel 1 daily. Vitamin D and B6, Evening Primrose **CEASE** Latuda (21/11-15/01/19)	Diarrhea,weak,low BP. Removing Latuda due to parkinsonian symptoms
04-Feb-19	**CONSULT**	**4th Feb 2019 - Consulted Professor Gordon Parker (Parnate to be removed due to side effects). Requested we see Neurologist to run extensive test to rule out other causes**					
08-Feb-19	Psychiatrist Paisley/Parker	**REMOVE** Parnate	**REDUCE 8/2/19** to NIL over 12 days		17/2/2019	Lithium 1250mg (500/750), Vitamin D and B6 plus Evening Primrose, Zinc, Magnesium. **CEASE** Neurofolin satchel (21/11/18-8/2/19)	
	CONSULT	**13th Feb 2019 - Neurologist A/Prof James Burrell - results came back ALL clear**					
		CT scan, MRI (brain), Lumber Puncture (Concord Hosp), RPA Pet Scan (brain and body), Blood Test (auto immune)					
17-Feb-19		NIL	NIL			Lithium 1250mg (500/750). **ADD** 17/2/19 Tertroxin 40mg. Vitamin D and B6, Evening Primrose, Zinc, Magnesium	

08-Mar-19	Psychiatrist Paisley	**NEW** Dosulepin (Dothiepin)	25mg daily to 200mg (morn/night) (50/150)	8/3/2019		Lithium 1250mg (500/750). Tertroxin 40mg. **ADD 8/3/19** Ritalin 10mg increase to 40mg every 5 days. Vitamin D and B6, Evening Primrose, Zinc, Magnesium	1st weak suicidal 10/10, Bad headaches (migraine), constipation, dry mouth, lots of dreams
10-Mar-19	**NOTE:**	**Bad headaches (likely migraine) which did not stop. likely Dothiepin side effect**					
21-Mar-19	Psychiatrist Paisley	Dosulepin (Dothiepin)	**INCREASE 21/3/19** to 225mg (75/150)			"as above"	Bad headaches (migraine), constipation, dry mouth, lots of dreams
25-Mar-19	**CONSULT**	**25th March 2019 - Consulted Professor Gordon Parker - suggested Franco "COME OFF" all medication**					
		Prof thoughts was Pseudo melancholic - totally deconstructed himself (catastrophised) Perfectionistic - Stress Response - Progressive rehab model recommended					
27-Mar-19	Psychiatrist Paisley/Parker	**REMOVE** Dosulepin (Dothiepin)	**REDUCE 27/3/19** to NIL over 9 days		1/4/2019	Vitamin D and B6, Evening Primrose, Zinc, Magnesium. **REDUCE 29/3/19** Lithium by 250mg every 3 days until 750mg, **REMOVE 26/3/19** Ritalin, **REMOVE 26/3/19** Tertroxin.	Increase Suicidal risk. Very bad migraines
04-Apr-19	**NOTE:**	**High SUICIDE risk. Left his earring with daughter and told her he was doing a "chicken run". Everyday got worse. Made a call to Prof Parker 9th April and he told us to see him straight away**					
09-Apr-19	**CONSULT**	**9th April 2019 - Consulted Professor Gordon Parker - Reduction of meds made Franco "SUICIDAL"**					
		Wrote letter to Marie Bashir (our local Hospital) to admit him					
10-Apr-19	**HOSPITAL**	**Admission to Marie Bashir 10th April 2019 - Dr Shannon Paisley consulted re MEDS**					
	Hospital Psych - Dr Medi	NIL				Temazepam 10mg, Diazepam 5mg **CEASE** Lithium to NIL (25/7/18 to 2/5/19).	

	NOTE:	**One psychiatrist wanted to move him to Concord for further ECT another wanted to start him on meds. In the end it was decided to monitor him and take Prof Parker advise of no meds and instead therapy. First 4 weeks were not great at all. Fifth week showed promising signs of improvement and was stable enough to go home. Mental health team to keep an eye on him**					
17-May-19		**Released from Marie Bashir 17th May 2019 (not feeling great but LOW risk of Suicide)**					
22-May-19	Psychiatrist Paisley	NIL				Olanzapine 5mg, Lorazapam 5mg	Very unwell, agitated, pacing
03-Jun-19	**CONSULT**	**3 June 2019 - Consulted Professor Gordon Parker - Script Alprazolam 2mg twice daily**					
	Psychiatrist Gordon Parker	NIL				Olanzapine 5mg, Alprazolam 2mg twice per day	Very unwell, agitated, pacing
17-Jun-19	**CONSULT**	**17th June 2019 - Consulted Professor Gordon Parker - suggested Quest for life "Healing your Life" - suggested getting back to work**					
25-Jun-19	**NOTE:**	**Moved to mothers to give me a break as he was constantly talking about wanted to end his life. His condition worseded and the mental health team came in to assess him and referred him to Canterbury Hospital for further assessment. Psychiatrist felt he was at riskd. I made a call to Dr Paisley and Franco was assessed as safe enough to go to St john of God instead of Concord. Franco was given Lorazapam 3 times per day which calmed him down but needed to come off before ECT started. It was a little rough but managed**					
27-Jun-19	**HOSPITAL**	**Admission to St John of God 27th June 2019 - Psychiatrist Dr Shannon Paisley care**					
	Psychiatrist Paisley	**NEW** Duloxetine (Cymbalta)	60mg	27/6/2019		Olanzapine 15mg, Lorazapam 2.5mg up to 3 times per day	
01-Jul-19	**PROCEDURE**	**Commenced ECT at St john of God Burwood (total 29 sessions bilateral) 1st July to 21st August 2019**					
		23 sessions inpatient and 7 as outpatient (1 per week)					
17-Jul-19	**NOTE:**	**After 8th ECT he had a better "seizure". He started to improve a little. Less agitated and able to start talking a little**					

	Psychiatrist Paisley	Duloxetine (Cymbalta)	**INCREASE 23/7/19** to 120mg			" as above"	
14-Aug-19	**NOTE:**	**After 20th ECT he was able to interact with other patients and participate in group therapy. Sleeping well**					
21-Aug-19		**Released from St John of God 21st August 2019 (feeling OK)**					
28-Aug-19	**NOTE:**	**After 24th ECT he was not so good. Had a few bad days on/off**					
13-Sep-19	Psychiatrist Paisley	Duloxetine (Cymbalta)	120mg			**REMOVE** Olanzapine	
16-Sep-19	**NOTE:**	**After 28th ECT started to improve and was engaging and started exercising etc. Franco still said he didn't feel right but that he wanted to live**					
20-Sep-19	Psychiatrist Paisley	Duloxetine (Cymbalta)	120mg			**ADD** Abilify 5mg	
18-Oct-19	Psychiatrist Paisley	Duloxetine (Cymbalta)	120mg			**INCREASE** Abilify to 10mg	
17-Dec-19	Psychiatrist Paisley	Duloxetine (Cymbalta)	120mg			**ADD** Ritalin 10mg (for energy) no change after a week so stopped. Abilify 10mg	
17-Feb-20	**RETREAT**	**Quest for Life 5 day retreat 17th Feb 2020 - "Healing your life" as per Prof Parker recommendation - No change**					
16-Mar-20	**NOTE:**	**Becoming negative, loosing hope, no motivation, stopped exercising**					
03-Apr-20	Psychiatrist Paisley	**REMOVE** Duloxetine (Cymbalta)	**REDUCE 4/4/20** to Nil by 30mg every 4th day		15/4/2020	Abilify 10mg	Brain "zaps", not good
16-Apr-20	Psychiatrist Paisley	**NEW** Vortioxetine (Brintellix)	5mg increase to 20mg every 4 days	16/4/2020		Abilify 10mg	no symptoms
26-May-20	Psychiatrist Paisley	Vortioxetine (Brintellix)	**REDUCE** 26/5/20 to 10mg		4/6/2020	Abilify 10mg. Lorazapam 2.5mg PRN	Started to need Lorazapam 28/5/20
02-Jun-20	**HOSPITAL**	**Admission to Northside St Leonards - Psychiatrist Professor Phillip Mitchell care**					

05-Jun-20	Psychiatrist Prof Phillip Mitchell	**NEW** Bupropion	150mg	5/6/2020		Abilify 10mg. Lorazapam 2.5mg PRN	no symptoms
10-Jun-20	Psychiatrist Prof Phillip Mitchell	Bupropion	**INCREASE** 10/06/20 to 150mg/150mg			**CEASE 12/6/20** Abilify 10mg. Lorazapam 2.5mg PRN	no symptoms
22-Jun-20	Psychiatrist Prof Phillip Mitchell	Bupropion	**INCREASE** 22/06/20 to 300mg/150mg			-	bad headaches
27-Jun-20	Psychiatrist Prof Phillip Mitchell	Bupropion	**REDUCE** 27/6/20 to 300mg			**ADD** Lithium 250/250 increased Lithium 3/7/20 to 500/500	bad headaches, very weak and extremely agitated
	Psychiatrist Prof Phillip Mitchell	Bupropion	CEASED to start ECT		8/7/2020	**Ceased** Lithium at the same time	
09-Jul-20	**PROCEDURE**	**Commenced ECT at Northside (total 20 sessions before moving to RNS) 9th July to 3rd September 2020**					
	Prof Colleen Loo consulted	**Only done twice weekly Tuesday (Prof Colleen Loo adminstering) and Thursday**					
		12 sessions bi-frontal with Ketamine anesthetic, 7 bi-temporal no ketamine, 1 high dose bi-temporal with ketamine)					
05-Sep-20	Psychiatrist Prof Phillip Mitchell	**NEW** Clomipramine	25mg INCREASE daily by 25mg until 150mg	1/9/2020		PRN either Lorazapam 5mg, Serequol 150mg and Olanzapine 10mg	started to become extremely agitated, very weak, confusion
06-Sep-20	**HOSPITAL**	**Transferred 6th September 2020 under mental health act to Royal North Shore Hospital**					

06-Sep-20	RNS consulting Psychiatrist Dr Amanda Brae	Clomipramine	150mg	6/9/2020		PRN Lorazapam	extremely agitated, very confused
	NOTE:	**suicidal - Acute Care 1 on 1 nurse 7th Sept to 18th Sept**					
	PROCEDURE	**Involuntary high dose (pulse width1 level8) Bi-Temporal ECT with Ketamine anesthetic (15 sessions).**					
		Commenced Monday 11 Sept 2020 - finished 26th Oct 2020 at RNS before transferring to St John of God					
22-Sep-20	**NOTE:**	**Moved to general ward 22nd Sept 2020**					
25-Sep-20	RNS consulting Psychiatrist Dr Amanda Brae	Clomipramine	**REDUCE 25/9/20** to NIL over 15 days		9/10/2020	PRN Lorazapam	Shaking of legs stopped and not having the urge to move all the time
06-Oct-20	**NOTE:**	**Cognitively very bad and at times delusional during my visits 6th October to 21st Oct**					
27-Oct-20		**27 Oct 2020 - Released from RNS into Dr Shannon Paisley care as an outpatient of St John Of God- continue ECT**					
28-Oct-20	Psychiatrist Paisley	NIL	28/10/2020			PRN Lorazapam 2.5mg	No executive function. Could not take any instructions. Very dosile
	PROCEDURE	**Continued ECT as Outpatient at St john of God Burwood (total 6 sessions bilateral twice weekly) 30th Oct to 16th Nov. None of the sessions were effective**					
03-Nov-20	**NOTE:**	**3rd November - Cognitive ability improved and was able to take instructions**					
05-Nov-20	**NOTE:**	**5th November felt extremely distressed. Did not want to do anything. Said it was all too hard and that he cant do it. Complained that life was no longer worth living. Unable to manage him**					
06-Nov-20	**NOTE:**	**After ECT morning of 6th November no change in his mood at all. Dr Paisley prescribes Alprazolam (Zanax 2mg)**					
06-Nov-20	Psychiatrist Paisley	NIL	6/11/2020			PRN Alprazolam 2mg up to 3 times per day if needed. Started with 1 tablet but now needs 1 in morning and 1/2 around 12	His mood is shocking in the morning. He is unbearable to be around. Within minutes of taking Zanax he is pacified & sleepy for a few hours
06-Nov-20	**NOTE:**	**Mood shocking. Unbearable to be around. Vanessa unable to deal with him - request he be admitted**					

06-Nov-20	**HOSPITAL**	**Admission 6th November 2020 - St John of God (Burwood) - Treating Psychiatrist Dr Shannon Paisley**					
	Psychiatrist Paisley	NIL				Alprazolam 2mg 3 times daily and Olanzapine for sleep	
16-Nov-20	**NOTE:**	**Not suicidal. Mood still very low. Good communicate but still shaking leg**					
18-Nov-20		**Released from SJOG Burwood 18th November 2020**					
18-Dec-20	Psychiatrist Paisley	**NEW** Desvenlafaxine 400mg (Pristiq)	50mg increased to 400mg (50mg increase every 5 days)	########			No side effects
08-Jan-21	Psychiatrist Paisley	Desvenlafaxine	150mg			**ADD** Olanzapine 15mg reduced to 7.5mg after 7 days	Unable to sleep so Olanzapine was given. Reduced to 7.5mg as too groggy next day
13-Jan-20	**NOTE:**	**Sounds a lot better on phone. Does not talk of Suicide. People saying his body language better. Not shaking Is however twisting hair on forehead**					
09-Feb-21	Psychiatrist Paisley	Desvenlafaxine	400mg			Olanzapine 7.5mg	BLOOD TEST done all ok. Blood Pressure 140/95 normally 115/75
13-Feb-21	Psychiatrist Paisley	Desvenlafaxine	400mg			**ADD** CBD Oil (1 drop 3 times daily increase drop each time weekly until 5 drops 3 times) Olanzapine 5mg	Blood pressure a little high
15-Feb-21	**NOTE:**	**Continues with OK Mood. STOPPED twisting hair at fron (did however have a cut). He is not fiddgy**					

19-Feb-21	Psychiatrist Paisley	Desvenlafaxine	400mg			Olanzapine 5mg plus CBD Oil	Bllod pressure a little high
05-Mar-21	**HOSPITAL**	**Admission 5th March 2021 - Marie Bashir RPA- Treating Psychiatrist Dr**					
	NOTE:	**Suicidal thoughts - has plan to go to Railway Station. Visited stations 3 times this week**					
08-Mar-21	Marie Bashir	Desvenlafaxine - Commence reduction					Nil side effects withdrawing 50mg every 4th day
18-Nov-20		**Released from 10Th March 2021**					

GallBladder emergency surgery - RPA - 13th to 15th March 2021

MIND MEDICINE
AUSTRALIA

Appendix D

Letter From Mr Graham Daniels about the immense suffering of his wife, Lianne Daniels, from treatment resistant depression, her large list of failed treatments over decades and Mr Daniels belief that psychedelic assisted therapy would give her a chance to lead a more normal life.

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PSYCHEDELICS SUBMISSION
by Graham Daniels

BACKGROUND

Leanne and I started our relationship in 1977 while she was still in high school. 3 years later we both said "I do" and are fortunate to still have an enviable relationship today. We partied and travelled for the first 6 years of our marriage, until we decided it was time to start a family. With much preparation and excitement our first child Taliah arrived in October 1986. 24 hours after delivery, Leanne and I did not know what had hit us. Leanne was staring at the wall in the hospital room, feeling lost, helpless and empty. Her doctor told her she had postnatal depression but it would lift in a few days. It did not. It got worse and Leanne remained in hospital for some time before coming home. At home her depression did not improve, and it wasn't long thereafter that Leanne stopped breast feeding and I, along with family support, became the carer for both Leanne and Taliah. Leannes's debilitating depression was a total bazaar occurrence as we had planned with keenness, everything in advance for our family to be.

It seemed that the hormonal drop after delivery had triggered what we now accept was the genetic predisposition to depression Leanne had inherited. Her mother, auntie and grandfather all suffered depression. It was now her turn. The depression that had been triggered by the post delivery hormonal plunge then took on a life of its own. Loving support, medication/supplements and time tended to improve her condition somewhat, so we made the decision to reduce medication and try for a second child. That pregnancy ended in miscarriage and the hormone monster exacerbated the depression. It was very bad, but we knew what it was this time. In time we tried for our second child again and in December 1988, Jake was born.
We were alive to what could happen and so managed Leanne's condition as best we could by utilising various treatments. Leanne's condition fluctuated with periods of "wellness" interspersed with times of total despair.

As 2010 approached, so did menopause and with it came the worst depression/anxiety/nausea ever. Leanne was admitted to a psychiatric hospital for many weeks as they tried to get her condition under control. It was severe. I would visit Leanne in hospital every day, and could sense the frustration of the medical team who were not getting the result they wanted.

TREATMENTS PRE 2010

In brief, prior to 2010 Leanne had tried various psychiatrists, medications, naturopaths, acupuncture, hormone treatments, eastern and western medicine, psychologists etc. all with limited or no relief. We had Leanne's genetic coding documented and discovered multiple single mutation genes and a polymorphism MTHFR A1298C which complicated her condition, but all attempts at a sustainable "patch" for Leanne's genetic defect(s) have failed.

TREATMENTS POST 2010

Post 2010 Leanne has had Electroconvulsive treatment in Adelaide, Trans Cranial Magnetic Stimulation when it was first pioneered in Melbourne (2011), and again in Queensland (2020), Ketamine infusion drip in Melbourne (2012), Esketamine nasal spray in Adelaide (2022). We have seen Doctors, professors, psychiatrists, psychologists and various specialists in many cities in Australia and Thailand, and have had numerous consults with specialists in UK and USA. For all this it is not unusual for Leanne to stay in a psychiatric hospital for 3 months at a time.

THE COST OF DEPRESSION & ANXIETY

The financial cost has been incredible, and I expect few with Leanne's condition could ever manage such out of pocket expenses which we estimate to be in excess of $300,000 so far. We are fortunate that we have been able to fund all her treatments and have sought the best treatments available... but still no lasting remedy. The emotional cost has been even greater, and the relationship vacuum for two children who know little of what it is to have a well mother is yet a greater loss still.

EVIDENCE IN SUPPORT OF "FAILED" TREATMENTS

We have disposed of many of the past treatment medications used by Leanne, however I went to the storage box yesterday where I keep Leanne's meds, and at the footer of this letter is the list of

what is in that box to give some evidence to what medications Leanne has been prescribed in recent times. [***OLD MEDS - From the box**]

LEANNE'S CURRNT TREATMENTS
Leanne's current medication and supplements are:

9:30am
Venlafaxine 100mg
Bupropion 300mg
Olanzapine 5mg
Buspirone 10mg
Turmeric - 10mg
B vitamin

6:30pm
Buspirone 10mg
Zinc
cod liver oil
vitamin D

10:15pm
Seroquel 200mg
Diazepam 2mg
Olanzapine 5mg
Bupropion 150mg
Mirtazapine 45mg
Magnesium 500mg
Testosterone cream
Estradot patch 2 x week
Melatonin 30mg gummies

PRN

Lorazepam 1mg	(1-4 x day)
Clonidine 100mcg	(1-4 x day)
Ondansetron 8mg	(1-2 x day)

THE CHALLENGE - PSYCHEDELICS... YOUR NEXT !
With Leanne being so unwell for so long, it is my understanding that the mind develops a "thinking rut' which becomes the dominating norm for current thought patterns and manifested actions and behaviours. In order to elevate thinking channels to "better thought pattens" and escape the "thinking rut" cycle, brain neuroplasticity needs to be activated. Copious studies in reputable psychiatric journals point to the role psychedelics can play in neural pathway regeneration. In some cases this benefit has been achieved after a single administration.

