MIND MEDICINE
AUSTRALIA

27 August 2020

Invitation to Lodge Submissions to Support Mind Medicine Australia's Applications for the Rescheduling of Medicinal Psilocybin and Medicinal MDMA as part of Therapy

We are inviting you to support our applications for the rescheduling of these two medicines.

1. Why is Rescheduling is so Important

The rescheduling will enable psychiatrists and specialist addiction physicians to more easily access these medicines to augment therapy for patients suffering from key mental illnesses such as depression, PTSD and the depression and anxiety often associated with a terminal illness diagnosis (and possibly in the future for substance abuse, OCD, anorexia and early stage dementia). It will also relieve a significant part of the regulatory burden associated with undertaking trials with these medicines in Australia.

Rescheduling is critical for a number of major reasons:

i. **To Expand the Medical Treatment Paradigm in Australia in a Major Way.** Trials to date have shown that these medicines when used with proper protocols in a medically controlled environment:
   - can provide high remission rates for key classes of mental illness (see above) when compared to current treatments (such as antidepressants and conventional therapy)
   - require only 2 -3 dosed sessions with the medicines (in contrast to a permanent or long-term use of pharmaceutical substances such as antidepressants)
   - have minimal side effects (again in contrast to pharmaceuticals such as antidepressants).

ii. **To Educate Australians.** To educate all key stakeholders in our medical system (eg medical practitioners, other health workers, politicians, regulators, people suffering from mental illness and other members of the general public) that these substances can be used positively and safely in a medically controlled environment to broaden the treatment paradigm for mental illnesses in Australia and substantially reduce the incidence of mental illness in our community.

iii. **To Remove Stigma.** To help the general community understand that the prohibition of psychedelics was politically motivated by a disgraced President of the United States (President Nixon), was not based on any scientific or medical rationale, and that the failure of our system to recognise that these substances can be used effectively as medicines in a medically controlled environment is detrimental to the health and welfare of a huge number of Australians.

2. What Does Rescheduling Mean?

MDMA and Psilocybin are currently Schedule 9 substances under the Commonwealth Standard for the Uniform Scheduling of Medicines and Poisons (often referred to as the Poisons Standard). This standard is designed to create a national system in Australia by classifying medicines and poisons into schedules for inclusion into relevant State and Territory legislation.

At the moment MDMA and Psilocybin are classified in the Poisons Standard as Schedule 9 substances. Schedule 9 substances are described as; "***Prohibited substances*** - *substances that may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except where required for medical or scientific research, or for analytical teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities".* This designation doesn't acknowledge that these substances can be used as medicines and, as a consequence, makes it much harder and more expensive for our medical practitioners and researchers to access these substances.

Mind Medicine Australia is seeking to have these medicines rescheduled to Schedule 8 of the Poisons Standard. Schedule 8 substances are described as; ***"Controlled Drug -*** *Substances which should be available for use but require restriction on manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence"*

The proposed rescheduling will make it easier for clinical trials to take place in Australia and for patients to access these medicines through their psychiatrists and specialist addiction physicians in a medically controlled environment under proper supervision.

Moving the medicines to Schedule 8 will acknowledge that these substances can be used as medicines. Many of the medicines prescribed by medical specialists are Schedule 8 medicines.

3. How Can I Get a Copy of Mind Medicine Australia's Rescheduling Applications?

A summary of each rescheduling application is available on the website of the Therapeutic Goods Administration (TGA)'s consultation document (see pages 23 - 28).

A full copy our applications can be found on the Mind Medicine Australia website [https://mindmedicineaustralia.org/important-resources/].

Our applications have been supported by leading psychiatrists, , physicians, general medical practitioners, psychologists, pharmacologists, researchers and other leading scientists.

4. What is the Timetable for Lodging a Submission ?

For your submission to be considered by the expert panel it must be sent to the TGA (through the TGA's Consultation Portal (explained below) by **no later than 5pm on *Monday the 28th of September.*** **Submissions lodged after this time will not be considered.** If you do not lodge a submission to the TGA during this period, you will not be able to comment on the interim decision on our applications that will be made in November.

