Clinical Memorandum

Therapeutic use of psychedelic substances

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The Royal Australian & New Zealand College of Psychiatrists

Your Health in Mind

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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 substances to assist in treating mental illness.

In Australia, the use of MDMA and psilocybin to treat any conditions other than post-traumatic stress disorder (PTSD) and treatment resistant depression (TRD),[1] respectively, remain restricted under the existing Schedule 9 classification. Please refer to the *Clinical Memorandum: Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression* for more information. All other psychedelic drugs remain in Schedule 9. This memorandum also excludes ketamine as the RANZCP has developed a separate *Clinical Memorandum: Use of ketamine in psychiatric practice*.

Key messages

- Further research is required to assess the efficacy and safety of psychedelic therapies to inform future potential use in psychiatric practice.
- There is limited but emerging evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses.
- Additional and larger randomised-control trials (RCTs) are needed to confirm initial promising results for all psychedelic therapies.
- Current evidence is drawn from research trials that feature psychotherapy as a core component of the treatment model. This requires trials to be carefully designed and led by researchers with appropriate training, experience, and supervision.

Definitions and scope

Psychedelic substances: A class of drug, also called hallucinogens, that can induce states of altered perception and thoughts[2]. Methylenedioxymethamphetamine (MDMA) is classified as an empathogen or entactogen but for simplicity it will be referred to as a psychedelic throughout this memorandum.[3]

Psychedelic therapy: refers to therapeutic practices involving psychedelic substances.

This statement is a general statement to inform psychiatrists about the potential utility of psychedelic substances in the treatment of mental illness, and considerations to inform their use. This statement does not cover the recreational use of psychedelic substances.

[1] This memorandum uses the term treatment resistant depression in line with regulatory frameworks but acknowledges that difficult-to-treat depression or other terms many be preferred.
[2] Source Encyclopaedia Britannica: https://www.britannica.com/science/psychedelic-drug
[3] Alcohol and Drug Foundation: https://adf.org.au/drug-facts/mdma/

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 was 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. [3]

There is emerging but limited evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses. Further research is needed to confirm initially promising results.

Psychedelic assisted psychotherapy

Unlike conventional psychotropic pharmacotherapy, psychedelic therapy includes intense psychotherapy sessions, in highly supportive and structure environments. This is known as 'psychedelic assisted psychotherapy'. This includes psychological preparation prior to administration and understanding of the subjective experience during treatment, as well as psychological support with assimilation and integration afterwards.[4]

The mechanism of how the therapy works is still developing. [5]. Both the classical psychedelics and MDMA appear to increase the affective bond between patient and therapist thereby enhancing the therapeutic alliance through increasing a sense of closeness, openness and trust. [4, 6]

Research findings indicate that the presence of psychological support is a core component of the psychedelic treatment model. [2,5]. It is unclear how much of the therapeutic effect comes from the psychedelic therapy and how much is derived from the psychological support surrounding the treatment. It appears that the interaction between the pharmacological action of both agents and concurrent psychotherapy is important for success.[4, 6] A major unknown is the degree to which the psychedelic/psychotherapy interaction is dependent on the specific type of psychotherapy administered. [5] This needs to be better defined and tested. [5]

Evidence and current research

- Recent research has been undertaken, and is ongoing, with results published to demonstrate potential utility and minimal side effects for a range of disorders when taken in controlled research environments, at therapeutic doses over short timeframes (1-2 sessions), when accompanied by psychotherapy.

- Worldwide, more than 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. Trials for the use of psychedelic therapy in Australia and New Zealand are now also underway with many in Australia funded under the 2021 Innovative Therapies for Mental Illness grants offered as part of the Medical Research Future Fund (MRFF) Clinical Trials Activity Initiative.

- Information about the use of MDMA for PTSD and psilocybin for TRD, respectively, is available in Clinical Memorandum: *Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression.*

- Evidence relating to the use of MDMA and psilocybin is outlined in recent systematic literature reviews and meta-analyses on the effect of psilocybin and MDMA on mental, behavioural or developmental disorders. [5, 7]

- MDMA has shown statistically significant improvements for treatment of social anxiety in adults with autism although participant numbers were low [8]. Future clinical research examining the

effectiveness of MDMA is necessary to test the hypothesised effectiveness of MDMA for social anxiety disorder. [9]

- Psychedelic therapy is being researched for use in anxiety or depression in end-of-life terminal illness and may show promise as potential therapeutic options in end-of-life treatment. [10] Statistically significant differences in two studies investigating psilocybin in the treatment of anxiety or depression due to end of life illness have been identified, but with limitations. [5] A systematic review found that recent (controlled) trials with LSD, psilocybin, and MDMA of higher methodological quality indicate positive effects on existential and spiritual well-being, quality of life, acceptance, and reduction of anxiety and depression in patients with terminal illness with few adverse and no serious adverse effects. [11] To draw final conclusions on effectiveness and safety, larger high-quality studies are needed. [11]

- Psychedelic therapy has not shown any significantly statistic effect for treatment of obsessive-compulsive disorder (OCD). [5, 6]