I have researched psilocybin and it is the obvious next treatment for Leanne. There appears to be a solid foundation of evidence from highly intelligent professionals that this treatment might give Leanne the opportunity she needs to get back to life. Under supervision there appears to be ZERO downside to allowing Leanne to take this treatment. Leanne's fear is that she will never recover and will die a depressed old woman. This would just add to the tragedy of her experience and seems totally unnecessary when a safe option that might assist, is being obfuscated by the very decision makers who have a duty of care obligation to administer such remedy to those in our community who need their proactive decision.

THE ARGUMENT AND THE SOLUTION
I fully understand the ***use*** versus ***abuse*** argument. We are confronted daily with health issues caused by the abuse of simple substances such as sugar and alcohol. It's not their use that are problematic and lead to illness and death, its their abuse. Obesity related deaths caused by abusive diets and gluttony are daily reminders of the detriment caused not by the use of foods, but by the abuse of foods. I expect with or without legislative guidelines, psychedelics will be, and no doubt are already, in the use/abuse arena. Surely legislative guidance on psychedelic

exploration and the health benefits they possess is a step in the right direction. I would encourage those who occupy the seat of decision on this issue to champion the cause in what I expect will be the cutting edge of psychiatric medicine in the near future and Australia could and should become a world leader in this field.

CONCLUSION

As I write this brief note (yes there is much more I could add) Leanne is in bed where she spends most of her day until I get her out of bed and take her for a drive which I do almost every day. As Leanne's husband and carer, I have both Power of Attorney and Power of Guardianship for Leanne and am available to discuss this matter further should there be benefit in so doing.

I have no doubt that psychedelics will become the silver bullet for many treatments in the future. In some respects it seems quite humorous that the "hippies" of the 60's were ahead of the trend in identifying the benefits of psychedelics, but surely our medical office bearers in Australia can build and improve on what has been learned since the 60's.

Let's just get on with removing the legislative blockages currently imposed on competent medicines. Impeding a potential remedy for cruel "dis-eases" has no place in an advanced and intelligent society like Australia.

Sincerely,

Graham Daniels
15 May 2022
Adelaide, South Australia
Phone: 0414 409186 Email: graham@danel.ch

***OLD MEDS - From the box**

Duloxetine
Temazepam
Escitalopram
Amitriptyline
Topiramate
Lamotrigine
Prometrium
Placil
Tevaripiprazole
Somac
Vyvance
Esomeprazole
Sifrol
Livial
Zopiclone
Oxycodone
Pericyazine
Candesartan
Zolpidem
Suvorexant
Modavigil
Guanfacine
Aripiprazole
Methadone
Amlodipine

Femoston
Prochlorperazine
Gabapentin
Dexmethazone
Phenobarb
Amantadine
Primidone
CBD
THC
Metoclopramide
Propranolol
Methylphenidate
Clonazepam
Thyroid extract
Alprazolaam
Benzatropine
Prednisolone
Dexamfetamine
Liothyronine

MIND MEDICINE
AUSTRALIA

Appendix E

Letter From Psychiatrist Dr Stuart Saker on the desperate plight and immense suffering of the ADF Veterans that he treats, the high levels of suicide risk amongst veterans with treatment resistant mental illnesses and the need for access to psychedelic assisted therapies on compassionate grounds.

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

28th February 2022

The Medicines Rescheduling Unit
Therapeutic Goods Administration
CANBERRA ACT

Dear Sir/Madam

Proposed Rescheduling of Psilocybin and MDMA

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

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

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

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

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

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Toronto Private Hospital

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

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

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

Yours Faithfully

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

MIND MEDICINE AUSTRALIA

Appendix F

Submission from Dr Simon Longstaff, the Executive Director of the Ethics Centre and Australia's preeminent ethicist.

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THE ETHICS CENTRE

THE SECRETARIAT **08.05.22**
MEDICINES RESCHEDULING UNIT
THERAPEUTIC GOODS ADMINISTRATION
CANBERRA ACT 2600

TO WHOM IT MAY CONCERN

It is some time since I last made a submission to the TGA on matters relating to Mind Medicine Australia's (MMA's) application to reschedule the medical use of psilocybin and MDMA as part of psychotherapy.

In making this further submission, I should again note that I continue to serve as 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.

The core arguments are essentially the same as those made in my earlier submission. However, given the passage of time, I would elevate my expression of concern about the ethics of allowing avoidable suffering to persist when adequate relief is at hand.

I note that MMA's latest submission proposes psilocybin and MDMA should only be rescheduled as Schedule 8 controlled medicines to the extent that;

1. They are prescribed by a psychiatrist with specific training in these therapies for use as part of psychotherapy for a treatment resistant patient;
2. The prescribing psychiatrist patient diagnosis and treatment plan are confirmed by two other psychiatrists;
3. The medicine dosing sessions take place in a medically-controlled environment with two trained therapists in the room at all times.
4. The patient will have given fully informed consent and will never be allowed to take the medicines away from the clinic or hospital where the medicine dosing session takes place.
5. The medicine is used as part of psychotherapy.

Furthermore, If the use of these substances is rescheduled to Schedule 8 in this manner access to these medicines will still require the prescribing psychiatrist to also seek approval from the TGA on a patient specific basis under the Special Access Scheme and from the Health Department of the State or Territory where the treatment is to occur.

All other uses of psilocybin and MDMA will remain in Schedule 9.

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I submit that this is a very conservative approach to the use of these emerging medicines – which, if anything, strengthens the ethical calculus in favour of approval.

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.

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.

As noted above, the submission before you do not request that psilocybin and MDMA be made available without restrictions. 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. Or, perhaps, to sharpen the point – there is a *prima facie* ethical obligation to alleviate avoidable suffering. That obligation can only be set aside in the face of compelling evidence that the means available to relieve suffering would cause more harm than the suffering itself. The current evidence does not support such a conclusion when it comes to the clinical use of MDMA and psilocybin.

On the scale of human ethical failings, the failure to relieve avoidable suffering ranks especially high. I would urge you to err on the side of compassion so that this modest proposal might be approved.

Yours sincerely,

DR SIMON LONGSTAFF AO
EXECUTIVE DIRECTOR

MIND MEDICINE AUSTRALIA

Appendix G

Offer from the Neuromedicines Discovery Centre at Monash University to host an independent clinical treatment registry to collate treatment information from psychiatrists and their patients if the medicines are rescheduled.

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

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Dear Colleagues,

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

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

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

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

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

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

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

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

Yours sincerely,

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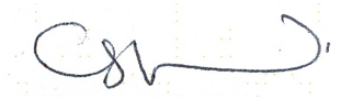

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Chair, Australasian Society of Bipolar and Depressive Disorders

MIND MEDICINE AUSTRALIA

Appendix H

Goodwin et al (2022) Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. The New England Journal of Medicine Vol 387 No 18 pages 1637 - 1648.

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The NEW ENGLAND JOURNAL of MEDICINE

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Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Bird, R.E. Blom, C. Brennan, D. Brusch, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, B.W. Dunlop, K. Eisen, D. Feifel, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, J. Kamphuis, J. Kawasaki, J.R. Kelly, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. Licht, J.L. Maples-Keller, J. Mars, L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirow, S. Mistry, T. Mletzko-Crowe, L.N. Modlin, R.E. Nielsen, E.M. Nielson, S.R. Offerhaus, V. O'Keane, T. Páleníček, D. Printz, M.C. Rademaker, A. van Reemst, F. Reinholdt, D. Repantis, J. Rucker, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. Somers, S.C. Stansfield, D. Sterling, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywema, S. Zisook, and E. Malievskaia

ABSTRACT

BACKGROUND

Psilocybin is being studied for use in treatment-resistant depression.

METHODS

In this phase 2 double-blind trial, we randomly assigned adults with treatment-resistant depression to receive a single dose of a proprietary, synthetic formulation of psilocybin at a dose of 25 mg, 10 mg, or 1 mg (control), along with psychological support. The primary end point was the change from baseline to week 3 in the total score on the Montgomery–Åsberg Depression Rating Scale (MADRS; range, 0 to 60, with higher scores indicating more severe depression). Secondary end points included response at week 3 (≥50% decrease from baseline in the MADRS total score), remission at week 3 (MADRS total score ≤10), and sustained response at 12 weeks (meeting response criteria at week 3 and all subsequent visits).

RESULTS

A total of 79 participants were in the 25-mg group, 75 in the 10-mg group, and 79 in the 1-mg group. The mean MADRS total score at baseline was 32 or 33 in each group. Least-squares mean changes from baseline to week 3 in the score were –12.0 for 25 mg, –7.9 for 10 mg, and –5.4 for 1 mg; the difference between the 25-mg group and 1-mg group was –6.6 (95% confidence interval [CI], –10.2 to –2.9; P<0.001) and between the 10-mg group and 1-mg group was –2.5 (95% CI, –6.2 to 1.2; P=0.18). In the 25-mg group, the incidences of response and remission at 3 weeks, but not sustained response at 12 weeks, were generally supportive of the primary results. Adverse events occurred in 179 of 233 participants (77%) and included headache, nausea, and dizziness. Suicidal ideation or behavior or self-injury occurred in all dose groups.

CONCLUSIONS

In this phase 2 trial involving participants with treatment-resistant depression, psilocybin at a single dose of 25 mg, but not 10 mg, reduced depression scores significantly more than a 1-mg dose over a period of 3 weeks but was associated with adverse effects. Larger and longer trials, including comparison with existing treatments, are required to determine the efficacy and safety of psilocybin for this disorder. (Funded by COMPASS Pathfinder; EudraCT number, 2017-003288-36; ClinicalTrials.gov number, NCT03775200.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Goodwin can be contacted at guy.goodwin@compasspathways.com.

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A Quick Take is available at NEJM.org

Treatment-resistant depression is a challenging disorder to treat, as shown in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial.[1] Incidences of remission became progressively lower from the first course of antidepressant treatment (36.8%) to the second course (30.6%), third course (13.7%), and fourth course (13.0%).[1,2] Failure of two courses of treatment has generally been considered to define a group of patients who have treatment-resistant depression. Patients with treatment-resistant depression have greater severity and duration of illness, disability, physical illness, incidences of hospitalization, risk of suicide, and economic costs than patients with treatment-responsive depression.[1-3]

Psilocybin is a tryptamine alkaloid found in several species of psilocybe mushrooms.[4] Its potential antidepressant efficacy was suggested by preliminary studies involving patients with life-threatening cancer.[5-7] Amelioration of symptomatic depression in pilot studies of major depressive disorder, including those that compared psilocybin with escitalopram[8,9] and that investigated its use in treatment-resistant depression,[10] has suggested therapeutic potential for this agent. The objective of the current trial was to identify an acceptable efficacious dose and assess the safety of a synthetic, proprietary formulation of psilocybin, administered together with psychological support,[11] in patients with a treatment-resistant major depressive episode.

METHODS

TRIAL OVERSIGHT

This was a phase 2 double-blind, dose-finding, parallel-group, randomized clinical trial. The sponsor, COMPASS Pathfinder, designed and funded the trial and provided a proprietary pharmaceutical-grade synthetic psilocybin formulation, COMP360, which was analyzed for stability and purity. A contract research organization (Worldwide Clinical Trials), paid by the sponsor, supervised the conduct of the trial. An independent contract research organization (MedAvante-ProPhase) was responsible for assessment of participants using the Montgomery–Åsberg Depression Rating Scale (MADRS),[12] performed by trained remote raters who were unaware of the details of the trial and the trial-group assignments. The statistical analysis of the data was performed by the contract research organization and reviewed by the sponsor, and the interpretation and post hoc statistical analyses of the data were performed by the sponsor. The sponsor paid for professional writing assistance for the first draft of the manuscript. All the authors reviewed and approved the manuscript before submission and vouch for the adherence of the trial to the protocol (available with the full text of this article at NEJM.org), the completeness and accuracy of the data, and the reporting of adverse events. Confidentiality agreements were in place between the investigators and COMPASS Pathfinder. The roles of the authors are listed in the Supplementary Appendix, available at NEJM.org.

The trial was conducted in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The trial protocol was approved by independent ethics committees or institutional review boards at each participating site. All the participants provided written informed consent.

PARTICIPANTS

Men and women 18 years of age or older were eligible if they met *Diagnostic and Statistical Manual of Mental Disorders* (fifth edition) criteria for a single or recurrent episode of major depressive disorder, without psychotic features, on the basis of clinical assessment and medical records and as documented by the Mini-International Neuropsychiatric Interview (version 7.0.2).[13] Recruitment was conducted through referrals from primary care and specialized psychiatry services, online advertisements, and word of mouth. Participants were outpatients who met criteria for the diagnosis of treatment-resistant depression and had a current episode of depression that had not responded to two to four adequate trials in terms of both dose and duration (≥8 weeks) of treatment according to the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ).[14] Augmentation agents, or other antidepressants not included in the MGH ATRQ, qualified as a treatment failure if they failed to ameliorate depression, provided they had local regulatory approval as a treatment for major depressive disorder. Additional selec-

tion criteria and screening procedures are summarized in the trial protocol.

TRIAL DESIGN AND PROCEDURES

The trial was conducted at 22 sites in 10 countries in Europe (the Czech Republic, Denmark, Germany, Ireland, the Netherlands, Portugal, Spain, and the United Kingdom) and North America (Canada and the United States) from March 1, 2019, through September 27, 2021. All but one of the principal investigators was a psychiatrist. Both assisting and lead therapists, whose roles are described below, were recruited as psychologists with at least master's-level qualifications, psychiatrists, master's-level practitioners, nurses, diploma-level cognitive behavioral therapists, or doctorate-level mental health specialists. These therapists had experience in adult mental health, addiction, dementia, physical health, child or developmental health, family therapy, or eating disorders and experience with patients having severe psychological distress. The therapist-training program that was expressly prepared for the trial had four components: an online learning platform, in-person training, clinical training, and ongoing individual mentoring and webinars. Therapists were required to complete the first three components of the training program before they could lead sessions independently and to engage in the fourth component to continue their professional development.[11] Therapists in training could act as assisting therapists so that there were always two therapists present on the day of drug administration. All the therapists were unaware of the trial-group assignments, did not collect efficacy assessments, and were discouraged from speculating about doses.

Eligible participants completed a run-in period of 3 to 6 weeks, during which antidepressants and other prohibited medications affecting the central nervous system were tapered and discontinued at least 2 weeks before the baseline visit (the day before psilocybin administration). During this period, the participant met with a therapist at least three times to build trust, receive psychoeducation, and prepare for the psychedelic experience. Participants who continued to meet eligibility criteria were randomly assigned in a 1:1:1 ratio to receive a single dose of psilocybin of 25 mg, 10 mg, or 1 mg (control). Randomization was performed at a central location and stratified according to country and the participant's previous experience with psilocybin. The administration session (day 1) lasted 6 to 8 hours, with the lead therapist who had prepared the participant for the intervention and an assisting therapist in attendance. A trial psychiatrist was available on site for consultation. Administration rooms were designed to provide a nonclinical, calming atmosphere. During the administration session, participants listened to a specially designed music playlist while wearing eyeshades to help direct attention internally. After at least 6 hours and when the psychedelic effects of the drug had fully dissipated, participants returned home.

The trial followed participants for 12 weeks after treatment. Participants received two integration sessions, with the same lead and assisting therapists at the day 2 visit and with the lead therapist at the week 1 visit. The goal of the integration sessions was to support participants in deriving their own insights and solutions from the experience with psilocybin. Therapists were advised to remain open and supportive, without active guiding.[11] Participants were requested to remain off antidepressant treatment during the first 3 weeks after the trial-drug administration; however, these medications could be started at any time during the trial if deemed clinically necessary by a physician investigator. (A schedule of the assessments is provided in Table S1 in the Supplementary Appendix.)

EFFICACY END POINTS

The primary end point was the change from baseline (day –1, the day before trial-drug administration) to 3 weeks in the MADRS total score (range, 0 to 60, with higher scores indicating greater severity of depression).[12] The primary analysis was of the 25-mg dose and 10-mg dose each compared with the 1-mg dose. The MADRS was administered by experienced mental health clinician raters by telephone at baseline, on day 2, and at weeks 1, 3 (primary end-point assessment), 6, 9, and 12. The Structured Interview Guide for the MADRS provided structured probes to ensure standardization of administration and comprehensive coverage of the 10 questions.[15] Three key secondary efficacy end points were response (≥50% decrease from baseline to week 3

in the MADRS total score), remission (MADRS total score ≤10 at week 3), and sustained response (week 3 response maintained through week 12).

SAFETY END POINTS

Adverse events were evaluated at every visit and were recorded and coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.0. All visits were in conducted in person except for the week 6 and 9 visits, which were conducted remotely. Adverse events that emerged or worsened after trial-drug administration were categorized as serious adverse events on the basis of the ICH Good Clinical Practice criteria and with the use of additional information from the Columbia Suicide Severity Rating Scale.[16] Suicidal ideation with intent or endorsement of any items in the suicidal-behavior section, including nonsuicidal self-injurious behavior, was reported as a serious adverse event. Safety assessments also included evaluation of vital signs (at screening, baseline, day 1, and day 2), clinical laboratory tests (including urine drug screening) (at screening, day 2, and week 3), and 12-lead electrocardiography (ECG) at screening and day 2.

STATISTICAL ANALYSIS

Using a two-sample t-test, we calculated that a sample of 216 participants (72 per group) would provide 90% power at a two-sided alpha level of 0.05 to detect a 6-point difference in the mean change from baseline to week 3 in the MADRS total score between the 25-mg group or the 10-mg group and the 1-mg group, assuming a common standard deviation of 11.0 (see the Supplementary Appendix). Efficacy analyses were performed in the modified intention-to-treat analysis set, which included all randomly assigned participants who received treatment and had at least one postbaseline efficacy assessment.

A "hypothetical strategy" estimand was applied in which MADRS total scores for participants who initiated a new antidepressant treatment were imputed at visits after initiation with the use of a missing-not-at-random mechanism that progressively worsened the MADRS total score. The aim was to hypothesize what would have happened to the MADRS total score had a new treatment for depression not been available to use. This same method was also applied to missing MADRS total scores after trial withdrawal for reasons of lack of efficacy or adverse events. All other missing data on MADRS total scores, both intermittent and after trial withdrawal for other reasons, were imputed with the use of a missing-at-random mechanism.

The primary efficacy end point (change from baseline to week 3 in the MADRS total score) was evaluated with the use of a mixed model for repeated measures (MMRM) analysis comparing the 25-mg dose with the 1-mg dose and comparing the 10-mg dose with the 1-mg dose. The MMRM analysis included treatment, visit, pooled trial site, treatment-by-visit interaction, baseline MADRS total score, and an unstructured correlation matrix. The estimates of the least-squares means and mean differences and 95% confidence intervals were then pooled with the use of Rubin's combination rules. This analysis method combined the between-imputation variability with the within-imputation variability to obtain one single point and confidence interval estimate to address imputation uncertainty.

Response and remission were analyzed with the use of a generalized linear mixed model, and sustained response was analyzed with the use of a logistic-regression model. A "composite strategy" estimand was applied, whereby participants who initiated a new antidepressant treatment or withdrew from the trial for reasons of lack of efficacy or adverse events were classified as not having a response, remission, or a sustained response at all visits after these events.