Key dates:

Wednesday the 26th August 2020	The TGA publishes our applications and opens the period for public submissions.
Monday the 28th September 2020	The final date for making a submission is September 28th 2020, closing at 5pm AEST. Our rescheduling applications and the public submissions will then be reviewed by the TGA's expert committee.
Wednesday the 3rd February 2021	The Expert Committee's interim decision on our rescheduling applications with be published on 3rd February 2020 after which there will be a further period for public submissions closing on 4th February 2021.
Thursday 4th of March 2021	Submissions for comments on the expert committee's interim decisions close at 5pm AEST. This is limited to people/organisations that lodged submissions during the earlier period.
Thursday 22 April 2021	Publication of notice of Final Decision.

5. How do I Lodge a Submission?

Your submission must be made through the TGA's online consultation hub [https://consultations.health.gov.au/tga/4159c547/] To make a submission click "Proposed amendments to the Poisons Standard - November 2020 ACMS/ACCS meetings " at the bottom of the page.

You can start and then save a draft and return to your submission at any time.
You will be asked to specify which medicine your submission is in relation to and your position of support before uploading your submission onto the portal. Please see screenshot of this page below (where a person's fully support for our psilocybin rescheduling application is shown).

Please select a maximum of one item in each row.

	Retain current scheduling	Fully support proposed amendment	Partially support proposed amendment	Other
Item 1.1 - amygdalin and hydrocyanic acid	○	○	○	○
Item 1.2 - cannabidiol	○	○	○	○
Item 1.3 - bilastine	○	○	○	○
Item 1.4 - budesonide + formoterol	○	○	○	○
Item 1.5 - psilocybin	○	◉	○	○
Item 1.6 - N, α-Dimethyl-3,4-(methylenedioxy)phenylethylamine (MDMA)	○	○	○	○
Item 2.1 - azoxystrobin	○	○	○	○
Item 2.2 - triticonazole	○	○	○	○
Item 3.1 - azelaic acid	○	○	○	○
Item 3.2 - 2-hydroxyethyl methacrylate	○	○	○	○
Item 3.3 - magnesium hydroxide	○	○	○	○
Item 3.4 - tetrahydrofurfuryl alcohol (THFA)	○	○	○	○

You will then be asked if you would like to make your submission public, unnamed or private. Please see the TGA's privacy policy for further information.

Finally, you will be asked to upload your submission. You can address your submission to:

The Secretary
Medicines Scheduling Secretariat
Therapeutic Goods Administration

Remember to keep your submission short, factual and to the point focusing on the matters that are important to you.

If you experience any challenges in using the consultation hub you can email the TGA directly with your queries: medicines.scheduling@health.gov.au

Please include "**Proposed amendments to the Poisons Standard (Medicines)"** in the subject line of the email.

Please remember that your submission must be received by the TGA by no later that 5pm on Monday the 28th of September.

6. Can I Combine My Submission for Psilocybin and MDMA in the One Document?

It is much better for you to do separate submissions for each medicine as the application and consideration process is medicine specific. Remember that Mind Medicine Australia's Rescheduling Application is limited to these medicines being prescribed by psychiatrists or specialist addiction physicians and being used as part of therapy in medically controlled environments.

7. What are some of the matters that I may want to put into my Submission?

You may want to deal with some or all of the following:

(i) Australia's terrible mental health statistics (1 in 5 Australians before the current COVID-19 pandemic, nearly 1 in 2 Australians during the course of their lives, a lack of scalable treatment innovation in the sector for decades, the inadequacy of current treatments for many Australians and the dependence on the long term use of pharmaceuticals that can have adverse side effects, an annual cost to the Australian economy of mental illness of around **$180 billion** and the untold and unacceptable suffering of so many people - suffering which will be getting even worse in the current COVID -19 pandemic).

(ii) The desperate need for innovation and an expansion of the available treatment paradigm for mental illness in Australia.

(iii) The high remission rates being achieved for people having access to these therapies in overseas trials.

