# Clinical Practice Guideline for the Appropriate Use of Methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy for Post-traumatic Stress Disorder - Draft for Public Consultation

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# Sections

# 1. Publication and Acknowledgements

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**Disclaimer**

This document is a general guide for appropriate use and practice, to be followed subject to a clinician or healthcare professional's judgement and the preferences and values of the person living with diagnosed post-traumatic stress disorder. The Guideline is designed to provide information to assist decision-making and is based on the best available evidence up until 20 February 2025.



**Acknowledgements**

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External reviewers have contributed their time and expertise to provide independent feedback and review on the Guideline. This includes organisations and individuals who provided submissions and responses to the public consultation and NHRMC-nominated independent reviewers.



Info Box

This version of the Guideline is a draft for public consultation. All recommendations are provisional and subject to change pending NHMRC approval.

If you wish to provide feedback on the draft Guideline, please submit your comments via the online form.

Public consultation will be open from 1 August 2025 to 31 August 2025.

## 2. Supporting Materials to Implement the Guideline

To support the implementation and dissemination of the Guideline, Monash University will develop the following resources.

### Companion Guide

The Companion Guide will be written in an easily accessible language for people impacted by post-traumatic stress disorder. This includes people living with PTSD, their carers, and families. The Companion Guide is also for the wider public. Health and care professionals may find the Companion Guide useful for shared decision-making.

### Alignment with other guidelines or guidance documents

This Guideline is intended to complement existing guidance on PTSD and psychedelic-assisted therapies (PAT). It should be read in conjunction with other relevant guidelines, memorandums, and guidance documents, including but not limited to:

- Australian Guidelines for the Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder, and Complex PTSD *[3]*
- Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Memorandum: Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression *[83]*
- Authorised Prescriber Scheme: Guidance for medical practitioners, Human Research Ethics Committees, specialist colleges and sponsors *[97]*
- Therapeutic Goods (Standard for MDMA) (TGO 112) Order 2024 *[127]*

## 3. Plain Language Summary

**What is this Guideline about?**

The Clinical Practice Guidelines for the Appropriate Use of MDMA-assisted psychotherapy (MDMA-AP) for Post-Traumatic Stress Disorder (PTSD) (hereafter Guideline) has been developed to support evidence-based use of MDMA-AP for people living with diagnosed PTSD. The Guideline provides recommendations and good practice statements based on the best available evidence.

**What does the Guideline address?**
The Guideline relates to the medical use of MDMA-AP as prescribed by authorised psychiatrists. The Guideline focuses on the benefits and harms of MDMA-AP for PTSD.

**What does the Guideline not cover?**
The Guideline does not address:

- the general management and treatment of PTSD
- the use of MDMA as a stand-alone treatment without psychotherapy
- the use of MDMA-AP for mental health conditions other than PTSD
- the use of MDMA-AP in palliative or end-of-life care settings
- quality, regulation, or manufacturing processes of MDMA itself
- MDMA obtained and used outside of clinical settings, which is illegal in Australia and may carry significant health risks

**Who is this Guideline for?**
The Guideline is primarily for healthcare professionals involved in the management of PTSD. People living with PTSD and other interested members of the public are also welcome to read the Guideline.

**How is the Guideline developed?**
The Guideline has been developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) process. The Guideline is informed by a systematic search of published literature up until February 2025. The 18-member multidisciplinary Guideline Development Group considered the benefits and harms, certainty of evidence, values and preferences, resources, equity, acceptability, and feasibility related to the topic.

**How will the Guideline be kept up to date?**
We plan to review and update the Guideline within five years. It may also be updated earlier if new evidence becomes available that could change current recommendations.

# 4. Executive Summary

*(All Recommendations and Good Practice Statements are pending NHMRC approval)*

## In people living with PTSD, should we use MDMA-AP or no MDMA-AP (other or no treatment)?

**Recommendation 1 (Conditional recommendation against)**
For people living with PTSD, the Guideline Development Group conditionally recommends against the routine use of MDMA-AP. If MDMA-AP is used, it should be limited to adults (≥18 years old) with PTSD symptoms for at least 6 months duration post-diagnosis, with moderate or severe PTSD symptoms in the past month (CAPS-5 total severity score ≥28), who have received an adequate trial of first-line evidence-based treatments, and who are not likely to be re-exposed to the index or other significant trauma during treatment.

**Recommendation 2 (Only in research settings)**
Do not use MDMA-AP for the treatment of PTSD outside of clinical trials with appropriate ethical approval in people less than 18 years old.

**Recommendation 3 (Only in research settings)**
Do not use MDMA-AP for the treatment of PTSD outside of clinical trials with appropriate ethical approval in people who 1) have not had PTSD symptoms for at least 6 months duration post-diagnosis; 2) did not have at least moderate PTSD symptoms in the past month (CAPS-5 total severity score ≥28); 3) have not received an adequate trial of first-line evidence-based treatments; or 4) are likely to be re-exposed to the index or other significant trauma during treatment.

**Recommendation 4 (Strong recommendation against)**
For people living with PTSD, the Guideline Development Group strongly recommends against the use of MDMA-AP in patient groups who have been excluded from existing clinical trials for safety reasons. These patient groups include but are not limited to those who are pregnant or breastfeeding, with cardiovascular disease (e.g., uncontrolled hypertension, cardiac arrhythmia), psychotic disorder, suicide-related distress (i.e., currently experiencing suicidal thoughts and/or behaviour), and people with current use of medications that may interact with MDMA.



**Good Practice Statement 1**

People living with PTSD have varying values, preferences, and lived experiences that should be central to the planning and delivery of MDMA-AP. Trauma-informed, participatory, and culturally-responsive care should be planned using a shared decision-making approach between the clinicians and patients. Care should be responsive to the needs of individuals from diverse cultural backgrounds, neurodivergent communities, and other priority populations.

**Good Practice Statement 2**

Prior to initiating MDMA-AP, appropriate medical, psychiatric, psychological, financial, and social screening should be conducted to maximise potential benefits and minimise potential harms. The screening process should be documented in appropriate records.

**Good Practice Statement 3**

Prior to initiating MDMA-AP, the treating psychiatrist is responsible for explaining to potential patients that the current evidence on the efficacy and safety of MDMA-AP is limited. The treating psychiatrist should also discuss the probability of treatment effectiveness and adverse events based on the clinical trial results. Potential patients should be provided with comprehensive information about what to expect before, during, and after treatment. Clinicians and people with lived experience of PTSD reported that some patients who have trialled established PTSD treatments without success may overestimate potential benefits and minimise potential risks.

**Good Practice Statement 4**

Prior to initiating MDMA-AP, the treating psychiatrist should obtain written informed consent from potential patients. This consent should address likely benefits and harms of treatment (including rare but serious adverse events); potential physical, psychological, and financial risks; and what to expect before, during, and after treatment. The psychiatrist is responsible for ensuring that any actual or potential conflicts of interest related to their association with companies that manufacture, market, or promote MDMA are declared to the patient. Obtaining informed consent should be treated as an ongoing process, with regular review and adaptation based on the patient's evolving needs and experiences. The consent should be documented in appropriate records.

**Good Practice Statement 5**

Patients should be given the option to involve a support person (such as a next of kin, family member, carer, or advocate) before and after treatment, including during the process of obtaining informed consent.

**Good Practice Statement 6**

Prior to initiating MDMA-AP, the treating psychiatrist should explore patient preferences around supportive touch. Evidence is lacking about the value of supportive touch during MDMA-AP. There are important ethical and clinical considerations related to supportive touch. MDMA may heighten suggestibility, increase the perceived pleasantness of touch, and impair a patient's capacity to provide or withdraw consent during dosing sessions. It is likely that people living with PTSD have variable values and preferences in relation to supportive touch. Clear boundaries, guided by patient preference, should be established during the informed consent process. This should be followed by a dynamic and ongoing consent process throughout treatment. In situations where supportive touch is offered, therapists must have received appropriate training in its ethical and therapeutic application.

**Good Practice Statement 7**

To ensure continuity of care, people who provide MDMA-AP should do so in consultation with the person's regular healthcare providers (e.g., general practitioners, psychologists, psychiatrists, therapists). MDMA-AP should be integrated into, rather than replace, a patient's broader treatment plan. Where possible, a designated provider (such as the patient's usual general practitioner) should remain primarily responsible for overall patient care.

**Good Practice Statement 8**

All clinicians involved in the delivery of MDMA-AP should develop a strong therapeutic alliance with patients prior to and throughout MDMA-AP for building trust, ensuring emotional safety, and supporting the effectiveness of therapy.

**Good Practice Statement 9**

Safeguarding measures should be implemented during MDMA-AP sessions, including ensuring that only authorised personnel are present during dosing sessions, video-recording sessions where appropriate for accountability, and having two trained therapists in the room during dosing sessions. The presence of two therapists is recommended as a risk mitigation strategy to provide a safeguard for both patients and therapists in the event of any concerns or allegations of misconduct.

**Good Practice Statement 10**

Clinics delivering MDMA-AP should ensure the presence of appropriately trained personnel, such as medical doctors, to oversee medical or pharmacological interventions in managing adverse events. Appropriate clinical support should be rapidly available in case of medical emergencies

**Good Practice Statement 11**

Clinicians should advise patients that MDMA may impair the ability to drive or operate heavy machinery. Patients should be informed of, and comply with, relevant State legislation regarding not driving under the influence of MDMA.

**Good Practice Statement 12**

Patients should only leave the treatment clinic once the acute effects of MDMA have fully worn off. This involves clinically assessing vital signs, level of awareness, mental stability, and ensuring a prearranged support person is available to accompany the patient home.

**Good Practice Statement 13**

A comprehensive communication plan should be developed to facilitate the patient's transition back to routine care after MDMA-AP treatment. People with lived experience report the importance of setting clear expectations from the outset of treatment. This includes discussion around the possible option to continue care with the therapist from MDMA-AP with whom a strong therapeutic alliance has been established. Clinicians should discuss potential post-treatment care models (such as peer support groups, group integration sessions, or regular check-ins with clinicians) to provide patients with ongoing support after completing MDMA-AP.

**Good Practice Statement 14**

The Guideline Development Group recognises that evidence in relation to MDMA-AP is rapidly evolving and there is potential value in a living evidence approach to future guideline development. Clinicians and people living with PTSD should make themselves familiar with the current best available research about possible benefits and harms as the basis for treatment decision-making.

**Good Practice Statement 15**

The Guideline Development Group concurs with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) that the clinicians involved in the delivery of MDMA-AP should be registered with the Australian Health Practitioner Regulation Agency (AHPRA) or their equivalent governing body and operate within their recognised scope of practice.

**Good Practice Statement 16**

Clinicians involved in the delivery of MDMA-AP should complete specific training. Psychiatrists should follow the Psychedelic Training Framework for Psychiatrists developed by the RANZCP. There is a need for formal and independent regulation or credentialing of training programs for psychiatrists and other clinicians to ensure consistent quality and standards for the delivery of MDMA-AP.

**Good Practice Statement 17**

Training should be available for the broader healthcare workforce to increase awareness and understanding of MDMA-AP, provide relevant and evidence-based information, and support making appropriate referrals. People with lived experience of PTSD emphasise the importance of clinician awareness, particularly among primary healthcare professionals who have an important role in providing evidence-based information to people with PTSD.

**Good Practice Statement 18**

Patient information about MDMA-AP should be provided in a format that is accessible to different target populations, including culturally and linguistically diverse (CALD) communities, Aboriginal and Torres Strait Islander peoples, and emergency service workers. With permission, this information should also be made available to the patient's support person.

# 5. Introduction

**What is Post-Traumatic Stress Disorder**

Post-Traumatic Stress Disorder (PTSD) is a group of stress- and trauma-related reactions that can develop after exposure to an actual or threatened horrific event or series of events. Traumatic events that may lead to PTSD include motor vehicle accidents, serious injuries, crime, sexual assault, natural disasters, terrorism, war, domestic violence, and emotional abuse *[19][3]*. DSM-5 and ICD-11 diagnostic criteria characterise PTSD by symptom clusters including re-experiencing the traumatic event or events (e.g., intrusive memories, flashbacks, nightmares), avoidance of reminders, and a persistent sense of current threat (e.g., hypervigilance, alterations in arousal or reactivity). The DSM-5 additionally describes negative alterations in cognition and mood (e.g., persistent negative beliefs, emotional numbness).

PTSD has a considerable impact on daily functioning *[45]* and may be associated with suicidal ideation *[52]*, chronic disease *[29][82][92]*, and premature death *[20]*. People living with PTSD also frequently struggle with alcohol and drug use *[115]*, which may create additional challenges for managing the disorder.

It has been estimated that up to 11% of Australians will experience PTSD in their lifetime *[11]*. Women are at almost twice the risk of men (14% and 8% respectively) *[9]*, while people who experience homelessness, refugees, people experiencing domestic violence, LGBTQIA+ people, First Nations people, and certain occupation groups (emergency services, armed forces, and veterans) are at higher risk of experiencing PTSD in their lifetime *[3]*.

**Treatments for PTSD**

The Australian Guidelines for the Treatment of Acute Stress Disorder, Post-traumatic Stress Disorder, and Complex PTSD provide "strong recommendations" for several psychological interventions for treating PTSD, including cognitive processing therapy (CPT), cognitive therapy (CT), eye movement desensitisation and reprocessing (EMDR), prolonged exposure (PE), and trauma-focused cognitive behavioural therapy (TF-CBT) *[3]*. These guidelines also include "conditional recommendations" for other psychological interventions such as guided internet-based trauma-focused CBT, narrative exposure therapy, present-centred therapy, stress inoculation training, and group-based TF-CBT. For pharmacological interventions, the guidelines provide "conditional recommendations" on the use of selective serotonin reuptake inhibitors (SSRIs) (e.g., sertraline, paroxetine, fluoxetine) and serotonin and noradrenaline reuptake inhibitors (SNRIs) (e.g., venlafaxine).

**What is MDMA**

3,4-methylenedioxymethamphetamine (MDMA) is a synthetic psychoactive compound that increases feelings of empathy or connectedness with others. MDMA is chemically related to amphetamine and mescaline; however, it produces a distinct combination of effects that differ from classical psychedelics such as psilocybin, lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), and mescaline. MDMA is classified as an empathogen (enhancing feelings of empathy or social connectedness with others) and entactogen (increasing introspection and self-awareness) *[122][119]***.** MDMA primarily acts by increasing the release of serotonin, noradrenaline, and dopamine in the brain, and it also stimulates the release of oxytocin, a hormone associated with social bonding *[123][124]*.

**Regulatory landscape of MDMA**

To date, no MDMA-containing product has been approved by any regulatory agencies worldwide. Following the Breakthrough Therapy Designation for MDMA-assisted psychotherapy (MDMA-AP) by the US Food and Drug Administration (FDA) in 2017, Lykos Therapeutics filed a new drug application for MDMA-AP to be used for adults with PTSD, which was granted a Priority Review by the FDA on 9 February 2024 *[59]*. However, the application was rejected as of 9 August 2024, with the FDA requesting additional Phase 3 trials to further investigate MDMA's safety and efficacy *[60]*.

**MDMA-assisted psychotherapy**

In clinical settings, MDMA is not administered as a stand-alone therapy; instead, MDMA is administered alongside psychotherapy. To date, most published trials, including both phase 3 randomised controlled trials (RCTs), have used a manualised therapeutic approach developed by the Multidisciplinary Association for Psychedelic Studies (MAPS) *[121]*. This approach was described as fundamentally "non-directive", with the therapist acting as an "non-invasive empathetic witness" to facilitate the patient's "innate capacity to heal from the wounds of trauma". The MAPS manual discussed other considerations in supporting the patient through MDMA-AP, including creating a safe and conducive physical setting, therapeutic use of music, and use of "nurturing touch", focused bodywork, and breathing techniques to support healing of somatic manifestations of trauma. Although described as standardised, the manual was described as being flexible, to allow therapists to "apply their own intuition and training" *[121]*. However, this flexibility has been described as a possible challenge for achieving standardisation and replicability across studies, especially when the therapists may have diverse training and backgrounds, and may opt to use techniques from a range of therapeutic modalities. This so-called "inner directed method" has not been investigated alone for PTSD and is not a treatment option recommended in current Australian PTSD treatment guidelines *[3]*. There are ongoing clinical trials evaluating the use of MDMA as an adjunct to established evidence-based psychotherapies, such as PE (NCT05709353, NCT06117306) and CPT (NCT05067244, NCT05837845).

Based on Lykos' Phase 3 clinical trial protocols, an MDMA-AP treatment course typically consisted of three phases: **preparatory, dosing, and integration sessions** (Figure 1).

- **Preparatory sessions:** The preparatory sessions involved building a therapeutic alliance and trust, preparing patients in terms of both expectations of MDMA-AP ("set") and logistics of dosing sessions, and providing guidance on managing memories and emotions that may arise during treatment. The Phase 3 trials used 3 preparatory sessions, each of 90 minutes duration.

- **Dosing sessions:** Phase 3 trial protocols used three 8-hour dosing/medication sessions. During the first dosing session, participants received 80mg of MDMA (as per Phase 3 clinical trial protocol), followed by a supplemental dose of 40 mg if the initial dose was well-tolerated and not declined by the patient. During the second and third dosing sessions (spaced ~1 month apart), the dose was escalated to 120mg (if well-tolerated and not declined), followed by a supplemental dose of 60mg. In the clinical trials, most participants stayed overnight at the study site, but some went home with a support person.

- **Integration sessions:** Each dosing session was followed by three integration sessions that were spaced approximately 1 week apart. The first integration session typically took place in the morning after the dosing session. These sessions helped participants understand and incorporate their experiences during the dosing sessions, and generalise these learnings into their everyday life. The therapeutic approach during integration was described as a "non-directive approach [which] pertains to inviting inquiry and providing suggestion rather than directing the participant in the therapeutic approach" in the Phase 3 clinical trial protocol. In the Phase 3 clinical trials, the entire treatment protocol involved **42 hours of contact time** with healthcare professionals (psychiatrists, psychologists, or therapists), including three preparatory sessions (1.5 hours each), three dosing sessions (8 hours each), and nine integration sessions (1.5 hours each).

In the control group, the intervention mirrored the treatment group, but MDMA was replaced by either an active or inactive placebo. In some Phase 2 trials, a low MDMA dose (25–40 mg) served as an active placebo to enhance the blinding effect.

Most published clinical trials on MDMA-AP for PTSD followed the process outlined above, with some variations in the MDMA dosage, the number of dosing and integration sessions, and the types of placebo used in the control group.

