Clinical Memorandum

Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression

The Royal Australian & New Zealand College of Psychiatrists

Your Health in Mind

Authorising Committee/Department:	Psychedelic-Assisted Therapy Steering Group
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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 psychedelic-assisted therapy (PAT) using MDMA to assist in treating PTSD and psilocybin to assist in treating treatment resistant depression (TRD).[1]

The RANZCP has developed this clinical memorandum with patient safety as the primary concern. These treatments are experimental, and a cautious initial approach is espoused, to help prevent serious adverse outcomes for patients. This field is developing, and the position adopted in this memorandum will be reviewed and updated as more data, and the experiences of practitioners and patients in delivering these treatments outside of clinical trial settings, becomes available.

The therapeutic use of psychedelic substances other than MDMA and psilocybin, and the treatment of conditions other than PTSD or TRD, are out of scope for this memorandum. Please refer to the Clinical Memorandum: *Therapeutic use of psychedelic substances* for information on other psychedelic substances and conditions.

Key messages

- Current evidence for PAT is drawn from research trials that feature psychotherapy as a core component of the treatment model. PAT is the use of a psychedelic drug as a tool to support or assist psychotherapy.
- The evidence base for PAT with either MDMA or psilocybin is limited and emerging. Patient safety is paramount and PAT carries unique risks that necessitates careful clinical judgement and clear communication with potential patients. The use of PAT with either MDMA or psilocybin is only recommended for those for whom established psychiatric treatment methods have been attempted without lasting success.
- Treatment protocols must be carefully designed and led by psychiatrists with appropriate training in PAT, including prior experience in treating at least one patient with PAT using the same psychedelic drug for the same indication in a clinical trial or in a clinical setting; failing this, the treating psychiatrists must be closely supervised by a psychiatrist who has prior experience with PAT.[2]
- The delivery of PAT using either MDMA or psilocybin must occur under highly controlled conditions and include the careful monitoring and reporting of efficacy and safety outcomes. Data, including on adverse events, must be collected systematically and longitudinally.

[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] When direct supervision is provided to the treating psychiatrist, this must be by a psychiatrist based in Australia or New Zealand who has prior experience in treating patients with PAT using the same psychedelic drug for the same indication in a clinical trial or in a clinical setting. The supervising psychiatrist must be named on any HREC submissions for any proposed clinical programs.

- The prescribing psychiatrist carries overall responsibility for the course of PAT, including patient selection, detailed assessment, obtaining informed consent, monitoring outcomes and progress of the therapy, and appropriate plans for follow up after the completion of treatment.
- Further research is required to assess the shorter and longer term safety and effectiveness of PAT using either MDMA or psilocybin.

Definitions and scope

Psychedelic substances: A class of drug, also called hallucinogens, that can induce states of altered perception and thoughts.[3] MDMA is classified as an empathogen or entactogen, but for simplicity it will be referred to as a psychedelic throughout this memorandum.[4]

Psychedelic-assisted therapy (PAT): A treatment focused on psychotherapy sessions, in highly supportive and structured environments, including the administration of a psychedelic drug as a tool to assist the psychotherapy. A course of treatment typically includes preparation sessions, active dosing session(s) where the psychedelic drug is administered, and integration sessions.[1]

This clinical memorandum is limited to addressing:

- PAT using 3,4-methylenedioxy-methamphetamine (MDMA) to assist in the treatment of post-traumatic stress disorder (PTSD), and
- PAT using psilocybin to assist in the treatment of treatment-resistant depression (TRD).[5]