(iv) The fact that these medicines have been shown to be safe and non-addictive when used in a medically controlled environment.

(v) The fact that these therapies only require two to three sessions with the medicines in contrast to pharmaceuticals like anti-depressants which can create lifetime dependence.

(vi) The fact that these therapies don't require long term therapy which is often required with conventional therapy (with associated high costs and long term commitment to the therapeutic process).

(vii) The fact that these medicines, when used properly, have minimal adverse side effects (in contrast to many pharmaceuticals and particularly anti-depressants).

(viii) The fact that MDMA and Psilocybin assisted therapies now have "Breakthrough Therapy Designation" with the Food and Drug Administration(FDA) in the United States. This designation is only granted by the FDA for medicines designed to treat a serious or life-threatening condition when the FDA believes that the medicine (based on clinical trials to date) may demonstrate substantial improvements over currently available therapies. This designation is given by the FDA to fast-track the regulatory approval process.

(ix) The fact that MDMA and Psilocybin are already being used by medical practitioners as part of expanded Access Schemes in the United States, Switzerland and Israel and that psilocybin assisted therapy for end of life distress and anxiety has been approved on a case by case basis in Canada.

(x) If you suffer from particular mental illnesses, your experience with Australia's mental health system and the inadequacy of existing treatments and your belief that you (and other people suffering from key mental illnesses) would benefit from these therapies and how inequitable it is that you can't access them.

(xi) Your personal experience (if this is the case) of the mental health benefits of these substances (if you have had direct experience of treatments with these therapies for mental illness). Note that having these treatments in Australia at the present time is illegal without specific Commonwealth and State-based approvals so you should be careful about any content that you use. *The use of these therapies overseas avoids this issue.*

Please note that the Appendices to this letter contain summary information covering (i) through to (ix) above and more detailed information is contained in our full rescheduling applications.

What is the TGA particularly interested in?

In the TGA's notice seeking submissions the TGA notes that it is particularly interested in submissions dealing with all of some of the specific matters covered by Section 52E of the Therapeutic Goods Act 1989:

- the risks and benefits of the use of a substance
- the purposes for which a substance is to be used and the extent of use of a substance
- the toxicity of a substance
- the dosage, formulation, labelling, packaging and presentation of a substance
- the potential for abuse of a substance
- any other matters necessary to protect public health

Submissions might also include:

- Suggested improvements
- An assessment of how the proposed change will impact on you, including the timing of implementation. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to provide your calculations of these costs and benefits

8. Is there easily accessible material that I could use to help me prepare my submission?

Yes, information is available as follows:

i. In Mind Medicine Australia's summary information attached as **Appendix A (Pertaining to both MDMA and Psilocybin), Appendix B (MDMA)** and **Appendix C (Psilocybin)**
ii. In the TGA's notice seeking submissions found here [https://www.tga.gov.au/sites/default/files/consultation-proposed-amendments-poisons-standard-acms-and-joint-acmsaccs-meetings-november-2020.pdf]
iii. In Mind Medicine Australia's actual rescheduling applications found here [www.mindmedicineaustralia.org/important-resources]

10. Final Comments.

Remember that this is your submission so please word it in your own way and cover the areas that are important to you. A range of diverse voices will offer powerful support.

Remember also that the TGA will prefer short, factually based and focused submissions.

Please could you let us know when you have lodged a submission and email a copy of it to us in a separate email. Please also advise whether you are happy for us to refer to it or include it on our website. Please also encourage others you know to lodge submissions.

Thank you for your support for creating positive change in Australia and helping so many people suffering from debilitating mental illnesses in this country.

With best wishes

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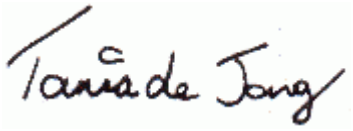

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Appendix A - Summary Information to Support the Rescheduling of Both MDMA and Psilocybin-Assisted Therapy.