To control the overall type I error rate, a hierarchical test procedure was applied across the primary and three key secondary efficacy end points. The 25-mg group and then the 10-mg group were sequentially examined for each end point before proceeding to the next end point. All testing was done at the two-sided 0.05 alpha level. Descriptive statistics were used to analyze safety data from all randomly assigned participants who received single-dose treatment (safety analysis set), including adverse events, concomitant medications, evaluation of vital signs, clinical laboratory tests, findings from 12-lead ECG, and suicidality assessments.

RESULTS

PARTICIPANTS

A total of 428 participants were screened, and 233 were enrolled, underwent randomization, and received psilocybin treatment (safety analy-

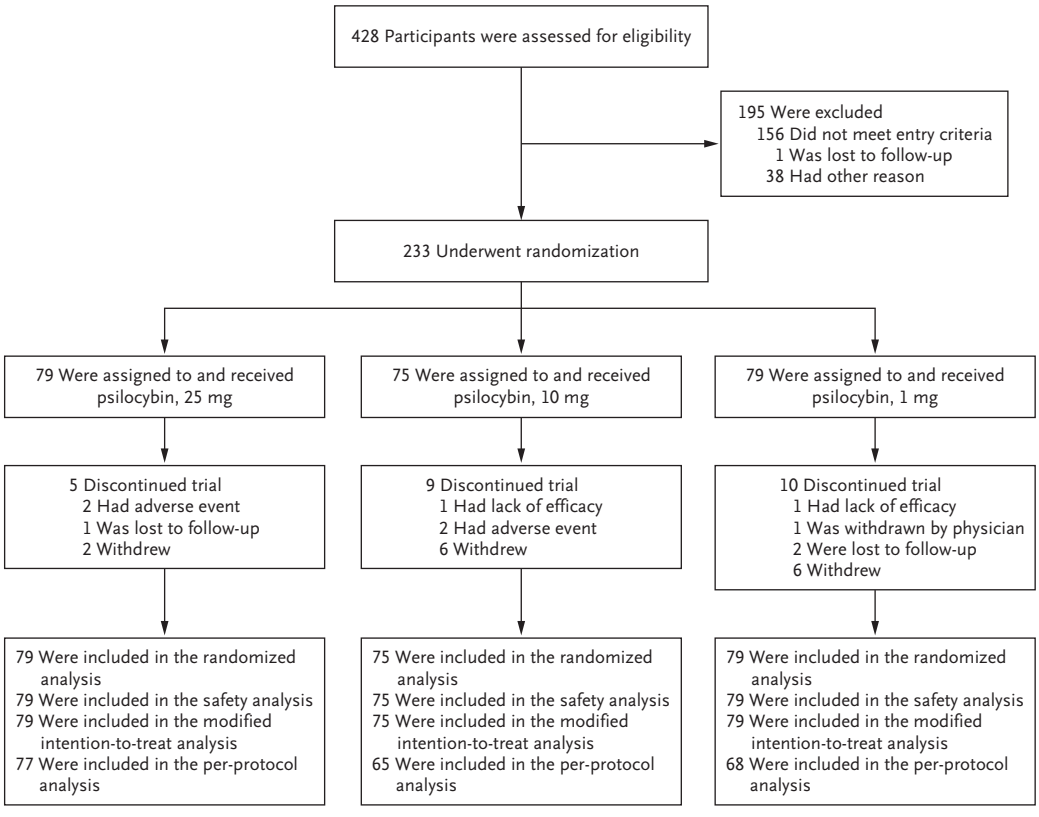

Figure 1. Enrollment, Randomization, and Follow-up of the Participants.

Randomly assigned participants received a single dose of a proprietary, synthetic formulation of psilocybin, which was administered together with psychological support.

sis set) and had at least one postbaseline efficacy evaluation (modified intention-to-treat analysis set). A total of 79 participants were assigned to the 25-mg group, 75 to the 10-mg group, and 79 to the 1-mg group (Fig. 1). By week 12, a total of 5 participants (6%) in the 25-mg group, 9 (12%) in the 10-mg group, and 10 (13%) in the 1-mg group had withdrawn from the trial.

The demographic and clinical characteristics of the participants at baseline were similar across the three groups (Table 1); the mean age was 39.8 years, 52% were female, and 92% were White. A total of 95% of the participants reported previous depressive episodes, with a mean of 6.9 lifetime depressive episodes, and 86% of the participants reported a duration of the current depressive episode of longer than 1 year. These characteristics were similar to what has been observed in population studies involving persons with treatment-resistant depression, and the representativeness of the trial population is shown in Table S11. Two thirds of the participants were receiving antidepressant treatment at screening. At baseline, depression was moderate (MADRS total score, 20 to 30) in 30% of the participants and severe (MADRS total score, ≥31) in 68% of the participants. Mean MADRS total scores at baseline were 31.9 in the 25-mg group, 33.0 in the 10-mg group, and 32.7 in the 1-mg group. A total of 6% of the participants had previous exposure to psilocybin.

Before the week 3 primary end-point assessment, initiation of treatment for depression was reported by 4 participants (5%) in the 25-mg group, 9 (12%) in the 10-mg group, and 14 (18%) in the 1-mg group. After week 3 and up to week 12, the number of participants initiating a treatment for depression was 26 (33%) in the 25-mg group, 18 (24%) in the 10-mg group, and 16 (20%) in the 1-mg group.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Safety Population).*

Characteristic	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)	Overall (N=233)
Demographic characteristics				
Female sex — no. (%)	44 (56)	41 (55)	36 (46)	121 (52)
Age — yr	40.2±12.2	40.6±12.8	38.7±11.7	39.8±12.2
White race — no. (%)†	70 (89)	72 (96)	73 (92)	215 (92)
Body-mass index‡	26.52±6.13	28.26±8.20	27.26±6.02	27.34±6.86
Previous psilocybin use — no. (%)	5 (6)	5 (7)	4 (5)	14 (6)
Psychiatric history				
Recurrent MDD episode — no. (%)	75 (95)	74 (99)	73 (92)	222 (95)
Lifetime depressive episodes — no.				
Mean	7.3±8.6	7.8±9.1	5.7±4.4	6.9±7.6
Median	5.0	4.0	4.0	5.0
Duration of current depressive episode — no. (%)				
<1 yr	12 (15)	10 (13)	10 (13)	32 (14)
1 yr to <2 yr	33 (42)	28 (37)	33 (42)	94 (40)
≥2 yr	34 (43)	37 (49)	36 (46)	107 (46)
Failed treatments for current depressive episode — no. (%)				
2	66 (84)	62 (83)	63 (80)	191 (82)
3 or 4	12 (15)	11 (15)	14 (18)	37 (16)
Withdrawn from antidepressant at trial entry — no. (%)	53 (67)	51 (68)	52 (66)	156 (67)
Failure of treatment trial of augmentation agent during current depressive episode — no. (%)	5 (6)	3 (4)	6 (8)	14 (6)
Depression scores				
MADRS total score§				
Mean	31.9±5.4	33.0±6.3	32.7±6.2	32.5±6.0
Moderate: 20–30 — no. (%)	33 (42)	19 (25)	18 (23)	70 (30)
Severe: ≥31 — no. (%)	46 (58)	54 (72)	59 (75)	159 (68)
HAM-D-17 total score¶				
Mean	21.8±3.0	22.4±2.8	22.2±2.9	22.2±2.9
Moderate: 18–23 — no. (%)	57 (72)	49 (65)	59 (75)	165 (71)
Severe: ≥24 — no. (%)	22 (28)	26 (35)	20 (25)	68 (29)

* Plus–minus values are means ±SD. Randomly assigned participants received a single dose of a proprietary, synthetic formulation of psilocybin, which was administered together with psychological support. Percentages may not total 100 because of rounding. MDD denotes major depressive disorder.

† Race was reported by the participants.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. Two participants in the 10-mg group and two participants in the 1-mg group had an MADRS total score of less than 20 at baseline.

¶ Total scores on the 17-item Hamilton Depression Rating Scale (HAM-D-17) range from 0 to 52, with higher scores indicating greater severity of depression.

EFFICACY

The least-squares mean change from baseline to week 3 in the MADRS total score was –12.0 points in the 25-mg group, –7.9 in the 10-mg group, and –5.4 in the 1-mg group. The difference in the least-squares mean change between the 25-mg group and the 1-mg group was –6.6 (95% confidence interval [CI], –10.2 to –2.9;

Table 2. Primary and Secondary Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
Primary efficacy end point			
Change from baseline to wk 3 in MADRS total score			
Least-squares mean	−12.0±1.3	−7.9±1.4	−5.4±1.4
95% CI of the least-squares mean	−14.6 to −9.3	−10.6 to −5.2	−8.1 to −2.7
Least-squares mean difference vs. 1 mg	−6.6±1.9	−2.5±1.9	—
95% CI of the least-squares mean difference	−10.2 to −2.9	−6.2 to 1.2	
P value vs. 1 mg	<0.001	0.18†	—
Secondary efficacy end points			
Response at wk 3‡			
No. of participants (%)	29 (37)	14 (19)	14 (18)
Odds ratio vs. 1 mg (95% CI)	2.9 (1.2 to 6.6)	1.2 (0.5 to 3.0)	—
Remission at wk 3§			
No. of participants (%)	23 (29)	7 (9)	6 (8)
Odds ratio vs. 1 mg (95% CI)	4.8 (1.8 to 12.8)	1.2 (0.4 to 3.9)	—
Sustained response at wk 12¶			
No. of participants (%)	16 (20)	4 (5)	8 (10)
Odds ratio vs. 1 mg (95% CI)	2.2 (0.9 to 5.4)	0.7 (0.2 to 2.0)	—

* Plus–minus values are standard errors.
† This nonsignificant P value terminated significance testing on the basis of the prespecified hierarchical test procedure, and all the subsequent secondary efficacy end points are considered to be not significantly different between the 25-mg group or 10-mg group and the 1-mg group.
‡ A response was defined as a decrease of at least 50% from baseline in the MADRS total score.
§ Remission was defined as an MADRS total score of 10 or less.
¶ A sustained response was defined as a week 3 response sustained through week 12.

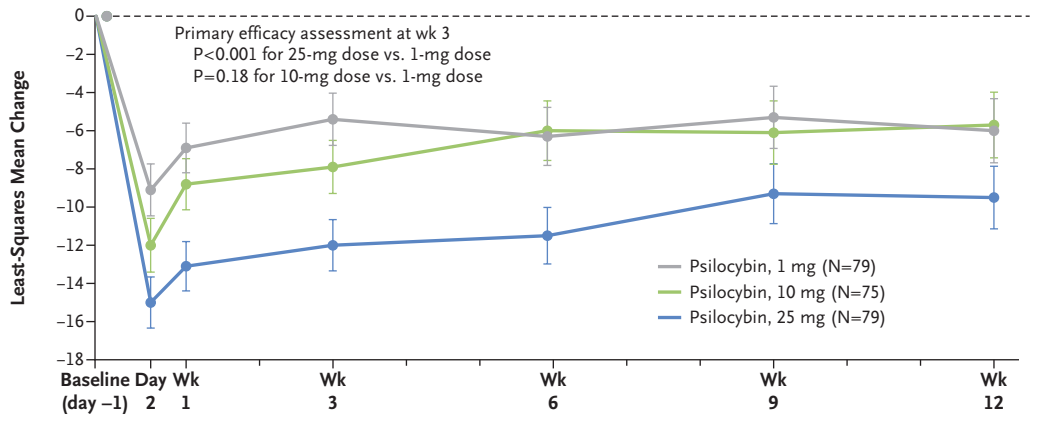

Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).
Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

P<0.001), and the difference between the 10-mg group and the 1-mg group was −2.5 (95% CI, −6.2 to 1.2; P=0.18) (Table 2 and Fig. 2). The nonsignificant finding for the comparison between the 10-mg group and the 1-mg group terminated significance testing on the basis of the prespecified hierarchical test procedure, and all the subsequent key secondary efficacy end points are considered to be not significantly different between the 25-mg group or the 10-mg group and the 1-mg group. Additional analyses for the primary efficacy end point are shown in Figure S2. These alternative data-handling strategies and analysis models provided results that were consistent with the findings for the primary efficacy end point.

The incidence of response at week 3 was 37% in the 25-mg group, 19% in the 10-mg group, and 18% in the 1-mg group (odds ratio in the 25-mg group vs. the 1-mg group, 2.9 [95% CI, 1.2 to 6.6]; odds ratio in the 10-mg group vs. the 1-mg group, 1.2 [95% CI, 0.5 to 3.0]) (Table 2). The incidence of remission at week 3 was 29% in the 25-mg group, 9% in the 10-mg group, and 8% in the 1-mg group (odds ratio in the 25-mg group vs. the 1-mg group, 4.8 [95% CI, 1.8 to 12.8]; odds ratio in the 10-mg group vs. the 1-mg group, 1.2 [95% CI, 0.4 to 3.9]). The incidence of sustained response at week 12 was 20% in the 25-mg group, 5% in the 10-mg group, and 10% in the 1-mg group (odds ratio in the 25-mg group vs. the 1-mg group, 2.2 [95% CI, 0.9 to 5.4]; odds ratio in the 10-mg group vs. the 1-mg group, 0.7 [95% CI, 0.2 to 2.0]). Because of the failure of hierarchical testing, no definite conclusions can be drawn from secondary end-point results. The confidence interval for the odds ratio for sustained response at week 12 for both the 25-mg dose and the 10-mg dose as compared with the 1-mg dose included 1. A post hoc analysis of the primary end point that included sex or the number of lifetime episodes of depression showed results similar to those for the primary analysis. The results from per-protocol analysis of the primary end point were also consistent with the modified intention-to-treat population (Fig. S2). Additional efficacy results are included in Tables S3 through S6 and Figures S1 and S2.

SAFETY

Adverse events occurred in 66 participants (84%) in the 25-mg group, 56 (75%) in the 10-mg group, and 57 (72%) in the 1-mg group. The most frequent adverse events reported in the 25-mg group with onset on the day of psilocybin administration (day 1) were headache (in 24% of the participants), nausea (in 22%), and dizziness and fatigue (in 6% each) (Table 3). Adverse events that were rated as severe on day 1 were reported by 4% of the participants in the 25-mg group, 8% of those in the 10-mg group, and 1% of those in the 1-mg group. Just one participant (in the 25-mg group) was treated with adjunctive medication (lorazepam for acute anxiety) on day 1. There were no serious adverse events reported on day 1.

From day 2 up to week 3 (primary end-point assessment), severe adverse events were reported by 9% of the participants in the 25-mg group, 7% of those in the 10-mg group, and 1% of those in the 1-mg group. The serious adverse events in the 25-mg group were suicidal ideation (in two participants) and intentional self-injury (nonsuicidal self-injurious behavior) (in two participants) and in the 10-mg group were suicidal ideation (in two participants), intentional self-injury (in one participant), and hospitalization (for severe depression, in one participant). No serious adverse events were reported from day 2 up to week 3 in the 1-mg group.

After week 3 and up to week 12 (end of trial), severe adverse events were reported by 3% of the participants in the 25-mg group, 4% of those in the 10-mg group, and no participants in the 1-mg group. Serious adverse events in the 25-mg group were suicidal behavior (in three participants), codeine withdrawal syndrome (in one participant), and adjustment disorder with anxiety and depressed mood (in one participant); in the 10-mg group were intentional self-injury (in one participant), depression (in one participant), and suicidal ideation (in one participant); and in the 1-mg group were intentional self-injury (in one participant). Severe adverse events during the trial period according to MedDRA system organ class and preferred term are shown in Table S7.

At the baseline visit, suicidal ideation (passive or active but with no intent or plan) was reported by 21 participants (27%) in the 25-mg group, 27 (36%) in the 10-mg group, and 19 (24%) in the 1-mg group. The number of participants who showed worsening of suicidal state from baseline to week 3 were 11 (14%) in the 25-mg group, 13 (17%) in the 10-mg group, and 7 (9%) in the 1-mg group (Table S8). Three

participants in the 25-mg group reported suicidal behavior after week 3. All three had a history of suicidal behavior or nonsuicidal self-injury before the trial and did not have a treatment response at week 3. No clinically significant changes in vital signs, clinical laboratory tests, or 12-lead ECGs were observed during the trial (see the Supplementary Appendix).

DISCUSSION

This phase 2 clinical trial showed the feasibility of psilocybin monotherapy for up to 12 weeks in patients with a treatment-resistant episode of major depression. The change from baseline to week 3 in the MADRS total score (primary end point) was significantly better with a 25-mg dose than with a 1-mg dose; there was not significant difference between the 10-mg dose and the 1-mg dose. In addition to headache, nausea, dizziness, and fatigue, some participants had suicidal ideation or self-injurious behavior, and the proportions of these participants were numerically higher in the 25-mg and 10-mg groups than in the 1-mg group. In view of the participants who showed worsening of suicidal state, suicidality demands clinical vigilance in future trials of psilocybin for depression. The incidences of response and remission at 3 weeks were generally in the same direction as the primary end-point results; however, the analyses of these end points were ordered in the prespecified hierarchical test procedure after the significance testing had terminated, and no definite conclusions can be drawn from these results. The confidence interval for the odds ratio for sustained response at week 12 for the 25-mg-group as compared with the 1-mg group included 1.

The current trial was designed to address some limitations of previous pilot studies and trials, including limited power, short-duration crossover design, reliance on single-site recruitment of participants, and interpretation of treatment effects that may be confounded by intensive concurrent psychological therapy. The current trial had a primary end point at 3 weeks but observed participants over 12 weeks of follow-up in a parallel-group design, included a trial population in which more than 90% of the participants did not have previous exposure to psilocybin, and used remote raters who were unaware of the details of the trial and the trial-group assignments to determine the primary end-point measure (MADRS total score). The manualized, time-limited approach to preparation, support, and integration of the psychedelic experience ensured safety and is not a stand-alone psychotherapy.

For participants in this trial, psilocybin therapy represented a third-, fourth-, or fifth-line treatment. The incidence of response at week 3 of 37% in the 25-mg group in our trial was numerically lower than that described for first-line treatment of major depressive disorder in several large trials of citalopram,[1] nefazodone, and escitalopram, sertraline, or venlafaxine[17] but was higher than the incidences of response reported in the STAR*D trial for second-line treatments and beyond. Pharmacokinetic research has shown dose-dependent increases in receptor occupancy and subjective effects of psilocybin across the dose range of 3 to 30 mg.[18] These findings may explain the differences in efficacy between the groups in the current trial.

Limitations of the current trial include the lack of an active comparator, the lack of an ethnically diverse participant sample, and the exclusion of persons judged to be at a clinically significant risk for suicide. The intensity of the acute subjective effect of the 25-mg and 10-mg doses, as compared with the 1-mg dose, reduces the effectiveness of the double-blind structure of the trial. We did not assess participants' ability to guess their dose assignment, and ensuring blinding is an inherent limitation of studies of drugs that produce psychedelic subjective effects. Whether other preparations of psilocybin than the proprietary one used in this trial would show the same effects cannot be determined.

