Clinical Memorandum

Therapeutic use of psychedelic substances

May 2020

The Royal Australian & New Zealand College of Psychiatrists

Your Health in Mind

Authorising Committee/Department:	Committee for Evidence-Based Practice and Committee for Research
Responsible Committee/Department:	Practice, Policy and Partnerships Department
Document Code:	**CM: Therapeutic use of psychedelic substances**

This Clinical Memorandum is under review. For up-to-date evidence relating to the use of MDMA and psilocybin the RANZCP refers to the report from the Australian Therapeutic Goods Administration (TGA) Independent Expert Panel on MDMA and psilocybin: Systematic literature review of the therapeutic value, benefits and risks of MDMA and psilocybin for the treatment of mental health conditions (2021).

The review of the Clinical Memorandum will take account of the TGA Advisory Committee of Medicines Scheduling final decision in regard to the scheduling of MDMA and psilocybin in Australia. Psychiatrists are recommended to check the regulatory authority communication directly.

Purpose

The Royal Australian and New Zealand College of Psychiatrists (RANZCP) has developed this memorandum to provide information for psychiatrists about the potential utility of psychedelic therapies for the treatment of certain mental illnesses.

Key messages

- There is limited but emerging evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses.
- Psychedelic substances are illicit substances and cannot be prescribed or administered outside of properly approved research trials.
- Current research confirms the presence of psychological support as an essential component of the psychedelic treatment model. This requires trials to be carefully designed and led by researchers with appropriate psychiatric and psychotherapy training.
- Further research is required to assess the efficacy, safety and effectiveness of psychedelic therapies to inform future potential use in psychiatric practice.
- Research into the clinical use of psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee and careful monitoring and reporting of efficacy and safety outcomes.

Definitions and scope

Psychedelic substances (also called psychedelic drugs or hallucinogens): any of the so-called mind-expanding drugs that are able to induce states of altered perception and thoughts, frequently with heightened awareness of sensory input but with diminished control over what is being experienced[1].

[1] Source Encyclopaedia Britannica: https://www.britannica.com/science/psychedelic-drug

Psychedelic therapy: refers to therapeutic practices involving psychedelic substances.

Most recent research into psychedelic therapy has focused on psilocybin ('magic mushrooms'), lysergic acid diethylamide ('LSD') and methylenedioxymethamphetamine ('MDMA').

Though technically not a psychedelic, MDMA is included as it is similar to psychedelics with regard to legal impediments to research and potential therapeutic methods. This statement excludes ketamine; the RANZCP has developed a separate Clinical Memorandum on the use of ketamine for treatment-resistant depression.

Background

There has been a recent resurgence in research trials into the potential utility of psychedelic therapies in the treatment of mental illness in adults. Used most notably as aids to psychotherapy for the treatment of mood disorders and alcohol dependence, a large amount of research into psychedelic therapies in the treatment of mental illness were undertaken in the 1950s and 1960s. Psychedelics were declared as prohibited substances in the mid-1960s which effectively ended all major psychedelic research programs. [1,2] Renewed interest in the utility of psychedelic therapies is relatively recent, increasingly steadily since the 1990s.

Recent research has been undertaken and research is ongoing into the following psychedelic therapies and disorders:

- psilocybin ('magic mushrooms') for end-of-life anxiety, treatment-resistant depression, obsessive compulsive disorders and smoking and alcohol dependence
- lysergic acid diethylamide ('LSD') for substance use disorders, anxiety and depression
- methylenedioxymethamphetamine ('MDMA') for Post Traumatic Stress Disorder (PTSD)

There is some evidence that, for some disorders, psychedelic substances may have therapeutic potential and minimal side effects when taken in controlled research environments, at therapeutic doses over short timeframes (1–2 sessions), when accompanied by psychotherapy. [1,3]

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

Psychedelic assisted psychotherapy

Much about the neuroscience of psychedelics remains unknown, although there are theories that they heighten emotional responses and encourage people to confront their disorder actively, which can prompt enduring shifts in mind-set. The purpose of psychedelic therapy is to harness this opportunity to achieve a healthy revision of pathological beliefs. [4] The psychedelic is therefore not a treatment in itself, but a tool to support psychotherapy.

Research findings indicate that the presence of psychological support is an essential component of the psychedelic treatment model. [2,5] This is known as 'psychedelic assisted psychotherapy'. It is unclear how much of the alleviation comes from the psychedelic therapy and how much is derived from the psychological support surrounding the treatment. This needs to be better defined and tested. Additionally, more research is needed to examine whether there are any long-term benefits or harms well as determining longer-term benefits. This mandates carefully designed trials within safe and comfortable settings led by researchers with appropriate psychiatric and psychotherapy training, including specific training in psychedelic psychotherapy [1] who understand the importance of maintaining professional boundaries.