The Safety of Psilocybin and MDMA compared to other drugs in epidemiological settings

A multi-criteria analysis of the harms of drugs in Australia based on both individual and societal costs (Bonomo et al., 2019). The paper showed that MDMA and Psilocybin caused less harm to users or society compared to several current Schedule 8 (buprenorphine, methadone, cannabis, ketamine, amphetamine) and Schedule 4 (anabolic steroids, benzodiazepines) drugs. Alcohol was ranked the most harmful substance overall, followed by cigarettes, crystal methamphetamine, cannabis, heroin and pharmaceutical opioids. This work built on a previous multi-criteria analysis of the harms of drugs in the UK which found similar results. Overall, psilocybin and MDMA were ranked among the least harmful of drugs. In Drugs – Without the Hot Air, Professor David Nutt calls psilocybin "among the safest drugs we know of" (Nutt, 2012).

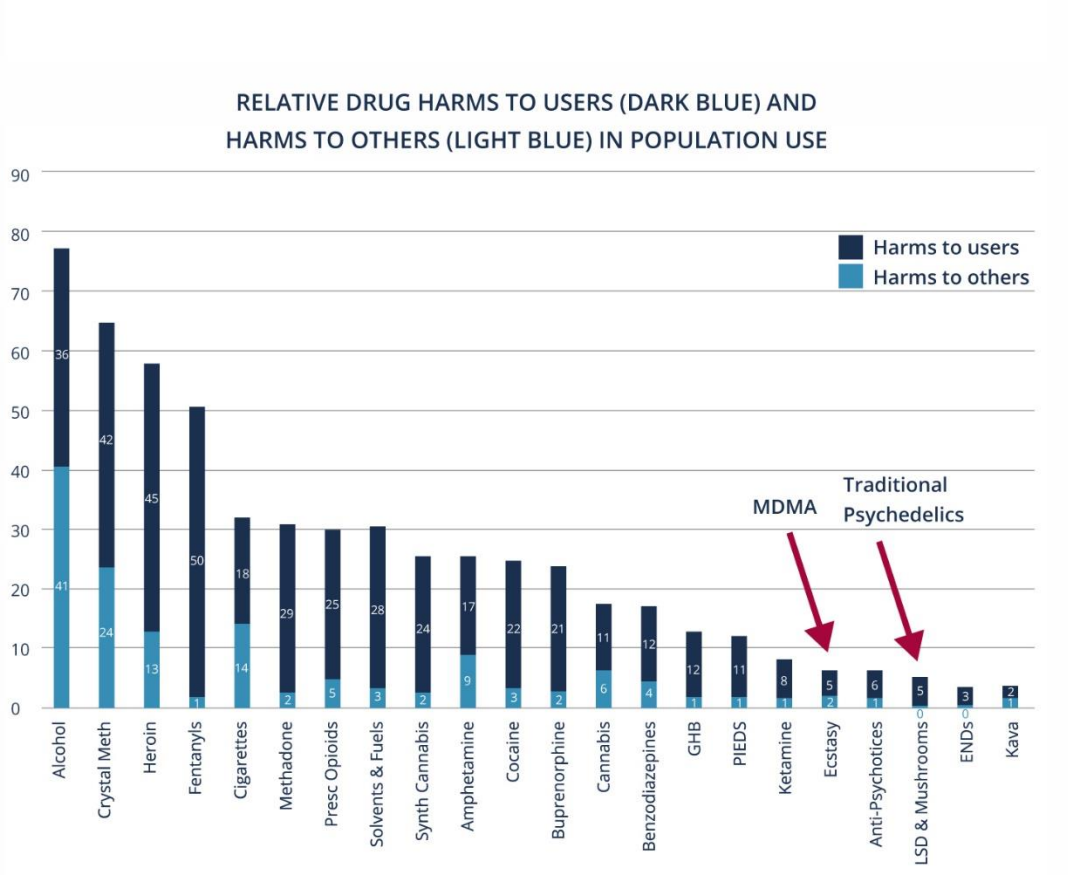

Table: The Australian Drug Harms Ratings Study examined the psychological, medical and social harms of substances (Adapted from Bonomo et al., 2019)

Risk Mitigation

Under Mind Medicine Australia's rescheduling applications these medicines will only be used in a clinical environment after patient screening by registered psychiatrists. These medicines will never be given to the patient to take home. They will remain under secure arrangements within the medical clinic until used, be ordered via prescription on a patient-by-patient basis and will be destroyed if not used.