In this trial of psilocybin administered in a single session with psychological support, a 25-mg dose but not a 10-mg dose resulted in a significantly greater reduction (improvement) in MADRS total scores than a 1-mg dose at 3 weeks in participants with treatment-resistant depression but was associated with adverse events. Secondary end-point results generally supported the primary analysis with the exception of 12-week sustained response, at which time point the observed numerical difference was not considered to be statistically significant. Longer and larger trials, including comparison with existing treatments for depression, are required to deter-

Table 3. Adverse Events Reported on Day 1, from Day 2 up to Week 3, and after Week 3 up to Week 12 (Safety Population).*

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Day 1			
Any adverse event	48 (61)	35 (47)	30 (38)
Any severe adverse event	3 (4)	6 (8)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	19 (24)	11 (15)	13 (16)
Nausea	17 (22)	5 (7)	1 (1)
Euphoric mood	4 (5)	5 (7)	3 (4)
Fatigue	5 (6)	2 (3)	4 (5)
Insomnia	2 (3)	3 (4)	5 (6)
Anxiety	3 (4)	6 (8)	0
Mood altered	4 (5)	3 (4)	0
Dizziness	5 (6)	1 (1)	0
Paresthesia	2 (3)	4 (5)	0
Abnormal thinking	0	4 (5)	0
Any serious adverse event	0	0	0
Day 2 up to wk 3			
Any adverse event	44 (56)	36 (48)	35 (44)
Any severe adverse event	7 (9)	5 (7)	1 (1)
Adverse events occurring in ≥5% of participants in any group			
Headache	9 (11)	5 (7)	9 (11)
Insomnia	4 (5)	5 (7)	8 (10)
Anxiety	4 (5)	6 (8)	3 (4)
Fatigue	6 (8)	2 (3)	3 (4)
Suicidal ideation	5 (6)	4 (5)	2 (3)
Depression	3 (4)	3 (4)	4 (5)
Mood altered	4 (5)	0	1 (1)
Any serious adverse event	4 (5)	4 (5)	0
Suicidal ideation	2 (3)	2 (3)	0
Intentional self-injury	2 (3)	1 (1)	0
Hospitalization	0	1 (1)	0
After wk 3 up to wk 12			
Any adverse event	23 (29)	24 (32)	24 (30)
Any severe adverse event	2 (3)	3 (4)	0
Adverse events occurring in ≥5% of participants in any group			
Headache	3 (4)	2 (3)	6 (8)
Any serious adverse event	4 (5)	3 (4)	1 (1)
Suicidal behavior	3 (4)	0	0

Table 3. (Continued.)

Adverse Event	Psilocybin, 25 mg (N=79)	Psilocybin, 10 mg (N=75)	Psilocybin, 1 mg (N=79)
		number (percent)	
Intentional self-injury	0	1 (1)	1 (1)
Adjustment disorder with anxiety and depressed mood	1 (1)	0	0
Depression	0	1 (1)	0
Drug withdrawal syndrome†	1 (1)	0	0
Suicidal ideation	0	1 (1)	0

* Shown are adverse events that emerged or worsened after trial-drug administration.
† The event involved codeine withdrawal.

mine the efficacy and safety of psilocybin for treatment-resistant depression.

The views expressed are those of the authors and not necessarily those of the NHS, the National Institute for Health or Care Research, or the Department of Health and Social Care in the United Kingdom.

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APPENDIX

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REFERENCES

1. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905-17.
2. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D project results: a comprehensive review of findings. Curr Psychiatry Rep 2007;9:449-59.
3. Pigott HE. The STAR*D trial: it is time to reexamine the clinical beliefs that guide the treatment of major depression. Can J Psychiatry 2015;60:9-13.
4. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. Addict Biol 2002;7:357-64.
5. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011;68:71-8.
6. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 2016;30:1165-80.
7. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 2016;30:1181-97.
8. Davis AK, Barrett FS, May DG, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 2021;78:481-9.
9. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of psilocybin versus escitalopram for depression. N Engl J Med 2021;384:1402-11.
10. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016;3:619-27.
11. Tai SJ, Nielson EM, Lennard-Jones M, et al. Development and evaluation of a therapist training program for psilocybin therapy for treatment-resistant depression in clinical research. Front Psychiatry 2021;12:586682.
12. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
13. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:Suppl 20:22-33.
14. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. Validation of the Massachusetts General Hospital Antidepressant Treatment History Questionnaire (ATRQ). CNS Neurosci Ther 2010;16:322-5.
15. Williams JB, Kobak KA. Development and reliability of a structured interview guide for the Montgomery Asberg Depression Rating Scale (SIGMA). Br J Psychiatry 2008;192:52-8.
16. Posner K, Brent D, Lucas C, et al. Columbia-suicide severity rating scale (C-SSRS). New York: Research Foundation for Mental Hygiene, 2008.
17. Saveanu R, Etkin A, Duchemin A-M, et al. The international Study to Predict Optimized Treatment in Depression (iSPOT-D): outcomes from the acute phase of antidepressant treatment. J Psychiatr Res 2015;61:1-12.
18. Madsen MK, Fisher PM, Burmester D, et al. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology 2019;44:1328-34.

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Appendix I

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MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

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Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma. After psychiatric medication washout, participants ($n = 90$) were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5, the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint) were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were tracked throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.0116$, $d = 0.43$). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

PTSD is a common and debilitating condition with immeasurable social and economic costs that affects the lives of hundreds of millions of people annually. There are a number of environmental and biological risk factors that contribute to the development and maintenance of PTSD[1], and poor PTSD treatment outcomes are associated with several comorbid conditions that include childhood trauma[2], alcohol and substance use disorders[3], depression[4], suicidal ideation[5] and dissociation[6]. It is therefore imperative to identify a therapeutic that is beneficial in those individuals with the comorbidities that typically confer treatment resistance.

The selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are Food and Drug Administration (FDA)-approved first-line therapeutics for the treatment of PTSD. However, an estimated 40–60% of patients do not respond to these compounds[7]. Likewise, although evidenced-based trauma-focused

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psychotherapies such as prolonged exposure and cognitive behavioral therapy are considered to be the gold standard treatments for PTSD[8], many participants fail to respond or continue to have significant symptoms, and dropout rates are high[9,10]. Novel cost-effective therapeutics are therefore desperately needed[11].

The substituted amphetamine 3,4-methylenedioxymethamphetamine (MDMA) induces serotonin release by binding primarily to presynaptic serotonin transporters[12]. MDMA has been shown to enhance fear memory extinction, modulate fear memory reconsolidation (possibly through an oxytocin-dependent mechanism), and bolster social behavior in animal models[13,14]. Pooled analysis of six phase 2 trials of MDMA-assisted therapy for PTSD have now shown promising safety and efficacy findings[15].

Here, we assess the efficacy and safety of MDMA-assisted therapy in individuals with severe PTSD. Participants were given three doses of MDMA or placebo in a controlled clinical environment and in the presence of a trained therapy team. Primary and secondary outcome measures (CAPS-5 and SDS, respectively) were assessed by a centralized pool of blinded, independent diagnostic assessors. MDMA-assisted therapy for PTSD was granted an FDA Breakthrough Therapy designation, and the protocol and statistical analysis plan (SAP) were developed in conjunction with the FDA[16].

Results

Demographics. Participants were recruited from 7 November 2018 to 26 May 2020, with the last participant visit conducted on 21 August 2020. A total of 345 participants were assessed for eligibility, 131 were enrolled, 91 were confirmed for randomization (United States, $n=77$; Canada, $n=9$; Israel, $n=5$), and 46 were randomized to MDMA and 44 to placebo (Fig. 1).

Study arms were not significantly different in terms of race, ethnicity, sex, age, dissociative subtype, disability or CAPS-5 score (Table 1). The mean duration of PTSD diagnosis was 14.8 (s.d. 11.6) years and 13.2 (s.d. 11.4) years in the MDMA and placebo groups, respectively. Of note, six participants in the MDMA group and 13 participants in the placebo group had the dissociative subtype according to CAPS-5 score.

Efficacy. MDMA significantly attenuated PTSD symptomology, as shown by the change in CAPS-5 total severity score from baseline to 18 weeks after baseline. Mixed model repeated measure (MMRM) analysis of the de jure estimand (that is, the effects of the drug if taken as directed) showed a significant difference in treatment arms ($n=89$ (MDMA $n=46$), $P<0.0001$, between-group difference = 11.9, 95% confidence interval (CI) = 6.3–17.4, d.f. = 71) (Fig. 2a). MMRM sensitivity analysis of the de facto estimand (that is, the effects of the drug if taken as assigned, regardless of adherence) showed a significant difference in treatment arms ($n=90$, $P<0.0001$, d.f. = 72).

The mean change in CAPS-5 scores from baseline to 18 weeks after baseline in the completers (per protocol set) was −24.4 (s.d. 11.6) ($n=42$) in the MDMA-assisted therapy group compared with −13.9 (s.d. 11.5) ($n=37$) in the placebo with therapy group.

The effect size of the MDMA-assisted therapy treatment compared with placebo with therapy was $d=0.91$ (95% CI = 0.44–1.37, pooled s.d. = 11.55) in the de jure estimand and $d=0.97$ (95% CI = 0.51–1.42) in the de facto estimand. When the within-group treatment effect (which included the effect of the supportive therapy that was administered in both arms) was compared between the MDMA and placebo groups, the effect size was 2.1 (95% CI = −5.6 to 1.4) in the MDMA group and 1.2 (95% CI = −4.9 to 2.5) in the placebo group.

Over the same period, MDMA significantly reduced clinician-rated functional impairment as assessed with the SDS. MMRM analysis of the de jure estimand showed a significant difference in treatment arms ($n=89$ (MDMA $n=46$), $P=0.0116$, d.f. = 71, effect size = 0.43, 95% CI = −0.01 to 0.88, pooled s.d. = 2.53) (Fig. 2b). The mean change in SDS scores from baseline to 18 weeks after baseline in the completers was −3.1 (s.d. 2.6) ($n=42$) in the MDMA-assisted therapy group and −2.0 (s.d. 2.4) ($n=37$) in the placebo with therapy group.

MDMA was equally effective in participants with comorbidities that are often associated with treatment resistance. Participants with the dissociative subtype of PTSD who received MDMA-assisted therapy had significant symptom reduction on the CAPS-5 (mean MDMA $\Delta=-30.8$ (s.d. 9.0), mean placebo $\Delta=-12.8$ (s.d. 12.8)), and this was similar to that in their counterparts with non-dissociative PTSD (mean MDMA $\Delta=-23.6$ (s.d. 11.7), mean placebo $\Delta=-14.3$ (s.d. 11.2)). The benefit of MDMA therapy was not modulated by history of alcohol use disorder, history of substance use disorder, overnight stay or severe childhood trauma. Results were consistent across all 15 study sites with no effect by study site ($P=0.1003$). In MMRM analysis there was no obvious impact of SSRI history on effectiveness of MDMA (Supplementary Table 2).

MDMA therapy was effective in an exploratory endpoint analysis of the reduction of depression symptoms (using the Beck Depression Inventory II (BDI-II)) from baseline to study termination of the de jure estimand (mean MDMA $\Delta=-19.7$ (s.d. 14.0), $n=42$; mean placebo $\Delta=-10.8$ (s.d. 11.3), $n=39$; $t=-3.11$, $P=0.0026$, d.f. = 79, effect size = 0.67, 95% CI = 0.22–1.12) (Fig. 2c).

Clinically significant improvement (a decrease of ≥10 points on the CAPS-5), loss of diagnosis (specific diagnostic measure on the CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score ≤ 11) were each tracked. At the primary study endpoint (18 weeks after baseline), 28 of 42 (67%) of the participants in the MDMA group no longer met the diagnostic criteria for PTSD, compared with 12 of 37 (32%) of those in the placebo group after three sessions. Additionally, 14 of 42 participants in the MDMA group (33%) and 2 of 37 participants in the placebo group (5%) met the criteria for remission after three sessions (Fig. 3).

Safety. Treatment-emergent adverse events (TEAEs, adverse events that occurred during the treatment period from the first experimental session to the last integration session) that were more prevalent in the MDMA study arm were typically transient, mild to moderate in severity, and included muscle tightness, decreased appetite, nausea, hyperhidrosis and feeling cold (Supplementary Table 3). Importantly, no increase in adverse events related to suicidality was observed in the MDMA group. A transient increase in vital signs (systolic and diastolic blood pressure and heart rate) was observed in the MDMA group (Supplementary Table 4). Two participants in the MDMA group had a transient increase in body temperature to 38.1 °C: one had an increase after the second MDMA session, and one had an increase after the second and third MDMA sessions.

Two participants, both randomized to the placebo group, reported three serious adverse events (SAEs) during the trial. One participant in the placebo group reported two SAEs of suicidal behavior during the trial, and another participant in the placebo group reported one SAE of suicidal ideation that led to self-hospitalization. Five participants in the placebo group and three participants in the MDMA group reported adverse events of special interest (AESIs) of suicidal ideation, suicidal behavior or self-harm in the context of suicidal ideation. One participant in the placebo group reported two cardiovascular AESIs in which underlying cardiac etiology could not be ruled out (Table 2). One participant randomized to the MDMA group chose to discontinue participation due to being triggered by the CAPS-5 assessments and to an adverse event of depressed mood following an experimental session; this participant met the criterion as a non-responder, which was defined as having a less than

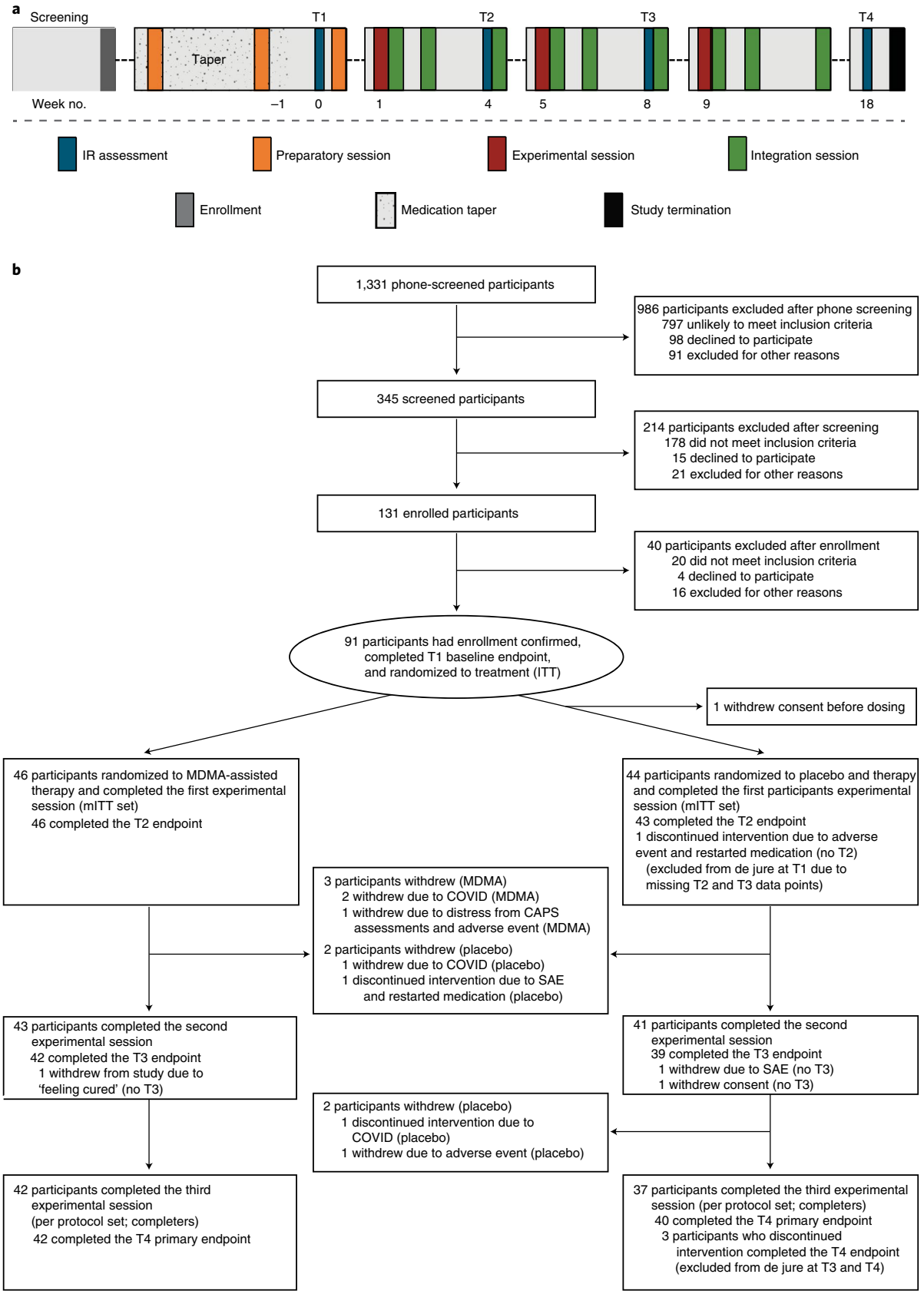


Fig. 1 | Procedure timeline and study flow diagram. a, Procedure timeline. Following the screening procedures and medication taper, participants attended a total of three preparatory sessions, three experimental sessions, nine integration sessions and four endpoint assessments (T1–4) over 18 weeks, concluding with a final study-termination visit. IR, independent rater; T, timepoint of endpoint assessment; T1, baseline; T2, after the first experimental session; T3, after the second experimental session; T4, 18 weeks after baseline. **b**, CONSORT diagram indicating participant numbers and disposition through the course of the trial.