Regulation

- In Australia from 1 July 2023, the Therapeutic Goods Administration (TGA) will amend the Poisons Standard to add MDMA and psilocybin, permitting their use as controlled drugs only in PTSD and TRD, respectively. The use of MDMA and psilocybin to treat any conditions other than PTSD and TRD, respectively, remain restricted under the existing Schedule 9 classification. Further information about this decision can be found in TGA documents, Notice of final decisions and Frequently Asked Questions. Prescription is permitted only by registered psychiatrists after Human Research Ethics Committee (HREC) approval of a detailed treatment protocol. TGA approval under the Authorised Prescriber Scheme is also required. Refer to TGA: Information for Psychiatrist Prescribers. In addition to the approval of the psychiatrist to prescribe, it is likely that a Schedule 8 permit from State or Territory regulators will be required to treat individual patients. The product to be prescribed must be specified, and must be manufactured according to principles of Good Manufacturing Practice (GMP). Psychiatrists are required to comply with all legislation of the State or Territory in which they practice.
- In New Zealand, the prescription of controlled substances is regulated by Section 8 of the Misuse of Drugs Act 1975, while the specific restrictions on Schedule 1 substances (including psilocybin and MDMA) are governed by Section 22(1)(a) of Misuse of Drugs Act Regulations 1977, which requires Ministerial approval. Under Section 29 of the Medicines Act a medical practitioner may apply to obtain an unapproved medicine in line with Medsafe guidelines.
- Regulation is subject to change and psychiatrists are advised to check with regulatory authorities directly to ensure they comply with relevant regulations.
- There is a need to collect data, including on adverse events, systematically and longitudinally in a manner that allows aggregated analyses. The RANZCP expects psychiatrists to support

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

[4] Alcohol and Drug Foundation: https://adf.org.au/drug-facts/mdma/

[5] TRD is defined in this memorandum as depression that has not responded to two or more antidepressant medications, provided at adequate dosage and duration.

and contribute data to any registry established for PAT. The RANZCP supports recording of outcome measures via independently run clinical quality registries and advocates that these need to be established and funded by government bodies as a matter of priority. The RANZCP recommends the use of outcomes measures as listed in Appendix 1 as a minimum.

Evidence and current research

Psychedelic Assisted Therapy (PAT)

- Current research findings come from clinical trials that have psychotherapy as a core component of the treatment model.[2, 3]
- The mechanism by which PAT works is still being researched.[1, 4]
- It is unclear how much of the therapeutic effect results from the inclusion of the psychedelic drug in the therapy and how much is derived from the psychotherapy itself and other psychological support surrounding the treatment.[1, 4]
- Until further clinical trials have been conducted, the integration of psychotherapy with the clinical use of MDMA or psilocybin must be treated as fundamental to PAT as this reflects the main evidence base to date.

Evidence for use

- For evidence relating to the use of MDMA and psilocybin the RANZCP refers to existing systematic literature reviews and meta-analyses on PAT, including the report made to the TGA.[5, 6] All studies referred to in the report made to the TGA were conducted in closely supervised settings and with psychotherapy as a core component of the treatment model.[5] Additional and larger randomised-control trials (RCTs) are needed to confirm or refute initial results.[6]

MDMA

- The TGA report identified six RCTs of MDMA to assist in treating PTSD.
- Data are mostly available for the use of MDMA in PTSD and this demonstrates an association of reduction in PTSD scores compared to active controls.[6]

PSILOCYBIN

- The TGA report identified two RCTs of psilocybin to assist in treating TRD.
- Patient selection for PAT using psilocybin needs to be considered in the context of TRD as a complex construct. Most studies have included only a subset of people who are able to come off psychotropic medications; this subset might not be generalisable to others with TRD. Patients experiencing depression with a high level of treatment resistance, such as those with depression that is not responsive to ECT, were also excluded.

Risks and side-effects

- There is potential for psychedelic substances to cause acute sensitivity to context and adverse psychological reactions or negative experiences (e.g. fear, panic and re-traumatisation).[7] Proper preparation and support of the person undergoing PAT, as well as an appropriate setting led by clinicians with appropriate training and experience in PAT, is important to help mitigate this risk.
- Current trials suggest there is a low risk of prolonged psychotic disorders in patients receiving PAT.[8] However, people with a personal or family history of psychosis (those with a first or second-degree relative with these disorders) have generally been excluded from clinical trials.[9]

MDMA

- The main adverse effects reported include anxiety, restlessness, fatigue, jaw-clenching, headache and transient increases in blood pressure.[6]

PSILOCYBIN

- The main adverse effects reported acutely were nausea, headache, anxiety, and transient increases in blood pressure. There is also a signal of increased suicidal ideation and behaviour, though the extent to which this was related to treatment is unclear given the small numbers to date in RCTs comparing psilocybin effects to a control condition.[3, 10, 11]

Study and evidence limitations

- Challenges to PAT study design have been highlighted.[12] For both MDMA and psilocybin trial quality varied and overall certainty of evidence was low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

- Given the current evidence base, generalisability to diverse populations is limited.