To date, research trials have done well to select appropriate participants and conduct trials in such a way as to ensure impressive levels of safety; for example, potential participants who have, or are at risk of, psychotic or personality disorders have been excluded due to risk of exacerbating their condition (Johnson et al, 2008). It is advised to continue to follow the strict exclusion criteria of leading clinical trials in the provision of MDMA for PTSD and psilocybin for depression.

In order to make these therapies available to broader mental health indications, more work is needed to understand the psychological risks and how to maintain the currently low levels of adverse events. It is therefore vital to ensure that research is facilitated and supported by policy as much as possible.

The following guidelines are advised for therapeutic use of MDMA and Psilocybin

- The provision of clinical support in the form of an appropriately trained psychiatrist and/or general practitioner, physician and/or psychologist, psychotherapist, counsellor, mental health social worker and /or nurse to conduct the psychotherapy in the preparatory, acute and integration sessions.
- Creation of the recommended clinical setting, including adherence to protocols for safety and security and the management of risk.
- Pre- and post-treatment clinical and psychological assessment to enable an evidence-based approach to reporting on outcomes, including the report of any adverse or unexpected events to the TGA
- Appropriate security measures for handling, safekeeping, and administration of these medicines.

Appendix B - Summary Information to Support the Rescheduling of MDMA-Assisted Therapy.

Efficacy of MDMA in a Medically Controlled Environment

Through a series of worldwide trials, The Multidisciplinary Association for Psychedelic Studies (MAPS) has finalised Phase 2 trials for the use of MDMA-assisted psychotherapy for the treatment of post-traumatic stress disorder (PTSD) (Mithoefer, 2019). The participants had previously had PTSD for an average of 18 years prior to their involvement in the trial. The data across these trials showed MDMA has a 54.2 % efficacy rate for treatment-resistant PTSD sufferers, compared to 23% in the placebo group. MDMA was well tolerated with only minor side effects reported in some cases. Overall, MAPS sponsored Phase 2 studies showed significant reductions in CAPS-IV scores of treatment-resistant PTSD patients, with a Cohen's d effect size of 1.58 (Jerome et al. 2020).

It was also found that once treated with MDMA, patients continued to improve as observed in subsequent follow ups, a year later (Jerome et al. 2020). A recent follow up study of patients at least 12 months after treatment exit of the Phase 2 studies showed further improvements at the time of follow-up. At treatment exit, 56% of participants no longer met the criteria for PTSD. This figure had increased to 67% at the follow-up. These results are all the more remarkable given the severe and previously intractable nature of the diagnosis among most of these participants. In consideration of these results the FDA designated MDMA-assisted therapy as a breakthrough treatment in 2017.

Internationally, Phase 3 trials are now in progress. Recently, an interim analysis of the early results was conducted, with FDA approval, by a third-party data monitoring committee (DMC). The DMC analysed data from the first 60 of 100 participants in current Phase 3 trials (MAPS, 2020). The DMC found "…a 90% or greater probability that the trial will detect statistically significant results when all participants have been treated, and that the trial will not require additional participants beyond the first 100".

Safety of MDMA in a Medically Controlled Environment

MDMA had been shown to be safe, non-toxic, and non-addictive in clinical settings (MAPS, 2019). There are numerous clinical studies of MDMA-assisted therapy that support its safety in this context (Bahji et al, 2020). Non-human studies of MDMA has observed neurotoxicity and organ toxicity at high doses. However at the doses used in human trials, MDMA is regarded as safe (Johnson, 2008).

Over 1,600 doses of clinical MDMA have being administered in research settings in the last 15 years, with only one report of a drug-related transient serious adverse event (which was quickly rectified) and no deaths (MAPS, 2019). Compared to other stimulants, dependence

is very rate in epidemiological settings and not reported in clinical settings (Sessa et al, 2019).