Table 1 | Demographics and baseline characteristics

	MDMA-assisted therapy ($n=46$)	Placebo with therapy ($n=44$)	Total ($n=90$)
Age (years), mean (s.d.)	43.5 (12.9)	38.2 (10.4)	41.0 (11.9)
Sex assigned at birth, *n* (%)			
Male	19 (41.3)	12 (27.3)	31 (34.4)
Female[a]	27 (58.7)	32 (72.7)	59 (65.6)
Ethnicity, *n* (%)			
Hispanic or Latino	5 (10.9)	3 (6.8)	8 (8.9)
Not Hispanic or Latino	41 (89.1)	40 (90.9)	81 (90.0)
Race, *n* (%)			
American Indian or native Alaskan	3 (6.5)	0 (0.0)	3 (3.3)
Asian	2 (4.3)	5 (11.4)	7 (7.8)
Black or African American	0 (0.0)	2 (4.5)	2 (2.2)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
White	39 (84.8)	30 (68.2)	69 (76.7)
Multiple	2 (4.3)	6 (13.6)	8 (8.9)
BMI ($kg\,m^{-2}$), mean (s.d.)	26.0 (4.8)	24.8 (4.2)	25.4 (4.5)
Duration of PTSD (years), mean (s.d.)	14.8 (11.6)	13.2 (11.4)	14.1 (11.5)
Dissociative subtype of PTSD, *n* (%)	6 (13.0)	13 (29.5)	19 (21.1)
Comorbid major depression, *n* (%)	42 (91.3)	40 (90.9)	82 (91.1)
Veteran	10 (21.7)	6 (13.6)	16 (17.8)
Trauma history, *n* (%)			
Developmental trauma	40 (87.0)	36 (81.8)	76 (84.4)
Combat exposure	6 (13.0)	5 (11.4)	11 (12.2)
Multiple trauma	41 (89.1)	38 (86.4)	79 (87.8)
Pre-study PTSD medications, *n* (%)[b]			
Sertraline	8 (17.4)	9 (20.5)	17 (18.9)
Paroxetine	3 (6.5)	3 (6.8)	6 (6.7)
Pre-study therapy, *n* (%)			
CBT	12 (26.1)	22 (50.0)	34 (37.8)
EMDR	17 (37.0)	13 (29.5)	30 (33.3)
Group therapy	19 (41.3)	14 (31.8)	33 (36.7)
Prolonged exposure therapy	1 (2.2)	0 (0)	1 (1.1)
Psychodynamic	11 (23.9)	10 (22.7)	21(23.3)
Other	41 (89.1)	38 (86.4)	79 (87.8)
None	1 (2.2)	1 (2.3)	2 (2.2)
Baseline CAPS-5 total score, mean (s.d.)	44.0 (6.01)	44.2 (6.15)	44.1 (6.04)
Baseline SDS modified score, mean (s.d.)	6.8 (2.07)	7.4 (1.63)	7.1 (1.9)
Lifetime C-SSRS, *n* (%)[c]			
Positive lifetime suicidal ideation	42 (91.3)	41 (93.2)	83 (92.2)
Serious lifetime suicidal ideation	20 (43.5)	17 (38.6)	37 (41.1)
Positive lifetime suicidal behavior	16 (34.8)	13 (29.5)	29 (32.2)
Baseline BDI-II total score, mean (s.d.)	30.5 (13.1)	34.9 (12.6)	32.7 (13.0)
AUDIT, mean (s.d.)	4.1 (4.2)	2.8 (3.2)	3.5 (3.8)
DUDIT, mean (s.d.)	2.7 (4.3)	3.5 (4.5)	3.1 (4.4)
ACE Questionaire score, mean (s.d.)	5.0 (2.7)	5.0 (2.9)	5.0 (2.8)
Prior report of MDMA use, *n* (%)			
Lifetime reported use	18 (39.1)	11 (25.0)	29 (32.2)
Reported use in the past 10 years	9 (19.6)	10 (22.7)	19 (21.1)

BMI, body mass index; CBT, cognitive behavioral therapy; EMDR, eye movement desensitization and reprocessing therapy. [a]Two participants included in the assigned female at birth MDMA group identified their gender as non-binary. [b]Medications were tapered down and washed out prior to baseline assessments and the first experimental session, in accordance with the protocol. [c]Lifetime accounts for all suicidal ideation and behavior prior to the study. Serious ideation is defined as a score of 4 or 5 in the suicidal ideation category.

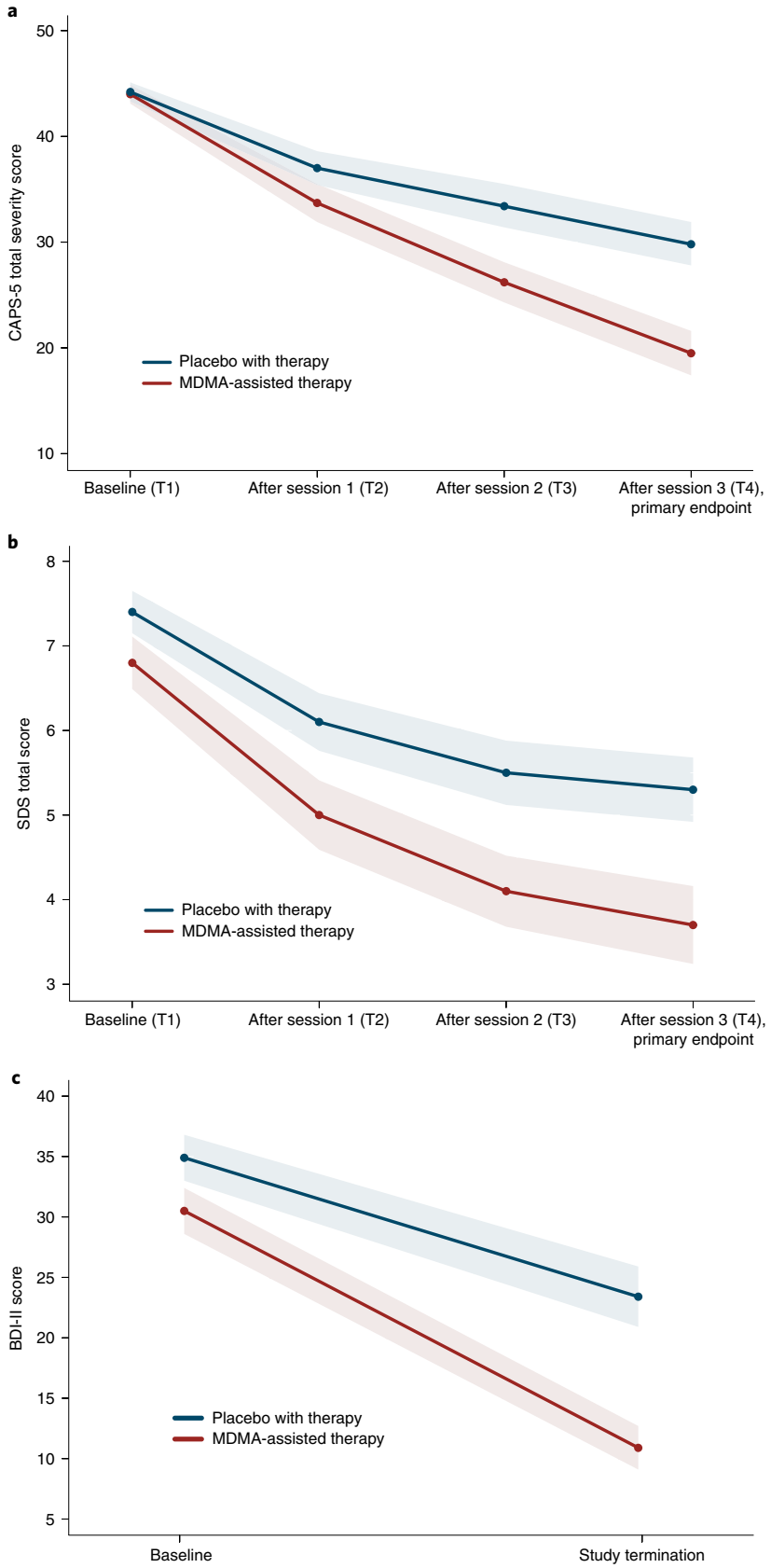


Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P < 0.0001$, $d = 0.91$, $n = 89$ (MDMA $n = 46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an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

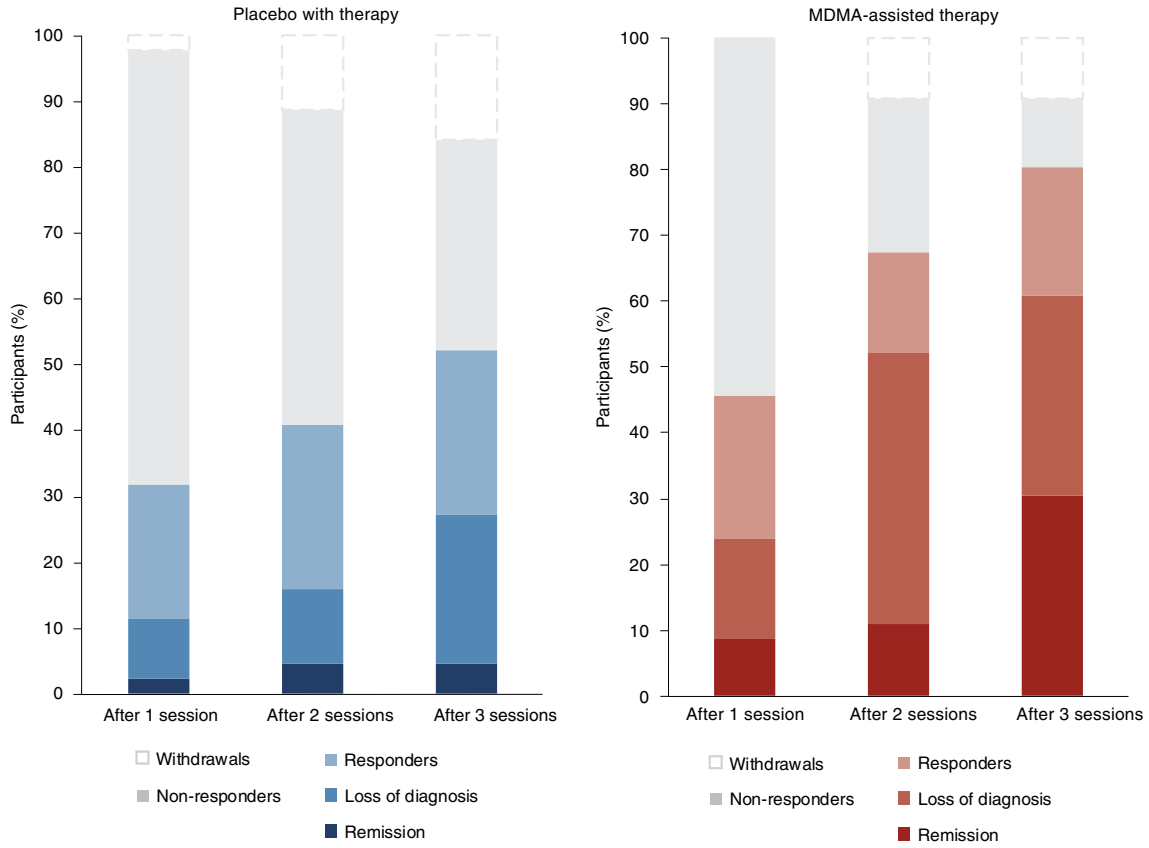


Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure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

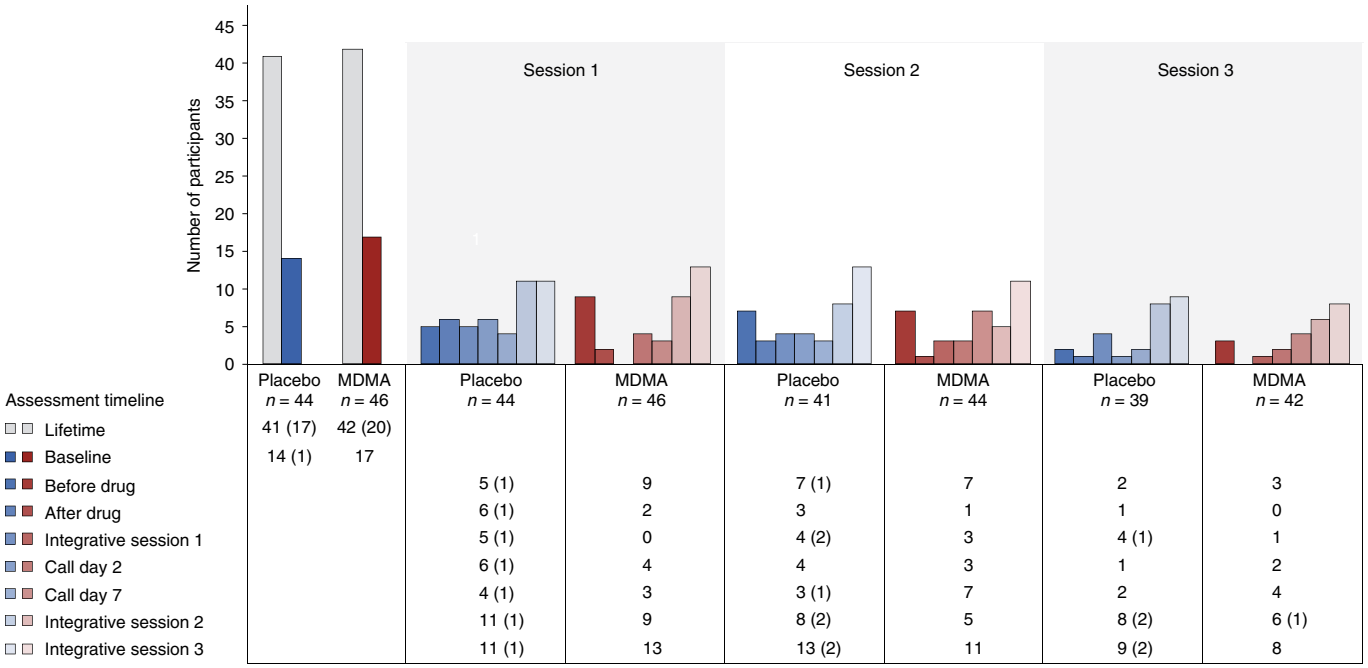
Table 2 | Participants with treatment-emergent SAEs and AESIs

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

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

10-point decrease in CAPS-5 score. MDMA sessions were not otherwise followed by a lowering of mood.

Suicidality was tracked throughout the study using the Columbia Suicide Severity Rating Scale (C-SSRS) at each study visit. More than 90% of participants reported suicidal ideation in their lifetime, and 17 of 46 participants (37%) in the MDMA group and 14 of 44 participants (32%) in the placebo group reported suicidal ideation at baseline. Although the number of participants who reported suicidal ideation varied throughout the visits, prevalence never exceeded baseline and was not exacerbated in the MDMA group.



	Placebo n = 44	MDMA n = 46	Placebo n = 44	MDMA n = 46	Placebo n = 41	MDMA n = 44	Placebo n = 39	MDMA n = 42
Lifetime	41 (17)	42 (20)						
Baseline	14 (1)	17						
Before drug			5 (1)	9	7 (1)	7	2	3
After drug			6 (1)	2	3	1	1	0
Integrative session 1			5 (1)	0	4 (2)	3	4 (1)	1
Call day 2			6 (1)	4	4	3	1	2
Call day 7			4 (1)	3	3 (1)	7	2	4
Integrative session 2			11 (1)	9	8 (2)	5	8 (2)	6 (1)
Integrative session 3			11 (1)	13	13 (2)	11	9 (2)	8

Fig. 4 | Number of participants reporting the presence of suicidal ideation as measured with the C-SSRS at each visit and separated by treatment group. C-SSRS ideation scores range from 0 (no ideation) to 5. A C-SSRS ideation score of 4 or 5 is termed 'serious ideation'. The number of participants endorsing any positive ideation (>0) is shown by the colored bars and noted in the table below the graph. The number of participants endorsing serious ideation is given in parentheses in the table.

Serious suicidal ideation (a score of 4 or 5 on the C-SSRS) was minimal during the study and occurred almost entirely in the placebo arm (Fig. 4).

Discussion

Here, we demonstrate that three doses of MDMA given in conjunction with manualized therapy over the course of 18 weeks results in a significant and robust attenuation of PTSD symptoms and functional impairment as assessed using the CAPS-5 and SDS, respectively. MDMA also significantly mitigated depressive symptoms as assessed using the BDI-II. Of note, MDMA did not increase the occurrence of suicidality during the study.

These data illustrate the potential benefit of MDMA-assisted therapy for PTSD over the FDA-approved first-line pharmacotherapies sertraline and paroxetine, which have both exhibited smaller effect sizes in pivotal studies[16]. Previous comparison of change in CAPS score between sertraline and placebo showed effect sizes of 0.31 and 0.37 (ref. [16]). Similarly, comparison of change in CAPS score between paroxetine and placebo showed effect sizes of 0.56, 0.45 and 0.09 (ref. [16]). By contrast, the effect size of 0.91 demonstrated in this study between MDMA-assisted therapy and placebo with therapy was larger than that for any other previously identified PTSD pharmacotherapy[16–18]. To directly assess superiority, a head-to-head comparison of MDMA-assisted therapy with SSRIs for PTSD would be needed. Although the present study tested the effects of MDMA using a model in which both treatment groups received supportive therapy, participants who received MDMA and supportive therapy ($d = 2.1$) had greater improvement in PTSD change scores compared with those who received placebo with supportive therapy ($d = 1.2$), suggesting that MDMA enhanced the effects of supportive therapy. In clinical practice, both MDMA and supportive therapy will be components of this PTSD treatment.

Previous research on MDMA for PTSD has suggested that those with a recent history of SSRI treatment may not respond as robustly to MDMA[18]. Given that 65.5% of participants in the current trial have a lifetime history of SSRI use, it is difficult to separate the ramifications of long-term SSRI treatment from the effects of treatment resistance. However, there was no obvious effect of previous SSRI use on therapeutic efficacy in this trial. Similarly, although years of PTSD diagnosis or age of onset may affect treatment efficacy, no obvious relationship was seen here between duration or onset of PTSD diagnosis and treatment efficacy.

Serotonin and the serotonin transporter are of particular importance in the generation, consolidation, retrieval and reconsolidation of fear memories[19,20]. Reduced serotonin transporter levels (which result in greater amounts of extracellular serotonin) have been shown to predict propensity to develop PTSD[21], increase fear and anxiety-related behaviors[22], and induce greater amygdalar blood oxygenation level-dependent (BOLD) activity in response to fearful images[23]. There is extensive serotonergic innervation of the amygdala, and amygdalar serotonin levels have been shown to increase following exposure to stressful and fear-inducing stimuli[24]. MDMA enhances the extinction of fear memories in mice through increased expression of brain-derived neurotrophic factor in the amygdala, and human neuroimaging studies have demonstrated that MDMA is associated with attenuated amygdalar BOLD activity during presentation of negative emotional stimuli[25]. Together these data suggest that MDMA may exert its therapeutic effects through a well-conserved mechanism of amygdalar serotonergic function that regulates fear-based behaviors and contributes to the maintenance of PTSD. Perhaps by reopening an oxytocin-dependent critical period of neuroplasticity that typically closes after adolescence[15], MDMA may facilitate the processing and release of particularly intractable, potentially developmental, fear-related memories.

It is intriguing to speculate that the pharmacological properties of MDMA, when combined with therapy, may produce a 'window of tolerance,' in which participants are able to revisit and process traumatic content without becoming overwhelmed or encumbered by hyperarousal and dissociative symptoms[26]. MDMA-assisted

therapy may facilitate recall of negative or threatening memories with greater self-compassion[27] and less PTSD-related shame and anger[28]. Additionally, the acute prosocial and interpersonal effects of MDMA[25,29] may support the quality of the therapeutic alliance, a potentially important factor relating to PTSD treatment adherence[30] and outcome[31]. Indeed, clinicians have suggested that "MDMA may catalyze therapeutic processing by allowing patients to stay emotionally engaged while revisiting traumatic experiences without becoming overwhelmed"[32].

Given that PTSD is a strong predictor of disability in both veteran and community populations[33], it is promising to note that the robust reduction in PTSD and depressive symptoms identified here is complemented by a significant improvement in SDS score (for example, work and/or school, social and family functioning). Approximately 4.7 million US veterans report a service-related disability[34], costing the US government approximately $73 billion per year[35]. Identification of a PTSD treatment that could improve social and family functioning and ameliorate impairment across a broad range of environmental contexts could provide major medical cost savings, in addition to improving the quality of life for veterans and others affected by this disorder.

PTSD is a particularly persistent and incapacitating condition when expressed in conjunction with other disorders of mood and affect. In the present study, perhaps most compelling are the data indicating efficacy in participants with chronic and severe PTSD, and the associated comorbidities including childhood trauma, depression, suicidality, history of alcohol and substance use disorders, and dissociation, because these groups are all typically considered treatment resistant[2–6]. Given that more than 80% of those assigned a PTSD diagnosis have at least one comorbid disorder[3], the identification of a therapy that is effective in those with complicated PTSD and dual diagnoses could greatly improve PTSD treatment. Additional studies should therefore be conducted to evaluate the safety and efficacy of MDMA-assisted therapy for PTSD in those with specific comorbidities.

