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 for mental illness.

Key messages

- There is limited but emerging evidence that psychedelic therapies may have therapeutic benefits in the treatment of a range of mental illnesses.
- MDMA and psilocybin are the most well studied, and may show promise in highly selected populations when administered in closely supervised settings and with intensive support. Additional and larger randomised-control trials (RCTs) are needed to confirm initial promising results.
- 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.
- 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\(^1\).

*Psychedelic therapy:* refers to therapeutic practices involving psychedelic substances.

Most recent research into psychedelic therapy has focused on methylenedioxymethamphetamine (MDMA), a chemical sometimes found in the drug ecstasy, and psilocybin, a compound in its natural form found in a number of species of psychedelic mushrooms. These substances are the primary focus for this memorandum, although it does cover use of other psychedelic substances in therapeutic use. This memorandum excludes ketamine as the RANZCP has developed a separate Clinical Memorandum on the use of ketamine. This statement does not cover the recreational use of psychedelic substances.

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\(^1\) Source Encyclopaedia Britannica: [https://www.britannica.com/science/psychedelic-drug](https://www.britannica.com/science/psychedelic-drug)
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. [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 structured 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. Psilocybin is an agonist of 5-HT2 receptors that may be critical for the psychedelic experience. MDMA, although not a classical psychedelic, has prominent action on transporters for 5-HT, noradrenaline and dopamine, as well as those for vesicular monoamines, which means it has similar subjective effects. [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 an essential component of the psychedelic treatment model. [2,5]. 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. It appears that the interaction between the pharmacological action of both agents and concurrent psychotherapy is important for success, although this has not been examined. [4, 6] 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 when taken in controlled research environments, at therapeutic doses over short timeframes (1-2 session), when accompanied by psychotherapy for the following psychedelic therapies and disorders:
  o MDMA for disorders including Post-Traumatic Stress Disorder (PTSD), mood disorders, obsessive-compulsive disorder (OCD), social anxiety in adults with autism, and anxiety or depression in life-threatening terminal illness.
  o psilocybin for disorders including anxiety or depression in life-threatening terminal illness, treatment-resistant depression, substance use disorders and OCD.
• Use of psychedelic substances for other disorders, including substance use disorders are also subject of ongoing research. Currently there are no RCTs on substance use disorders.
• For up-to-date evidence relating to the use of MDMA and psilocybin the RANZCP refers to existing systematic literature reviews and meta-analyses on the effect of psilocybin and MDMA on mental, behavioural or developmental disorders, including the Systematic literature review of the therapeutic value, benefits and risks of MDMA and psilocybin for the treatment of mental health conditions report made to the Therapeutic Good Administration (TGA) in Australia [5, 7].
The TGA report identified eight studies on MDMA and six on psilocybin that were randomised, double-blind, placebo-controlled trials of psilocybin and MDMA for mental health conditions. Of these, nine had data that could be combined in a meta-analysis of either beneficial or adverse effects. All of these studies were conducted in closely supervised settings and with intensive psychotherapy support. The report concluded that MDMA and psilocybin may show promise in highly selected populations when administered in closely supervised settings and with intensive support. Additional and larger randomised-control trials (RCTs) are needed to confirm initial promising results.

- Most quality data are available for the use of MDMA in PTSD and this demonstrates the strongest association for changes in PTSD scores compared to active controls, especially in doses over 100mg. Small benefits for the use of MDMA in social anxiety in adults with autism were also reported.

- Psilocybin was found to be superior to wait-list but not niacin (active control) in life-threatening disease anxiety or depression. It was equally as effective as escitalopram in long-standing depression for the primary study outcome and superior for most of the secondary outcomes in analyses uncorrected for multiple comparison. Many of the studies on psilocybin use a crossover design, such that only the outcomes prior to the crossover at 5-7 weeks could be reliably due to the drug.

- For both MDMA and psilocybin trial quality varied and for both MDMA and psilocybin overall certainty of evidence was low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. This makes the therapeutic value, benefits and risks difficult to determine, and further long-term data are needed. As identified in the systematic reviews, limitations to research studies for MDMA and psilocybin include:
  - the limited number of quality studies from which data can be combined and small samples, largely restricted to white/European populations, none of which were conducted in Australia or New Zealand. This is particularly relevant given the high rates of PTSD in Indigenous Australians and Māori.
  - in several trials, only a small proportion of potential participants were included in the randomised phase. Further, despite studies being described as double–blinded, in some cases, it appeared on questioning that observers and/or patients may have been aware of their treatment allocation.
  - the exclusion criteria limit the findings to people with PTSD, depression, anxiety and obsessive-compulsive disorders, but not those with a family or past history of other psychiatric disorders (particularly schizophrenia and bipolar disorder). Further research is also needed on predictors of response.
  - in most of the studies psilocybin and MDMA were combined with psychotherapy. A major unknown is the degree to which the psychedelic/psychotherapy interaction is dependent on the specific type of psychotherapy administered.

- The potential use of other psychedelics is also being investigated. The use of LSD in psychedelic therapy is not currently being pursued in many research trials and evidence for its potential as a treatment is based on historical research. Therefore evidence for its use and any associated risks are not well understood. 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. Treatment outcomes in New Zealand, where ibogaine can be prescribed as a non-approved medicine, confirm the need for more research. Trials into the use of ayahuasca, particularly for the treatment of depression and addiction, are also of research interest.
• 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. [15-17]

• 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.

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]

• MDMA is well tolerated in all studies. The main adverse effects reported include anxiety, restlessness, fatigue, jaw-clenching, headache and transient increases in blood pressure. A meta-analysis from the results of five of the most common side effects found the only statistically difference was that participants receiving MDMA were more likely to experience jaw clenching immediately after administration. There were similar findings for adverse events up to 7 days after drug administration except that participants who received MDMA were more likely to report a reduced appetite. Biochemical or haematological changes have not been assessed. [5]

• Psilocybin adverse events were similar to those of MDMA and well tolerated in all studies. The main effects were anxiety, headache and transient increased in blood pressure. None were coded as serious. It was not possible to combine the results quantitatively. [5]

• Practical steps (e.g. patient screening, concomitant medication management, and psychiatrist support) have been taken to minimise risks in psychedelic trials. [2, 18] 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). [19] 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. [18] 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**

Psychedelic substances are not registered for any use by the Therapeutic Goods Administration (TGA) in Australia. In New Zealand, only ibogaine is registered by Medsafe and can be prescribed as a non-approved medicine. 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.

MDMA and psilocybin are not currently registered as a medicine for therapeutic use in any country for any condition, although 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. 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.

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 the treatment of mental disorder**

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 whether there are any long-term benefits or harms as 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 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. 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. Issues ranging from training and accreditation to regulation and economics are all emerging as the approach is being explored anew. Given these concerns it is critical to avoid the pitfalls of the past, and give due attention to possible pathways from clinical trials to community clinics.
• 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.

• A major unknown is the degree to which the psychedelic/psychotherapy interaction is dependent on the specific type of psychotherapy administered. This raises the question as to whether clinical practice would need to follow a specific protocol. [5]

• The RANZCP supports psychiatrists continuing to expand knowledge 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. 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. [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, 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). 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.

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DISCLAIMER
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proper assessment with respect to the merits of each case and the needs of the patient. The RANZCP endeavours to
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