International Policy

A number of other countries have adopted various measures to permit the use of MDMA-assisted psychotherapy in the treatment of PTSD. Early access schemes for MDMA-assisted psychotherapy have been approved in the USA, Israel, Switzerland and Australia, on compassionate grounds, in recognition of the strong evidence base and patient need. This provides a clear precedence for MDMA being used as a quality medicine.

Current Treatments for PTSD

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

PTSD is notoriously hard to treat, with current antidepressant pharmacotherapy achieving relief from symptoms in only about 20%-30% of sufferers (Stein et al. 2009). While 44% of patients experience some clinical improvement in their PTSD symptoms from trauma focused psychotherapies, 60-72% still retain the PTSD diagnosis, with 35% still experiencing debilitating symptoms (Bradley, 2005; Lee et al. 2016; Steenkamp et al; 2015). A significant impediment to the treatment of PTSD is the high drop-out rate ranging from 30-50% across clinical trials, significantly higher than for other mental health disorders (Schottenbauer et al., 2008).

Current anti-depressant pharmacotherapy achieving relief from symptoms in about 20% of sufferers.

Positive Psychological Effects

As an adjunct to the treatment of PTSD , MDMA-assisted therapy has been found to increase feelings of safety and self-acceptance whilst decreasing fear and defensiveness, allowing patients to revisit traumatic memories and reintegrate them (Sessa et al, 2019). All memories are encoded by the brain with the emotional tone of the experience, which is re-encoded each time the memory is recalled. A key challenge for treating PTSD is that reactivating traumatic memories can induce fearful responses, increasing the risk of re-traumatisation (Feduccia & Mithofer, 2018). MDMA allows a substantial increase in a patient's ability to tolerate traumatic memories, and these memories are subsequently associated with an entirely different emotional state of ease and acceptance.

Outcomes for psychotherapy rely on a strong therapeutic alliance between patient and therapist which can be challenging for many patients with PTSD, with many facing disconnection and disassociation (Schottenbauer et al., 2008). MDMA releases the social bonding neurohormones of oxytocin, prolactin and vasopressin as well as serotonin (Hysek et

al, 2014). Oxytocin, prolactin and vasopressin have been described as a key modulators of trust and bonding. This increase in these pro-social hormones may underlie the increase in emotional safety precipitated by MDMA which enhances the therapeutic alliance and increases a patient's felt sense of safety when approaching challenging emotional memories.

Appendix C - Summary Information to Support the Rescheduling of Psilocybin-Assisted Therapy.

Efficacy of Psilocybin in a Medically Controlled Environment

There is a broad range of studies highlighting the efficacy of psilocybin-assisted psychotherapy for the treatment of a range of conditions, most extensively treatment-resistant depression and major depressive disorder but also obsessive-compulsive disorder (OCD), anxiety disorders and addiction (Johnson & Griffiths, 2017). It is crucial that the evidence relating to this is paramount in considering whether Australia should reschedule Psilocybin from Schedule 9 to Schedule 8.

Phase 2 trials have illustrated significant efficacy for psilocybin in cases of depression, end-of-life distress and alcohol addiction, showing that treatment groups showed significantly improved outcomes compared to controls (Schenberg, 2018). Trials to date have shown that psilocybin-assisted therapy can lead to remission in 60-80% of cases of anxiety and depression, whereas current existing treatments lead to remission in a maximum of 35-42% of cases.

Large multi-site Phase 2b and Phase 3 clinical trials have commenced internationally. Results from the preceding Phase 2 clinical trials have been so compelling that the Food and Drug Administration (FDA) in the United States recently assigned psilocybin with two designations as a 'Breakthrough Therapy". This designation highlights the FDA's anticipation that these therapies may offer substantial advantage over current treatments.