Considerations for use of psychedelic-assisted therapy (PAT)

- Patients must have the capacity to understand the potential risks and benefits of PAT using either MDMA or psilocybin in the context of their diagnosis, duration of current episode, previous treatment history, and ability to provide informed consent. Other considerations include medical, psychological, and social factors.

- Patients must have the capacity to consent. Informed consent must be obtained before commencing treatment in line with Principle 5 of the RANZCP Code of Ethics. Details relating to the current evidence base, alternative treatments, description of the treatment process, acute and longer-term efficacy (including response and remission data), safety considerations including uncertainty about longer term outcomes and the effects of repeated courses of treatment, side effects, and cost must be provided. Patients must be informed of what to expect before, during, and after treatment. During the consent process, psychiatrists must ensure patients understand that therapeutic outcomes cannot be guaranteed. It would usually be appropriate for whānau, families and carers to be involved in this process depending on the patient's preference.

- Practitioners must undertake comprehensive training in PAT. This must include both knowledge of the medical effects of MDMA and psilocybin, encompassing adverse effects, potential interactions with other medications; as well as training in practical aspects of delivering PAT. Specific training in psychedelic psychotherapy must recognise the importance of maintaining professional boundaries, given that patients will be in close physical contact with the therapist during the treatment session. RANZCP has not currently developed or endorsed any particular training program but will provide further information as resources are developed [please refer to the Psychedelic-assisted therapy information hub].

- The psychotherapeutic approach must be an established model drawn from the published evidence base.

- The psychotherapy must be delivered by a treating dyad of health professionals, one of whom is a medical practitioner. Patient preference can, if necessary, guide the choice of the therapists.

- Psychiatrist prescribers must consider extra pharmacological safety factors. These include:[13]
    - Recognising the impact of the context in which MDMA or psilocybin is taken, i.e., the set (the mindset of the patient) and the setting (the physical and social environment).
    - Managing patient expectations regarding treatment outcomes.
    - Remaining vigilant regarding the conduct of practitioners and the safe delivery of psychotherapy as patients can be particularly vulnerable during PAT.
    - Discussing the potential use of touch with a patient prior to any dosing sessions and obtaining specific consent about the nature and timing of appropriate touch.

- The TGA have stated on page 10 of the Access to MDMA (3,4-methylenedioxy-methamphetamine) and psilocybin for therapeutic purposes – information for psychiatrist prescribers that they expect "the HREC reviewing the treatment protocols would consider the training and experience of all staff involved in the treatment. It is likely that a minimum standard of training of others involved in patient oversight would be that of clinical psychologists."[14] This statement is rather ambiguous, and the RANZCP recommendation is that practitioners involved with PAT must hold registration with AHPRA or their equivalent governing body, as well as current medical indemnity insurance. If one of the treating dyad is a trainee, the other member of the dyad must meet these criteria.

- Practitioners delivering the psychotherapy component of the treatment are recommended to engage in ongoing supervision from a relevant expert, demonstrate fidelity to the model in which they have been trained, and participate in continuing professional development relevant to the treatment being delivered.

- Psychiatrist prescribers must ensure they are familiar with and practise within all relevant legislation and follow the prescribing pathway required in their Country and State or Territory.

    - In Australia, this includes complying with advice published by the TGA, including Information for Psychiatrist Prescribers, and relevant State or Territory Poisons legislation.

    - In New Zealand, this includes complying with the requirements of the Medicines Act 1981 and Misuse of Drugs Act 1975.

- Appropriate infrastructure for PAT is required. PAT must be delivered as part of holistic, wrap-around care. Services providing PAT must have clear practice policies and guidelines overseen by an appropriate clinical governance committee. This includes outlining appropriate use of a multidisciplinary team, processes for monitoring and management of acute and severe side-effects, and escalation mechanisms in the treatment of adverse events.

- Psychiatrist prescribers must be aware that, as a developing field, there is no clarity on protocols with regard to optimum dose, duration of treatment, or accompanying psychotherapy.[6, 15] Advice must be sought from the latest published evidence/treatment protocols of the same substance for the same indication.

- All practitioners must comply with regulations for legal supply and storage.

Public education and awareness

- The out-of-pocket costs of psychedelic-assisted therapy are unknown.