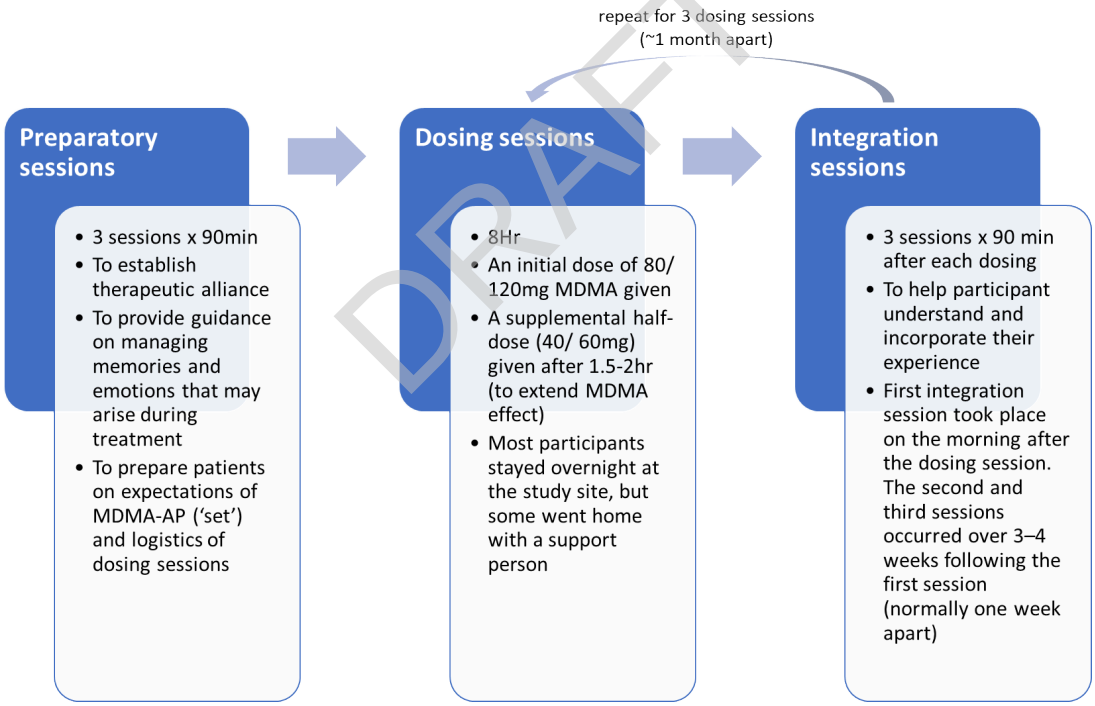



**Figure 1.** Treatment process of MDMA-AP based on Phase 3 clinical trial protocols.

## 5.1 Purpose of Guideline

The Guideline has been developed to support evidence-based use of MDMA-AP for people living with diagnosed PTSD. In Australia, patients can access MDMA-AP in specific private specialist clinics. However, the efficacy of specific MDMA products has not yet been established through the routine drug approval pathway. This Guideline is intended to support clinical use. The Guideline has been developed to support clinicians in understanding the existing evidence, and deliver appropriate care, while also supporting patients to make informed decisions about MDMA-AP treatment.

Specifically, the objectives of this Guideline are to:

- Provide clinicians with evidence-based recommendations
- Provide people living with PTSD and their carers with clear, accessible, and evidence-based information about MDMA-AP for diagnosed PTSD treatment
- Highlight current gaps in knowledge and propose directions for future research

## 5.2 Scope of Guideline

The Guideline relates to the medical use of MDMA-AP under the Authorised Prescriber scheme. The Guideline does not provide guidance in relation to the overall management of PTSD. This Guideline should be read in conjunction with other evidence-based resources related to the management of PTSD.

The Guideline addresses the clinical question "In people living with PTSD, should we use MDMA-AP or no MDMA-AP (other or no treatment)?".

The Guideline focuses on the safety and efficacy of MDMA-AP in adults (aged 18 years and over) living with PTSD. The evidence review process did not identify any evidence relating to the use of MDMA-AP in people aged under 18 years.

The use of MDMA outside of clinical settings for PTSD is illegal in Australia. MDMA obtained illicitly is often of unknown dose and purity and might result in harm or death. Possession, manufacture, or supply of MDMA without authorisation is a legal offence. Under the current approval framework, MDMA-AP in Australia should only occur in controlled conditions, under the supervision of an authorised psychiatrist, and with close monitoring for efficacy and safety.

**What the Guideline does not address**

This Guideline does not address the use of MDMA as a stand-alone treatment without psychotherapy.

The Guideline is focused solely on the use of MDMA-AP for PTSD and does not extend to other mental health conditions such as depression, anxiety disorders, obsessive-compulsive disorder, substance use disorders, or eating disorders. The use of MDMA-AP in the context of end-of-life or palliative care is beyond the scope of this Guideline. The Guideline is not intended to address the quality and regulatory requirements in the manufacturing, processing, procurement, storage, or supply of the active pharmaceutical ingredients and finished product related to MDMA.

**Target audience**

The Guideline is mainly intended for clinicians, including general practitioners, nurses, pharmacists, psychiatrists, psychologists, therapists, and other medical/allied health professionals involved in the management of PTSD. The Guideline will be supported by a Companion Guide produced in a concise and easily accessible format for people living with PTSD, carers, family members, other support persons, and members of the public. A Guideline implementation and dissemination plan has been developed in consultation with various stakeholders.

**Updating the Guideline**

We intend that the Guideline will be updated within five years or earlier if and when new evidence emerges that is likely to impact or change one or more of the recommendations. The Guideline has been developed on the MAGICapp platform, which facilitates updates if required.

## 5.3 Considerations of Issues for Specific Population Groups

This Guideline has been developed with a strong emphasis on inclusivity, recognising that population groups such as Aboriginal and Torres Strait Islander peoples, individuals from culturally and linguistically diverse (CALD) backgrounds, people living in rural and remote areas, and veterans and emergency service workers, may be disproportionately affected by trauma and face unique challenges in accessing mental healthcare.

An umbrella review of 33 systematic reviews identified being female, of Indigenous heritage (in the United States of America), and low socioeconomic status as key sociodemographic risk factors for developing PTSD *[99]*. However, to date, there has been limited research on the safety and efficacy of MDMA-AP in the interest groups outlined in this Guideline. A systematic review of psychedelic studies (including 1393 participants) reported that 85% were identified as non-Hispanic White *[42]*. There is also a lack of data relating to the pharmacokinetics, pharmacodynamics, and safety of MDMA-AP in non-White, minority, and vulnerable population groups. Where possible, the Guideline Development Group (GDG) has considered issues related to delivery of MDMA-AP in these population groups as part of the Evidence-to-Decision framework, particularly in the domains of values and preferences, equity, acceptability, and feasibility. This Guideline aims to promote safe, equitable, and culturally-responsive care in the use of MDMA-AP for PTSD.

**Aboriginal and Torres Strait Islander peoples**

Aboriginal and Torres Strait Islander peoples have been reported to be three times more likely than other Australians to experience potentially harmful traumas and develop PTSD, with a 12-month prevalence of PTSD at 13.3% *[69]*. The delivery of MDMA-AP to Aboriginal and Torres Strait Islander peoples should be grounded in an understanding of the diverse cultural perspectives of Aboriginal and Torres Strait Islander peoples.

Classical psychedelics have played a role in the rituals of specific Indigenous groups worldwide, used for healing, ceremonies, or other practices that foster a sense of collective belonging or aid in the transmission of cultural values and beliefs *[28][34]*. In recognition of these connections, it has been proposed that spiritual, existential, religious, and theological components be integrated in PAT to honour traditional knowledge systems and support cultural safety *[34][120]*.

However, due to its distinct effects, MDMA is not typically considered a classical psychedelic. In Australia, the use of MDMA is not known to be a current practice among the Aboriginal and Torres Strait Islander peoples.

It is important that therapy offered to Aboriginal and Torres Strait Islander peoples is provided in a way that is culturally responsive. To ensure that MDMA-AP does not cause further inequity, treatment must be culturally safe and tailored to the community *[81][98]*. This requires authentic partnership with Aboriginal and Torres Strait Islander peoples in the development, implementation, monitoring, and evaluation of treatment protocols.

This Guideline should be used in tandem with other published resources and tools that support the mental healthcare of Aboriginal and Torres Strait Islander peoples, such as:

- National Strategic Framework for Aboriginal and Torres Strait Islander Peoples' Mental Health and Social and Emotional Wellbeing 2017-2023 *[25]*
- Aboriginal and Torres Strait Islander Peoples in Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder (2020) *[125]*
- Primary Health Networks (PHNs) and Aboriginal Community Controlled Health Organisations – Guiding Principles *[26]*
- Stolen Generations Collective Healing Initiatives Rounds 1–6: impacts and findings *[95]*
- Local or state guidelines and tools, such as the Aboriginal Mental Health Consultation Guideline *[101]*, Aboriginal Mental Health Clinical Practice Guideline and Pathways *[35]*
- Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice *[118]*

**Culturally and linguistically diverse (CALD) populations**

There is limited recent data on the prevalence of mental health conditions among people from culturally and linguistically diverse (CALD) backgrounds in Australia. However, individuals from these communities may be at increased risk due to factors such as low socioeconomic status, underemployment, cultural or language barriers, housing distress, experiences of racism or discrimination, and limited access to mental health services *[31]*. Adults seeking asylum may be at particularly high risk, with studies suggesting asylum seekers are up to 10 times more likely to experience PTSD than the general population, with reported prevalence rates ranging from 37% to 77% *[31]*.

The Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder highlight additional considerations while providing services to people from CALD backgrounds, particularly refugees and asylum seekers, including additional assessments, practices to facilitate engagement, and potential barriers to access mental healthcare *[77]*.

The GDG recognised the importance of providing culturally responsive care. This may include, but is not limited to, providing information using culturally inclusive language; pairing patients with clinicians of the same ethnoracial background, particularly in cases involving race-based trauma; and creating a culturally inclusive environment for treatment sessions, such as through the setup of overnight rooms or the use of inclusive music *[63][81][22]*.

The importance of training in cultural competency for clinicians has been described *[110]*, as people may be especially physically and emotionally vulnerable during treatment sessions *[113]*. This necessitates high standards of cultural awareness and sensitivity when discussing issues related to race, gender, sexuality, and spirituality *[90] [103]*. The potential role of interpreters in MDMA-AP has not been explored in current research, and it is not clear to what extent interpreter use may impact therapeutic effectiveness and engagement.

**Rural and remote areas**

Living in rural and remote areas has been associated with lower use of mental health services *[64]*. Limited resourcing is considered a major barrier to care, in addition to complexity in using and navigating the system, technological limitations, distance to services, insufficient culturally-sensitive practice, and lower mental health literacy. Such systemic barriers can cause delays in accessing care and increase the associated cost *[49]*.

There are workforce and other resource considerations associated with implementing clinical practice guideline recommendations in rural and remote areas. Travel and accommodation costs are inherent common barriers for many treatments, and are not unique to MDMA-AP. In developing the Guideline, resource, equity, and feasibility issues were considered as part of the Evidence-to-Decision framework.

**Veterans and emergency service workers**

Emergency services workers, military personnel, and members of the veteran community are among the occupational groups at highest risk of experiencing PTSD *[126]*. Cumulative exposure to work-related traumatic events is associated with increased risk of PTSD. In 2015, a survey reported that the estimated 12-month prevalence of PTSD among current serving members of the Australian Defence Force (ADF) was 8%, while the estimated prevalence among members who had transitioned from full-time service between 2010 and 2014 was 18% *[3][100]*. The prevalence of PTSD among emergency service workers based on the Answering the Call national survey was estimated at around 10% in Australia *[108]*.

The Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder highlight that veterans often experience multiple (and repeated) traumatic exposures over prolonged periods *[126]*. Veterans may also experience unique challenges associated with transitioning into and out of military service, stigma surrounding seeking help for mental health conditions, poorer treatment responses to some PTSD therapies compared to civilians, and higher rates of comorbidity (e.g., substance use disorders, sleep disturbance, emotional numbing, physical symptoms including chronic pain) *[126]*. Similarly, the presentation of PTSD in emergency service workers may differ from the general population due to the nature of repeated trauma exposure, resulting in different initial symptom presentation at diagnosis and delayed diagnosis *[134]*. Uncertainties remain about how these factors might influence both the overall safety and effectiveness of MDMA-AP in veterans and emergency service workers.

There may be stigma-related barriers associated with PAT among veterans. In one survey on the beliefs and perceived barriers regarding PAT among American service members and veterans (n=21), common stigma-related barriers identified were fear of workplace consequences (29%) and fear of judgment (24%) *[109]*.

The need for tailored approaches that respect the core values, align with the communication styles, and enhance cultural awareness and understanding of potential barriers and clinical complexities has been described *[112][111]*.

# 6. Methods

The Guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) process *[94],* in accordance with National Health and Medical Research Council (NHMRC) Guidelines for Guidelines and 2016 Standards for Guidelines *[71]*. The intent to develop the Guideline was registered by NHMRC on 7 February 2024 and NHMRC appointed a guideline liaison person.

The methods used to develop this Guideline were pre-specified and published *[131].* Part of the methods have been reproduced in Sections 6.1 and 6.2. The GRADE Evidence-to-Decision framework was used to make recommendations from the evidence and other information *[5][6]*. The criteria considered in the GRADE Evidence-to-Decision framework are (1) benefits and harms, (2) certainty of the evidence, (3) values and preferences, (4) resources, (5) equity, (6) acceptability, and (7) feasibility *[5][6]*. GRADE methods were used to summarise and assess evidence about benefits and harms.

## 6.1 Governance

# Governance Structure

The Guideline was developed by the Guideline Development Group (GDG), supported by a Stakeholder Group, Expert Group, Conflict of Interest (COI) Oversight Committee, and Evidence Review Team (Figure 2).

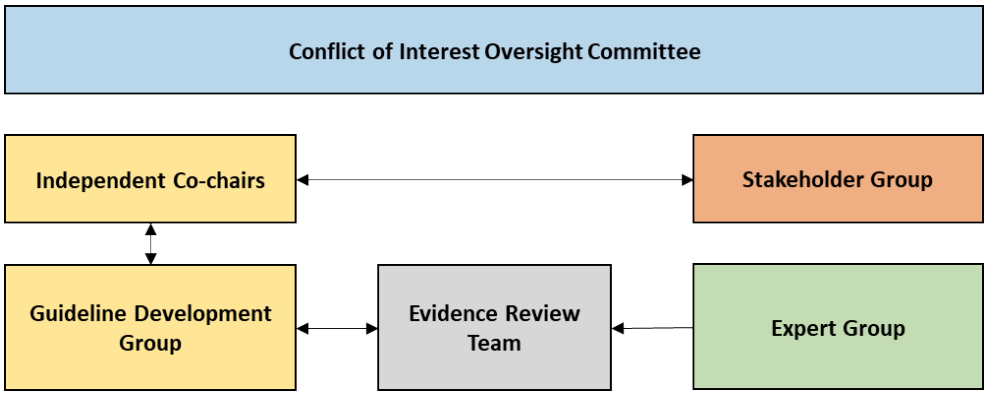



**Figure 2.** Guideline governance structure.

## Guideline Development Group

The GDG comprised members with clinical (e.g., general practice, nursing, pharmacy, psychiatry, psychology, psychotherapy), health economics, knowledge translation, mental health policy, methodological, neuroscience, pharmacology, and legal expertise, and lived experience. GDG members were offered training in Aboriginal and Torres Strait Islander cultural awareness provided by the Australian Indigenous Doctors' Association (Australian Indigenous Doctors' Association) or the Royal Australian College of General Practitioners (Royal Australian College of General Practitioners). GDG members were also offered the opportunity to undertake We Al-li Trauma-informed Aboriginal and Torres Strait Islander Cultural Capability training (We Al-li). Recommendations and good practice statements were formulated by the GDG using the GRADE Evidence-to-Decision framework (refer to Section 5.2 for details). Each GDG member completed a declaration of interests form, which was assessed by the COI Oversight Committee to ensure that members were not conflicted or that conflicts were managed according to a management plan in compliance with NHMRC requirements.

The GDG was co-chaired by a pharmacist and guideline methodologist with no direct or indirect financial interactions with any companies (or their foundation) involved in the development, production, or delivery of MDMA, another psychedelic, psychedelic-like drug, or related services. In line with NHMRC requirements, the co-chairs were appointed based on their independence and expertise in chairing and facilitating guideline meetings using GRADE methodology *[72]*. Both co-chairs were experienced in leading or guiding the development of NHMRC-approved guidelines. The two independent co-chairs did not vote at GDG meetings or on the formulation of recommendations. All recommendations were made collectively by the GDG members through majority vote. Having two co-chairs helped to maintain balance and independence, and is consistent with standard guideline development practice by the Guidelines International Network and GRADE. Having a chair with content expertise and another with methodological expertise is consistent with The Guideline Participant Tool by Piggott et al. (2021) *[107]***.** The co-chairs led GDG and Stakeholder Group meetings, promoted balanced participation of group members, and facilitated best practice application of the GRADE process. The guideline methodologist had a non-voting role, and no direct or indirect financial or non-financial interests, and therefore had primary responsibility for ensuring compliance with the conflict-of-interest policy.

## Stakeholder Group

The Stakeholder Group comprised government agencies, professional organisations, peak bodies or research organisations, and consumer representatives. The Stakeholder Group provided strategic advice on the project, advised on barriers and risks, was invited to provide feedback during the public consultation process, and assisted in disseminating the Guideline. Organisations represented on the Stakeholder Group may be invited to endorse the Guideline.

## Expert Group

The Expert Group comprised authorised prescribers, consumers and carers, general practitioners, psychiatrists, psychologists, social workers, researchers, and others with relevant expertise. This included but was not limited to clinicians and consumers with direct experience providing and receiving MDMA-AP but who could not be part of the GDG due to involvement in industry-sponsored psychedelic clinical trials, private clinics, or other COIs. The Expert Group also included consumers without potential COIs. This facilitated a more in-depth exploration of consumer experience and perspectives than would have been possible through GDG participation alone. The Expert Group was not a decision-making body but existed to provide input without compromising the actual or perceived integrity of the recommendation process. The Expert Group did not meet and discuss together as a group. Perspectives from the Expert Group were solicited via one-on-one interviews (or, in the case of consumers, one-on-two interviews) facilitated by the Project Manager. All consumer representatives were offered the opportunity for a debrief session separately after each meeting and were reimbursed for their time on an hourly basis. The interviews were audiotaped, transcribed *verbatim,* and thematically analysed following

the process outlined by Braun and Clarke (2021) *[21]*. Ethics approval was obtained from the Monash University Human Research Ethics Committee for the in-depth interviews (Project ID: 44868). The interview findings were presented to the GDG by a member of the ERT. A member of the COI Oversight Committee reviewed the material to be presented in advance of the meeting to ensure that the GDG was made aware of the COIs of the Expert Group. Except for the co-chairs and ERT, the GDG did not have direct contact in relation to the Guideline with the Expert Group members. Communication between the GDG and the Expert Group relevant to the guidelines was via the Project Manager.

## Conflict of Interest Oversight Committee

The COI Oversight Committee included two guideline methodologists with no direct or indirect interests relevant to the Guideline topic. The COI Oversight Committee advised on the COI policy and process, reviewed the declarations of prospective GDG candidates, evaluated the interests of each GDG member, assessed whether an interest reflected a conflict, and devised appropriate conflict management plans. A COI was defined in accordance with the Australian Code for the Responsible Conduct of Research as a "situation where an independent observer might reasonably conclude that the professional actions of a person are or may be unduly influenced by other interests" *[8]*. Potential COIs included financial, organisational, or intellectual interests (refer to Supplementary material 1 for the COI Policy). All potential GDG members were asked to complete a Declaration of Interests Form prior to appointment. Disclosed interests were updated and reviewed by the COI Oversight Committee prior to the start of each GDG meeting. Each disclosed interest was individually assessed for its level of conflict risk based on the COI matrix adapted from the Clinical Guidelines Committee of the American College of Physicians *[80]* (Supplementary material 1). The COI Oversight Committee notified the members of their management plans before each meeting. Individuals with interests assessed as serious COIs were not appointed to the GDG but, in some cases, were invited to join the Expert Group. Members with moderate-risk COIs could contribute to discussions and were permitted to vote independently ahead of meetings. This vote was only used to elicit the perspectives of members of the GDG and facilitate discussion. Members with a moderate risk were not permitted to vote in the meeting on either the judgements required in the GRADE Evidence-to-Decision framework or the recommendations. Members with low-risk COIs were permitted to contribute to discussion and voting without restriction.