Safety of Psilocybin

Psilocybin had been shown to be safe, non-toxic, and anti-addictive (Passie, 2008). There has been no evidence of any physiological harm in animal, clinical or epidemiological studies (Johnson, 2008). It has been noted that hallucinogens can raise the pulse and blood pressure, but no patients have ever experienced a serious spike in blood pressure or receive any medical intervention (Johnson et al, 2008)

Despite previous stigma, two recent large-scale studies have shown that people who have used psychedelics such as psilocybin may be less likely to suffer from serious mental illness or experience suicidality (Hendricks et al, 2018). In 2015 Johansen and Krebs published a paper that reviewed over 135,000 adults of which 19,299 had used psychedelics, such as psilocybin. It was found those who had used these substances were no more likely to have experienced psychological distress or received in-patient psychiatric treatment compared to non-users (Johnansen & Krebs, 2015).

Due to the way psilocybin increases sensitivity to context (see therapeutic mechanisms below), in unsupervised and uncontrolled settings, some individuals may experience anxiety and psychological distress. The experience of anxiety can be minimised in trials through careful preparation and guiding during the dosed session (Johnson et al, 2008). No major psychological complications have resulted from any clinical trials involving psilocybin.

International Policy

A number of other countries have adopted various measures to permit the use of psilocybin-assisted psychotherapy in the treatment of depressive disorders. Early access schemes for psilocybin-assisted psychotherapy have been approved in the USA, Canada, Switzerland and Australia, on compassionate grounds, in recognition of the strong evidence base and patient need. This is a clear precedence of psilocybin being used as a quality medicine.

Current Treatments for Depression

Around the world, the use of antidepressants has doubled from 2000 to 2015 and continues to rise (OECD, 2015). However, there is a growing body of literature calling into question the efficacy of medications used to treat these conditions, addressing a range of factors such as selective reporting has diminished the larger effect sizes initially reported for antidepressants (Hillhouse & Porter, 2017). The World Health Organisation has recommended that certain antidepressants be considered in adults with a 'moderate to severe depressive episode/disorder', but this recommendation is qualified as being a 'conditional' recommendation with 'low' quality of evidence (WHO, 2012). Additionally, adverse effects were more pronounced with current antidepressants than non-pharmacological treatments (Kwawam, 2006). A recent, meta-analysis of 116 trials found current evidence in support of antidepressants is lacking (Cipriani, 2018).

Mechanisms of Psilocybin

It is important to emphasise the fundamental role of 'set' and 'setting'. Surmised under the umbrella term 'context'. 'Set' is referring to the psychological factors brought forth by the patient, such as intention and predisposed beliefs of psychedelics (Carhart-Harris et al, 2018). 'Setting' is related to the comfortability of the environment in which the medicinal experience takes place. It is proposed that the sensitising effects of psilocybin are related to the activation of the serotonin 2A (5HT2A) receptor (Carhart-Harris & Nutt, 2017). Psilocybin's main effects are believed to be mediated by the 5HT2a receptor. Recent research suggests that the 5HT2a receptor aids adaptivity through enhancing sensitivity to the environment, cognitive flexibility and pro-plasticity effects (Carhart-Harris, 2018).

In clinical trials, patients who show clinically significant outcomes report that the most 'salient' acute effect of psilocybin is a distinct shift in the quality of their consciousness (Watts et al, 2017). Psilocybin temporarily create a labile brain state by de-coupling large-scale brain networks and increasing connectivity between novel neural networks within the brain (Carhart-Harris, 2017). These changes may help shift patients out of pathological patterns of belief and make it easier to revise old beliefs and create new ones about the self (Carhart-Harris & Friston, 2019). These mechanisms underlie psilocybin's ability to alleviate depressive, anxious, and addictive disorders by allowing the brain and mind to 'break out' of maladaptive, fixed styles of thinking, feeling, and behaving.

Increased Sense of connection

In clinical psychedelic sessions, classical psychedelics like psilocybin frequently produce profound personal or existential insights, feelings of empathy and self-compassion, and a sense of connection or unity with other people and the natural world (Watts et al. 2017). Research shows that these characteristics are correlated to therapeutic outcomes. After psilocybin-assisted therapy, patients have been shown to experience greater wellbeing and social connectedness, which has been shown to increase in the weeks after the experience (Carhart-Harris et al, 2017)

For Further Reading

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