- A systematic review investigating treatment using psilocybin, ibogaine, and ayahuasca, alone or adjunct with psychotherapy for the treatment of substance use disorder or substance misuse found no sufficient research evidence to suggest effectiveness of any of the psychedelics on any specific substance use disorder or substance misuse. [12] A further systematic review on psilocybin with some form of psychotherapy identified four studies showing a beneficial effect of psilocybin-assisted therapy in patients with alcohol and tobacco use disorder, but the risk of bias ranged from some concerns to critical. [13] Both reviews conclude that further research (double-blinded, placebo-controlled RCTs) using rigorous effectiveness evaluation methods with larger sample sizes and longer-term follow-up is required. [12, 13]

- Research into the use of ibogaine in substance use disorders (particularly opioid dependence) is in its infancy and there are safety concerns. [14] 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. [15]

- Potential use of LSD as a treatment is largely based on historical research. Risks associated with the use of LSD require further investigation. [3, 13, 16, 17]

- Trials into the use of ayahuasca, particularly for the treatment of depression and addiction, are also of research interest. [17-19]

- A systematic review evaluating evidence related to the therapeutic potential of psychedelics in individuals diagnosed with eating disorders and body dysmorphic disorder highlight that more research is needed to determine the safety and efficacy. [20]

- 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. Recent studies suggest the perceived benefits associated with microdosing may outweigh the challenges and may have utility for a variety of uses while having minimal side effects. [21] However, evidence for this is currently limited. [22-25]. Double-blind, placebo-controlled experiments are required to substantiate these reports. [21] Constraints on study design that prohibit outpatient use of psychedelics may explain failure of several microdosing studies to reproduce grey literature reported benefits (from recreational and self-medicating users) and limit translatability of any findings. [26]

Risks and side effects

- 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.[2, 3]

- Practical steps (e.g. patient screening, concomitant medication management, and psychiatrist support) have been taken to minimise risks in psychedelic trials. [2, 26, 27] As well as positive effects there is potential for psychedelic substances to elicit acute sensitivity to context and psychologically toxic reactions or 'bad trips' (e.g. fear, panic and re-traumatisation). [28] 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 suggest there is minimal risk of prolonged psychotic disorders in patients using psychedelic therapy. [2] 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. [27] Giving psychedelic substances to these populations presents a potential risk for the precipitation or exacerbation of a psychotic disorder. 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). [2]

- There remain 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. Potential long-term risk factors following psychedelic therapy, including risks for developing psychosis (hallucinogen induced psychotic disorder) as well as Hallucinogen Persisting Perception Disorder (HPPD) have not been investigated. There is an ongoing need to collect adverse event data systematically and longitudinally in a manner that allows aggregated analyses.

- 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.

- Taking into account recent media attention highlighting the potential therapeutic benefits of psychedelic substances, broader societal strategies may be required to deter illicit use and self-medication.

Regulation

- In Australia, the use of MDMA and psilocybin to treat any conditions other than PTSD and TRD, respectively, remain restricted under the existing Schedule 9 classification. Please refer to the Clinical Memorandum: *Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression* for more information. All other psychedelic drugs remain in Schedule 9. 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.

- In New Zealand, only ibogaine is registered by Medsafe and can be prescribed as a non-approved medicine. A psychiatrist wishing to use any other psychedelic substance would need to comply with the requirements of the Medicines Act and Misuse of Drug Act.

- Regulation governing use varies internationally. 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. Breakthrough designation by the Food and Drug Administration (FDA) in the USA of MDMA for PTSD and psilocybin for

treatment-resistant depression 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.

- Regulation is subject to change and psychiatrists are advised to check with regulatory authorities directly to ensure they comply with relevant regulation for psychedelic use.

Considerations for use of psychedelic therapy in treatment

- 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. Active research is encouraged to build on the current evidence-base.

- More research is needed to examine long term effects of the clinical use of psychedelic substances. This mandates carefully designed trials within safe and comfortable settings led by researchers with appropriate training, including specific training in psychedelic psychotherapy, who understand the importance of maintaining professional boundaries.

- Community and media interest in psychedelic therapy as a promising therapeutic modality in the face of worsening mental health statistics has led to strong pressure from some advocacy groups to fast-track, or even bypass, clinical research and rapidly implement psychedelic assisted therapy in community settings. [29] However, undue haste in translation to community clinics could compromise essential aspects of efficacy, safety and equity, ultimately threatening the sustainability of psychedelic assisted therapy. It is critical to avoid the pitfalls of the past, and give due attention to possible pathways from clinical trials to community clinics. [29]

- Regulatory approval of psychedelic therapy should not pre-empt the adequate evidence-base of the treatment. In addition, prior to any regulatory approval or movement into use outside of research trials, there is need for appropriate treatment methodologies, adequate training by those delivering the treatment, and an ethical and legal framework that provides appropriate safeguards.

- The RANZCP supports psychiatrists continuing to expand their knowledge and to contribute within the framework of current research practice to help inform the future use of psychedelic therapy.

- It is acknowledged that research into the therapeutic potential of psychedelic substances has been limited by legal restrictions and practical difficulties. 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. [5]

- The RANZCP welcomes further research into this area, including through initiatives such as the MRFF Clinical Trials Activity Initiative in Australia to examine whether substances such as psychedelic drugs, used in conjunction with psychological/psychiatric care, are effective and safe for mental illness that has not responded to standard therapies.

Summary

While there is emerging evidence for the use of psychedelic therapies in the treatment of mental illness in adults, the evidence is still in development. Further research is required to assess the efficacy and safety 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). 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 effectiveness and safety outcomes. Such trials should be led by researchers with appropriate 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.

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