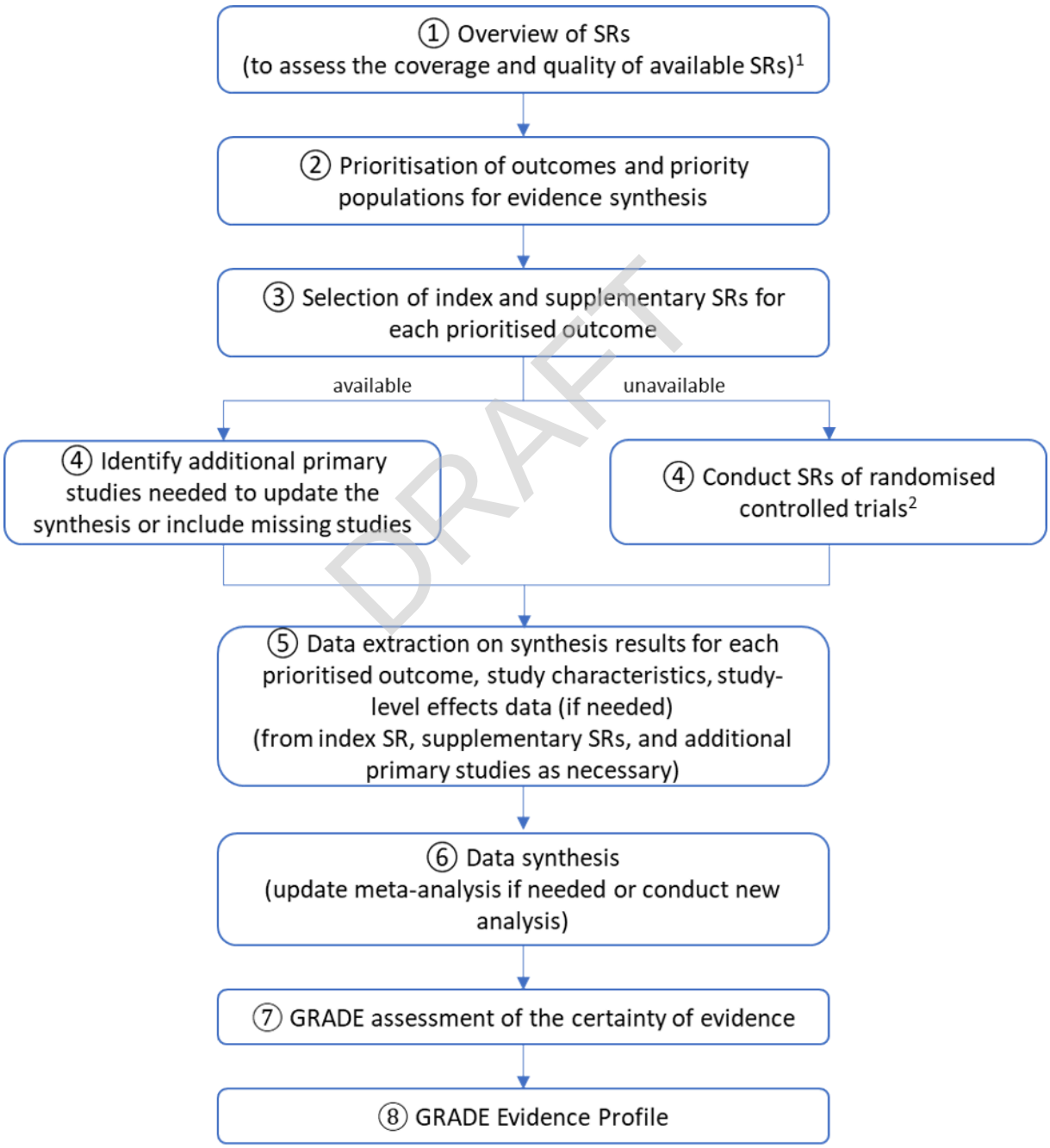
## Evidence Review Team

The ERT was comprised of the Project Manager and researchers with experience in evidence synthesis. The ERT collated evidence on benefits and harms, which was used by the GDG to formulate recommendations and good practice statements. The ERT provided evidence to support the GDG's decision-making and, where necessary, provided clarifying information during the GDG meetings, but did not contribute to the decision-making process itself. The ERT conducted literature searches, formulated an overview of systematic reviews, and extracted relevant data.

## 6.2 Methodology for Evidence Synthesis

A precis of the questions, criteria, and methods for synthesis of evidence evaluating effects on health outcomes follows. See Technical Reports 1 and 2 (attached in Section 9) for detailed methodology and results of the evidence synthesis.

In brief, an overview of systematic reviews and meta-analyses was undertaken as background research to critically evaluate the coverage and quality of existing systematic reviews *[104]* (Figure 3). From this overview, index systematic reviews were identified for consideration in the Guideline. The evidence review was based on existing systematic reviews that addressed the Guideline's Participants, Interventions, Comparators, and Outcomes (PICO) criteria and that met minimum methodological criteria. Evidence from these systematic reviews was supplemented with additional primary studies to address any gaps in the PICO questions covered by existing systematic reviews and to ensure that the evidence is up to date. The certainty of evidence was independently assessed using GRADE methods. The evidence review includes available results for primary studies identified from systematic reviews and supplemental searches up to the date of the last search (20 February 2025).






[1] Manuscript published in peer-reviewed journal *[104]*.

[2]This was planned, but the step was not needed because high-quality systematic reviews that met the PICO criteria were identified.

**Figure 3.** The process of synthesising evidence for benefits and harms. SR, systematic review

## Question Addressed in the Guideline

The Guideline addressed a single clinical question "In people living with PTSD, should we use MDMA-AP or no MDMA-AP (other or no treatment)?".

## Criteria for Considering Studies for the Evidence Review

The PICO and study design criteria for the evidence review are summarised in Table 1 (see Technical Report 1 for the explanation and rationale for criteria).

**Table 1.** Summary of criteria for inclusion of studies in the evidence review.

| Element | Criteria |
|---|---|
| Types of studies | Systematic reviews of:<br>• randomised trials (for all outcomes)<br>• non-randomised studies (for adverse events and safety outcomes only)<br>To be eligible, systematic reviews had to:<br>• address one or more of the PICO questions of interest (i.e. report a meta-analysis addressing an eligible comparison and one of the prioritised outcomes), and<br>• meet a minimum threshold for methodological-quality (AMSTAR-2 overall rating as high)<br>Supplemental primary studies (including trials and non-randomised studies) were eligible to address gaps in the coverage of included systematic reviews (i.e. to update or address aspects of the guideline PICO not covered by a systematic review). |
| Population | People of any age living with post-traumatic stress disorder (PTSD) of any severity, duration of diagnosis, and nature of trauma.<br>When making recommendations, the GDG considered specific populations for whom treatment needs and outcomes may differ. Specifically:<br>• Aboriginal and Torres Strait Islander peoples,<br>• military and ex-military personnel,<br>• emergency services personnel,<br>• age (children, adolescents, older people),<br>• culturally and linguistically diverse peoples,<br>• neurodivergent individuals such as people with autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD),<br>• people with mental health co-morbidities, and<br>• PTSD severity, duration of diagnosis, and nature of trauma. |
| Intervention | Methylenedioxymethamphetamine-assisted Psychotherapy (MDMA-AP)<br>MDMA is typically combined with psychotherapy components and is not used as a standalone therapy, hence MDMA in the absence of psychotherapy was ineligible.<br>There were no restrictions on the treatment course (or protocols) of MDMA-AP. It was anticipated that most trials would use the typical treatment course (described below). |
| Comparators | Other treatments including:<br>• psychological interventions,<br>• pharmacological interventions,<br>• watchful waiting |

| | |
|---|---|
| | Inactive or active placebos in combination with psychotherapy<br>• Active placebos included low-dose MDMA as used in Phase 2 MDMA trials to mimic some of the physiological or psychological effects of MDMA at a dose lower than expected to provide therapeutic effects.<br>• For suicide risk, adverse events, and safety outcomes, only data from comparisons with an inactive placebo were included for analysis to avoid underestimation of potential MDMA-related adverse events. |
| Outcomes | Outcome prioritised by the GDG for decision making were:<br>• PTSD symptoms [critical]<br>• daily functioning [critical]<br>• self-organisation/emotional regulation (e.g., interpersonal problems, negative self-concept) [critical]<br>• depression symptoms [critical]<br>• health-related quality of life [critical]<br>• anxiety symptoms [important]<br>• impact on productivity (e.g., employment and education) [important]<br>• sleep quality [important]<br>Adverse effects and safety outcomes:<br>• suicide risk (e.g., suicide; suicide attempts, planning and ideation; self-harm associated with suicidal ideation) [critical]<br>• cardiac-related adverse events [critical]<br>• diversion or misuse of MDMA [important]<br>• adverse events related to MDMA-AP (e.g., muscle tightness, decreased appetite, jaw clenching, excessive sweating, fatigue, restlessness, insomnia, nausea, blurred vision, chills) [important]<br>• treatment-related discontinuation/withdrawal [important] |



## Evidence-to-Decision Framework

Evidence for domains 1 and 2 (benefits and harms, certainty of the evidence) was derived from the GRADE Evidence Profile. Narrative literature reviews were conducted to identify evidence for domains 3 to 7 (values and preferences, resources, equity, acceptability, and feasibility). A summary of findings from the semi-structured interviews with each member of the Expert Group that were relevant to the framework was presented to the GDG. Input derived from the discussions among the GDG members was also captured. Table 2 lists the domains of the Evidence-to-Decision framework, the evidence considered by the GDG for each domain and the corresponding judgments.

**Table 2.** GRADE Evidence-to-Decision (EtD) framework domains, considerations, and judgements as implemented in MAGICapp.

| **Domains of EtD framework** | | **GDG Judgment** | | |
|---|---|---|---|---|
| | **GDG considers** | **Favours the intervention (MDMA-AP)** | **A close balance between options** | **Favours the alternative** |
| Benefits and harms | Whether the balance between benefits and harms favours MDMA-AP or the alternative, considering[a] the magnitude of: | Substantial net benefits of the recommended alternative | Small net benefit, or little difference between alternatives | Important harms |

| | | | | |
|---|---|---|---|---|
| | • desirable effects (benefit)<br>• undesirable effects (harm) | | | |
| Certainty of evidence | Certainty of evidence of effects across all critical outcomes | Influences the strength of recommendation | | |
| Values and preferences | Whether there is important variability (or uncertainty) in how much people with PTSD value the main outcomes | No substantial variability expected | Substantial variability is expected or uncertain | We expect few to want the intervention |
| Resource | Whether the cost-effectiveness favours MDMA-AP or no-MDMA and the certainty of evidence of resource requirements | No important issues with the recommended alternative | Important issues, or potential issues not investigated | Important negative issues |
| Equity | Whether recommending MDMA-AP could impact health equity considering potential differences in treatment effects; differences in baseline risk; priority of PTSD among certain disadvantaged populations | No important issues with the recommended alternative | Important issues, or potential issues not investigated | Intervention likely increases inequity |
| Acceptability | Acceptability of MDMA-AP among key stakeholders, which include patients and healthcare providers. Where relevant, perspectives from a broader range of stakeholders such as policymakers and the general public are considered. | No important issues with the recommended alternative | Important issues, or potential issues not investigated | Intervention is likely poorly accepted |
| Feasibility | Whether MDMA-AP is practical to implement in real-world settings | No important issues with the recommended alternative | Important issues, or potential issues not investigated | Intervention is likely difficult to implement |



[a] In making their overall judgement about the balance between benefits and harms, the panel also considers the certainty of evidence and values.

## Development of Recommendations

The Evidence Profile and findings from the narrative review and in-depth interviews were presented to the GDG at a series of GDG meetings. Prior to group discussion, each GDG member was asked to independently judge whether the evidence and other information for each domain in the Evidence-to-Decision framework support a recommendation for the intervention (MDMA-AP) or the alternative option. The summary judgements for each domain are shown in Table 2. Anonymous voting was conducted using electronic polls. This ensured that each member voted without the influence of others. The co-chairs then facilitated a group discussion about each domain to explore possible differences in voting. The voting process was repeated after the group discussion.

The GDG first made a judgment about the balance between the benefits and harms (domains 1 and 2). When the balance clearly favoured one option, it drove the direction of the recommendation (for/against the intervention). However, when there was a close balance or trade-off between the benefits and harms, the GDG considered all other criteria in the Evidence-to-Decision framework (domains 3 to 7). Depending on the recommendation, the group chose to place more or less emphasis on certain domains. Ultimately, the Evidence-to-Decision framework was a tool for group decision-making; all judgments and their rationale, including any disagreements, were transparently documented.

After voting on each domain within the Evidence-to-Decision framework was completed, the GDG voted on the direction (for or against MDMA-AP) and strength (strong or conditional) of the overall recommendation (Table 3) *[7]*. Where possible, voting on the overall recommendation was by unanimous agreement or consent by all members. If unanimity could not be achieved, the group discussed any concerns and reservations, which in some cases led to modification or rewording of the recommendation. If unanimity was not reached after discussion, a majority vote was sought. The reasons for disagreement or objection of members were documented.

**Table 3**. Types of possible recommendations and their definitions based on the GRADE Handbook.

| Recommendation | Definition |
|---|---|
| Strong Recommendation for | The GDG is confident that the benefits of an intervention outweigh its harms. The intervention will likely benefit most or all individuals. |
| Strong Recommendation against | The GDG is confident that the harms of an intervention outweigh its benefits. The intervention will likely not benefit most or all individuals. |
| Conditional Recommendation for | The benefits probably outweigh the harms, but appreciable uncertainty exists. The intervention may not be suitable for all individuals. There is a need to carefully consider the individual patient's circumstances, preferences, and values. |
| Conditional Recommendation against | The harms probably outweigh the benefits, but appreciable uncertainty exists. The intervention may not be suitable for all individuals. There is a need to carefully consider the individual patient's circumstances, preferences, and values. |
| Recommendations to use interventions only in research | There is to date insufficient evidence to support a decision for or against an intervention. Further research has large potential for reducing uncertainty about the effects of the intervention. Further research is considered to be of good value for the anticipated costs. |

## Development of Good Practice Statements

A series of Good Practice Statements related to principles important to follow prior to, during, and after the initiation of MDMA-AP for PTSD were formulated, where there was clear indirect evidence that their implementation will provide unequivocal benefits. Good Practice Statements are actionable statements grounded in either: (1) ethical principles or human rights (e.g., the right to health and to make decisions about treatment with informed consent), (2) essential principles, practices, and protocols (e.g., to guide standards for infection control), or (3) established scientific evidence. The Evidence-to-Decision criteria were considered for each Good Practice Statement to decide if there was high certainty that the desirable effects outweigh undesirable effects or that the opposite course of action would be clearly inappropriate *[27]*). All recommendations and Good Practice Statements were discussed, drafted, and approved by the GDG. These recommendations and Good Practice Statements did not require endorsement by Monash University, the funders, or any of the other GDG member organisations in order to be published.

## Dissemination and Implementation

The Guideline will be disseminated to medical and allied health professionals via digital dissemination, professional networks, conferences, and member organisations of the Stakeholder Group. A Companion Guide will be developed and disseminated to people living with PTSD and their carers, family members, and other supports. The detailed Dissemination Plan can be found in Section 9.

# 7. Benefits and Harms of Methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in Post-traumatic Stress Disorder

Conditional recommendation against

**Recommendation 1** (draft pending NHMRC approval)

For people living with PTSD, the Guideline Development Group conditionally recommends against the routine use of MDMA-AP. If MDMA-AP is used, it should be limited to adults (≥18 years old) with PTSD symptoms for at least 6 months duration post-diagnosis, with moderate or severe PTSD symptoms in the past month (CAPS-5 total severity score ≥28), who have received an adequate trial of first-line evidence-based treatments, and who are not likely to be re-exposed to the index or other significant trauma during treatment.

### Practical info

1. Authorised prescribers must ensure that the MDMA used in clinical settings complies with the national quality requirements. Since there are currently no MDMA products included in the Australian Register of Therapeutic Goods and no internationally recognised quality standards available for MDMA, the Australian Therapeutic Goods Administration (TGA) has established national quality standards for MDMA through Therapeutic Goods Orders (TGOs).

2. Clinicians involved in MDMA-AP must adhere to regulatory requirements governing the lawful supply, storage, and handling of MDMA. Clinicians should adhere to the relevant State Medicines and Poisons Regulation for Schedule 8 medications. Pharmacists should dispense or supply MDMA directly to authorised prescribers only and in accordance with the guidance from TGA. MDMA products should not be supplied directly to patients.

3. MDMA for the treatment of PTSD is a Schedule 8 therapeutic good (controlled drug). Advertising therapeutic goods included in Schedule 8 to the general public is prohibited under the Therapeutic Goods Act (1989). The Therapeutic Goods Administration (TGA) updated their advice in September 2024 to clarify that advertising of health services must not promote the use of therapeutic goods for which advertising is prohibited. The TGA advises that any reference to a therapeutic good in an advertisement for a health service risks that advertisement being considered an advertisement for the therapeutic good.

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

#### Research evidence

**Balance of Effects**

To decide on the balance of effects, the GDG group initially considered and made separate judgements about:

- the size of desirable anticipated effects (benefit)
- the size of undesirable anticipated effects (harm)
- the overall certainty of the evidence for critical outcomes
- whether there is important variability (or uncertainty) in how much people value the main outcomes

The GDG reached a decision after discussion that the balance between desirable and undesirable effects (benefits and harms) probably favours not using MDMA-AP for PTSD. The polling showed that GDG members had different opinions on the balance between benefits and harms (the second poll indicated 5/14 voted for 'probably favours no MDMA-AP'; 5/14 voted for 'favours or probably favours MDMA-AP'; 3/14 voted for 'does not favour either'; 1/14 voted for 'varies'), but the decision was reached after discussion that the evidence was too uncertain to determine whether benefit outweighs the harm (detailed below).

Although high value was placed on findings that MDMA-AP may reduce PTSD symptom severity and improve daily functioning at 18 weeks, the evidence was deemed to be of low certainty, and it was unknown whether these effects on PTSD symptoms and functioning are sustained. The evidence was also deemed to be of very low certainty for other critical outcomes (e.g., suicidality, emotional regulation, depression). In terms of undesirable effects, evidence was of very low certainty that MDMA-AP may increase cardiac events indicative of QT prolongation and adverse events. Long-term risks of MDMA-AP (beyond 18 weeks) and the effects on the diversion or misuse of MDMA were uncertain. No studies reported on health-related quality of life, productivity, or anxiety.

**Desirable effects (benefits)**

The GDG members judged the desirable effects of MDMA-AP (as interpreted below) to be moderate (voted by 9/14), based on the high value placed on improvement in function by people living with PTSD and carers, and the size of the observed effects (consensus achieved after polling, discussion, and re-polling). The GDG noted their concerns about the low certainty of the clinical trial evidence for these outcomes, and the very low certainty or absence of evidence for other critical outcomes (detailed below).

Compared with no MDMA-AP, MDMA-AP at 18 weeks:

- may reduce PTSD symptom severity [CRITICAL]
- may improve daily functioning [CRITICAL]

There is also very low certainty evidence that MDMA-AP may improve:

- suicidal ideation or behaviour [CRITICAL]
- self organisation / emotional regulation [CRITICAL]
- depression symptoms [CRITICAL]
- sleep quality slightly [IMPORTANT]
- treatment discontinuation [IMPORTANT]



The GDG was uncertain about the long-term effects of MDMA-AP (beyond 18 weeks). There were non-interventional follow-up studies (beyond 6 months), but the findings were too uncertain to interpret.

No studies reported on:

- health-related quality of life [CRITICAL]
- productivity [CRITICAL]
- change in anxiety symptoms [IMPORTANT]

**Undesirable effects (harms)**

The GDG members judged the undesirable effects of MDMA-AP (as interpreted below) to be small but important (voted by 10/15). This was based on the potential cardiovascular risks if MDMA-AP were applied in routine use and the size of the observed effects (consensus achieved after discussion and polling). The GDG noted the very low certainty of evidence for critical outcomes (detailed below).

Compared with no MDMA-AP, MDMA-AP at 18 weeks:

- may increase cardiac events indicative of QT prolongation [CRITICAL]. One serious adverse event of cardiac arrhythmia (ventricular extrasystoles) was reported in the MDMA-AP arm during a phase 2 study (MP-8).
- may increase adverse events [IMPORTANT]. 17 serious adverse events were reported across all Phase 2 and 3 trials, but only one was deemed by the trial investigators as probably related to MDMA-AP, which was the ventricular extrasystole.