Although recent research suggests that dissociative subtype PTSD is difficult to treat[36], participants with the dissociative subtype who received MDMA-assisted therapy had significant symptom reduction that was at least similar to that of their counterparts with non-dissociative PTSD. Given that this covariate was significant, it warrants further study. Furthermore, given that other treatments for PTSD are not consistently effective for those with the dissociative subtype, these data, if replicated, would indicate an important novel therapeutic niche for MDMA-assisted therapy for typically hard-to-treat populations.

Importantly, there were no major safety issues reported in the MDMA arm of this study. Although abuse potential, cardiovascular risk and suicidality were recorded as AESIs, MDMA was not shown to induce or potentiate any of these conditions. In addition, although there was often a transient increase in blood pressure during MDMA sessions, this was expected based on phase 2 data and previous studies in healthy volunteers[37]. These data suggest that MDMA has an equivalent, if not better, safety profile compared with that of first-line SSRIs for the treatment of PTSD, which are known to carry a low risk of QT interval prolongation[38].

There are several limitations to the current trial. First, due to the coronavirus disease 2019 (COVID-19) pandemic, the participant population is smaller than originally planned. However, given the power noted in this study, it is unlikely that population size was an impediment. Second, the population is relatively homogeneous and lacks racial and ethnic diversity, which should be addressed in future trials. Third, this report describes the findings of a short-term pre-specified primary outcome, 2 months after the last experimental session and 5 weeks since the final integrative therapy session; long-term follow-up data from this controlled trial will be collected to assess durability of treatment. Fourth, safety data were by necessity collected by site therapists, perhaps limiting the blinding of the data. To eliminate this effect on the primary and secondary outcome measures, all efficacy data were collected by blinded, independent raters. Last, given the subjective effects of MDMA, the blinding of participants was also challenging and possibly led to expectation effects[14]. However, although blinding was not formally assessed during the study, when participants were contacted to be informed of their treatment assignment at the time of study unblinding it became apparent that at least 10% had inaccurately guessed their treatment arm. Although anecdotal, at least 7 of 44 participants in the placebo group (15.9%) inaccurately believed that they had received MDMA, and at least 2 of 46 participants in the MDMA group (4.3%) inaccurately believed that they had received placebo.

We may soon be confronted with the potentially enormous economic and social repercussions of PTSD, exacerbated by the COVID-19 pandemic. Overwhelmingly high rates of psychological and mental health impairment could be with us for years to come and are likely to impart a considerable emotional and economic burden. Novel PTSD therapeutics are desperately needed, especially for those for whom comorbidities confer treatment resistance.

In summary, MDMA-assisted therapy induces rapid onset of treatment efficacy, even in those with severe PTSD, and in those with associated comorbidities including dissociative PTSD, depression, history of alcohol and substance use disorders, and childhood trauma. Not only is MDMA-assisted therapy efficacious in individuals with severe PTSD, but it may also provide improved patient safety. Compared with current first-line pharmacological and behavioral therapies, MDMA-assisted therapy has the potential to dramatically transform treatment for PTSD and should be expeditiously evaluated for clinical use.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01336-3.

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References

1. Yehuda, R. et al. Putative biological mechanisms for the association between early life adversity and the subsequent development of PTSD. *Psychopharmacology (Berl.)* **212**, 405–417 (2010).
2. Widom, C. S. Posttraumatic stress disorder in abused and neglected children grown up. *Am. J. Psychiatry* **156**, 1223–1229 (1999).
3. Kessler, R. C., Sonnega, A., Bromet, E., Hughes, M. & Nelson, C. B. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch. Gen. Psychiatry* **52**, 1048–1060 (1995).
4. Hegel, M. T. et al. Impact of comorbid panic and posttraumatic stress disorder on outcomes of collaborative care for late-life depression in primary care. *Am. J. Geriatr. Psychiatry* **13**, 48–58 (2005).
5. Tarrier, N., Taylor, K. & Gooding, P. Cognitive-behavioral interventions to reduce suicide behavior: a systematic review and meta-analysis. *Behav. Modif.* **32**, 77–108 (2008).
6. Wolf, E. J., Lunney, C. A. & Schnurr, P. P. The influence of the dissociative subtype of posttraumatic stress disorder on treatment efficacy in female veterans and active duty service members. *J. Consult. Clin. Psychol.* **84**, 95–100 (2016). Jan.
7. Steenkamp, M. M., Litz, B. T., Hoge, C. W. & Marmar, C. R. Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA* **314**, 489–500 (2015).
8. Watkins, L. E., Sprang, K. R. & Rothbaum, B. O. Treating PTSD: a review of evidence-based psychotherapy interventions. *Front Behav. Neurosci.* **12**, 258 (2018).
9. Bisson, J. I., Roberts, N. P., Andrew, M., Cooper, R. & Lewis, C. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst. Rev.* **2013**(12), CD003388 (2013).

10. Gutner, C. A., Gallagher, M. W., Baker, A. S., Sloan, D. M. & Resick, P. A. Time course of treatment dropout in cognitive-behavioral therapies for posttraumatic stress disorder. *Psychol. Trauma* **8**, 115–121 (2016).
11. Marseille, E., Kahn, J. G., Yazar-Klosinski, B. & Doblin, R. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. *PLoS ONE* **15**, e0239997 (2020).
12. Rudnick, G. & Wall, S. C. The molecular mechanism of "ecstasy" [3,4-me thylenedioxy-methamphetamine(MDMA)]: serotonin transporters are targets for MDMA-induced serotonin release. *Proc. Natl Acad. Sci. USA* **89**, 1817–1821 (1992).
13. Hake, H. S. et al. 3,4-Methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiol. Behav.* **199**, 343–350 (2019).
14. Nardou, R. et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature* **569**, 116–120 (2019).
15. Mithoefer, M. C. et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl.)* **236**, 2735–2745 (2019).
16. Feduccia, A. A. et al. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Front. Psychiatry* **10**, 650 (2019).
17. Lee, D. J. et al. Psychotherapy versus pharmacotherapy for posttraumatic stress disorder: systematic review and meta-analyses to determine first-line treatments. *Depress. Anxiety* **33**, 792–806 (2016).
18. Feduccia, A. A., Jerome, L., Mithoefer, M. C. & Holland, J. Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy. *Psychopharmacology* (*Berl.*) **238**, 581–588 (2021).
19. Bauer, E. P. Serotonin in fear conditioning processes. *Behav. Brain Res.* **277**, 68–77 (2015).
20. Johnson, P. L. et al. Assessment of fear and anxiety associated behaviors, physiology and neural circuits in rats with reduced serotonin transporter (SERT) levels. *Transl. Psychiatry* **9**, 33 (2019).
21. Lee, H. J. et al. Influence of the serotonin transporter promoter gene polymorphism on susceptibility to posttraumatic stress disorder. *Depress. Anxiety* **21**, 135–139 (2005).
22. Lesch, K. P. et al. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* **274**, 1527–1531 (1996).
23. Hariri, A. R. et al. Serotonin transporter genetic variation and the response of the human amygdala. *Science* **297**, 400–403 (2002).
24. Kawahara, H., Yoshida, M., Yokoo, H., Nishi, M. & Tanaka, M. Psychological stress increases serotonin release in the rat amygdala and prefrontal cortex assessed by in vivo microdialysis. *Neurosci. Lett.* **162**, 81–84 (1993).
25. Bedi, G., Phan, K. L., Angstadt, M. & de Wit, H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology (Berl.)* **207**, 73–83 (2009).
26. Frewen, P. A. & Lanius, R. A. Toward a psychobiology of posttraumatic self-dysregulation: reexperiencing, hyperarousal, dissociation, and emotional numbing. *Ann. NY Acad. Sci.* **1071**, 110–124 (2006).
27. Kamboj, S. K. et al. Recreational 3,4-methylenedioxy-N-methylamphetamine (MDMA) or 'ecstasy' and self-focused compassion: preliminary steps in the development of a therapeutic psychopharmacology of contemplative practices. *J. Psychopharmacol.* **29**, 961–970 (2015).
28. Dewey, D., Schuldberg, D. & Madathil, R. Do peritraumatic emotions differentially predict PTSD symptom clusters? Initial evidence for emotion specificity. *Psychol. Rep.* **115**, 1–12 (2014).
29. Hysek, C. M. et al. MDMA enhances emotional empathy and prosocial behavior. *Soc. Cogn. Affect. Neurosci.* **9**, 1645–1652 (2014).
30. Keller, S. M., Zoellner, L. A. & Feeny, N. C. Understanding factors associated with early therapeutic alliance in PTSD treatment: adherence, childhood sexual abuse history, and social support. *J. Consult. Clin. Psychol.* **78**, 974–979 (2010).
31. Imel, Z. E., Laska, K., Jakupcak, M. & Simpson, T. L. Meta-analysis of dropout in treatments for posttraumatic stress disorder. *J. Consult. Clin. Psychol.* **81**, 394–404 (2013).
32. Mithoefer M. MDMA-assisted psychotherapy; promising treatment for PTSD. American Psychiatric Association Annual Meeting, Toronto, Ontario, Canada (2015).
33. Fortenbaugh, F. C. et al. The impact of common psychiatric and behavioral comorbidities on functional disability across time and individuals in post-9/11 veterans. *J. Trauma. Stress* **33**, 750–761 (2020).
34. Bureau of Labor and Statistics. Employment Situation of Veterans—2020. News release, 18 March 2021; https://www.bls.gov/news.release/pdf/vet.pdf
35. Congressional Budget Office. *Possible Higher Spending Paths for Veterans' Benefits* (2018); https://www.cbo.gov/publication/54881
36. Cloitre, M., Petkova, E., Wang, J. & Lu Lassell, F. An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD related to childhood abuse. *Depress. Anxiety* **29**, 709–717 (2012).
37. Vizeli, P. & Liechti, M. E. Safety pharmacology of acute MDMA administration in healthy subjects. *J. Psychopharmacol.* **31**, 576–588 (2017).
38. Funk, K. A. & Bostwick, J. R. A comparison of the risk of QT prolongation among SSRIs. *Ann. Pharmacother.* **47**, 1330–1341 (2013).

Methods

Study design. This was a randomized double-blind study designed to compare the efficacy of MDMA-assisted therapy with that of placebo with therapy. Fifteen study sites, consisting of 11 in the United States, two in Canada and two in Israel, included both institutional sites and private clinics. Ethics approval was obtained from Copernicus Group Independent Review Board, Western Institutional Review Board, University of British Columbia Providence Healthcare Research Ethics Board, and the Helsinki Committees of Be'er Ya'akov Ness Ziona Mental Health Center and Chaim Sheba Medical Center. This clinical study was conducted in accordance with the principles of the Declaration of Helsinki. The public study protocol is available at http://maps.org/mapp1. The therapist manual is available at http://maps.org/treatment-manual.

Participants. Participants were recruited through print and internet advertisements, referrals from treatment providers, and by word of mouth. Participants were required to initiate contact with the study sites themselves, even if recommended by a provider. After providing written informed consent, participants were screened for eligibility. The criteria for inclusion consisted of meeting the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria for current PTSD with a symptom duration of ≥6 months at screening (as assessed with the Mini International Neuropsychiatric Interview (MINI) for DSM-5), and a CAPS-5 total severity score of ≥35 at baseline. Exclusion criteria consisted of primary psychotic disorder, bipolar I disorder, dissociative identity disorder, eating disorders with active purging, major depressive disorder with psychotic features, personality disorders, current alcohol and substance use disorders, pregnancy or lactation, and any medical condition that could make receiving a sympathomimetic drug harmful due to increased blood pressure and heart rate, including uncontrolled hypertension, history of arrhythmia, or marked baseline prolongation of QT and/or QTc interval. Participants with other mild, stable, chronic medical problems (for example, type 2 diabetes mellitus or well-controlled hypertension) were eligible for enrollment if the site physician, clinical investigator and medical monitor agreed that the condition would not increase the risk associated with MDMA administration. Participants were required to comply with lifestyle modifications, including a medically supervised discontinuation of psychiatric medications for a minimum of five half-lives plus one additional week before the baseline assessments (see the study protocol for inclusion and exclusion criteria).

The study protocol was amended on three occasions during study enrollment: first, to add clarity to eligibility criteria related to comorbid medical conditions; second, to add terms of suicidal ideation and behavior as AESIs, as requested by the FDA; and third, to increase the frequency of suicidality assessments following experimental sessions, as requested by the FDA, and to add an option for some telemedicine visits following the COVID-19 pandemic. Given that the study was at full enrollment ($n=105$) when COVID-19 shut down in-person interactions at most of the study sites, the FDA and sponsor concluded that a reduced sample size of 90 participants, instead of the planned 100, would maintain sufficient statistical power to meet study objectives and would avoid COVID-19 delays of experimental sessions, which might confound the assessment of treatment effects.

Study drug. The study drug was manufactured in accordance with Current Good Manufacturing Practice (CGMP) standards by Onyx Scientific and compounded by Sharp Clinical Services. Assays for chemistry, manufacturing and controls were completed in accordance with the CGMP and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards, and reported to the FDA, Health Canada and the Israel Ministry of Health.

Randomization, masking and bias minimization. Participants were randomized in a blinded fashion and were allocated 1:1 to either the MDMA-assisted therapy group or the placebo with therapy group. Randomization was stratified by site and occurred following enrollment confirmation (after preparatory visits). Randomization was managed via an interactive web randomization system—ITClinical IWRS, version 11.0.1 (ITClinical, LDA)—based on a centralized randomization schedule developed by an independent third-party vendor to maintain blinding. Participants, site staff and the sponsor were blinded to participant group assignment until after the database was locked.

An inactive placebo with therapy was utilized as the comparator to isolate the efficacy of the MDMA itself. Although low-dose MDMA improved blinding in phase 2 studies, it led to decreased effectiveness compared with an inactive placebo in a PTSD population, making it easier to detect a difference between the active and comparator groups[15]. The use of inactive placebo also allows for uncontaminated comparison of safety data between groups. Therefore, an inactive placebo was determined in partnership with the FDA as a more conservative statistical comparison, and the study utilized observer-blinded efficacy assessments to minimize bias in efficacy measurements.

An observer-blind and centralized independent rater pool was used to administer the primary and secondary outcome measures, that is, the CAPS-5 and the SDS for functional impairment, the latter of which was adapted to limit missing item-level data as per the FDA requirements and included use of the three-item mean as the total score and imputation of work-related impairment as the maximum score, if caused by PTSD. The independent rater measurements were conducted at baseline and following each experimental session via live video interviews. Independent raters did not repeatedly see the same participant and the independent rater pool was blinded to the complete study design, visit number, treatment assignment, and all data collected by the therapy team after baseline, with the exception of safety data related to suicidality. Participants were instructed to withhold their opinion on treatment group assignment from independent raters and to refrain from sharing details regarding the study design and their number of completed visits. To ensure that all site and sponsor staff were shielded from study outcome measures, primary and secondary outcome measures were collected from the blinded independent rater pool and stored in a dedicated database that was separate from the blinded, clinical database.

Procedures. Following an initial phone screening, participants provided written informed consent and underwent further screening assessments for eligibility. These included the PTSD Checklist for DSM-5 (PCL-5), the MINI for DSM-5, the Structured Clinical Interview for DSM-5 Screening Personality Questionnaire and Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-SPQ and -PD), the Lifetime C-SSRS, medical history, and pre-study medications. Study staff contacted outside providers, ordered medical records, and conducted a physical examination, laboratory testing (including pregnancy and drug tests), electrocardiogram, and 1-min rhythm strip. Eligible participants were enrolled in the study and began psychiatric medication taper (Table 1) if needed, and collection of adverse events. Anticipated effects of MDMA, such as euphoria, stimulation and feelings of closeness[39], were intentionally not solicited as adverse events to avoid biasing the collection of adverse event data. Participant medication taper was variable, lasting from 0 d (no taper needed) to 103 d. Clinical data were electronically captured using Medrio EDC versions R40–R40.7.

In accordance with FDA guidance, we paid special attention to a subset of adverse events, termed AESIs, relating to cardiac function that could be indicative of QT interval prolongation or cardiac arrhythmias, abuse liability, and suicidal ideation and behavior. All adverse events that included signs or symptoms potentially associated with a cardiovascular event such as palpitations or dizziness were further evaluated for reporting as a cardiovascular adverse event. To assess signs of MDMA abuse potential, any adverse event terms such as 'behavioral addiction', 'drug abuser', 'substance abuser', 'dependence', 'intentional product misuse', 'overdose' (accidental, intentional or prescribed) or 'drug diversion' were collected and coded as AESIs. Suicidal ideation that was judged as serious or severe by the investigator, serious ideation defined as a C-SSRS suicidal ideation score of a 4 or 5, self-harm in the context of any suicidal ideation, and any suicide attempts were reported as AESIs.

Enrolled participants underwent three 90-min preparatory sessions of therapy with a two-person therapist team in preparation for experimental sessions (Fig. 1). The preparatory sessions focused on establishing therapeutic alliance and trust, and also provided guidance on how to respond to the memories and feelings that could arise during treatment. Participants who failed to meet all eligibility criteria were withdrawn during this preparatory period. Baseline CAPS-5 assessment (to confirm PTSD diagnosis and total severity score of ≥ 35 for randomization) was performed by the independent rater pool after completion of two preparatory sessions and any necessary psychiatric medication taper to establish baseline symptom severity following removal of psychiatric medications. At the end of the preparatory period, participants were assessed for final eligibility and enrollment was confirmed prior to randomization (Fig. 1).

The treatment period consisted of three 8-h experimental sessions of either MDMA-assisted therapy or therapy with inactive placebo control, spaced ~4 weeks apart. Following a 10-h fast, experimental sessions began with a qualitative urine drug screen, pregnancy screen if applicable, and C-SSRS, as well as measurement of baseline blood pressure, body temperature and heart rate immediately before the initial drug dose. Any positive findings on the urine drug screen that could not be attributed to pre-approved concomitant medications were reviewed by the medical monitor to assess compliance with ongoing eligibility criteria and for possible AESIs. Experimental sessions were conducted following a circadian rhythm-adjusted dosing schedule for a morning (~10:00 hours) initial dose.

In each experimental session the participants received a single divided dose of 80–180 mg MDMA or placebo. In the first experimental session, an initial dose of 80 mg was followed by a supplemental half-dose of 40 mg 1.5–2.5 h after the first dose. In the second and third experimental sessions, an initial dose of 120 mg was followed by a supplemental half-dose of 60 mg. If tolerability issues emerged with the initial dose or if participants declined, the protocol permitted the supplemental dose and/or dose escalation to be withheld. There were no instances in which the supplemental dose was withheld due to tolerability issues. Six participants chose either not to take the supplemental dose ($n=3$, 1 MDMA) or not to escalate to the 120 mg dose ($n=3$, 2 MDMA) in a total of six experimental sessions (2.3% of the total sessions across the study). Blood pressure, body temperature and heart rate were measured before the supplemental dose was given[14].

Manualized therapy was conducted in accordance with the MDMA-assisted therapy treatment manual (http://maps.org/treatment-manual). Therapy was inner-directed and designed to invite inquiry and to facilitate therapeutic effect

by providing support for approaching difficult material in a manner that would not interfere with the participant's spontaneous experience. Every therapist held a Master's degree or above, and the protocol requirement was that one person per therapy team was licensed to provide psychotherapy in accordance with state and local requirements. Therapists were additionally required to take part in the sponsor's five-part training process, which consisted of an online course (15 h), a training course (5 d), experiential learning (3 d), role playing (1 d), and supervision (52 h).