Evidence and current research

- Since 2006, there have been several pilot trials and randomised controlled trials using psychedelics in various non-psychotic psychiatric disorders. These have provided encouraging results that provide initial evidence of safety and efficacy [1] although most have not been appropriately designed to demonstrate this conclusively. [2]

- Medicinal psilocybin, used as an adjunct to psychotherapy in controlled clinical environments, has demonstrated clinical effect sizes and safety in the treatment of depression, anxiety, and addiction with Phase 1 and 2 trials completed and Phase 3 approved across North America and Europe. [1,3,6,7,8,9] A recent review [3] demonstrated significant efficacy for psilocybin for depression, psilocybin for end-of-life distress, and psilocybin for alcohol addiction - in which patient groups treated with psilocybin showed significantly improved outcomes compared to control groups.

- Medicinal MDMA, used as an adjunct to psychotherapy in controlled clinical environments, has demonstrated significant clinical effect sizes and safety in the treatment of Post-Traumatic Stress Disorder (PTSD) with Phase 1 and 2 trials completed, and Phase 3 active across North America and Europe. [3,10]

- Psilocybin-assisted therapy for depression and MDMA-assisted therapy for PTSD have been given ‘breakthrough therapy’ designation from the Food and Drug Administration (FDA) in the United States. 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 Phase 3 results).

- The use of LSD in psychedelic therapy is not currently being pursued in many research trials [3] and evidence for its potential as a treatment is based on historical research. [11] Therefore evidence for its use and any associated risks are not well understood.

- Worldwide, about 100 psychedelic trials are currently active for the treatment of depression and anxiety in the terminally ill, alcohol and drug use disorders, dementia, anorexia and chronic pain. The UK, Canada, the United States and Israel are active research hubs and research is informed by international collaboration. The first psilocybin-assisted psychotherapy trial has been approved in Australia, targeting depressive and anxious symptoms in terminal patients, and is hosted at St Vincent’s Hospital, Melbourne.

- The potential use of other psychedelics is also being investigated. For example, research into the use of ibogaine in substance use disorders (particularly opioid dependence) is in its infancy and there are safety concerns. A range of observational and retrospective trials suggest there may be potential for Phase 2 trials for further determining efficacy with a particular focus on managing cardiac safety [3]. Treatment outcomes in New Zealand, where ibogaine can be prescribed as a non-approved medicine, confirm the need for more research [12]. Trials into the use of ayahuasca, particularly for the treatment of depression and addiction, are also of research interest. [2, 3, 13]

- Research is being conducted into ‘microdosing’ psilocybin or LSD, which involves low-dose regular consumption of psychedelic substances, without concurrent psychotherapy, to determine impact on mental health. Evidence for this is currently limited. [14,15]

Risks and side effects

- There is an ongoing need to collect adverse event data systematically in a manner that allows aggregated analyses. [1] To date in controlled trials, with psychedelic substances given at therapeutic doses, psychedelic therapies demonstrate an initial high safety ratio and low risk profile with limited physiological concerns. [1,3] Psilocybin particularly is very neutral in regard to physiological effects, as is MDMA but it can cause tachycardia and transient increases in blood pressure.

- Frequent high dose MDMA can be neurotoxic (damaging to the nervous system) [16] although such doses would be well in excess of any clinical protocol. Clinical trials have demonstrated safety profile, for example 760 individuals have participated in the MAPS' MDMA trials with only one serious adverse event reported [17] relating to tachycardia and increased blood pressure.

- Psychedelics can elicit acute sensitivity to context and psychologically toxic reactions or 'bad trips' (e.g. fear, panic and re-traumatisation). Practical steps (e.g. patient screening, concomitant medication management, and psychiatrist support) have been taken to minimise risks in psychedelic trials. [1,5] Proper preparation and support of the person undergoing psychedelic therapy, as well as an appropriate setting led by researchers with appropriate psychiatric and psychotherapy training, including specific training in psychedelic psychotherapy, is crucially important to help mitigate risk.

- Current trials for psychedelic therapy generally exclude people with a personal or family history of psychosis, personal history of mania, repeated violence towards others, and a recent personal history of a suicide attempt serious enough to require hospitalisation, as well as those with current drug or alcohol use disorders (unless this is the target for intervention). [1]

- Current trials suggest there is minimal risk of prolonged psychotic disorders in patients using psychedelic therapy. [1] However, people with a personal or family history of psychosis (those with a first or second-degree relative with these disorders) are generally excluded from such trials because they have a higher risk of developing a psychotic disorder. [5] Giving psychedelic substances to these populations presents a potential risk for the precipitation or exacerbation of a psychotic disorder.

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

- There remain many unknown factors and side effects, including long-term side effects, when using psychedelic substances in trials for psychiatric treatment. Further, different people will experience varying effects in response to psychedelics.

- The selection of appropriate patients requires careful consideration. Patients should have capacity to understand the risks and benefits of the treatment in the context of their disorder, duration of current episode, previous treatment history, and ability to provide valid consent. In addition to these diagnostic considerations, other considerations include medical, psychological and/or social factors.

Regulation

- Psychedelic substances are illicit and are not registered for any use by the Therapeutic Goods Administration (TGA) in Australia or Medsafe in New Zealand. They cannot be prescribed or administered outside of properly approved research trials. In Australia, it is possible to provide psychedelic substances under the TGA Special Access Scheme (pathway B) or the Authorised Prescriber Scheme although, as schedule 9 substances, additional state or territory permissions are required and the primary purpose of approval is for research including clinical trials.