- has very uncertain effects on the diversion or misuse of MDMA [IMPORTANT]

The GDG was uncertain about the long-term adverse events of MDMA-AP (beyond 18 weeks). No studies reported on the possible effect of MDMA-AP on other outcomes identified as important by the GDG members, such as the diversion or misuse of other drugs or alcohol, and comorbid symptoms (e.g., symptoms of numbing, problems with concentration, irritability).

**Summary**

**Balance of Effects**

GDG members discussed the difficulty in voting on the balance of effects. This was because the evidence suggested moderate desirable effects and small undesirable effects, indicating apparent net benefit, yet GDG members were not confident to vote in favour of MDMA-AP due to the low certainty of evidence for PTSD symptoms and function, and very low certainty evidence for all other critical outcomes. The GDG had important concerns about potential adverse events, given the very low certainty evidence, and the absence of evidence about longer-term outcomes. Some GDG members, particularly clinicians, noted their hesitance to implement a treatment with low to very low certainty evidence on critical outcomes when other PTSD treatments have stronger evidence supporting their efficacy. Conversely, GDG members were also reluctant to vote 'against' MDMA-AP, recognising that it may offer benefits to certain individuals with treatment-resistant PTSD for whom other options have been unsuccessful, and therefore should remain an option.

The chairs clarified that a conditional recommendation against the routine use of MDMA-AP would not remove MDMA-AP as a treatment option. The chairs also explained that the GDG discussions could inform the development of Good Practice Statements to guide the conditional use of MDMA-AP should a 'conditional recommendation against routine use' be made.

**Desirable effects (benefits)**

GDG members were cautious in interpreting the effect sizes, noting that only symptom severity and daily functioning had evidence of sufficient certainty to interpret the results for decision-making, though 18 weeks may be an insufficient length of follow-up. No longer-term data (beyond 18 weeks) from randomised controlled studies were currently available. The GDG noted the limitations of the current evidence base for clinical practice, as the comparator (non-directive psychotherapy) is not considered standard clinical practice in Australia *[3]*.

An initial poll of GDG members about the overall magnitude of effects showed a near-even split between 'small' (voted by 7/15) and 'moderate' (voted by 5/15) anticipated desirable effects. GDG members with lived-experience expertise emphasised the high value of improvement in the critical outcomes, especially function, and also provided context about the burden of care and 'ripple effects' around the people living with PTSD. GDG members discussed the importance of improvement in daily functioning and quality of life to people living with PTSD, but no data were available on the impact on quality of life. The standardised mean differences (SMDs) for PTSD symptoms were 0.86. GDG members also discussed reported effect sizes with other treatments, such as eye movement desensitization and reprocessing (SMD of 0.99) and trauma-focused cognitive behavioural therapy (SMD of 1.08) *[1]*. After a second poll, GDG members voted that the overall desirable effects were moderate (voted by 9/14).

**Undesirable effects (harms)**

GDG members expressed caution that, despite the small effect sizes, the potential harms, particularly cardiovascular, could be a cause for concern if MDMA-AP were routinely used. One GDG member noted that given sufficient screening, the acute effects of MDMA are likely physiologically well-tolerated in a controlled setting, as demonstrated in animal models and Phase 1 human studies. The GDG was advised to be cautious in interpreting safety data from animal models or Phase 1 human studies because this evidence did not form part of the Evidence Summary (different population and study design) and had

not been formally evaluated using the GRADE methods (e.g., considering whether the population was comparable, risk of bias).

GDG members discussed the potential use of published observational/population data (specifically, about the harms of illicit MDMA use) as supplementary information to inform the safety profile of MDMA-AP. The Evidence Review Team reported that the FDA had reviewed harms associated with illicit/non-medical MDMA using poison centre data, toxicologist consultations, and a scoping literature review. The FDA Meeting Report mentioned that "we identified adverse events associated with illicit MDMA use, including specific cardiovascular, respiratory, hepatic, and neuropsychiatric outcomes, as well as various laboratory abnormalities". However, the FDA Advisory Committee concluded that interpretation is difficult because "use of other substances may accompany illicit MDMA use, the purity and dosage of the MDMA product consumed is usually not known, and what is believed to be MDMA might include non-MDMA ingredients that could substantially impact clinical effects and outcomes" *[2]*.

GDG members agreed that data on adverse events from illicit MDMA use have limited relevance to the medical use of MDMA-AP due to the unknown purity and dose, and were typically used in populations (e.g., younger, healthier individuals with lesser comorbidities) different from those who might receive MDMA-AP. Hence, the GDG agreed to consider data from clinical trials or observational data on MDMA-AP (if any) when forming the recommendation.

**Certainty of the evidence**

Very low



**Research evidence**

The GDG judged the overall certainty of evidence to be 'very low' based on the very low certainty of evidence for multiple outcomes considered as critical for decision making.

The GDG considered the certainty of evidence for each outcome as assessed by the Evidence Review team (see Evidence profile for complete assessments). Pre-specified decision thresholds, as agreed by the GDG, were used to interpret effects and rate certainty (see Technical Report 1 for details).

In brief, the certainty of evidence for critical outcomes was:

- Low for PTSD symptoms (due to risk of bias and imprecision), daily functioning (due to risk of bias and imprecision)
- Very low for suicidal ideation or behaviour (due to risk of bias, imprecision, indirectness and publication bias), self-organisation / emotional regulation (due to risk of bias, imprecision and indirectness), depression symptoms (due to risk of bias, imprecision and inconsistency), cardiac events indicative of QT prolongation (downgrade on all domains).

Health-related quality of life and productivity were not reported in any eligible studies.

These GRADE ratings align with the Institute for Clinical and Economic Review's (ICER) evidence rating of "Insufficient", indicating a low level of certainty in evidence for MDMA-AP compared to psychotherapy alone *[4]*. The GRADE ratings also reflect concerns raised by the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) following their rejection of Lykos Therapeutics' New Drug Application for MDMA-assisted therapy for PTSD *[2]* and summarised in a commentary by Marks on the FDA review *[128]*.

Many of the concerns raised in the ICER report - authored by Mustafa et al - and in the FDA review, relate to methodological limitations of the studies. These study limitations are addressed in the GRADE rating under "risk of bias". The main concerns, and their implications for the assessment of risk of bias, are summarised below.

Risk of bias

All trials were rated as being at high risk of bias (mainly ROB2 assessments from Mustafa et al 2024 *[4]* and Colcott et al 2024 *[24]*, with verification by the Evidence Review Team).

Two major concerns relating to risk of bias were described in the ICER report (Mustafa et al, 2024)*[4]* and a commentary on the FDA review *[128]*:

- Unblinding of participants and those delivering the therapy, which must be considered because of the potential to introduce bias through deviations from the intended intervention and bias in the measurement of the outcome. The latter was a particular concern for participant-reported outcomes, including outcomes where participants are interviewed by an outcome assessor who is unaware of the treatment received (Sterne et al., 2019). In the MAPP1 and MAPP2 trials, there were concerns about inadequate or a lack of blinding of participants and therapists due to MDMA's psychoactive effects.
- The high proportion of trial participants with prior experience using MDMA (40% of all participants) raised concerns about the potential to introduce bias in the measurement of the outcome. The concern was that those who have had a "positive" prior experience with MDMA (e.g. perceiving that they have experienced benefit, not having experienced serious adverse events, or being "accustomed" to adverse events), will provide more favourable reports of outcomes (referred to as "expectancy bias") leading the trials to overestimate benefit, underestimate harm, or both.

Specific concerns about bias arising from deviations from the intended intervention in the MAPP1 and MAPP2 trials (precis from Mustafa et al 2024 risk of bias assessment) *[4]*:

- "Participants were aware of their assigned intervention during the trial, as blinding participants to receiving MDMA vs placebo was challenging given the psychoactive and physiological effects of MDMA. For these same reasons, it is likely that therapists were aware of the treatment arm that their participants were in."
- "Blinding was formally assessed in MAPP2"; 94.2% and 75% of participants in the intervention and control groups, respectively, guessed which treatment they had received correctly."

Specific concerns about bias arising from the measurement of the outcome:

- Overall, Mustafa et al reported that methods for administering CAPS-5 were appropriate. "CAPS-5 is considered the gold standard as an outcome measure for PTSD and was appropriately used as the primary outcome measure in this study, though it may not be ideally suited for assessing non-military populations and individuals whose PTSD did not originate from a singular traumatic trigger event."
- Functional unblinding, combined with the participants' expectancy towards MDMA-AP, might lead to an overestimation of benefits (and, possibly, an underestimation of adverse effects) among those who believed they were in the MDMA-AP group. It might also contribute to nocebo effects (where negative expectations about placebo reduce perceived benefit) among those who believed they were in the control group.
- Electrocardiogram was not routinely monitored after MDMA dosing in the phase 2 and 3 studies, potentially leading to under-reporting of cardiac events.

Other concerns were raised through public consultation and in interviews ICER conducted with people who had "…firsthand or secondhand knowledge of the trials and related events" *[4]*:

- There were reports of "participants who improved on the CAPS-5 outcome while worsening overall" leading ICER to comment that "participants overall response to MDMA-AP" may not have been detected (Mustafa et al 2024, p4)
- There were reports of participants feeling "pressure to have the results of the MAPP trials be favourable" i.e. "to report good outcomes and suppress bad outcomes" (Mustafa et al 2024, p5)

- Marks summarised other concerns from the FDA review: "During a public comment period, speakers alleged that Lykos failed to report serious adverse events and discouraged some participants from enrolling in the long-term follow-up study". This raises concern about the risk of bias that could be introduced through under-reporting of harms, and, possibly, overestimation of beneficial effects in the long-term *[128]*.

Rating down of other GRADE domains

The full explanation for the GRADE rating for all outcomes and domains is reported in the GRADE Evidence Profile. Results for all critical outcomes were imprecise such there is uncertainty about whether effects on these outcomes are important or not. For suicide risk and cardiac events indicative of QT prolongation, there were additional concerns about bias arising from missing results (publication bias).

For some population groups, the evidence relating to safety outcomes is less certain, which the GDG considered in making their recommendations:

- Cardiovascular risk factors: The safety profile of MDMA-AP in individuals with cardiovascular risk factors was considered unknown because people with a history of a medical condition that could make receiving a sympathomimetic drug harmful were excluded from Phase 3 clinical trials.
- Suicide risk: People with PTSD have a higher risk of suicide: suicide rates are 6.7 times higher in women and around 4 times higher in men with PTSD, compared to people without PTSD (Fox et al., 2021). The safety profile of MDMA-AP in individuals with increased/active suicidality remains unknown due to their exclusion from trials.
- Comorbidities: Individuals with PTSD often have comorbidities such as substance use disorders (65% of men and 32% of women), personality disorders (4-28%), and psychotic symptoms (over 30%) *[114]*. There were concerns that adverse events may be underestimated because the trials did not include people with these common comorbidities.
- Current illicit MDMA use: The safety profile of MDMA-AP in individuals with current illicit MDMA use was considered unknown due to their exclusion from trials, including people with active illicit (other than cannabis) or prescription drug substance use disorder at any severity within the past 12 months.

Other concerns raised by the FDA *[2]*

Data collection related to illicit MDMA use during MDMA-AP treatment was considered limited despite illicit use being identified as an adverse event of special interest in Phase 3 clinical trials. The FDA raised concerns in 2017 about the need for measures of "abuse-related adverse events", recommending measurement of "…subjective effects that could be perceived as neutral or beneficial, such as euphoria, which the FDA believes increase the risk of abuse" (Marks 2024, p963). However, "in the NDA [new drug application], the Applicant [Lykos Therapeutics] stated that they did not collect as adverse events any 'effects of treatment that were considered to be neutral, positive, or favorable by the participant and the therapist and study physician…' This is not consistent with FDA advice provided to the Applicant in 2017 regarding the collection of adverse events in clinical studies." (Food and Drug Administration, 2024, p56) *[2]*.

**Summary**

In accordance with GRADE methodology, the GDG judged the overall certainty of evidence to be very low based on the very low certainty of evidence for multiple outcomes considered as critical for decision making. All GDG members agreed.

**Values and preferences**

Substantial variability is expected or uncertain

**Research evidence**

The GDG members judged that the value placed on the outcomes of MDMA-AP will vary importantly among people living with PTSD. There was uncertainty about patient preferences (i.e., willingness to accept risks for potential benefit) and the complexity in treatment decision-making (because of uncertain evidence). 11/14 GDG members voted for 'It would vary importantly'; 3/14 voted for 'we don't know- there is important uncertainty'.

Findings from Narrative Review

- No study has examined how people with PTSD value or trade off between different benefits and harms.
- In qualitative studies, efficacy and therapeutic mechanisms appear to guide treatment decision-making more frequently than adverse events *[23][88]*.
- In a survey with 254 Australian mental health service users, 75% expressed a desire to access PAT [a] and 55% preferred PAT over conventional therapy. However, there were still significant concerns about its safety and negative effects (60% expressed concerns about its negative effects) *[56]*.
- In another survey with 502 Australians from the general population (including 64.5% mental health service users) - 52.4% agreed/strongly agreed that they were open to trying PAT [vs 17% who disagreed/strongly disagreed] *[68]*.

Findings from Expert Group [b]

- Both clinicians and patients reported the possible tendency for some people with PTSD who are "desperate" to access MDMA-AP to overemphasise treatment benefits and downplay the risks.
- Some patients may have reservations towards MDMA-AP influenced by social stigma, loss of productivity, professional reservations (veterans), and cultural preferences (Indigenous and CALD communities)

[a] No studies specific to MDMA-AP were identified, hence the narrative review was broadened to include PAT. In Louie 2025 *[56]* and Nadeem 2024 *[68]*, MDMA was classified as a psychedelic.

[b] Findings are based on the perspectives of patients who have received MDMA-AP for PTSD and may not fully reflect the views of those who have not undergone this treatment. See Technical Report 3 for details.

**Summary**

People with lived-experience expertise highlighted that individuals living with PTSD may weigh the risks and benefits of MDMA-AP differently based on their previous experience with other established treatments. People living with PTSD who have unsuccessfully tried other treatment options might place more weight on the potential benefits, which may reflect desperation for symptom improvement rather than efficacy of the therapy. The GDG acknowledged this variability in patient perspectives and emphasised the critical role of informed consent processes.

The GDG also discussed the potential influence of media reporting individual 'miracle stories' of recovery following MDMA-AP, which might lead to bias in decision-making. The chairs shared findings from interviews with the Expert Group that there might be an overemphasis on the promise of successful treatment. Additionally, the decision-making process might be variable based on access to information – some people may seek out more information prior to referral.

**Resources** Important negative issues

**Research evidence**

The poll recorded a majority vote for 'large' (voted by 7/15) or 'moderate' costs (voted by 4/15) of MDMA-AP compared with other therapies (4/15 voted for 'Don't know'). All GDG members agreed that the cost-effectiveness of MDMA-AP compared to other treatment options could not be established because of the absence of evidence in the Australian context and uncertainty around applying cost-effectiveness data from US studies.

Findings from Narrative Review

- No economic evaluation specific to the Australian healthcare context was identified.
- US studies reported that MDMA-AP may be more cost-effective than no short-term intervention (incremental cost-effectiveness ratio of US$83,845 per QALY) *[92]*. However, the findings of these economic evaluations are uncertain due to the low certainty of evidence around the underlying clinical trial outcomes.

Findings from Expert Group

- Delivery of MDMA-AP (as per the existing Phase 3 clinical trials protocol) requires more human resources (2 therapists/session) and time (42 hours of therapy per patient) than other PTSD treatments.
- Interviewees reported that some patients were asked to pay out-of-pocket costs amounting to A$20,000-30,000.
- Providers might require resources to create the setting for the therapeutic experience (e.g., music, ambient temperature and lighting, comfortable seating/beds). Interviewees reported that the benefits of treatment (reducing the social and financial burden of PTSD) might justify the cost. Reducing cost was perceived as potentially compromising treatment efficacy and safety (e.g., one therapist, video-conferencing, fewer sessions).

**Summary**

Some GDG members expressed concerns about the internal and external validity of the cost-effectiveness analyses conducted from a US payer's perspective. The available cost-effectiveness analyses *[92][4]* were based on modelling, rather than trial-based economic evaluations, which may limit their internal validity. The external validity was limited as the analyses and ICER threshold used might not be generalisable to the way MDMA-AP would be delivered in Australia, considering the local healthcare resource profile and the public/private funding structure. Additionally, concerns were raised regarding extrapolating clinical outcomes from clinical trials (two phase 3 and one long-term follow-up of one year) to construct a 5-year model for the economic evaluation. One GDG member highlighted ongoing RCTs evaluating the efficacy of delivering MDMA-AP in the Australian context that include economic evaluation components. These studies may provide more relevant evidence as to the cost-effectiveness of MDMA-AP. GDG members also noted the additional costs incurred by service providers to comply with current storage and supply regulations, such as having a medical safe at the treatment delivery site.

**Equity**

Important issues, or potential issues not investigated

**Research evidence**

The GDG members considered that the implementation of MDMA-AP would have a mixed impact on health equity. 5/13 voted that MDMA-AP 'reduced/probably reduced' health equity, 2/13 voted for 'probably no impact', 2/13 voted for 'increased/ probably increased', 2/13 voted for 'varies', and 2/13 voted for 'don't know'.

Findings from Narrative Review

- Access may be influenced by sociodemographic factors, such as place of residence, cultural background, occupation, gender, and socioeconomic status, which are not unique to MDMA-AP, but reflect existing systemic inequities in accessing mental health services.
- Potentially increases inequity to people living in rural areas because clinics delivering MDMA-AP are typically located in major metropolitan regions.
- The cost of treatment could be prohibitive to many people living with PTSD.
- There are different potential avenues for funding support for MDMA-AP, such as the Department of Veterans' Affairs *[57]*, not-for-profit organisations, or private health insurance.

Findings from Expert Group

- People who decide to pay for treatment might face possible financial hardship and potential loss of income during treatment (e.g., inability to work/drive during treatment).
- Adaptation to the standard treatment protocol might be necessary in some populations (e.g., culturally and linguistically diverse communities, LGBTQIA+ communities, Aboriginal and Torres Strait Islander peoples, veterans) to ensure equitable access.

**Summary**

The GDG members discussed how MDMA-AP could improve or worsen health equity. MDMA-AP was perceived to potentially promote equity by offering a new therapeutic option for individuals with treatment-resistant PTSD, who may have come from disadvantaged backgrounds. It was noted that for some individuals, MDMA-AP could improve functioning to the point of being able to return to work. Some GDG members from rural settings also noted that travel and accommodation costs are inherent common barriers for many mental health treatments, not unique to MDMA-AP. For patients considering self-funding the treatment, informed consent and the provision of sufficient information to weigh the financial risks against the potential loss of productivity due to PTSD was deemed important.

On the other hand, several concerns were raised about the treatment potentially increasing inequity. The cost of MDMA-AP is high, and certainty around its efficacy and cost-effectiveness remains low. Publicly funding such a resource-intensive intervention for a small proportion of patients may divert resources from other treatments with established effectiveness, thereby limiting access for others. Additional concerns were raised about inequity arising from the financial burden placed on patients who pursue MDMA-AP as a last resort, especially when public funding is not available. Some members raised concerns about worsening inequity due to barriers related to cultural safety and treatment costs among the Aboriginal and Torres Strait Islander peoples (who experience higher rates of trauma than the general population).



**Acceptability**

Important issues, or potential issues not investigated

**Research evidence**

Most GDG members agreed that MDMA-AP would probably be acceptable (7/12 voted for 'yes' or 'probably yes'; 4/12 voted for 'varies'; 1/12 voted for 'probably no') to key stakeholders. However, the GDG recognised the uncertainties and limited evidence regarding acceptability. This was considered in making the final recommendation.