Blood pressure, body temperature and heart rate were measured at the end of each experimental session prior to discharging the participant.

Each experimental session was followed by three 90-min integration sessions that were spaced ~1 week apart to allow the participant to understand and incorporate their experience. The first integration session always occurred on the morning after the experimental session, and the remaining two integration sessions occurred over the following 3–4 weeks (Fig. 1).

Independent raters conducted CAPS-5 and SDS assessments ~3 weeks after each of the first two experimental sessions. The primary outcome assessment was conducted ~8 weeks after the third experimental session (18 weeks after the baseline assessment), in which the independent raters collected the final CAPS-5 and SDS assessments. Twenty per cent of independent rater assessments were randomly selected and reviewed for fidelity. Lead independent raters evaluated the fidelity of all assessments related to enrollment failures as well as an additional 20% of remaining baseline CAPS-5 assessments. Diagnostic concordance between the raters had a Cohen's kappa coefficient of 0.94, and reliability analysis of the CAPS-5 total severity scores showed a Spearman correlation coefficient of 0.98 ($P < 0.0001$), demonstrating high inter-rater reliability between the independent raters. The independent raters were all mental health professionals with graduate-level training in psychology, social work or counseling, at least 1 year of experience working with trauma-exposed populations, and had previous experience administering structured assessments.

Cases of non-compliance, protocol deviations, loss to follow-up, and other reasons for participant dropout were assessed for the presence of AESIs. There were two major protocol deviations (defined as the eligibility criteria not being met by the randomized participants during the course of the study). In the first protocol deviation a participant was not compliant with drug use lifestyle modifications on study, and in the second protocol deviation a participant disclosed cannabis use at study entry but abstained for the duration of the study. There was one dosing error in which a participant in the placebo group received 80 mg placebo as an initial dose and 100 mg as a supplemental dose ($n = 1$). Additionally, 14 participants (10 of whom were in the MDMA arm) requested further integrative visits, as permitted by the protocol.

Objectives. The primary objective of this trial was to evaluate the efficacy and safety of MDMA-assisted therapy for PTSD compared with placebo with therapy, based on comparison of CAPS-5 total severity score at baseline with that at 18 weeks after baseline. The CAPS-5 is a semi-structured interview that assesses the index history of DSM-5-defined traumatic event exposure, including the most distressing event, to produce a diagnostic score (presence versus absence) and a PTSD total severity score. The CAPS-5 rates intrusion symptoms (intrusive thoughts or memories), avoidance, cognitive and mood symptoms, arousal and reactivity symptoms, duration and degree of distress, and dissociation. The CAPS-5 is scored on a scale from 0 to 80, with moderate PTSD defined from a rationally derived severity range of 23–34 (ref. [40]), and severe PTSD as ≥35.

The secondary objective of this trial was to evaluate the efficacy of MDMA-assisted therapy for PTSD compared with placebo with therapy in clinician-rated functional impairment, as measured by the mean change in SDS total scores from baseline to 18 weeks after baseline. Exploratory outcome measures included the BDI-II, the Alcohol Use Disorders Identification Test (AUDIT), the Drug Use Disorders Identification Test (DUDIT) and the Adverse Childhood Experiences (ACE) Questionnaire.

Follow-up. Participants agreed to be recontacted for potential enrollment in a long-term follow-up study, which will include follow-up measures to assess the durability of the treatment. These data will be published at a later date.

Statistics and reproducibility. Statistical power calculations for the initial sample size were made by fitting an MMRM of CAPS-4 data (converted to the CAPS-5 scale and pooled from the phase 2 studies) to obtain variance and covariance parameter estimates. Using the estimated effect size and variance and covariance parameters, the sample size was calculated to achieve a power of 90% at an alpha of 0.049.

The intent-to-treat (ITT) set consisted of 91 randomized participants, however, one participant declined dosing on the morning of the session and provided no additional data, and therefore it was not possible to complete this analysis. Participants were randomized in a blinded fashion with 1:1 allocation as described in the section on randomization, masking and bias minimization above. The modified intent-to-treat (mITT) set consisted of 90 randomized participants who had completed at least one blinded experimental session and at least one post-treatment assessment. The mITT set consisted of 46 participants randomized to the MDMA group and 44 participants randomized to the placebo group, with identical therapy. The per protocol set (completers) consisted of all participants who completed three experimental sessions and assessments (MDMA, $n = 42$; placebo, $n = 37$) (Fig. 1).

The SAP was guided by the ICH E9 (R1) guidelines, which describe the use of estimands and sensitivity analyses to measure the effects of the drug if taken as directed (de jure, assessment of efficacy), and the effects of the drug if taken as assigned, regardless of adherence (de facto, assessment of effectiveness). The SAP was developed in accordance with FDA requirements and was approved by the European Medicines Agency to meet the requirements for future marketing applications. The primary and secondary efficacy analyses therefore utilized a de jure estimand of the mITT set for assessing treatment efficacy from the CAPS-5 and SDS data while on the study drug. The de jure dataset did not include outcome measurements taken after treatment discontinuation in the analysis of treatment efficacy. Missing data were not imputed.

One participant in the placebo group completed only the baseline assessment, and discontinued intervention but provided CAPS data at the T4 timepoint, ~18 weeks after baseline. Given that no endpoint assessment was collected prior to treatment discontinuation, this participant is excluded from the de jure estimand (leaving $n = 89$) but is included in the de facto estimand sensitivity analysis (for a total of $n = 90$). Two additional CAPS data points at the T4 timepoint, ~18 weeks after baseline, from two participants in the placebo group who provided these data following discontinuation of treatment, were not included in the de jure estimand (Supplementary Table 1).

The de facto estimand assessed the impact of these missing data points in the mITT set. That is, the CAPS measures at the T4 timepoint, ~18 weeks after baseline for the three placebo participants who discontinued treatment but provided off-treatment outcome assessments were included in a sensitivity analysis, which determined that inclusion of these measures in the model did not significantly alter the results.

The primary and secondary efficacy analyses were carried out using an MMRM that included all outcome data from baseline and the first, second and third experimental sessions. The efficacy of treatment was tested by comparing the change from baseline to the third experimental session in CAPS-5 and SDS scores between treatment groups in two-sided tests. The fixed effects were treatment (MDMA or placebo), baseline CAPS score, dissociative subtype and investigational site, with random effect specified as study participant.

A hierarchical testing strategy was used to control for type I error, such that the hypothesis for the key secondary endpoint (SDS) would be tested only if the statistical test for the primary efficacy comparison rejected the null hypothesis. An analysis of covariance (ANCOVA) to test the effects of study participation before versus after the COVID-19 pandemic declaration by the World Health Organization indicated a non-significant interaction and therefore was not included in the primary outcome model (Supplementary Table 2). The primary outcome analysis was replicated independently by one blinded programmer and one unblinded programmer.

An independent data monitoring committee monitored adverse events for safety and conducted one administrative interim analysis, after completion of enrollment and of 60% of primary endpoints to examine the adequacy of the sample size. The data monitoring committee recommended that no additional participants should be added, based on conditional power calculations supporting 90% statistical power, but in keeping with the SAP did not provide the sponsor with any information on the conditional power or effect size. The alpha level was set to 0.05, and 2% of the alpha (0.001) was spent on the interim analysis and 98% (0.0499) was left for the final analysis.

Statistics for the primary and secondary efficacy comparisons (CAPS and SDS) are reported as P values from the results of the MMRM analysis. In exploratory analyses, additional baseline covariates of age, gender, ethnicity, prior use of SSRIs, depression as measured by the BDI-II, adverse childhood experiences, and alcohol and substance use disorders were assessed in the model, with the threshold of significance set at $P < 0.05$ (Supplementary Table 1). BDI-II score was also assessed as an exploratory efficacy outcome measure with a paired, two-tailed t-test. Results are reported as mean (s.d.) throughout the text. Between-group effect size was calculated with Cohen's d, and 95% CIs are reported. SAS version 9.4 (SAS Institute) was used for analyses.

The safety analysis included all participants who were given at least one dose of the study drug or placebo. The primary safety analysis evaluated TEAEs as a participant-level analysis. An association with MDMA was determined based on the relative incidence of TEAEs with at least a twofold difference between the MDMA and placebo groups.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are available from the sponsor (MAPS). However, restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available from the authors upon reasonable request and with the

permission of MAPS at http://maps.org/datause. All requests for raw and analyzed data are promptly reviewed by the sponsor delegate and trial organizer, MAPS PBC, to verify if the request is subject to any confidentiality obligations. Patient-related data not included in the paper were generated as part of clinical trials and may be subject to patient confidentiality. Any data that can be shared will be released via a data use agreement.

Code availability

Commercially available software (SAS version 9.4, SAS Institute) was used for analyses, in keeping with the SAP.

References

39. Bershad, A. K., Miller, M. A., Baggott, M. J. & de Wit, H. The effects of MDMA on socio-emotional processing: does MDMA differ from other stimulants? *J. Psychopharmacol.* **30**, 1248–1258 (2016).
40. Weathers, F. W. et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol. Assess.* **30**, 383–395 (2018).

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Author contributions

J.M.M., B.Y.-K., S.H. and A.C. had full access to all of the data in the study and take responsibility for the integrity of the data and for the accuracy of the data analysis. R.D., M.M., B.Y.-K., A.E., R.M., C.H. and A.L. conceived and designed the study. M.O.G., B.P., W.G., S.Q., C.P., I.G., R.W., J.M.M., S.S., G.W., B.V.D.K., C.M., Y.G., S.S.K., E.H., S.A., M.B., R.A., Y.W., C.N., R.B. and K.T. collected the data. S.C., M.M., A.M., M.O.G., B.P., S.K., K.P.-G. and K.T. carried out supervision and training. C.H., R.M., A.L., B.Y.-K., A.E. and A.D.B. carried out sponsor oversight of data collection. J.M.M., A.C. and B.Y.-K. drafted the paper. J.M.M., B.Y.-K., A.D.B., M.B., A.L., C.H., S.K., K.P.-G., A.C., S.H., R.D., J.B.W., B.V.D.K., M.O.G., W.G., C.P., I.G., C.N., M.M., S.C., B.P., G.W., S.S.K., E.H., A.E., J.D.W., S.S., Y.G., S.A., R.W. and C.M. critically revised the paper for important intellectual content. S.H., J.B.W., B.Y.-K., A.C., S.K. and A.D.B. carried out statistical analysis and interpretation of data. R.D. obtained funding.

Competing interests

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Additional information

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Reporting Summary

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For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
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☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Commercially available software was used for data collection through the study including: electronic data capture (EDC) software (Medrio Version 40.5), and interactive web randomization system (IWRS) software (IT Clinical Version 11.0.1).
Data analysis	Commercially available software (SAS software version 9.4 (SAS Institute Inc., Cary, N.C.)) was used for analyses in keeping with the Statistical Analysis Plan.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The data that support the findings of this study are available from the sponsor (MAPS). However, restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of MAPS at maps.org/datause. All requests for raw and analyzed data are promptly reviewed by the sponsor delegate & trial organizer, MAPS Public Benefit Corporation to verify if the request is subject to any confidentiality obligations. Patient-related data not included in the paper were generated as part of clinical trials and may be subject to patient confidentiality. Any data that can be shared will be released via a Data Use Agreement.

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☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Statistical power calculations for the initial sample size were made by fitting a mixed-effect repeated measure model (MMRM) of CAPS-4 data, converted to the CAPS-5 scale, pooled from the Phase 2 studies to obtain variance/covariance parameter estimates. Using the estimated effect size and variance/covariance parameters, the sample size was calculated to achieve a power of 90% at an alpha of 0.049.
Data exclusions	The intent-to-treat (ITT) set included n = 91 randomized participants, however one participant declined dosing on the morning of the session and provided no additional data, and therefore it was not possible to complete this analysis. The modified intent-to-treat (mITT) set included n = 90 randomized participants, defined as those who completed at least one blinded experimental session and at least one post-treatment assessment. The mITT set included a total of n = 46 participants randomized to MDMA and n = 44 to Placebo with identical therapy. The per protocol set (completers) included all participants who completed three experimental sessions and assessments (n = 42 MDMA, n = 37 Placebo). One placebo participant completed only Baseline T1, discontinued intervention but provided T4 CAPS data. As no endpoint assessment was collected prior to treatment discontinuation, this participant is excluded from the de jure estimand (leaving n = 89) but included in the de facto estimand sensitivity analysis (for a total of n = 90). Two additional T4 CAPS data points from placebo participants who provided this data following discontinuation of treatment were not included in the de jure estimand (see Supplementary Table 1).
Replication	This Phase 3 RCT replicates previous findings in a series of previously published controlled Phase 2 trials (Mithoefer 2019).
Randomization	Participants were randomized in a blinded fashion and 1:1 allocation to either the MDMA-assisted therapy group or the placebo with therapy group. Randomization was stratified by site and occurred following enrollment confirmation (after preparatory visits). Randomization was managed via an Interactive Web Randomization System (IWRS) based on a centralized randomization schedule developed by an independent third-party vendor to maintain blinding.
Blinding	Participants, site staff, and the sponsor were blinded to participant group assignment until after the database was locked. An observer-blind and centralized Independent Rater (IR) pool was used to administer the Primary and Secondary Outcome measures.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	Study arms were not significantly different in terms of race, ethnicity, sex, age, dissociative subtype, disability, and CAPS-5 score (see Table 1). The mean The mean duration of PTSD diagnosis was 14.8 (11.6) years and 13.2 (11.4) years in the MDMA and placebo groups, respectively. Of note, six participants in the MDMA group and 13 participants in the placebo group qualified as dissociative subtype per the CAPS-5.
Recruitment	Participants were recruited through print and internet advertisements, referrals from treatment providers, and by word of mouth. Participants were required to initiate contact with the study sites themselves, even if recommended by a provider. Since study participants often self-referred, self-selection bias must be considered. Participants may have been intrigued by the novelty or character of the therapeutic, may have had previous positive recreational experience with the therapeutic, or - since participants all were shouldering severe and sometimes dissociative PTSD - may have been willing to consider a

	therapeutic that they may not have been willing to consider under less intractable circumstances. All participants provided written informed consent.
Ethics oversight	Ethics approval was obtained from Copernicus Group Independent Review Board, Western Institutional Review Board, University of British Columbia Providence Healthcare Research Ethics Board, and the Helsinki Committees of Beer Yaakov Ness Ziona Mental Health Center and Chaim Sheba Medical Center.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov NCT03537014
Study protocol	The public study protocol is available at maps.org/mapp1. To protect data integrity and study blind and to minimize bias, specific eligibility criteria and timing of assessments have been redacted from the public protocol.
Data collection	Fifteen study sites across the US (11), Canada (2), and Israel (2) included both institutional sites and private clinics. Participants were recruited from November 07, 2018 through May 26, 2020, with the last participant visit conducted on August 21, 2020. The final database was locked on October 27, 2020.
Outcomes	The Primary Outcome measure, the change in Clinician Administered PTSD Scale (CAPS-5), and the Secondary Outcome measure, the change in the Sheehan Disability Scale (SDS) were assessed by a blinded centralized Independent Rater (IR) pool multiple times throughout the study.

MIND MEDICINE AUSTRALIA

Appendix J

Email from MAPS dated 14th April 2022 advising on the estimated number of patients in MDMA trials pre and post prohibition.

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From: MAPS Public Relations <media@maps.org>
Sent: Thursday, 14 April 2022 7:43 AM
To: Charleen Justice <charleen@maps.org>; Tania de Jong <tania@taniadejong.com.au>
Cc: Peter Hunt <peter@phunt.com.au>; Ilan Hayman <ilan@mindmedicineaustralia.org>; Rick Doblin <rick@maps.org>
Subject: Re: quick question

Hi Tania,

Here is a paragraph from our Development Safety Update Report which covers how many participants have undergone an experimental session:

"As of the reporting period, 358 individuals are known to have been exposed to MDMA in sponsored studies, all under US-IND 063384. The sponsor does not have access to the primary data, but previous experience with MDMA includes an additional 1441 individuals by reference to scientific literature as of 01 October 2021, for a total of 1,799 research participants who have been exposed to MDMA in clinical or research studies conducted with or without sponsor support."
I don't have a specific number on how many MDMA therapy sessions occurred pre-prohibition, but, here are some key graphs from this paper by Torsten Passie (2018) that might be helpful:

> After Shulgin introduced Zeff to MDMA in 1977, Zeff responded enthusiastically and started therapeutic work. During the next 12 years, Zeff administered MDMA to about 4000 people and trained more than 150 therapists (Stolaroff, 2004: 86).

Obviously, it can't reliably be estimated how much MDMA was used in underground psychotherapeutic work. My more than 10 knowledgeable informants gave evidence that it is likely that a few hundred therapists worldwide have ever used it underground. A realistic estimate would assume that in Europe alone, five to ten underground therapists which use MDMA-assisted therapy were active in the ten largest European countries. If these therapists are each giving 10 MDMA-assisted weekend group therapy sessions per year, with 12 to 15 patients each (the usual format), this results in approximately 10,000 therapeutic applications of MDMA per year. If the average number of sessions per patient is assumed to be five, this (probably conservative) estimate suggests that more than 2,000 people have been treated each year. If this is true, more than 60,000 patients may have been treated underground with MDMA-assisted therapy during the 1985–2017 timespan.

I hope this helps!

Thanks,

Kevin Cranford & Grace Cepe
Communications Team

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Multidisciplinary Association for Psychedelic Studies

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MIND MEDICINE AUSTRALIA

Appendix K

Submission from the Australia Institute and the trauma charity Fearless to the TGA on Diversion Risk dated May 2022.

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FEARLESS
RESTORING CONTROL TO VICTIMS OF TRAUMATIC STRESS

The Australia Institute
Research that matters.

Amendment to the Poisons Standard

Joint submission on application to reschedule psylocibin and MDMA

Rescheduling psilocybin and MDMA from Schedule 9 to Schedule 8 of the Poisons Standard is a small step likely to significantly improve the mental health of a number of treatment-resistant patients. Concern about substances being diverted to the black market is unwarranted.

May 2022

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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 rescheduling psilocybin and MDMA from Schedule 9 to Schedule 8 of the Poisons Standard as set out in their respective applications to the TGA. The potential risks from rescheduling are small while the benefits are potentially large. As the TGA has recognised, evidence for the benefit is growing rapidly and when used in a clinical environment the risks are very small. We believe the risk from 'diversion' into the black market is also very small:

- Medical grade psylocibin and MDMA are likely to cost 5-15 times more than the black market, making diversion an uneconomic undertaking. The substances would not be taken home and would be prescribed and administered by psychiatrists. Given their high income and social standing they face strong disincentives not to allow diversion.
- Because the psilocybin and MDMA will only be available under the SAS-B, the amount of medical psylocibin and MDMA at issue will be very small compared to the overall black market and would have little impact on overall illicit drug usage even if some diversion does take place.
- Even if some substance was diverted, drug harm experts rate the potential harm from these substances *outside* a clinical setting as low.

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 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.

We are puzzled by the contradiction between the TGA being prepared to give access to treatment-resistant patients under its SAS-B but not being prepared to downgrade the scheduling of psylocibin and MDMA so that patients approved under the SAS-B can be treated.

We made an earlier submission on this issue when earlier applications were made to reschedule psilocybin and MDMA. We have updated this submission with recent data and focussed on the risks versus benefits, the limitations from relying entirely on random-controlled trails, and the risk of diversion.