- Currently psychedelic therapy is not regulated for use in any country, although the Israeli Defence Force has approved the use of MDMA-assisted psychotherapy for PTSD based on 'compassionate grounds', ahead of seeking regulatory approval.

- Regulatory approval of psychedelic therapy as a treatment for mental illness would require the therapy to be deemed safe and evidence-based. This includes appropriate treatment methodologies, adequate training by those delivering the treatment, and an ethical and legal

framework that provides appropriate safeguards. The risk for potential abuse of these substances in the illicit market is a particular consideration.

Summary

While there is emerging evidence for the use of psychedelic therapies in the treatment of mental illness in adults, the RANZCP notes that the evidence for effectiveness and safety is still in development. Further research is required to assess the efficacy, safety and effectiveness of psychedelic therapies to inform future potential use in psychiatric practice. There may be particular utility in this treatment for people who have not responded to conventional treatments for mental illness. There are insufficient data on safety for individuals with psychotic illness (or vulnerability to it by for example familial risk). These individuals may be at risk of development of psychotic symptoms in the context of psychedelic therapies. Research into medicines containing psychedelic substances should only occur under research trial conditions that include oversight by an institutional research ethics committee and careful monitoring and reporting of effectiveness and safety outcomes. Such trials should be led by researchers with appropriate psychiatric and psychotherapy training, including specific training in psychedelic psychotherapy, to ensure appropriate management of risks and side effects.

As the evidence for the use of psychedelic therapies continues to evolve, this memorandum will be reviewed and revised.

References

1. Rucker JJ, Iliff J, Nutt DJ. Psychiatry & the psychedelic drugs. Past, present & future. Neuropharmacology. 2018 Nov 1;142:200-18.

2. Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs: past, present, and future. Neuropsychopharmacology. 2017 Oct;42(11):2105.

3. Schenberg EE. Psychedelic-assisted psychotherapy: A paradigm shift in psychiatric research and development. Frontiers in pharmacology. 2018 Jul 5;9:733.

4. Carhart-Harris RL. How do psychedelics work? Current opinion in psychiatry. 2019 Jan 1;32(1):16-21.

5. Johnson MW, Richards WA, Griffiths RR. Human hallucinogen research: guidelines for safety. Journal of psychopharmacology. 2008 Aug;22(6):603-20

6. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry. 2016 Jul 1;3(7):619-27.

7. Carhart-Harris RL, Bolstridge M, Day CM, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology. 2018 Feb 1;235(2):399-408.

8. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of psychopharmacology. 2016 Dec;30(12):1181-97.

9. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of psychopharmacology. 2016 Dec;30(12):1165-80.

10. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, Holland J, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R. 3, 4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. The Lancet Psychiatry. 2018 Jun 1;5(6):486-97.

11. Fuentes JJ, Fonseca F, Elices M, Farre M, Torrens M. Therapeutic use of LSD in psychiatry: A systematic review of randomized-controlled clinical trials. Frontiers in Psychiatry. 2019;10:943. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6985449/

12. Hamill J, Hallak J, Dursun SM, Baker G. Ayahuasca: Psychological and physiologic effects, pharmacology and potential uses in addiction and mental illness. Current neuropharmacology. 2019 Feb 1;17(2):108-28.

13. Noller GE, Frampton CM, Yazar-Klosinski B. Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. The American journal of drug and alcohol abuse. 2018 Jan 2;44(1):37-46.

14. Anderson T, Petranker R, Rosenbaum D, Weissman CR, Dinh-Williams LA, Hui K, Hapke E, Farb NA. Microdosing Psychedelics: Personality, mental health, and creativity differences in microdosers. Psychopharmacology. 2019 Feb 14;236(2):731-40.

15. Kuypers KP, Ng L, Erritzoe D, Knudsen GM, Nichols CD, Nichols DE, Pani L, Soula A, Nutt D. Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. Journal of Psychopharmacology. 2019 Sep;33(9):1039-57.

16. Boyle NT, Connor TJ. Methylenedioxymethamphetamine ('Ecstasy')-induced immunosuppression: a cause for concern?. British journal of pharmacology. 2010 Sep;161(1):17-32.

17. MAPS (Multidisciplinary Association for Psychedelic Studies), 2019. MDMA-Assisted Psychotherapy Study Protocols Infographic. Accessed October 2019 via: *https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/PTSDandMDMA.png*

18. Martinotti G, Santacroce R, Pettorruso M, Montemitro C, Spano MC, Lorusso M, Di Giannantonio M, Lerner AG. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. Brain sciences. 2018 Mar;8(3):47.

19. Murrie B, Lappin J, Large M, Sara G. Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. Schizophrenia Bulletin. 2019 Oct 16.

REVISION RECORD

Contact: Executive Manager, Practice, Policy and Partnerships Department

Date	Version	Approver	Description
05/2020	1.0	B2020/7 R5	New document
12/2021	1.1	PPPC Chair	Updated only to include text box note that the CM is under review.
2022			**NEXT REVIEW**