Findings from Narrative Review

- A survey of Australian mental health service users reported that 52-75% were open to trying PAT. However, there were still considerable concerns about its safety and negative effects *[56][68]*.
- Most healthcare professionals agreed that psychedelics show promise in treating psychiatric disorders (65-85%), but had concerns about safety and efficacy (~70%) *[17][131]*.

- An online survey reported that Australian mental health researchers, psychiatrists, and psychologists (n=94) showed no general bias against MDMA-AP compared to a neutrally labelled pharmacotherapy trial, though psychiatrists and more experienced mental health professionals were more likely to show hesitancy in recommending trials of MDMA-AP *[132]*.
- In 2023, the Royal Australian and New Zealand College of Psychiatrists espoused a "cautious initial approach" to help prevent serious adverse outcomes for patients because the evidence base for MDMA-AP is limited and emerging *[84]*.

Findings from Expert Group

- All clinicians and patients recognised the importance of having MDMA-AP as a treatment option for PTSD, but some wanted more flexibility in treatment protocols.
- Many clinicians recognised the need for clearer guidelines and more specific training.
- Several interviewees highlighted potential professional reservations or stigma around MDMA, particularly among veterans and emergency service workers.

**Summary**

The GDG members acknowledged potential variability in the acceptability of MDMA-AP among patients- some individuals appear open and optimistic about the treatment, some might have concerns, while others may reject it. Some GDG members raised concerns that evidence regarding acceptability based on surveys might be prone to bias based on the participants' understanding of MDMA-AP. It was discussed how "acceptability" is defined—whether it reflects individual experience or public opinion/ perceptions, which could be altered in many ways, such as how information is presented. One member with previous trial experience noted that while the public generally seems accepting of MDMA-AP, some felt that the acceptability of the current treatment protocol should be improved, such as adjusting the timing between sessions according to patients' needs or exploring alternative models like group therapy.



**Feasibility**

Important issues, or potential issues not investigated

**Research evidence**

The GDG members considered that the feasibility of implementing MDMA-AP would vary (4/11 voted for 'probably no'; 4/11 voted for 'yes/ probably yes'; 3/11 voted for 'varies').

Findings from Narrative Review

- Surveys showed that healthcare providers generally feel unprepared to deliver PAT due to perceived gaps in knowledge and training *[17][131]*.
- Nationwide/broad-scale implementation is probably not feasible at this stage due to constraints on human resources and the need for training to equip relevant healthcare providers.
- TGA reports 14 Authorised Prescribers for MDMA as of 14/02/2025 (WA-6, NSW-3, VIC-2, SA-1, ACT-1, QLD-1).

Findings from Expert Group

- Some interviewees felt that MDMA-AP may be more effective if offered earlier in the illness trajectory or with more flexible treatment structures, but the scope was perceived to be limited within existing regulations.
- Some interviewees discussed the need to integrate patients back into routine care after treatment completion (e.g., by keeping other health providers, such as GPs and existing therapists, informed of the treatment).

**Summary**

GDG members discussed the feasibility of implementing MDMA-AP at both the service provider level and on a broader system-wide scale. While it was perceived as feasible for providers who have already set up specialist clinics, it was considered likely to be less feasible for others. Currently, implementation appears realistic only in metropolitan settings where resources are more readily available. Members also noted that Australia's mental health workforce is already under considerable strain, and MDMA-AP is a resource-intensive intervention, especially in terms of required therapy hours. Substantial training for health professionals would be necessary to improve feasibility. It was also acknowledged that feasibility is largely shaped by broader healthcare system factors, rather than by the nature of MDMA-AP itself. Similar to other health services, nationwide implementation of MDMA-AP would require significant investment in workforce development, public sector implementation frameworks, governance structures, and equity-focused strategies.

**Rationale**

Most GDG members agreed on a 'conditional recommendation against the routine use of MDMA-AP' (voted by 9/12), whereas some voted on a 'conditional recommendation for the routine use of MDMA-AP' (3/12).

Several GDG members expressed support for a 'conditional recommendation against the routine use of MDMA-AP' due to concerns around the low certainty of evidence for PTSD symptoms and daily functioning (very low certainty overall for critical outcomes), and the need for more evidence on long-term safety and efficacy. Members emphasised the importance of outlining specific conditions under which MDMA-AP might be appropriate. Due to the variability in patient value and preferences, the GDG members stressed the importance of fully informed consent and empowering the individual to weigh the benefits and harms. The GDG members acknowledged the rapidly evolving evidence base surrounding psychedelic therapies and emphasised the importance of regularly updating the Guideline to ensure it remains aligned with emerging evidence.

For members who voted for a 'conditional recommendation for the routine use of MDMA-AP', the view was that MDMA-AP may offer meaningful benefits to certain individuals with PTSD, especially those who have not responded to existing treatments. These members emphasised the importance of individual autonomy in weighing potential benefits against potential risks, noting that the severity and impact of PTSD may make the risks of this 'experimental' treatment acceptable for some. They also cautioned against excluding any population from the recommendation, stressing that treatment options should not be taken away from individuals who may benefit, provided that decision making and consent is fully informed.



**Clinical question/ PICO**

**Population:** Adults with PTSD
**Intervention:** MDMA-assisted psychotherapy
**Comparator:** Placebo with psychotherapy

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo with psychotherapy | **Intervention** MDMA-assisted psychotherapy | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Suicidal ideation or behaviour** [1] 18 weeks 8 Critical | Relative risk 0.72 (CI 95% 0.26 — 2.01) Based on data from 194 participants in 2 studies. (Randomized controlled) | 84 per 1000 Difference: | 60 per 1000 **24 fewer per 1000** ( CI 95% 62 fewer — 85 more ) | **Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [2] | MDMA-AP may decrease suicide ideation or behaviour, but the evidence is very uncertain. |
| **Cardiac events indicative of QT prolongation** 18 weeks | Relative risk 1.47 (CI 95% 0.14 — 15.48) Based on data from 194 participants in 2 studies. (Randomized controlled) | 21 per 1000 Difference: | 31 per 1000 **10 more per 1000** ( CI 95% 18 fewer — | **Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Due to | MDMA-assisted psychotherapy may increase cardiac events indicative of QT prolongation (i.e., palpitations) but the evidence is very uncertain. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo with psychotherapy | **Intervention** MDMA-assisted psychotherapy | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 7 Critical | | | 304 more ) | serious publication bias, Due to serious inconsistency [3] | |
| **Treatment discontinuation** 18 weeks 6 Important | Relative risk 0.38 (CI 95% 0.15 — 0.94) Based on data from 282 participants in 6 studies. (Randomized controlled) | **132** per 1000 Difference: | **50** per 1000 **82 fewer per 1000** ( CI 95% 112 fewer — 8 fewer ) | **Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [4] | MDMA-assisted psychotherapy may reduce treatment discontinuation but the evidence is very uncertain. |
| **Adverse events** 18 weeks 6 Important | Relative risk 2.85 (CI 95% 2.27 — 3.59) Based on data from 194 participants in 2 studies. (Randomized controlled) | **51** per 1000 Difference: | **145** per 1000 **94 more per 1000** ( CI 95% 65 more — 132 more ) | **Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious publication bias [5] | MDMA-assisted psychotherapy may increase adverse events but the evidence is very uncertain. |
| **Diversion or misuse of MDMA** 18 weeks 5 Important | Relative risk Based on data from 194 participants in 2 studies. (Randomized controlled) | **0** per 1000 | **0** per 1000 | **Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [6] | The evidence is very uncertain about the effect of MDMA-AP on the diversion or misuse of MDMA. |
| **PTSD symptoms** 18 weeks 8 Critical | Measured by: Clinician-Administered PTSD Scale for DSM-4 or DSM-5 (CAPS-4 or CAPS-5) Lower better Based on data from 249 participants in 7 studies. (Randomized controlled) | Difference: | **SMD 0.86 lower** ( CI 95% 0.59 lower — 1.12 lower ) | **Low** Due to serious risk of bias, Due to serious imprecision [7] | MDMA-assisted psychotherapy may reduce PTSD symptoms. |
| **Daily functioning** 18 weeks 8 Critical | Measured by: Sheehan Disability Scale (SDS) or Global Assessment of Functioning (GAF) Lower better Based on data from 200 participants in 4 studies. (Randomized controlled) | Difference: | **SMD 0.54 lower** ( CI 95% 0.25 lower — 0.83 lower ) | **Low** Due to serious risk of bias, Due to serious imprecision [8] | MDMA-assisted psychotherapy may improve daily functioning. |
| **Health-related quality of life** 7 Critical | | | | | No studies were found that looked at health-related quality of life. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo with psychotherapy | **Intervention** MDMA-assisted psychotherapy | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Self-organisation/ emotional regulation** 18 weeks 7 Critical | Measured by: Self-Compassion Scale (SCS) Scale: 0 — 5 High better Based on data from 90 participants in 1 studies. (Randomized controlled) | Difference: | **MD 0.84 higher** ( CI 95% 0.48 higher — 1.2 higher ) | **Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious indirectness [9] | MDMA-assisted psychotherapy may improve self-organisation/ emotional regulation, but the evidence is very uncertain. |
| **Depression symptoms** 18 weeks 7 Critical | Measured by: Beck Depression Inventory (BDI-II) Scale: 0 — 63 Lower better Based on data from 137 participants in 4 studies. (Randomized controlled) | Difference: | **MD 11.13 lower** ( CI 95% 2.92 lower — 19.35 lower ) | **Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [10] | MDMA-assisted psychotherapy may reduce depression symptoms but the evidence is very uncertain. |
| **Productivity** 6 Important | | | | | No studies were found that looked at productivity. |
| **Anxiety symptoms** 6 Important | | | | | No studies were found that looked at anxiety symptoms. |
| **Sleep quality** 18 weeks 6 Important | Measured by: Pittsburgh Sleep Quality Index (PSQI) Scale: 0 — 21 Lower better Based on data from 46 participants in 3 studies. (Randomized controlled) | Difference: | **MD 3.67 lower** ( CI 95% 7.7 lower — 0.36 higher ) | **Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [11] | MDMA-assisted psychotherapy may improve sleep quality slightly but the evidence is very uncertain. |



1. including suicidal ideation and non-suicidal self-injurious behaviour
2. **Risk of Bias: serious.** There have been concerns about inadequate/lack of blinding of participants and therapists due to MDMA's psychoactive effects, which could lead to potential performance and detection biases, even with blinded outcome assessors. In the MAPP2 study, 94.2% and 75% of participants in the intervention and control groups, respectively, guessed their assignment correctly. Since most of the measurement tools used in the trials involved patient-reported outcomes, this functional unblinding might have increased participants' expectancy, potentially leading to an underestimation of harms. Additionally, there are reports of participants feeling pressured to not disappoint others in the 'community' given the high hopes on MDMA-AP being a new treatment option and concerns that therapists might encourage positive reports and discourage negative ones, which may have caused under-reporting of harms.. **Inconsistency: no serious.** No serious concerns. Consistent effects in both studies (CI overlap, I2 = 0%, p = 0.63). **Indirectness: serious.** Research shows people with PTSD have a higher risk of suicidal thoughts, suicide attempts, and suicide. About 14% of trauma survivors and nearly one in three people with PTSD have reported a suicide attempt. The safety profile of MDMA-AP in individuals with increased/ active suicidality remains unknown due to their exclusion from trials.. **Imprecision: serious.** 95% CI's include both an important benefit and important harm (assuming 1% threshold for suicidal ideation and 0.1% threshold for suicide/ suicide attempt); only 14 events reported across both arms (6 in MDMA-AP; 8 in control group). **Publication bias: serious.** Strongly suspected (-1). The index SR, Colcott (2024), reported discrepancies between the adverse events reported on ClinicalTrial.gov versus those in published articles: 56% of non-serious and 31% of serious adverse events recorded on ClinicalTrial.gov were not reported in published articles. For instance, there were 13 serious adverse events recorded on ClinicalTrial.gov but only 9 in published articles, including an event of suicide behaviour in the MDMA-AP arm..
3. **Risk of Bias: serious.** There have been concerns about inadequate/lack of blinding of participants and therapists due to MDMA's psychoactive

effects, which could lead to potential performance and detection biases, even with blinded outcome assessors. In the MAPP2 study, 94.2% and 75% of participants in the intervention and control groups, respectively, guessed their assignment correctly. Since most of the measurement tools used in the trials involved patient-reported outcomes, this functional unblinding might have increased participants' expectancy, potentially leading to an underestimation of harms. Additionally, there are reports of participants feeling pressured to not disappoint others in the 'community' given the high hopes on MDMA-AP being a new treatment option and concerns that therapists might encourage positive reports and discourage negative ones, which may have caused under-reporting of harms; Electrocardiogram was not routinely monitored after MDMA dosing in the phase 2 and 3 studies, potentially leading to under-reporting of cardiac events. **Inconsistency: serious.** Inconsistent effects across studies. **Indirectness: serious.** The safety profile of MDMA-AP in individuals with increased cardiovascular risks remains unknown because people with history of any medical condition that could make receiving a sympathomimetic drug harmful were excluded from trials. This included those with current uncontrolled essential hypertension, a history of arrhythmia, any history of ventricular arrhythmia, and Wolff-Parkinson-White syndrome or any other accessory pathway that had not been successfully eliminated by ablation.. **Imprecision: serious.** 95% CI's include both an important harm and a negligible effect; only 6 events reported across both arms (4 in MDMA-AP; 2 in control group). **Publication bias: serious.** Strongly suspected. The index SR, Colcott (2024), reported discrepancies between the adverse events reported on ClinicalTrial.gov versus those in published articles: 56% of non-serious and 31% of serious adverse events recorded on ClinicalTrial.gov were not reported in published articles. For instance, there were 13 serious adverse events recorded on ClinicalTrial.gov but only 9 in published articles, including an event of suicide behaviour in the MDMA-AP arm.

4. **Risk of Bias: serious.** There have been concerns about inadequate/lack of blinding of participants and therapists due to MDMA's psychoactive effects, which could lead to potential performance and detection biases, even with blinded outcome assessors. In the MAPP2 study, 94.2% and 75% of participants in the intervention and control groups, respectively, guessed their assignment correctly. Since most of the measurement tools used in the trials involved patient-reported outcomes, this functional unblinding might have increased participants' expectancy, potentially leading to an underestimation of harms. Additionally, there are reports of participants feeling pressured to not disappoint others in the 'community' given the high hopes on MDMA-AP being a new treatment option and concerns that therapists might encourage positive reports and discourage negative ones, which may have caused under-reporting of harms. Unblinding might increase participant's expectancy towards the treatment, leading to higher treatment continuation among those who believed they were in the MDMA-AP group and higher dropout among those who believed they were in the control group.. **Inconsistency: no serious.** Consistent effects across studies (CI overlap). **Indirectness: no serious. Imprecision: serious.** 95% CI's include both an important benefit and a little or no effect (assuming 10% threshold). **Publication bias: serious.** (same as the reason(s) provided for Suicidality).

5. **Risk of Bias: serious.** (same as the reason(s) provided for Suicidality). **Inconsistency: no serious.** Consistent effects across studies (CI overlap). **Indirectness: serious.** Individuals with PTSD often have co-morbidities such as substance use disorders (65% of men and 32% of women), personality disorders (4-28%), and psychotic symptoms (over 30%). There are concerns that adverse events may be underestimated because the trials did not include people with these common co-morbidities.. **Imprecision: no serious.** Assuming 50 in 1000/ 5% as threshold for an important effect). **Publication bias: serious.** Strongly suspected (same as the reason(s) provided for Suicidality).

6. **Risk of Bias: serious.** (same as the reason(s) provided for Suicidality). **Inconsistency: no serious. Indirectness: serious.** Individuals with PTSD often have substance use disorders (65% of men and 32% of women). The safety profile of MDMA-AP in individuals with increased risk of MDMA misuse remains unknown due to their exclusion from trials, including people with active illicit (other than cannabis)/ prescription drug substance use disorder at any severity within the past 12 months. In addition, there are serious concerns that the measurement of the outcome was insufficient (addressed under publication bias).. **Imprecision: serious.** No events were reported.. **Publication bias: serious.** strongly suspected (-1). Even though MDMA abuse/misuse was identified as adverse events of special interests in Phase 3 clinical trials, there was limited data collection. Lykos Therapeutics was advised by US FDA to systematically record adverse events that were considered "neutral, positive, or favourable" because drug effects that may have been perceived as positive (such as euphoria, stimulation, or somnolence) could indicate drug-liking and would be important for the assessment of misuse potential. However, this was not done during the Phase 3 trials (Food and Drug Administration, 2024)..

7. **Risk of Bias: serious.** There have been concerns about inadequate/lack of blinding of participants and therapists due to MDMA's psychoactive effects, which could lead to potential performance and detection biases, even with blinded outcome assessors. In the MAPP2 study, 94.2% and 75% of participants in the intervention and control groups, respectively, guessed their assignment correctly. This functional unblinding might have increased participants' expectancy, potentially leading to an overestimation of benefits. Additionally, there are reports of participants feeling pressured to not disappoint others in the 'community' given the high hopes on MDMA-AP being a new treatment option and concerns that therapists might encourage positive reports and discourage negative ones, which may have influenced the reporting of benefits and harms. **Inconsistency: no serious.** No evidence of significant heterogeneity; All studies overlap (CI overlap, I2 = 0%, p = 0.87). **Indirectness: no serious.** Some are concerned that effects may differ among people with no experience of MDMA (40% of trial participants had a history of illicit MDMA use; 22% in the past 10 years). Long-term recreational use of ecstasy/MDMA may result in neurotoxicity, chronic tolerance, and lasting changes in cognition, memory, and broader neurobiological functions, particularly serotonergic pathways. However, the specific level and duration of exposure required to cause these effects remain uncertain. Changes appear to be more closely associated with the environmental factors of repeated recreational use rather than the controlled, repeated dosing employed in research settings. Subgroup analysis (index SR, Mustafa 2024) did not support indirectness, finding no important difference in in CAPS-5 between subgroups with a history of MDMA (MD -10.9 [-16.9, -5.0], n=94) and MDMA-naive (MD-9.5 [-14.5, -4.6], n=79).. **Imprecision: serious.** The upper and lower bound of the 95% CI of the SMD are above the typical threshold used for an important effect (assuming SMD 0.4 as a threshold), suggesting no imprecision. However, when re-expressed on the CAPS-5 scale, the 95% CI crosses the threshold for a minimally important difference (using an MID on CAPS-5 of 10-points), so is compatible with benefit (17 point reduction) and a trivial effect (9 point reduction) (assuming population SD of 15 on CAPS-5). A sensitivity analysis of trials that used the CAPS-5 score showed an effect size of MD=−9.65 [−13.13 to −6.16]. This result falls short of the MID of a 10-points, and the confidence interval overlaps the threshold for little to no clinically meaningful benefit.. **Publication bias: no serious.** Publication bias: undetected. Mustafa (2024) conducted a systematic search of MDMA trials on ClinicalTrials.gov and identified three phase 2 trials that were reported in the clinical trial registry, but not published in peer-reviewed journals: MP-3/ NCT00402298 (terminated early), MP-4/NCT01958593 (terminated early), and MP-9/NCT01689740 (included in meta-analysis of this Guideline). Since MP-3 and MP-9 only had 10 participants in total, inclusion of their results in the meta-analyses is unlikely to cause notable change to the summary effect estimate. Hence, there is unlikely to be publication bias due to missing results..