- The illicit use of psychedelics, even when intended to be therapeutic, poses signficant risk to the community and is illegal in Australia and New Zealand. Unlike pharmaceutical-grade psychedelics, illicitly-accessed MDMA and psilocybin are of unknown composition. Improperly screened patients may suffer adverse physical and/or mental health effects with limited or no support from medical practitioners. There is no oversight of the credentials, training, or ethical behaviour of unregulated 'practitioners'. Broader social strategies, including education and direction to licit paths of access, are required to prevent harm from illicit PAT to the community.

- Education for the community and medical practitioners, including general practitioners who may be asked for referrals for treatment, must be available.

Summary

The evidence base for PAT with either MDMA or psilocybin is limited and emerging. Patient safety is paramount and PAT carries unique risks that necessitates careful clinical judgement and clear communication with potential patients.

Treatment protocols must be carefully designed and led by psychiatrists with appropriate training in PAT, including prior experience in treating at least one patient with PAT using the same psychedelic drug for the same indication in a clinical trial or in a clinical setting; or to be supervised by a colleague who meets such criteria. The prescribing psychiatrist carries overall responsibility for the course of PAT, including patient selection, detailed assessment, obtaining informed consent, monitoring outcomes and progress of the therapy, and appropriate plans for follow up after the completion of treatment. Data, including on adverse events, must be collected systematically and longitudinally.

The RANZCP has developed this clinical memorandum with patient safety as the primary concern. This memorandum will be reviewed and updated as more data, and the experiences of practitioners and patients in delivering these treatments outside of clinical trial settings, becomes available.

Appendix 1: RANZCP Framework for recording safety and quality when using MDMA and psilocybin as part of Psychedelic-Assisted Therapy (PAT)

Patient selection

Required reporting before treatment course commences:

	Please complete/give details
Diagnoses	Tick all that apply [ ] Major Depressive Disorder [ ] Bipolar Disorder [ ] Schizophrenia [ ] Schizoaffective disorder [ ] Personality disorder [ ] Autism Spectrum Disorder [ ] Anxiety Disorder [ ] PTSD [ ] Mild neurocognitive disorder [ ] Major neurocognitive disorder [ ] Substance use disorder (specify substances): _____ [ ] Obsessive-compulsive disorder (OCD) [ ] Feeding and eating disorder [ ] Neurological condition (specify): _____ [ ] Other (specify): _____
Treatment failed prior to PAT treatment (medications, therapy, other)	[List]
Concurrent medications	[List]

PAT administration

Requires reporting for each dosing session:

	Please complete/give details
Date of treatment	
Drug and formulation	
Manufacturer	
Route of administration	
Dose range	
Dose number (e.g. 1st, 2nd)	
Concurrent medications	
Type of psychotherapy / therapy approach	
Number of hours of psychotherapy	
(i) Before dose	
(ii) After dose	
Professional background, training, and qualification of therapists – specify for each therapist	
(i) Present in dosing sessions	
(ii) Delivering psychotherapy	

Safety evaluation

Requires reporting before each dosing session:

	Y/N [give details]
Suicidal ideation+/- behaviour	

Requires reporting for each dosing session:

	Y/N [give details]
Any adverse effect requiring medical intervention	

Requires reporting over the course of PAT treatment:

	Y/N [give details]

'Negative experiences' or/or post-dosing 'flashbacks'	
Suicide attempt	
Significant increase in suicide risk	
Significant worsening of clinical condition	
Any other clinically significant side effects	
Treatment cessation due to adverse effects, including worsening of clinical condition, increased suicide risk	

Recommended scales

Scale	**Pre-course**	**End dosing treatment period**	**3 month follow up**
Columbia Suicide Severity Rating Scale (CSSR-S) - assessed by clinician	✓	✓	✓
Clinical Global Impressions Scale (CGI-S) - assessed by clinician	✓	✓	✓
Clinical Global Impressions – Improvement (CGI – I) - assessed by clinician	✓	✓	✓
Quick Inventory of Depressive Symptomatology – Self Rated (QIDS-SR)	✓	✓	✓
Recovering Quality of Life - Self-Rated (REQOL 10) – Self Rated	✓	✓	✓
World Health Organization Disability Assessment Schedule 2.0 -Self-Rated (WHODAS 2.0)	✓	✓	✓
Leisure Time Satisfaction scale (LTS)	✓	✓	✓
Depression			
Montgomery–Åsberg Depression Rating Scale (MADRS)	✓	✓	✓
PTSD			

PTSD Checklist for *DSM-5* Self-Rated (PCL-5)	✓	✓	✓

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