RISK AND BENEFITS OF PSYLOCIBIN AND MDMA

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 in terms of healthcare and lower economic output of mental ill health is estimated by the Productivity Commission at up to $70 billion *per year* and a further $151 billion *per year* relating to diminished health and reduced life expectancy**.**[1] This is huge, it amounts to around 40% of the Australian Federal Government's 2022 budget.[2] Given this, even a small improvement in mental health treatment would provide a large economic benefit.

Such an improvement could be assisted by this rescheduling, as based on trials to date, psilocybin and MDMA-assisted therapy could provide relief to treatment-resistant patients who, by definition, have had no success with current mainstream treatments. These patients bear severe costs from mental illness and are particularly vulnerable to self-harm and suicide.

We note that in its commentary on an earlier rescheduling application the TGA found few adverse events when used in a clinical environment. The clinical environment is important due to the importance of mindset and environment ('set' and 'setting') to the outcomes from psychedelic-assisted therapy. Set and setting are much more controlled in a clinical setting than when these substances are used illicitly.

RANDOMISED CONTROLLED TRIALS ARE NOT THE ONLY EVIDENCE

We note the TGA commentary on the decision not to downgrade was based on the lack of evidence from randomised controlled trials and only on this evidence, it appears the TGA did not consider any other evidence. We note the importance of randomised controlled trials (RCT) for many decisions that the TGA makes. We support this. It is wise to rely on RCT when approving a new drug from a pharmaceutical company advocating strongly to make huge sales often funded by the government. Rigorous evidence is needed in these cases. Also because it is a new drug there is little other evidence to look at.

Relying on RCT alone normally causes little problem, as most new drugs are developed by pharmaceutical companies who are willing to invest the millions of dollars in running RCT, because they will benefit from the exclusive sales if approval comes. However psilocybin

[1] Productivity Commission (2019), *Mental Health* https://www.pc.gov.au/inquiries/completed/mental-health/draft

[2] Parliamentary Library (2022) *Australian Government Expenditure,* https://www.aph.gov.au/About_Parliament/Parliamentary_Departments/Parliamentary_Library/pubs/rp/BudgetReview202021/AustralianGovernmentExpenditure

and MDMA are not attractive for large pharmaceutical companies to run RCT because psychedelic therapy does not fit their usual business model.

- Psilocybin and MDMA are generally not regarded as patentable so companies will not get exclusive sales if approval comes.
- Not only will sales be lower but profit margins will be considerably lower because of the price competition from other manufacturers.
- Furthermore psilocybin and MDMA-therapy only involve 2-3 treatments with medicine, so the revenue stream from psilocybin and MDMA would be substantially less than other drugs which require daily dosage for weeks, months and often years.

Not only is the 'RCT is the only evidence' approval model not suited to psychedelic-assisted therapy approval but there is substantial evidence to look at apart from RCT and if one looks only at RCT evidence, you are choosing to see only a small part of the picture. It is also not necessary to not rely exclusively on the very high standard required by RCT as downgrading will not lead to mainstream usage, let alone require large government funding. Indeed the TGA has already looked at the wider evidence and decided to grant psychedelic-assisted therapy SAS-B status.

For this reason it is sensible to look at the wider evidence to ensure the best decision is made. This evidence is extensive and although each of points below is on its own not conclusive, in the manner of say Phase 3 trials, taken together they clearly point to the effectiveness of psychedelic therapy.

- Regulators in Canada, Israel, Switzerland the US have already granted access to psychedelic therapy for patients under special access schemes for treatment-resistant patients. In 2019, the Israeli government approved its first Compassionate Use Program for MDMA-assisted psychotherapy, shortly followed by FDA approval for an Expanded Access program in the US. Switzerland has permitted compassionate use of MDMA and lysergic acid diethylamide (LSD) since 2014.[3] In Canada, a growing number of permissions have been granted by the federal government to use psilocybin for existential distress, and for therapist training purposes.[4]
- We presume the TGA regards these regulators as competent.

[3] Argento et al (2021) Psychedelic-Assisted Psychotherapy After COVID-19: The Therapeutic Uses of Psilocybin and MDMA for Pandemic-Related Mental Health Problems, https://www.frontiersin.org/articles/10.3389/fpsyt.2021.716593/full

[4] Gilman (2022) *Health Canada Grants Special Access to Restricted Drugs for Psychedelic Therapy,* https://psychedelicspotlight.com/health-canada-psychedelic-therapy-special-access-programme-amendment/

- There was a large number of studies done in the 1950s and 1960 which, while they might not be up to the standards of today's RCT, point to the effectiveness of psychedelic-assisted therapy.
- Imaging studies have shed light on how psychedelics work.
- Around the world there are some seven or so universities, some very prestigious, that have felt sufficiently compelled by the evidence to date to accept the reputational risk and invest in centres of excellence to study psychedelic-assisted therapy.
- There is the anecdotal history of many people alive today and in the past that credit psychedelics for changing their life for the better.
- Furthermore, the willingness of these people to give their support, time and money so others can gain the benefit from psychedelic-assisted therapy attests to the veracity of their experience.

POTENTIAL FOR MISUSE OF THE SUBSTANCES

The risk arising from diversion of substances from clinical use has a number of aspects.

- The likelihood of substances being diverted from clinical use
- The size of the possible amount that would be diverted compared to overall illicit use
- The harm that would come from people using that diverted substance compared to benefit that would come from the substances being available under the SAS-B.

THE LIKELIHOOD OF DIVERSION

We assume the TGA sets appropriate standards for storage and usage of the substances by practitioners under its SAS-B. Regardless there do not appear to be strong forces acting to draw substances into the illicit market. Psilocybin and MDMA are already relatively cheap and easy to obtain.

MDMA in the form of ecstasy capsules is already considered "easy or very easy to obtain" by 84% of ecstasy users in 2020 and 92% of users in 2019. Tablets sell for a low price. Nationally, the price for a single MDMA tablet/capsule ranged between $10 and $30 in 2019-20 with a median price of $22.50 . Prices have declined from 2010-11 when the price was $33.25 indicating ecstasy is now easier to obtain.[5]

Data on the ease of obtaining psilocybin and its price is quite limited, likely reflecting its low harm and low priority for drug enforcement efforts. The *Illicit Drug Data Report 2019-20* does not contain any information on the ease of obtaining psilocybin. The Report does note

[5] Australian Criminal Intelligence Commission (2021) *Illicit Drug Data Report 2019-20*, p45-48 *https://www.acic.gov.au/publications/illicit-drug-data-report*

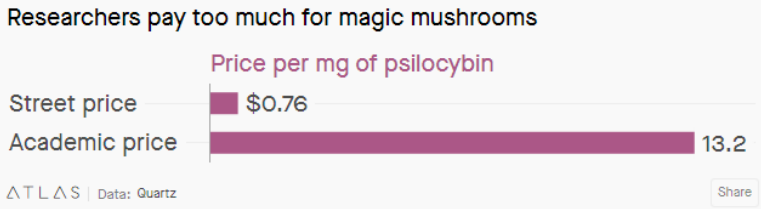
that there are some twenty species of psilocybin that grow naturally in Australia, indicating easy seasonal access for people with some mycology knowledge (and potential risks for those that lack such expertise).[6] We easily found articles which tell you where to look, and what to look for, when searching for psilocybin mushrooms in Australia.[7]

In 2019 South Australia was the lone state to report a price for psilocybin - one gram of psilocybin for $15. However it but stopped doing that in 2020, further indicating psilocybin's low priority for law enforcement.

The low prices and easy availability of street psilocybin and MDMA significantly diminish the attraction of diversion to the recreational market. It would also be a very uneconomic proposition to supply medical psilocybin and MDMA. It is estimated medical psilocybin and MDMA cost some 5-15 times more than the street price (Figure 1).

Figure 1: Medical psilocybin is expensive

Matthew Johnson, a psychiatry and behavioral sciences professor at John Hopkins University who's conducted extensive research on psilocybin, says he and his colleagues pay between $7,000 and $10,000 per gram. The typical street price for magic mushrooms is $35 per eighth of an ounce, so $10 per gram. To be fair, those hoping to get high recreationally typically buy dried mushrooms rather than pure psilocybin. Though it varies, 5,000 mg of dried mushrooms roughly equals 66 mg of psilocybin. Academics, though, are still paying over 13 times the price of the drug as its sold on the street.



That high cost is due in part to the processes involved in synthesizing a form of psilocybin that meets standards set by the US Food and Drug Administration's Good Manufacturing Practice (GMP) regulations. Johnson says the chemists who create the drugs have never given him a line-item breakdown of exactly where all the money goes, but they do say that absolutely everything is tested and retested. The people doing the work, the chemistry procedures used to synthesize the compound, the purity of pre-cursors, and the equipment being used in the manufacturing process all have to meet certified standards.

[6] Australian Criminal Intelligence Commission (2021), p68

[7] Barlow (2021) *Psilocybe subaeruginosa: Australia's Most Famous Magic Mushroom,* https://doubleblindmag.com/psilocybe-subaeruginosa/

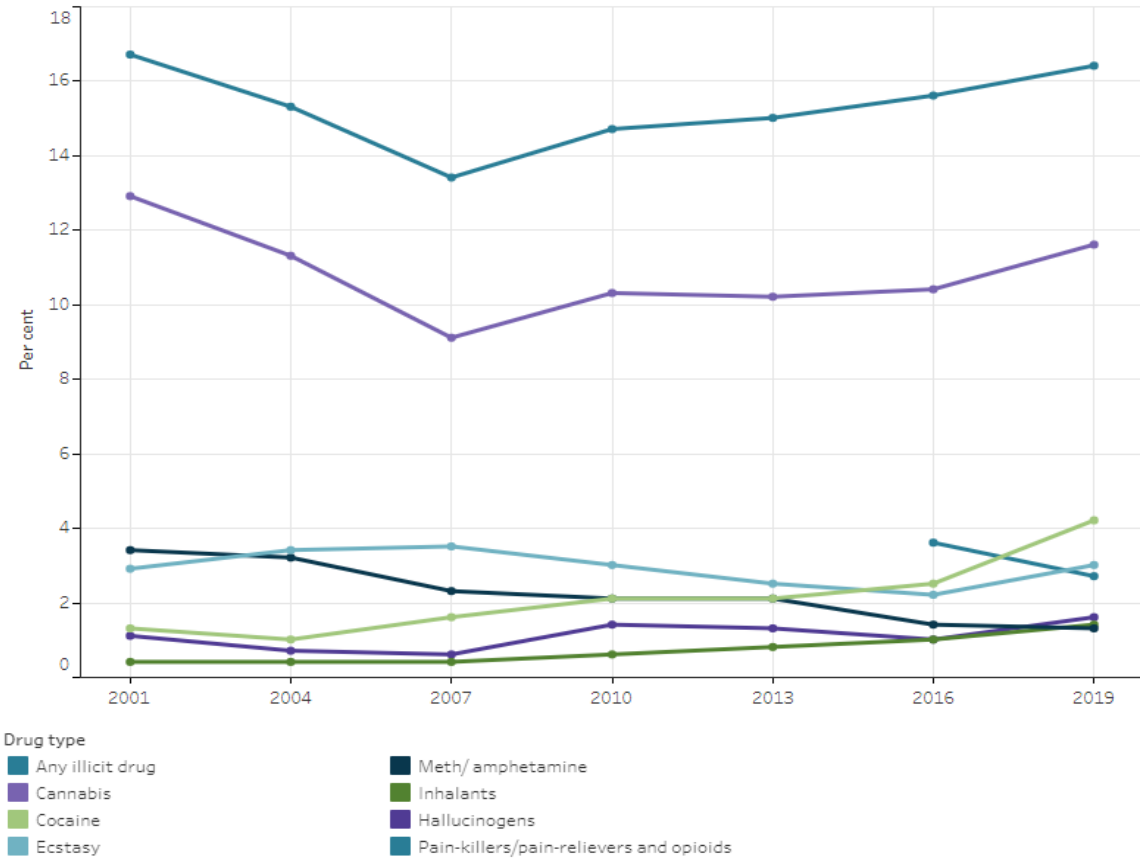
Source: Goldhill (2018) *Scientists who want to study psychedelic mushrooms have to pay $7,000 per gram* https://qz.com/1235963/scientists-who-want-to-study-psychedelic-mushrooms-have-to-pay-7000-per-gram/

Under the current application, psilocybin- and MDMA- assisted therapy would be prescribed and administered by psychiatrists. They enjoy high incomes and high social standing but face the serious risk of deregistration if diversion takes place under their responsibility, either intentionally or unintentionally. In contrast the rewards from allowing diversion to place are small given the psilocybin and MDMA markets are already very well supplied and prices are low. In summary the incentives to stop diversion are strong.

We note patients will not take the substances home.

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, and only 1.6% of the population had used hallucinogens (which includes LSD as well as psilocybin),[8] as shown in Figure 3 below:

Figure 3: Use of illicit drugs in the last 12 months



Source: AIHW (2020) *Illicit drug use*. Percentage of population aged over 14.

[8] Australian Institute of Health and Welfare (2020) *Illicit Drug use,* https://www.aihw.gov.au/reports/australias-health/illicit-drug-use

IMPACT IF DIVERSION WAS TO OCCUR

We consider that even if diversion was to take place it would have an unnoticeable impact on overall illicit psilocybin and MDMA usage as the quantities that would be diverted would be insignificant compared to overall market.

There would be only a limited number of psychiatrists willing to undertake psychedelic-assisted therapy under the SAS-B. In turn there would be only a limited number of treatment-resistant patients willing to undertake psychedelic-assisted therapy. We doubt there would be more than 10,000 patients a year initially for MDMA-assisted therapy. Given the treatment will be expensive, 10,000 patients a year is probably an over-estimate. Treatment will be expensive because it will not be government subsidised and will require 15 or more hours or therapist time (two therapists are usually present at medicine sessions),

Patients are only given 2-3 sessions for treatment. Assume the equivalent of 0.5 grams of street ecstasy is used per patient. (Patients in the recent Phase 3 trial of MDMA-assisted therapy were given 480mg of medicinal MDMA across three sessions).[9] Total annual usage of medical MDMA under the SAS-B would then be the equivalent of 5 kg of street ecstasy (10,000 patients at 0.5 grams each). Assume an amount equal to 10 % of this gets diverted ie 500 grams.

The National Wastewater During Monitoring Program estimated that 2.2 tonnes of MDMA is consumed annually in Australia.[10] 500 grams is imperceptible in comparison. Even if the whole amount of MDMA (5kg) we assume is used under the SAS-B is diverted it would still be imperceptible.

Just as there is no information collected on psilocybin price or ease of availability (because of its low priority for law enforcement), we could find no information on the size of the overall illicit psilocybin usage in Australia. However the fact that psilocybin mushrooms can be grown at home or picked in forests and open areas[11] (and then dried for storage) indicates that the amount of medical psilocybin, if it were to be diverted, is also likely to be inconsequential compared to overall illicit psilocybin usage.

[9] Mitchell et al (2021*) MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study,* https://www.nature.com/articles/s41591-021-01336-3

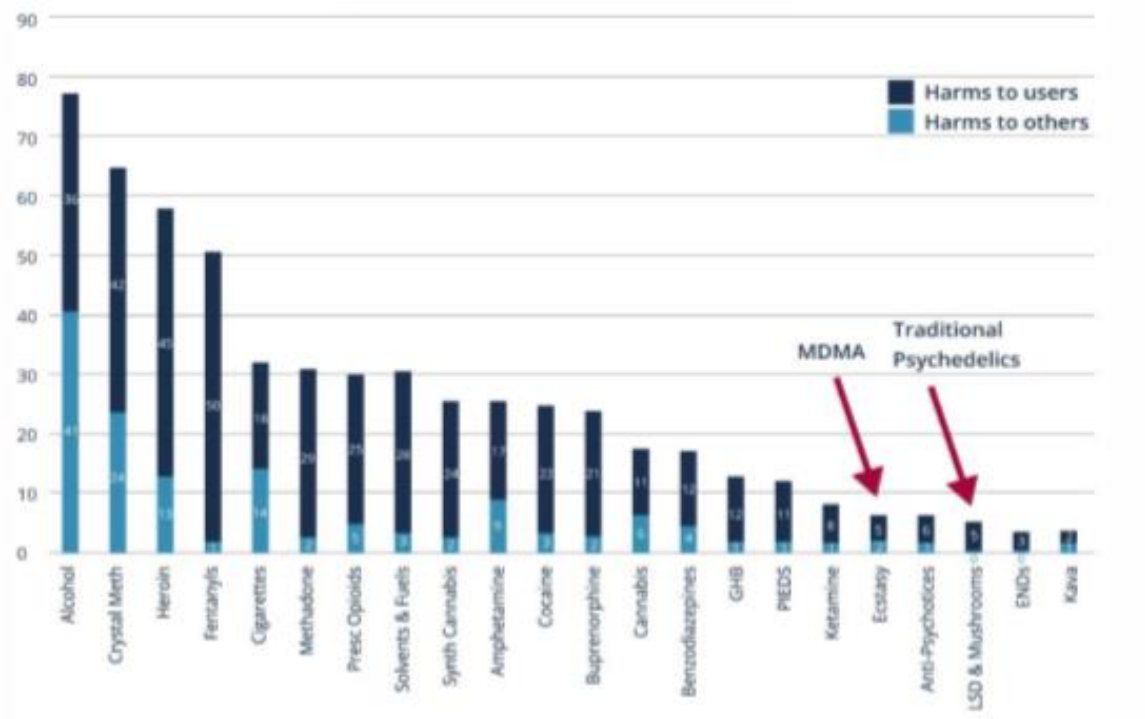
[10] Australian Criminal Intelligence Commission, *Ninth wastewater report reveals Australians spend over $11.3 billion a year on drug*s, https://www.acic.gov.au/media-centre/media-releases-and-statements/ninth-wastewater-report-reveals-australians-spend-over-113-billion-year-drugs#:~:text=Australians%20spent%20an%20estimated%20%2411.3,aspects%20of%20illicit%20drug%20markets.

[11] Barlow (2021)

HARM FROM NON-CLINICAL USE

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).[12] Figure 2 below shows that psilocybin and MDMA are among the least harmful substances analysed by the *Australian drug harms ranking study*. Similar studies overseas have made similar findings.

Figure 2: 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.

The low harm ranking comes despite the fact that psilocybin and MDMA are considered "easy or very easy" to obtain as discussed below.

[12] Bonomo et al (2019) *The Australian drug harms ranking study,* https://journals.sagepub.com/doi/abs/10.1177/0269881119841569

The low harm ranking is also because they are non-addictive. 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.[13]

CONCLUSION

The amount of diversion, it were to take place, would be imperceptible compared to overall illicit usage. There is relatively little harm caused by psilocybin and MDMA. As such the harm from diversion would be imperceptible. This should be measured against the benefit that would come from SAS-B treatments actually taking place. The people being treated are treatment-resistant patients. They suffer serious mental illness and each year many of them engage in self-harm or suicide. A reduction in harm from successful treatment of even some of these patients under the SAS-B would significantly outweigh the likely harm from diversion, if it were to take place.

The cost of not doing anything to treat mental illness is not nothing. In money terms, if such a narrow measure can be used, it costs Australia $220 billion *each year* – equal to 40% of the Federal Government budget. Rescheduling seems a small, measured step in comparison.

[13] 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