8. **Risk of Bias: serious.** (same as the reason(s) provided for PTSD symptoms). **Inconsistency: no serious.** No serious concerns. Consistent effects across studies (CI overlap, I2 = 19%, p = 0.3). **Indirectness: no serious.** (same as the reason(s) provided for PTSD symptoms). **Imprecision: serious.** 95% CI crossed the threshold for an important effect, and so was compatible with both an important benefit and little or no effect (assuming SMD>0.4 as threshold). **Publication bias: no serious.** (same as reason(s) provided for PTSD symptoms).
9. **Risk of Bias: serious.** (same as the reason(s) provided for PTSD symptoms). **Inconsistency: no serious. Indirectness: serious.** Single small study and it is uncertain whether similar effects would be seen in other populations.. **Imprecision: serious.** Data from a single small study, showing a large effect (review information size not met).. **Publication bias: no serious.** Not detected (same as the reason(s) provided for PTSD symptoms).
10. **Risk of Bias: serious.** (same as the reason(s) provided for PTSD symptoms). **Inconsistency: serious.** Even though CIs of all studies overlap, there is significant statistical heterogeneity (I2 = 72%, p = 0.008). While the overall effect size shows an important benefit, the results are mixed: three studies suggest an important benefit, while one suggests no important effect. **Indirectness: no serious.** (same as the reason(s) provided for PTSD symptoms). **Imprecision: serious.** 95% CI crossed the threshold for an important effect, and so was compatible with both an important benefit and little or no effect (assuming 3-point change in BDI-II score as threshold). **Publication bias: no serious.** Not detected (same as the reason(s) provided for PTSD symptoms).
11. **Risk of Bias: serious.** (same as the reason(s) provided for PTSD symptoms). **Inconsistency: serious.** Even though CIs of all studies overlap, there is significant statistical heterogeneity (I2 = 65%, p = 0.07). While the overall effect size shows little or no benefit, the results are mixed: one study suggests an important benefit, while two suggests little or no benefit.. **Indirectness: no serious.** (same as the reason(s) provided for PTSD symptoms). **Imprecision: serious.** 95% CI crossed the threshold for an important effect, and so was compatible with both an important benefit and little or no effect (assuming a 5-point change in PSQI as threshold; the result is still imprecise if a lower threshold of 3 points is used). **Publication bias: no serious.** (same as the reason(s) provided for PTSD symptoms).

Only in research settings

**Recommendation 2** (draft pending NHMRC approval)

Do not use MDMA-AP for the treatment of PTSD outside of clinical trials with appropriate ethical approval in people less than 18 years old.



### Rationale

The GDG members agreed on a Research-only Recommendation for the use of MDMA-AP in people less than 18 years old. Since existing clinical trials for MDMA-AP in PTSD excluded people less than 18 years old, the possible risks and safety for this population could not be determined due to the absence of data. 11/12 voted for 'research only recommendation'; 1/12 voted for 'conditional recommendation for use'.

The chairs suggested that in the absence of existing evidence, a recommendation to use an intervention 'only in a research setting' could be made when the research has real potential to reduce uncertainty about the beneficial and harmful effects of the intervention, and the research is acceptable and feasible *[118]*. A RCT is the study design most likely to achieve this, because non-randomised studies are likely to generate low or very low certainty evidence. However, some GDG members expressed concerns about limiting research to RCTs, noting that the field is still in its infancy. Other study designs may be necessary to first generate preliminary data on safety and feasibility before RCTs can be conducted. Restricting research to RCTs alone was perceived to potentially hinder progress and limit opportunities for researchers to explore this emerging area. One GDG member also highlighted that without initial pilot safety and feasibility data, securing funding for larger randomised trials is challenging. A decision was made to amend the language of the recommendation to remove 'randomised' from clinical trials to allow other types of research studies. This could include qualitative research, conducted alongside a pilot randomised trial, to examine views on the treatment and outcome assessment, including whether MDMA-AP is acceptable and feasible.

The GDG members also discussed the limitations of setting an explicit age threshold (i.e., 18 years) because it may delay access to a potential treatment option that some younger patients and their families are actively seeking, particularly at a critical stage in their lives (i.e., at 16 or 17 years). One member raised the caveat that a patient may wait to turn 18 years old to access a treatment [MDMA-AP] that was not guaranteed to work.

Only in research settings

**Recommendation 3** (draft pending NHMRC approval)

Do not use MDMA-AP for the treatment of PTSD outside of clinical trials with appropriate ethical approval in people who 1) have not had PTSD symptoms for at least 6 months duration post-diagnosis; 2) did not have at least moderate PTSD symptoms in the past month (CAPS-5 total severity score ≥28); 3) have not received an adequate trial of first-line evidence-based treatments; or 4) are likely to be re-exposed to the index or other significant trauma during treatment.

### Rationale

The GDG members agreed on a 'Research-only Recommendation' because the possible risk and safety beyond this population cannot be determined due to the absence of data. 10/11 voted for 'research-only recommendation'; 1/11 voted for 'conditional recommendation against'.

Existing Phase 3 clinical trials for MDMA-AP in PTSD included people who have had PTSD symptoms for at least 6 months duration and have at least moderate PTSD symptoms in the past month (CAPS-5 total severity score ≥28). The GDG suggested the inclusion of 'Research Recommendations' on the safety and efficacy of MDMA-AP in specific populations currently excluded from clinical trials.

The chairs suggested that a 'research-only recommendation' would allow the collection of data in population groups currently excluded from clinical trials, with the potential to inform and revise the recommendation as new evidence emerges. The chairs clarified that a 'research-only recommendation' would essentially be a 'strong recommendation against', but allows people to access MDMA-AP via trials. Some GDG members were concerned that a 'research-only recommendation' may restrict access to clinical trials only. Other members clarified that the restriction would only apply to populations where there are no existing data, whereas patients who meet the severity and 6-month duration post-diagnosis criteria would still be able to access the treatment outside of clinical trials. The chairs suggested that the GDG could make separate 'Research Recommendations' to address the inclusion of excluded populations in future clinical trials.

Some GDG members agreed that evidence is limited as trials have primarily been conducted in patients with 'treatment-resistant' PTSD. The lack of a clear definition of treatment resistance in PTSD was discussed. It was determined to be difficult to define "adequate trial" or suggest a minimum number of sessions of first-line treatment because some patients might not be able to tolerate first-line treatments, such as prolonged exposure. Several members supported reserving MDMA-AP for patients who have exhausted other treatment options, given the low certainty of existing evidence. On the other hand, some members raised concerns that individuals with more severe or complex PTSD might face greater risks of negative outcomes from MDMA-AP, and hence, MDMA-AP may be safer in people with moderate symptoms. GDG members discussed the need for further research in less severe populations.

There was a discussion on whether MDMA-AP should be limited only to people who have had PTSD symptoms for "at least 6 months". Some members felt that specifying a fixed duration placed an unfair value judgement on an individual's symptom severity without considering the impacts and risks of the PTSD on an individual. Some members argued that there might be potential benefits in offering the treatment at an earlier phase of PTSD to prevent the symptoms from worsening. These members suggested that rather than imposing a fixed time frame, treatment eligibility could be guided by symptom severity, as measured by CAPS-5 scores. The chairs explained that the 6-month limitation used in clinical trials may be related to the requirement for patients to have tried and not responded to other treatments. Some members agreed that a 6-month time frame was reasonable to allow patients try other established first-line treatments, hence ensuring MDMA-AP was not being used as a first-line treatment. It was highlighted that if the six-month time frame was not stated, MDMA-AP might be used within six months of diagnosis, for which there was currently no research evidence. The 6-month limit was also perceived to be important to avoid over-recommending MDMA-AP as a first-line treatment to patients who may remit without treatment or respond to established evidence-based and less expensive treatments.

There was a discussion on the rationale of excluding individuals who are "likely to be re-exposed to their index trauma or other significant trauma" from clinical trials. Some lived experience members questioned the need for the criterion because triggers could occur throughout the MDMA-AP treatment course (e.g., the use of PTSD assessment tools). Another GDG member commented that "re-exposure" was considered as an exclusion criterion for clinical trials due to safety reasons. Instead of people at risk of being re-exposed to trauma being offered MDMA-AP, the GDG determined that a higher priority would likely be to ensure a safe environment and support system for patients (e.g., for exposure related to combat PTSD, domestic violence). This might better prepare people for subsequent MDMA-AP if required.

Strong recommendation against

**Recommendation 4** (draft pending NHMRC approval)

For people living with PTSD, the Guideline Development Group strongly recommends against the use of MDMA-AP in patient groups who have been excluded from existing clinical trials for safety reasons. These patient groups include but are not limited to those who are pregnant or breastfeeding, with cardiovascular disease (e.g., uncontrolled hypertension, cardiac arrhythmia), psychotic disorder, suicide-related distress (i.e., currently experiencing suicidal thoughts and/or behaviour), and people with current use of medications that may interact with MDMA.

### Rationale

The GDG members agreed on a 'strong recommendation against' the use of MDMA-AP in the listed patient groups because the safety profile had not been established in clinical trials, and these conditions are considered too high-risk to warrant the use of MDMA-AP. 9/12 voted for 'strong recommendation against'; 2/12 voted for 'conditional recommendation against'; 1/12 voted for 'conditional recommendation for'.

The GDG initially considered whether to make a strong recommendation against the use of MDMA-AP in all populations excluded from clinical trials. Following the discussion summarised below, two separate recommendations were made. Recommendation 4 includes a more concise list of contraindications, specifically recommending against the use of MDMA-AP in populations with significant safety concerns. Other population groups excluded from existing clinical trials are considered in Research Recommendation 8.

The GDG members suggested stratifying the exclusion criteria into 'strong', 'conditional', and 'research-only recommendations' based on the level of risk and safety concerns.

There was a suggestion to change "serious suicide risk" to "people in suicide distress" or "at imminent risk of suicide". Some members were concerned that the word "serious" might oversimplify the complexity of suicide risk, which is dynamic and can fluctuate rapidly. This may lead to patients being unfairly excluded from accessing MDMA-AP. One GDG member shared that suicide risk stratification (e.g., high, medium, low) is increasingly viewed as unhelpful, because international studies have shown that 82-85% of people who die by suicide were assessed as "low or no risk" at last contact - an issue known as the "low risk paradox". While some members observed that people who have suicidal ideation or behaviours may choose to receive MDMA-AP in the hope of improving symptoms, others raised concerns that if the treatment does not provide the anticipated relief, it might exacerbate the risks for these patients.

Practice Statement

The Good Practice Statements represent the consensus of the Guideline Development Group and were developed based on the GRADE Evidence-to-Decision Framework for the benefits and harms of MDMA-AP, review of the Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Memorandum 'Therapeutic use of MDMA for PTSD and Psilocybin for Treatment Resistant Depression', and interviews with an Expert Group of clinicians, researchers, or patients with direct experience of MDMA-AP or PTSD.

## Prior to initiating MDMA-AP

**Good Practice Statement 1**

People living with PTSD have varying values, preferences, and lived experiences that should be central to the planning and delivery of MDMA-AP. Trauma-informed, participatory, and culturally-responsive care should be planned using a shared decision-making approach between the clinicians and patients. Care should be responsive to the needs of individuals from diverse cultural backgrounds, neurodivergent communities, and other priority populations.

**Good Practice Statement 2**

Prior to initiating MDMA-AP, appropriate medical, psychiatric, psychological, financial, and social screening should be conducted to maximise potential benefits and minimise potential harms. The screening process should be documented in appropriate records.

**Good Practice Statement 3**

Prior to initiating MDMA-AP, the treating psychiatrist is responsible for explaining to potential patients that the current evidence on the efficacy and safety of MDMA-AP is limited. The treating psychiatrist should also discuss the probability of treatment effectiveness and adverse events based on the clinical trial results. Potential patients should be provided with comprehensive information about what to expect before, during, and after treatment. Clinicians and people with lived experience of PTSD reported that some patients who have trialled established PTSD treatments without success may overestimate potential benefits and minimise potential risks.

**Good Practice Statement 4**

Prior to initiating MDMA-AP, the treating psychiatrist should obtain written informed consent from potential patients. This consent should address likely benefits and harms of treatment (including rare but serious adverse events); potential physical, psychological, and financial risks; and what to expect before, during, and after treatment. The psychiatrist is responsible for ensuring that any actual or potential conflicts of interest related to their association with companies that manufacture, market, or promote MDMA are declared to the patient. Obtaining informed consent should be treated as an ongoing process, with regular review and adaptation based on the patient's evolving needs and experiences. The consent should be documented in appropriate records.

**Good Practice Statement 5**

Patients should be given the option to involve a support person (such as a next of kin, family member, carer, or advocate) before and after treatment, including during the process of obtaining informed consent.

**Good Practice Statement 6**

Prior to initiating MDMA-AP, the treating psychiatrist should explore patient preferences around supportive touch. Evidence is lacking about the value of supportive touch during MDMA-AP. There are important ethical and clinical considerations related to supportive touch. MDMA may heighten suggestibility, increase the perceived pleasantness of touch, and impair a patient's capacity to provide or withdraw consent during dosing sessions. It is likely that people living with PTSD have variable values and preferences in relation to supportive touch. Clear boundaries, guided by patient preference, should be established during the informed consent process. This should be followed by a dynamic and ongoing consent process throughout treatment. In situations where supportive touch is offered, therapists must have received appropriate training in its ethical and therapeutic application.

## When providing MDMA-AP

**Good Practice Statement 7**

To ensure continuity of care, people who provide MDMA-AP should do so in consultation with the person's regular healthcare providers (e.g., general practitioners, psychologists, psychiatrists, therapists). MDMA-AP should be integrated into, rather than replace, a patient's broader treatment plan. Where possible, a designated provider (such as the patient's usual general practitioner) should remain primarily responsible for overall patient care.

**Good Practice Statement 8**
All clinicians involved in the delivery of MDMA-AP should develop a strong therapeutic alliance with patients prior to and throughout MDMA-AP for building trust, ensuring emotional safety, and supporting the effectiveness of therapy.

**Good Practice Statement 9**
Safeguarding measures should be implemented during MDMA-AP sessions, including ensuring that only authorised personnel are present during dosing sessions, video-recording sessions where appropriate for accountability, and having two trained therapists in the room during dosing sessions. The presence of two therapists is recommended as a risk mitigation strategy to provide a safeguard for both patients and therapists in the event of any concerns or allegations of misconduct.

**Good Practice Statement 10**
Clinics delivering MDMA-AP should ensure the presence of appropriately trained personnel, such as medical doctors, to oversee medical or pharmacological interventions in managing adverse events. Appropriate clinical support should be rapidly available in case of medical emergencies

**Good Practice Statement 11**
Clinicians should advise patients that MDMA may impair the ability to drive or operate heavy machinery. Patients should be informed of, and comply with, relevant State legislation regarding not driving under the influence of MDMA.

## Post-treatment care

**Good Practice Statement 12**
Patients should only leave the treatment clinic once the acute effects of MDMA have fully worn off. This involves clinically assessing vital signs, level of awareness, mental stability, and ensuring a prearranged support person is available to accompany the patient home.

**Good Practice Statement 13**
A comprehensive communication plan should be developed to facilitate the patient's transition back to routine care after MDMA-AP treatment. People with lived experience report the importance of setting clear expectations from the outset of treatment. This includes discussion around the possible option to continue care with the therapist from MDMA-AP with whom a strong therapeutic alliance has been established. Clinicians should discuss potential post-treatment care models (such as peer support groups, group integration sessions, or regular check-ins with clinicians) to provide patients with ongoing support after completing MDMA-AP.



## Education and training

**Good Practice Statement 14**
The Guideline Development Group recognises that evidence in relation to MDMA-AP is rapidly evolving and there is potential value in a living evidence approach to future guideline development. Clinicians and people living with PTSD should make themselves familiar with the current best available research about possible benefits and harms as the basis for treatment decision-making.

**Good Practice Statement 15**
The Guideline Development Group concurs with the Royal Australian and New Zealand College of Psychiatrists (RANZCP) that the clinicians involved in the delivery of MDMA-AP should be registered with the Australian Health Practitioner Regulation Agency (AHPRA) or their equivalent governing body and operate within their recognised scope of practice.

**Good Practice Statement 16**
Clinicians involved in the delivery of MDMA-AP should complete specific training. Psychiatrists should follow the Psychedelic Training Framework for Psychiatrists developed by the RANZCP. There is a need for formal and independent regulation or credentialing of training programs for psychiatrists and other clinicians to ensure consistent quality and standards for the delivery of MDMA-AP.

**Good Practice Statement 17**
Training should be available for the broader healthcare workforce to increase awareness and understanding of MDMA-AP, provide relevant and evidence-based information, and support making appropriate referrals. People with lived experience of PTSD emphasise the importance of clinician awareness, particularly among primary healthcare professionals who have an important role in providing evidence-based information to people with PTSD.

**Good Practice Statement 18**
Patient information about MDMA-AP should be provided in a format that is accessible to different target populations, including culturally and linguistically diverse (CALD) communities, Aboriginal and Torres Strait Islander peoples, and emergency service workers. With permission, this information should also be made available to the patient's support person.

### Rationale

**Good Practice Statement 1 (Shared decision-making)**
GDG members emphasised the importance of patient engagement during pre-treatment consultation. Drawing on lived experience perspectives can support a participatory and collaborative process between clinicians and patients to create a care plan that fits each patient's preferences. GDG members discussed that patient preferences around supportive touch should be explicitly discussed in advance of dosing to ensure that care is compassionate, trauma-informed, age-, and culturally-appropriate.

**Good Practice Statements 3 & 5 (Involvement of support person)**
The GDG members discussed the importance of involving the person's carer/support system/ advocate during the process of explaining the potential risks, safety, and efficacy. Some GDG members highlighted the legal considerations and the need to document the informed consent process to ensure that the patient is fully-informed.

**Good Practice Statements 6 (Supportive touch)**
There was a discussion on how 'supportive touch' should be addressed in the Guideline. While the Lykos/MAPS clinical trial protocols permitted supportive touch, some GDG members noted that these protocols may not be the most appropriate reference for establishing clinical practice standards. There is a lack of evidence on the use of supportive touch and it is not commonly practised in Australian settings. Some GDG members suggested that the Guideline could exclude the information on the practice of supportive touch until further evidence becomes available, while others argued that because these practices are already in use in clinical settings, it is important to acknowledge them while emphasising the need for evidence-informed protocols and adequate training. It was suggested that the statement should explicitly explain the risks and ethical concerns surrounding the use of supportive touch due to MDMA's direct pharmacological effects (e.g., enhancing the pleasantness of touch). Hence, there is a need for trauma-informed practice around the use of touch. Some GDG members supported the use of supportive touch, provided that the therapists have undergone proper training (e.g., somatic psychotherapy). A lived experience member shared a case where the patient gave permission for supportive touch, but the therapist was uncomfortable providing it - an example where insufficient training caused harm rather than benefit. One member discussed the broader importance of integrating body-mind approaches into clinical practice, particularly in the context of trauma therapy, to treat the whole person rather than just the symptoms. Some GDG members with lived experience suggested that family members and carers should be involved in discussions and consent process about the use of touch to ensure transparency.

**Good Practice Statements 9 (Safeguard measures)**
The GDG members discussed the role and the gender dynamics of the male-female 'dyad' commonly adopted in previous clinical trials of MDMA-AP. Some members with lived experience suggested that rather than focusing on the gender of the dyad, greater attention should be paid to the qualifications and training of the practitioners, such as ensuring at least one of them is trained in somatic psychology. From a legal perspective, the use of the dyad was discussed as a safeguard not only for the patient, but also for the clinicians, in the event of potential allegations of misconduct. It was noted that while the MAPS treatment manual used two co-therapists of opposite gender for preparation, dosing, and integration sessions; there are other ongoing trials exploring the use of single therapists for certain components of the treatment. Some members cautioned that the Guideline should not be seen as endorsing the MAPS protocols, but rather remain open to their potential limitations and be guided by ongoing developments in empirical evidence.

**Good Practice Statements 15 (Professional registration of clinicians)**
Some members noted that specifying Australian Health Practitioner Regulation Agency (AHPRA) registration might be too restrictive, as some practitioners involved in this work are licensed counsellors who are registered with the Psychotherapy and Counselling Federation of Australia (PACFA) but not AHPRA.

Implications for research

**Research Recommendation 1**
It should be mandatory for data on treatment outcomes, including adverse events, to be collected using a systematic and structured approach and recorded in an independently funded registry. With appropriate privacy safeguards in place, registry data should be made available for research, guideline development, and regulatory decision-making.

**Research Recommendation 2**
Further research is needed to determine the most appropriate psychotherapeutic approach to be used alongside MDMA in the treatment of PTSD. This includes evaluating whether MDMA can enhance the effectiveness of existing evidence-based psychotherapies, and identifying which therapeutic modalities or techniques are the safest and most effective when combined with MDMA.

**Research Recommendation 3**
Future research is needed to understand the extent to which symptoms may worsen before improving in people who receive MDMA-AP, and whether temporary worsening of symptoms is associated with significant distress or harm.

**Research Recommendation 4**
Evidence from current clinical trials relates to a single course (3 dosing sessions, 80-120mg MDMA with supplemental half dose at each dosing) of MDMA-AP delivered over an 18-week period. There is a lack of safety and efficacy data on the use of MDMA for a longer or shorter term or at a different dosage. Further research is needed into the benefits and harms of delivering more than one course of MDMA-AP.

**Research Recommendation 5**
Future research is needed to investigate the safety and efficacy of MDMA-AP in people with PTSD who are re-exposed to their index or other significant trauma during the course of treatment. Current clinical trials have excluded people likely to be re-exposed to trauma.

**Research Recommendation 6**
Future research is needed into the role of MDMA-AP in relation to other evidence-based treatments for PTSD, including whether earlier use of MDMA-AP may improve treatment outcomes.

**Research Recommendation 7**
Future research should explore the possible value of adapting treatment protocols according to the complexity of each patient's PTSD presentation. This may include variations in treatment duration, intervals between dosing sessions, number of dosing and integration sessions, or group integration sessions.

**Research Recommendation 8**
Future research should investigate the safety and efficacy of MDMA-AP for PTSD in the context of specific comorbid conditions for which the therapeutic value of MDMA-AP is currently being evaluated (e.g., alcohol use disorders, eating disorders without active purging, substance use disorders).

**Research Recommendation 9**
Existing phase 3 clinical trial protocols for MDMA-AP in PTSD used fixed-dose regimens and excluded individuals who weighed less than 48 kg. Further research should be conducted into the possible value of weight-based dosing (e.g,. concentration-response, pharmacokinetic-pharmacodynamic simulations).

**Research Recommendation 10**
The Guideline Development Group recognises that people from different cultures might view MDMA-AP differently. Future research should investigate the acceptability of treatment protocols for MDMA-AP in different cultural groups, including Aboriginal and Torres Strait Islander peoples.

**Research Recommendation 11**
Future research should investigate whether there is a need for tapering or discontinuation of all other medications prior to MDMA-AP. People with lived experience report significant challenges in discontinuing other mental health medications prior to MDMA-AP.

## 8. Abbreviations

| | |
|---|---|
| **APS** | Authorised Prescriber Scheme |
| **CALD** | Culturally and Linguistically Diverse |
| **CAPS-5** | Clinician-Administered PTSD Scale for DSM-5 |
| **CPT** | Cognitive Processing Therapy |
| **CT** | Cognitive Therapy |
| **EMDR** | Eye Movement Desensitisation and Reprocessing |
| **ERT** | Evident Review Team |
| **FDA** | US Food and Drug Administration |
| **GDG** | Guideline Development Group |
| **GPS** | Good Practice Statement |
| **GRADE** | Grading of Recommendations, Assessment, Development and Evaluation |
| **ICER** | Institute for Clinical and Economic Review |
| **LGBTQIA+** | Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, and Asexual + other identities |
| **MDMA** | 3,4-methylenedioxymethamphetamine |
| **MDMA-AP** | MDMA-assisted psychotherapy |
| **NHMRC** | National Health and Medical Research Council |
| **PACFA** | Psychotherapy and Counselling Federation of Australia |
| **PAT** | Psychedelic-assisted therapy |
| **PDAC** | Psychopharmacologic Drugs Advisory Committee |
| **PTSD** | Post-Traumatic Stress Disorder |
| **QALY** | Quality-Adjusted Life Year |
| **RCT** | Randomised Control Trial |
| **RoB 2** | Cochrane risk-of-bias tool for randomized trials |
| **SNRIs** | Serotonin and Noradrenaline Reuptake Inhibitors |
| **SR** | Systematic Review |
| **SSRIs** | Selective Serotonin Reuptake Inhibitors |
| **TF-CBT** | Trauma-focused Cognitive Behavioural Therapy |

**TGA** Therapeutic Goods Administration

## 9. Glossary

| Term | Definition |
|---|---|
| **Aboriginal and Torres Strait Islander peoples** | According to the High Court of Australia (1983), a person of Aboriginal or Torres Strait Islander descent who identifies as an Aboriginal or Torres Strait Islander and is accepted as such by the community in which the person lives. Also referred to as Indigenous or First Nations peoples. |
| **Adverse event** | Any undesirable experience associated with a medication or health intervention. Adverse events can be serious and result in hospitalisations, persistent disability or death. Adverse events are sometimes known as side effects. |
| **Authorised prescriber** | A medical practitioner who, in the context of this Guideline, is a psychiatrist who has been granted approval by the Therapeutic Goods Administration (TGA) to prescribe a specified unapproved therapeutic good (e.g., MDMA) to patients with particular medical conditions (e.g., PTSD). The psychiatrist must have obtained Human Research Ethics Committee (HREC) approval and operate within their scope of practice, supported by appropriate training and clinical protocols. |
| **Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)** | A 30-item semi-structured interview assessing PTSD in the past month through diagnostic and symptom severity scores anchored to a DSM-5-defined traumatic event. The CAPS-5 produces a Total Severity Score based on the severity of PTSD domains described in the DSM-5, as well as a categorical rating indicating whether a participant meets PTSD diagnostic criteria. The total symptom severity scores range from 0 to 80, with higher values indicating greater symptom severity. CAPS-5 assigns PTSD diagnosis as being present or absent. |
| **Carer / Support person** | People who provide the primary ongoing support and care in a non-professional, unpaid capacity for a person living with PTSD. The carer is generally a spouse/ partner, child, other family member, relative or friend. Not everyone in this role prefers to be referred to as 'carer' and the person's preferences should be sought before using the term. Carers are distinguished from care workers. |
| **Clinical question** | The key questions about treatment and care. The clinical question in the current Guideline was addressed by systematic reviews of the evidence. |
| **Consumers** | In the context of this Guideline, consumers are people with lived or living experience with PTSD and/or their carers. |
| **Culturally and linguistically diverse populations** | The Australian Institute of Health and Welfare has defined culturally and linguistically diverse populations as those born overseas, have a parent born overseas or who speak a variety of languages. Pham (2021) suggested that CALD status be defined according to being born in a non-English speaking country and/or not speaking English at home. |
| **Culturally-responsive care** | Culturally-responsive refers to the capacity for healthcare professionals to effectively provide healthcare services that acknowledge, respect, and meaningfully integrate patients' and families' cultural values, beliefs, and practices into care. Here, "culture" extends beyond the identification of a person's race and ethnicity to include other variables such as faith/religion, occupation, sexual orientation, region of residence, and level of acculturation, and closely related factors such as socioeconomic status and literacy level. |
| **Cultural safety** | According to the Australian Institute of Health and Welfare, cultural safety refers to healthcare that is provided in a way that is safe, accessible and responsive for individuals from all cultural backgrounds, as determined by the experience of the individual receiving care. It requires practitioners to reflect on and address their own cultural values, beliefs and attitudes that consciously or unconsciously affect their behaviours, and to actively work toward creating an environment that respects all cultural identities and addresses racism and inequity. |

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| **First-line treatment** | APA Dictionary of Psychology defines first-line treatment as an intervention (such as a specific therapy, procedure, or medication used alone or in combination) that is recommended as the initial choice for treating a particular condition. This recommendation is typically based on high-quality evidence of safety and efficacy demonstrating that it is the most effective and has the lowest likelihood of causing harm compared with other available options. |
| **Emergency services workers** | Workers who protect public health and safety by responding to and preventing emergency situations. In Australia, these include police, fire and rescue, and ambulance services, along with individuals who perform these functions in a volunteer capacity (e.g., coast guard, rural fire service). Workers and volunteers in these roles are often exposed to potentially traumatic events as part of their duties. |
| **Index trauma** | The specific traumatic event(s) used as the basis for diagnosing and assessing the severity of PTSD symptoms *[132]*. When someone has experienced multiple traumatic events, the "index trauma" can be defined as the worst single incident, or it can include up to three qualitatively distinct traumatic events. |
| **Informed consent** | A process of communication between a patient and healthcare professional about options for treatment, care processes or potential outcomes. This communication results in the patient's authorisation or agreement to undergo a specific intervention and participate in planned care. The communication should ensure that the patient has an understanding of the care they will receive, all the available options and the expected outcomes, including success rates and side effects for each option. |
| **MAPS (Multidisciplinary Association for Psychedelic Studies)** | A nonprofit organisation that 'develops medical, legal, and cultural contexts for people to benefit from the careful uses of psychedelics and marijuana'. MAPS formed Lykos Therapeutics, a drug-development public benefit company that submitted the New Drug Application for MDMA-AP to be used for adults with PTSD to the US FDA. |
| **MDMA (3,4-methylenedioxymethamphetamine)** | A synthetic compound classified as an entactogen or empathogen (a compound that increases feelings of empathy or connectedness with others), with minor psychedelic properties. Also known as midomafetamine (the United States Adopted Name, USAN), and colloquially as ecstasy. |
| **MDMA-Assisted Psychotherapy** | A combined pharmacologic and psychotherapeutic intervention, in which MDMA is administered as an adjunct to psychotherapy sessions to enhance therapeutic outcomes. A course of treatment typically includes preparatory sessions, active dosing session(s) where MDMA is administered, and integration sessions. Also known as MDMA-assisted therapy. |
| **Post-Traumatic Stress Disorder (PTSD)** | DSM-5 and ICD-11 diagnostic criteria describe PTSD as a trauma- and stressor-related disorder that develops following exposure to a threatening or horrific event or series of events (e.g., actual or threatened death, serious injury, or sexual violence). PTSD is characterised by symptoms including re-experience the traumatic event(s) (e.g., intrusive memories, flashbacks, nightmares), avoidance of reminders, and a persistent sense of current threat (e.g. hypervigilance, alterations in arousal/reactivity). The DSM-5 additionally describes negative alterations in cognition and mood (e.g., persistent negative beliefs, emotional numbness). These symptoms cause significant distress or impairment in functioning. |
| **Psychedelics** | Psychedelics (also known as hallucinogens) are a class of psychoactive substances that produce changes in perception, mood and cognitive processes. Examples of psychedelics include psilocybin, ayahuasca, LSD, DMT, NBOMes, and mescaline. MDMA is classified as an empathogen or entactogen, but for simplicity, it will be referred to as a psychedelic throughout this Guideline. |
| **Randomised controlled trial (RCT)** | A prospective study design used to evaluate the effectiveness of an intervention or treatment. Participants are randomly assigned to either the intervention or comparator group, which balances participant characteristics and reduces bias. |

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| | The study population, interventions and outcomes are carefully selected, and experimental conditions are often blinded. RCTs are generally considered to provide the strongest level of evidence below a systematic review. |
| **Safeguard measures** | Actions taken to protect the rights and dignity of people living with mental illness or psychological distress. |
| **Shared decision making** | A collaborative and participatory process in which clinicians and patients work together to make healthcare decisions and develop a care plan that aligns with the patient's individual preferences, values, and goals. |
| **Supportive touch** | Physical contact intended to communicate empathic care to participants during psychedelic-assisted dosing/experimental sessions. This is different from safety, procedural, and therapeutic forms of touch found in other healthcare disciplines, and is not intended to have direct healing purposes beyond empathic support *[133]*. |
| **Trauma-informed care** | The Australian Institute of Family Studies defined trauma-informed care as a framework for human service delivery that is based on knowledge and understanding of how trauma affects people's lives, their service needs and service usage. |
| **Veterans** | According to the Australian Institute of Health and Welfare, veterans are people who have any experience in the Australian Defence Force, including permanent, reserve, and former (ex-serving) personnel. Australian Defence Force members have unique experiences as a result of their service in the military, which can influence their health and wellbeing relative to the rest of the Australian population. |

## 10. Supporting Guideline Reports

### Dissemination and Implementation Plan
The detailed Dissemination and Implementation Plan can be found HERE.

### Administrative Report
Non-technical information relating to the Guideline development process can be found in the Administrative Report HERE.

### Technical Reports
Technical Report 1 - Evidence Review of Benefits and Harms of MDMA-AP for PTSD

Technical Report 2 - Evidence Review of Evidence-to-Decision Framework Domains

# References

1. Coventry PA, Meader N., Melton H., Temple M., Dale H., Wright K., et al. Psychological and pharmacological interventions for posttraumatic stress disorder and comorbid mental health problems following complex traumatic events: Systematic review and component network meta-analysis. PLoS Med 2020;17(8):e1003262 Pubmed Journal

2. Food and Drug Administration. FDA Briefing Document: Psychopharmacologic Drugs Advisory Committee Meeting. null: (null) 2024. Website

3. Phoenix Australia. Australian Guidelines for the Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder, and Complex PTSD. 2020.

4. Mustafa RA, McQueen B, Nikitin D, Nhan E, Zemplenyi A, DiStefano MJ, et al. MDMA-Assisted Psychotherapy for Post-Traumatic Stress Disorder: Effectiveness and Value. null: (Evidence Report.) 2024. Website

5. Alonso-Coello P, Oxman AD, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. Gaceta sanitaria 2017;32(2):167. e1-167. e10

6. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. BMJ 2016;353:i2016 Journal Website

7. Andrews J., Guyatt G., Oxman AD, Alderson P., Dahm P., Falck-Ytter Y., et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66(7):719-25 Pubmed Journal

8. Australia Universities. Australian code for the responsible conduct of research. null: (null) 2018.

9. Australian Bureau of Statistics. National Study of Mental Health and Wellbeing. (null) 2020-2022. Website

10. Australian Indigenous Doctors' Association. Cultural Awareness – Online Training. Website

11. Australian Institute of Health and Welfare. Stress and trauma. (null) 2024. Website

12. Bahji A., Forsyth A., Groll D., Hawken ER. Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology & Biological Psychiatry 2020;96:109735 Pubmed Journal Website

13. Bahji A., Lunsky I., Gutierrez G., Vazquez G.. Efficacy and Safety of Four Psychedelic-Assisted Therapies for Adults with Symptoms of Depression, Anxiety, and Posttraumatic Stress Disorder: A Systematic Review and Meta-Analysis. J Psychoactive Drugs 2023;1-16 Pubmed Journal Website

14. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. Journal of clinical

epidemiology 2011;64(4):401-406

15. Barnett BS, Beaussant Y., King FT, Doblin R.. Psychedelic Knowledge and Opinions in Psychiatrists at Two Professional Conferences: An Exploratory Survey. J Psychoactive Drugs 2022;54(3):269-277 Pubmed Journal Website

16. Barnett BS, Siu WO, Pope HGJ. A Survey of American Psychiatrists' Attitudes Toward Classic Hallucinogens. J Nerv Ment Dis 2018;206(6):476-480 Pubmed Journal Website

17. Berger JJ, Fitzgerald PB. The prescription of psychedelic therapies in Australia and New Zealand: A brief survey of psychiatrists. Australas Psychiatry 2023;31(2):190-194 Pubmed Journal Website

18. Bisson JI, Berliner L, Cloitre M, Forbes D, Jensen TK, Lewis C, et al. The international society for traumatic stress studies new guidelines for the prevention and treatment of posttraumatic stress disorder: Methodology and development process. Journal of traumatic stress 2019;32(4):475-483

19. Black Dog Institute. Understanding post-traumatic stress disorder. 2025. Website

20. Boscarino JA. Posttraumatic stress disorder and mortality among U.S. Army veterans 30 years after military service. Ann Epidemiol 2006;16(4):248-56 Pubmed Journal

21. Braun V, Clarke V. Thematic analysis: a practical guide. (null) 2021.

22. Buchanan NT. Ensuring the psychedelic renaissance and radical healing reach the Black community: Commentary on Culture and Psychedelic Psychotherapy. Journal of Psychedelic Studies 2021;4(3):142-145 Journal Website

23. Chen JA, Keller SM, Zoellner LA, Feeny NC. "How will it help me?" Reasons underlying treatment preferences between sertraline and prolonged exposure in posttraumatic stress disorder. J Nerv Ment Dis 2013;201(8):691-7 Pubmed Journal Website

24. Colcott J., Guerin AA, Carter O., Meikle S., Bedi G.. Side-effects of mdma-assisted psychotherapy: a systematic review and meta-analysis. Neuropsychopharmacology 2024. Pubmed Journal Website

25. Commonwealth of Australia. National Strategic Framework for Aboriginal and Torres Strait Islander Peoples' Mental Health and Social and Emotional Wellbeing 2017-2023. 2017.

26. Department of Health and Aged Care. Primary Health Networks (PHNs) and Aboriginal Community Controlled Health Organisations – Guiding Principles. 2016.

27. Dewidar O, Lotfi T, Langendam MW, Parmelli E, Saz Parkinson Z, Solo K, et al. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. BMJ Evidence-Based Medicine 2023;28(3):189-196 Journal Website

28. Dupuis D.. Psychedelics as Tools for Belief Transmission. Set, Setting, Suggestibility, and Persuasion in the Ritual Use of Hallucinogens. Front Psychol 2021;12:730031 Pubmed Journal

29. Edmondson D., Kronish IM, Shaffer JA, Falzon L., Burg MM. Posttraumatic stress disorder and risk for coronary heart disease: a meta-analytic review. Am Heart J 2013;166(5):806-14 Pubmed Journal

30. Ford N., Thomas R., Grove J.. Transparency: A central principle underpinning trustworthy guidelines. J Clin Epidemiol 2022;142:246-248 Pubmed Journal

31. Fozdar F, Salter K. A review of mental ill health for culturally and linguistically diverse communities in Western Australia. null: (null) 2019. Website

32. Gagliardi AR, Berta W, Kothari A, Boyko J, Urquhart R. Integrated knowledge translation (IKT) in health care: a scoping review. Implementation Science 2016;11(1):38 Journal Website

33. Gagliardi AR, Kothari A, Graham ID. Research agenda for integrated knowledge translation (IKT) in healthcare: what we know and do not yet know.

Journal of Epidemiology and Community Health 2017;71(2):105-106 Journal Website

34. George JR, Michaels TI, Sevelius J, Williams MT. The psychedelic renaissance and the limitations of a White-dominant medical framework: A call for indigenous and ethnic minority inclusion. Journal of Psychedelic Studies 2020;4(1):4-15 Journal Website

35. Government of South Australia. Aboriginal Mental Health Clinical Practice Guideline and Pathways. 2017. Website

36. Graham ID, Tetroe JM. Getting evidence into policy and practice: perspective of a health research funder. J Can Acad Child Adolesc Psychiatry 2009;18(1):46-50 Pubmed

37. Green WM, Raut SB, James FLJ, Benedek DM, Ursano RJ, Johnson LR. MDMA-Assisted Psychotherapy Decreases PTSD Symptoms, Dissociation, Functional Disability, and Depression: A Systematic Review and Meta-Analysis. medRxiv preprint 2023. Journal

38. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. Journal of clinical epidemiology 2011;64(4):395-400

39. Heath L, Gonzales V, Luloh M, Marble Q, Henkels R, Knippenberg K, et al. MDMA-assisted therapy for post-traumatic stress disorder: Phase 2 evidence synthesis- A report to the UTAH Psychotherapy Drug Task Force. (null) 2022. Website

40. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions, null, null 2019;205-228 Journal Website

41. Hoskins MD, Sinnerton R., Nakamura A., Underwood JFG, Slater A., Lewis C., et al. Pharmacological-assisted Psychotherapy for Post-Traumatic Stress Disorder: a systematic review and meta-analysis. Eur J Psychotraumatol 2021;12(1):1853379 Pubmed Journal Website

42. Hughes ME, Garcia-Romeu A. Ethnoracial inclusion in clinical trials of psychedelics: a systematic review. eClinicalMedicine 2024;74 Journal Website

43. Illingworth BJ, Lewis DJ, Lambarth AT, Stocking K., Duffy JM, Jelen LA, et al. A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: A systematic review and meta-analysis. J Psychopharmacol 2021;35(5):501-511 Pubmed Journal Website

44. International Society for Traumatic Stress Studies. ISTSS Prevention and Treatment Guidelines. 2018. Website

45. Jellestad L, Vital NA, Malamud J, Taeymans J, Mueller-Pfeiffer C. Functional impairment in Posttraumatic Stress Disorder: A systematic review and meta-analysis. Journal of Psychiatric Research 2021;136:14-22 Journal Website

46. Jerome L., Feduccia AA, Wang JB, Hamilton S., Yazar-Klosinski B., Emerson A., et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology (Berl) 2020;237(8):2485-2497 Pubmed Journal Website

47. Jull J, Giles A, Graham ID. Community-based participatory research and integrated knowledge translation: advancing the co-creation of knowledge. Implementation Science 2017;12(1):150 Journal Website

48. Karatzias T., Murphy P., Cloitre M., Bisson J., Roberts N., Shevlin M., et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. Psychol Med 2019;49(11):1761-1775 Pubmed Journal

49. Kavanagh BE, Corney KB, Beks H., Williams LJ, Quirk SE, Versace VL. A scoping review of the barriers and facilitators to accessing and utilising mental health services across regional, rural, and remote Australia. BMC Health Serv Res 2023;23(1):1060 Pubmed Journal Website

50. Kisely S, Connor M, Somogyi AA, Siskind D. A systematic literature review and meta-analysis of the effect of psilocybin and methylenedioxymethamphetamine on mental, behavioural or developmental disorders. Australian & New Zealand Journal of Psychiatry 2023;57(3):362-378 Pubmed Journal Website

51. Kothari A, Wathen CN. A critical second look at integrated knowledge translation. Health Policy 2013;109(2):187-191 Journal Website

52. Krysinska K, Lester D. Post-Traumatic Stress Disorder and Suicide Risk: A Systematic Review. Archives of Suicide Research 2010;14(1):1-23 Journal Website

53. Kucsera A., Suppes T., Haug NA. Psychologists' and psychotherapists' knowledge, attitudes, and clinical practices regarding the therapeutic use of psychedelics. Clin Psychol Psychother 2023;30(6):1369-1379 Pubmed Journal Website

54. Kunstler B., Hatty M., Genat A., Smith L., Goodwin D., Langmead C.. Attitudes and beliefs about the medically supervised use of psychedelic medications for the treatment of mental health conditions. (null) 2022.

55. Kunstler B, Smith L, Langmead C, Goodwin D, Wright B, Hatty M. "We don't want to run before we walk": the attitudes of Australian stakeholders towards using psychedelics for mental health conditions. Public Health Research & Practice 2023;33(3) Journal

56. Louie E., Towers E., Morse AR, Watt J., Bryant Z., Haber P., et al. The Acceptability of Psychedelic-Assisted Therapy Amongst Mental Health Consumers: Utilising the Theory of Planned Behaviour. International Journal of Mental Health Nursing 2025;34(1):e70010 Pubmed

57. Lucas F. Psychedelic therapy may soon be funded for veterans with PTSD, depression. ABC News 2025. Website

58. Luoma JB, Chwyl C., Bathje GJ, Davis AK, Lancelotta R.. A Meta-Analysis of Placebo-Controlled Trials of Psychedelic-Assisted Therapy. J Psychoactive Drugs 2020;52(4):289-299 Pubmed Journal Website

59. Lykos Therapeutics. Lykos Therapeutics Announces FDA Acceptance and Priority Review of New Drug Application for MDMA-Assisted Therapy for PTSD. 2024a. Website

60. Lykos Therapeutics. Lykos Therapeutics Announces Complete Response Letter for Midomafetamine Capsules for PTSD. 2024b. Website

61. Mackey KM, Anderson JK, Williams BE, Ward RM, Parr NJ. VA Evidence-based Synthesis Program Reports. Evidence Brief: Psychedelic Medications for Mental Health and Substance Use Disorders, null, Department of Veterans Affairs (US) 2022. Pubmed

62. Mavranezouli I., Megnin-Viggars O., Daly C., Dias S., Welton NJ, Stockton S., et al. Psychological treatments for post-traumatic stress disorder in adults: a network meta-analysis. Psychol Med 2020;50(4):542-555 Pubmed Journal Website

63. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. BMC Psychiatry 2018;18(1):245 Journal Website

64. Mills V., Van Hooff M., Baur J., McFarlane AC. Predictors of mental health service utilisation in a non-treatment seeking epidemiological sample of Australian adults. Community Ment Health J 2012;48(4):511-21 Pubmed Journal Website

65. Mitchell JM, Bogenschutz M., Lilienstein A., Harrison C., Kleiman S., Parker-Guilbert K., et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med 2021;27(6):1025-1033 Pubmed Journal Website

66. Mitchell JM, Ot'alora GM, van der Kolk B., Shannon S., Bogenschutz M., Gelfand Y., et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med 2023;29(10):2473-2480 Pubmed Journal Website

67. Mocanu V., Mackay L., Christie D., Argento E.. Safety considerations in the evolving legal landscape of psychedelic-assisted psychotherapy. Subst Abuse Treat Prev Policy 2022;17(1):37 Pubmed Journal

68. Nadeem Z, Parker S, McGovern H, Oestreich LK. Attitudes toward psychedelics and psychedelic-assisted therapy among potential mental health service users and the general population in Australia. Australian & New Zealand Journal of Psychiatry 2024;58(10):904-913 Pubmed Journal Website

69. Nasir BF, Black E, Toombs M, Kisely S, Gill N, Beccaria G, et al. Traumatic life events and risk of post-traumatic stress disorder among the Indigenous population of regional, remote and metropolitan Central-Eastern Australia: a cross-sectional study. BMJ Open 2021;11(4):e040875 Journal Website

70. National Health and Medical Research Council. Guidelines for Guidelines Handbook. Website

71. National Health and Medical Research Council. 2016 NHMRC Standards for Guidelines. 2016. Website

72. National Health and Medical Research Council. Guidelines for Guidelines: Identifying and managing conflicts of interest. 2018. Website

73. National Health and Medical Research Council. Disclosure of interests and management of conflicts of interest: A guide supporting the Australian Code for the Responsible Conduct of Research. (null) 2019.

74. Neumann I., Quiñelen E., Nahuelhual P., Burdiles P., Celedón N., Cerda K., et al. Using Explicit Thresholds were valuable for judging Benefits and Harms in partially contextualized GRADE Guidelines. J Clin Epidemiol 2022;147:69-75 Pubmed Journal

75. Oehen P., Gasser P.. Using a MDMA- and LSD-Group Therapy Model in Clinical Practice in Switzerland and Highlighting the Treatment of Trauma-Related Disorders. Front Psychiatry 2022;13:863552 Pubmed Journal

76. Page LA, Rehman A., Syed H., Forcer K., Campbell G.. The Readiness of Psychiatrists to Implement Psychedelic-Assisted Psychotherapy. Front Psychiatry 2021;12:743599 Pubmed Journal Website

77. Phoenix Australia - Centre for Posttraumatic Mental Health. Specific Populations and Trauma Types: Refugee and asylum seekers. Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder, null, Phoenix Australia 2020. Website

78. Pieper D., Antoine SL, Mathes T., Neugebauer EA, Eikermann M.. Systematic review finds overlapping reviews were not mentioned in every other overview. J Clin Epidemiol 2014;67(4):368-75 Pubmed Journal

79. Psychedelic Alpha. Psychedelic Legalization & Decriminalization Tracker. Website

80. Qaseem A., Wilt TJ, Forciea MA, Kansagara D., Crandall CJ, Fitterman N., et al. Disclosure of Interests and Management of Conflicts of Interest in Clinical Guidelines and Guidance Statements: Methods From the Clinical Guidelines Committee of the American College of Physicians. Ann Intern Med 2019;171(5):354-361 Pubmed Journal

81. Rea K., Wallace B.. Enhancing equity-oriented care in psychedelic medicine: Utilizing the EQUIP framework. Int J Drug Policy 2021;98:103429 Pubmed Journal Website

82. Roberts AL, Agnew-Blais JC, Spiegelman D., Kubzansky LD, Mason SM, Galea S., et al. Posttraumatic stress disorder and incidence of type 2 diabetes mellitus in a sample of women: a 22-year longitudinal study. JAMA Psychiatry 2015;72(3):203-10 Pubmed Journal

83. Royal Australian and New Zealand College of Psychiatrists. Clinical Memorandum: Therapeutic use of MDMA for PTSD and psilocybin for treatment resistant depression. null: (null) 2023. Website

84. Royal Australian College of General Practitioners. Cultural awareness and cultural safety training. Website

85. Santesso N., Glenton C., Dahm P., Garner P., Akl EA, Alper B., et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-135 Pubmed Journal Website

86. Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, et al. Guidelines International Network: principles for disclosure of interests and management of conflicts in guidelines. Annals of Internal Medicine 2015;163(7):548-553

87. Schwartzkopff L., Gutermann J., Steil R., Muller-Engelmann M.. Which Trauma Treatment Suits me? Identification of Patients' Treatment Preferences for Posttraumatic Stress Disorder (PTSD). Front Psychol 2021;12:694038 Pubmed Journal Website

88. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008 Journal Website

89. Siegel JS, Daily JE, Perry DA, Nicol GE. Psychedelic Drug Legislative Reform and Legalization in the US. JAMA Psychiatry 2023;80(1):77-83 Pubmed Journal

90. Smith DT, Faber SC, Buchanan NT, Foster D., Green L.. The Need for Psychedelic-Assisted Therapy in the Black Community and the Burdens of Its Provision. Front Psychiatry 2021;12:774736 Pubmed Journal Website

91. Stanicic F., Zah V., Grbic D., De Angelo D.. Cost-effectiveness of midomafetamine-assisted therapy (MDMA-AT) in chronic and treatment-resistant post-traumatic stress disorder of moderate or higher severity: A health-economic model. PLoS ONE [Electronic Resource] 2024;19(11):e0313569 Pubmed Website

92. Sumner JA, Kubzansky LD, Roberts AL, Gilsanz P., Chen Q., Winning A., et al. Post-traumatic stress disorder symptoms and risk of hypertension over 22 years in a large cohort of younger and middle-aged women. Psychol Med 2016;46(15):3105-3116 Pubmed Journal

93. Tedesco S., Gajaram G., Chida S., Ahmad A., Pentak M., Kelada M., et al. The Efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for Post-traumatic Stress Disorder in Humans: A Systematic Review and Meta-Analysis. Cureus 2021;13(5):e15070 Pubmed Journal Website

94. The GRADE Working Group. The GRADE Book. null: (null) 2024. Website

95. The Healing Foundation. Stolen Generations Collective Healing Initiatives Rounds 1–6: impacts and findings. null: (null) 2022. Website

96. Therapeutic Goods Administration. Update on MDMA and psilocybin access and safeguards from 1 July 2023. 2023. Website

97. Therapeutic Goods Administration. Authorised Prescriber Scheme: Guidance for medical practitioners, Human Research Ethics Committees, specialist colleges and sponsors. 2024. Website

98. Thrul J, Garcia-Romeu A. Whitewashing psychedelics: racial equity in the emerging field of psychedelic-assisted mental health research and treatment. Drugs: Education, Prevention and Policy 2021;28(3):211-214 Journal Website

99. Tortella-Feliu M, Fullana MA, Pérez-Vigil A, Torres X, Chamorro J, Littarelli SA, et al. Risk factors for posttraumatic stress disorder: An umbrella review of systematic reviews and meta-analyses. Neuroscience & Biobehavioral Reviews 2019;107:154-165 Journal Website

100. Van Hooff M, Lawrence-Wood E, Hodson S, Sadler N, Benassi H, Hansen C, et al. Mental Health Prevalence, Mental Health and Wellbeing Transition Study. 2018. Website

101. WA Country Health Service. Aboriginal Mental Health Consultation Guideline. 2023. Website

102. We Al-li. Culturally Informed Trauma Integrated Healing Approach. Website

103. Williams MT, Reed S, George J. Culture and psychedelic psychotherapy: Ethnic and racial themes from three Black women therapists. Journal of Psychedelic Studies 2020;4(3):125-138 Journal

104. Yong ASJ, Bratuskins S, Sultani MS, Blakeley B, Davey CG, Bell JS. Safety and efficacy of methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in post-traumatic stress disorder: An overview of systematic reviews and meta-analyses. Australian & New Zealand Journal of Psychiatry 2025;59(4):339-360 Journal

105. Zeng L., Brignardello-Petersen R., Hultcrantz M., Siemieniuk RAC, Santesso N., Traversy G., et al. GRADE guidelines 32: GRADE offers guidance on choosing targets of GRADE certainty of evidence ratings. J Clin Epidemiol 2021;137:163-175 Pubmed Journal

106. Neumann I, Brennan S, Meerpohl J, Davoli M, Alonso Coello P, Akl E, et al. Overview of the GRADE approach. The GRADE Book 2025. Website

107. Piggott T., Baldeh T., Akl EA, Junek M., Wiercioch W., Schneider R., et al. Supporting effective participation in health guideline development groups: The Guideline Participant Tool. J Clin Epidemiol 2021;130:42-48 Pubmed Journal

108. Beyond Blue Ltd. Answering the call national survey, National Mental Health and Wellbeing Study of Police and Emergency Services – Final report. null: (null) 2018. Website

109. Gray JC, Murphy M., Carter SE, Johnson MW, Wolfgang AS, Roy MJ, et al. Beliefs and Perceived Barriers Regarding Psychedelic-assisted Therapy in

a Pilot Study of Service Members and Veterans With a History of Traumatic Brain Injury. Mil Med 2023;188(11-12):e3356-e3362 Pubmed Journal

110. Williams MT, Reed S, Aggarwal R. Culturally informed research design issues in a study for MDMA-assisted psychotherapy for posttraumatic stress disorder. Journal of Psychedelic Studies 2020;4(1):40-50 Journal Website

111. Yong ASJ, Freeburn A, Bratuskins S, Bedi G, Bell JS. MDMA-assisted psychotherapy for post-traumatic stress disorder: Experience of Australian clinicians, researchers, and patients. [Manuscript submitted for publication].

112. Arjmand HA, O'Donnell ML, Putica A., Sadler N., Peck T., Nursey J., et al. Mental health treatment for first responders: An assessment of mental health provider needs. Psychol Serv 2024;21(3):489-499 Pubmed Journal

113. Meikle S, Carter O, Bedi G. Psychedelic-assisted psychotherapy, patient vulnerability and abuses of power. Australian & New Zealand Journal of Psychiatry 2024;58(2):104-106 Pubmed Journal Website

114. Qassem T., Aly-ElGabry D., Alzarouni A., Abdel-Aziz K., Arnone D.. Psychiatric Co-Morbidities in Post-Traumatic Stress Disorder: Detailed Findings from the Adult Psychiatric Morbidity Survey in the English Population. Psychiatr Q 2021;92(1):321-330 Pubmed Journal

115. Hinojosa CA, van Rooij SJH, Fani N., Ellis RA, Garrison-Desany HM, House SL, et al. The reciprocal relationship between posttraumatic stress disorder symptoms and alcohol use in a large multisite longitudinal sample stratified by sex: A random-intercept cross-lagged panel model. Alcohol Clin Exp Res (Hoboken) 2025. Pubmed Journal

116. Fox V., Dalman C., Dal H., Hollander AC, Kirkbride JB, Pitman A.. Suicide risk in people with post-traumatic stress disorder: A cohort study of 3.1 million people in Sweden. J Affect Disord 2021;279:609-616 Pubmed Journal

117. Lotfi T., Hajizadeh A., Moja L., Akl EA, Piggott T., Kredo T., et al. A taxonomy and framework for identifying and developing actionable statements in guidelines suggests avoiding informal recommendations. J Clin Epidemiol 2022;141:161-171 Pubmed Journal

118. Dudgeon P., Milroy H., Walker R.. Working Together: Aboriginal and Torres Strait Islander Mental Health and Wellbeing Principles and Practice. null: (null) 2014.

119. Barber GS, Aaronson ST. The Emerging Field of Psychedelic Psychotherapy. Curr Psychiatry Rep 2022;24(10):583-590 Pubmed Journal Website

120. Palitsky R., Kaplan DM, Peacock C., Zarrabi AJ, Maples-Keller JL, Grant GH, et al. Importance of Integrating Spiritual, Existential, Religious, and Theological Components in Psychedelic-Assisted Therapies. JAMA Psychiatry 2023;80(7):743-749 Pubmed Journal Website

121. Mithoefer MC. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. (null) 2017.

122. Stocker K., Liechti ME. Methylenedioxymethamphetamine is a connectogen with empathogenic, entactogenic, and still further connective properties: It is time to reconcile "the great entactogen-empathogen debate". J Psychopharmacol 2024;38(8):685-689 Pubmed Journal

123. Sottile RJ, Vida T. A proposed mechanism for the MDMA-mediated extinction of traumatic memories in PTSD patients treated with MDMA-assisted therapy. Frontiers in Psychiatry 2022;Volume 13 - 2022 Journal Website

124. Sessa B, Higbed L, Nutt D. A Review of 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy. Frontiers in Psychiatry 2019;Volume 10 - 2019 Journal Website

125. Phoenix Australia - Centre for Posttraumatic Mental Health. Specific Populations and Trauma Types: Aboriginal and Torres Strait Islander Peoples. Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder, null, Phoenix Australia 2020. Website

126. Phoenix Australia - Centre for Posttraumatic Mental Health. Specific Populations and Trauma Types: Military and Ex-military Personnel. Australian Guidelines for the Prevention and Treatment of Acute Stress Disorder, Posttraumatic Stress Disorder and Complex Posttraumatic Stress Disorder, null, Phoenix Australia 2020. Website

127. Department of Health DAA,. Therapeutic Goods (Standard for MDMA) (TGO 112) Order 2024. 2024. Website

128. Marks M. Psychedelic Therapy Scrutinized by FDA Advisory Committee?. JAMA 2024;332(12):963-964 Journal Website

129. Nadeem , Parker , McGovern , Sebben , Oestreich K. Attitudes toward psychedelics and psychedelic-assisted psychotherapy among Australian mental healthcare providers. Aust N Z J Psychiatry 2025;00048674251346679 Journal Website

130. Wright DJ, Colagiuri B, Glozier N. Evaluating the attitudes of mental health professionals towards trials of MDMA: a randomised vignette trial. BMJ Open 2022/11/01;12(11):e060360 Journal Website

131. Yong ASJ, Brennan SE, Bratuskins S, Freeburn A, Bedi G, Burke R, et al. Development of an Australian Clinical Practice Guideline on methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy for Post-traumatic Stress Disorder. Journal of Affective Disorders 2025;119866 Journal Website

132. Priebe K, Kleindienst N, Schropp A, Dyer A, Krüger-Gottschalk A, Schmahl C, et al. Defining the index trauma in post-traumatic stress disorder patients with multiple trauma exposure: impact on severity scores and treatment effects of using worst single incident versus multiple traumatic events. European Journal of Psychotraumatology 2018;9(1):1486124 Journal Website

133. Neitzke-Spruill L, Beit C, Averill LA, McGuire AL. Supportive Touch in Psychedelic Assisted Therapy. The American Journal of Bioethics 2025;25(1):29-39 Journal Website

134. Black Dog Institute, UNSW School of Psychiatry. Expert Guidelines: Diagnosis and Treatment of PTSD in Emergency Service Workers. 2024. Website