Psychedelic-assisted psychotherapy: The Australian and general practice perspective

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Background
Since Australia's Therapeutic Goods Administration down-scheduled two psychedelic medicines from July 2023, psychotherapeutic treatment using these medicines has become available in the private sector, making it possible for general practitioners (GPs) to refer their patients with treatment-resistant depression or post-traumatic stress disorder (PTSD). Several other psychedelic medicines are also legally in use as off-label or unapproved medicines.

Objective
The aim of this article is to help GPs make sense of this new type of treatment by discussing the Australian context, with focus on what a GP can expect for their patient and the GP's potential role.

Discussion
Psychedelic medication, when used to facilitate a psychotherapy process, can provide a very different and powerful way to allow patients to access emotions, thoughts, beliefs and traumatic memories that may otherwise remain subconscious or hard to access. This treatment is currently available privately in Australia for patients with treatment-resistant PTSD and depression. Meta-analyses of clinical trial results to date have shown some substantial effect sizes. Such trials continue to clarify and expand indications, efficacy and safety, as not everyone is suited to, safe for or will respond to psychedelic treatment.

HUMAN SOCIETIES since antiquity have used naturally derived substances to induce out-of-ordinary experiences, for example for religious or initiation ceremonies, practices that continue today in some cultures.[1] In Western medicine, an initial burst of research on psychedelic substances starting in the 1950s was shut down by the 'war on drugs', and it has only been in recent years that clinical research has resumed and flourished.[2,3]

Australian context

The Australian Government, in setting up a $15 million research fund for psychedelics, referred to 'a strong and emerging body of international evidence that shows that substances such as ketamine, psilocybin, and 3,4-methylenedioxymethamphetamine (MDMA), when used in a controlled environment and supported by psychological/psychiatric care, offer a promising new approach to effectively treating pernicious mental illnesses that are resistant to first-line treatments'.[4]

Although some Australian psychedelic researchers thought the decision premature,[5] Australia's Therapeutic Goods Administration (TGA) decided to down-schedule two psychedelic medicines – psilocybin and MDMA – from July 2023. Although they are not TGA-approved medications, they are now Schedule 8 (S8) medicines and can be prescribed outside of research trials for specific conditions (treatment-resistant depression [TRD] and post-traumatic stress disorder [PTSD]) and only by TGA-authorised psychiatrists through the Authorised Prescriber pathway.[6] Table 1 gives some detail on the current state of evidence regarding psychedelic treatment for those specific conditions.

These medications must be used together with psychotherapy from psychotherapists trained and qualified specifically in psychedelic-assisted psychotherapy (PAT) and in an appropriately supervised environment.[7] The TGA also regulates the quality of the supplied psychedelic medication.

Rescheduling was based on human clinical trial evidence, some of which is included in Table 1. General practitioners (GPs) can now refer suitable patients to a TGA-authorised psychiatrist for private treatment for these conditions.

Apart from this TGA rescheduling, ketamine (parenteral and sublingual) is offered as part of PAT at some private clinics in Australia under the supervision of specialist psychiatrists for conditions such as TRD and comorbid PTSD. This is an off-label use of an approved drug, using ketamine in dissociative doses to facilitate the psychotherapy, rather than the much more common use for its pharmacological actions alone. Some therapists also use tetrahydrocannabinol (THC)-dominant cannabis for PAT,[8] a medication that is legal but not TGA approved.

What are psychedelics?

A psychedelic can be defined as a substance that induces temporary but significant

altered states of consciousness, including sensory perception, thoughts and emotions.[9] These experiences can include sensory hyperacuity, dissociation, hallucinatory perceptions and expressions from the subconscious.[3] They can be intense and challenging experiences, as well as inducing profound feelings of peace and connection with others, within oneself and with a broader, more universal reality. These effects can produce major shifts in previously rigid perspectives and patterns of thought, self-image and emotion, including to the emotional and somatic intensity of traumatic memories.[10] Refer to Table 2 for psychedelics in common clinical use.

Do psychedelics work?

Clinical trials continue to clarify indications, efficacy and safety. For now, it is important to understand that not everyone is suited to, safe for or will respond to PAT, and some people may feel worse during or after treatment. Randomised trials must overcome problems of unblinding and patient pre-expectation, but overall meta-analyses of trial results have shown some substantial effect sizes.

In depression, for example, one could compare the benefit found in a meta-analysis of psilocybin trials (standardised mean difference [SMD] =–0.78, $P<0.001$)[11] with the effect size consistently reported in antidepressant trials of approximately –0.3.[12,13] Similarly, one can compare in PTSD the effect size on symptom score in a meta-analysis of MDMA (SMD=–0.78)[14] with that in a meta-analysis of selective serotonin reuptake inhibitors (SSRIs; SMD=–0.28).[15]

Evidence suggests that approximately two-thirds of patients with PTSD will experience remission on MDMA,[16] whereas 57% of patients with depression will respond and 45% will experience remission on psilocybin.[11] On an individual level, many patients experience in short time frames (ie weeks) substantial improvements in clinical symptoms that had remained refractory after years of conventional

Table 1. Some psychedelic-assisted psychotherapy clinical trial results[11,14,33–40]

Psychedelic	Patient group	Type of study (for RCT, what was the control)	n	Psychedelic vs comparator[A]	Reference
Psilocybin	Depression	Meta-analysis	596	Large effect size in favour of psilocybin (SMD=–0.78, $P<0.001$)	11
	Long-standing, moderate-to-severe MDD	RCT (vs escitalopram)	59	Non-significant greater fall in depression and significant greater rise in wellbeing scores at 12/52	33
	MDD	RCT (vs waitlist)	27	71% significant improvement, 54% remission at 4/52	34
	TRD	RCT (25 mg vs 10 mg vs 1 mg dose)	233	Improved patient-reported depression severity, anxiety, affect and functioning at 3/52	35
	Anxiety, depression in life-threatening cancer	RCT (vs placebo)	29	Enduring anxiolytic and antidepressant effects at 6.5/12	36
MDMA	PTSD	Meta-analysis	286	Significant reduction in PTSD symptoms (CAPS score Hedges' g=–1.532, $P=0.004$; RR of remission=2.587, $P=0.002$)	14
	Moderate-to-severe PTSD	RCT (vs placebo)	104	Significantly greater PTSD score drop at 18/52 ($P<0.001$, Cohen's d effect size=0.7)	37
	Alcohol or cannabis use disorder (with PTSD)	RCT (vs placebo)	90	Significantly greater drop in alcohol use ($P<0.05$, Hedges' g=0.45)	38
	Eating disorder symptoms (with PTSD)	RCT (vs placebo)	89	Significant reduction in total EAT-26 scores ($P=0.03$)	39
Ketamine	PTSD	Meta-analysis	34	Significant reduction in CAPS-5 ($P=0.005$) and PCL-5 scores ($P<0.001$)	40

[A]CAPS-5 and PCL-5 are commonly used PTSD scales; Hedges' g and Cohen's d are measures of effect size.

CAPS-5, Clinician-Administered PTSD Scale for DSM-5; EAT-26, Eating Attitudes Test; MDD, major depressive disorder; PCL-5, PTSD Checklist for DSM-5; PTSD, post-traumatic stress disorder; RCT, randomised controlled trial; RR, relative risk; SMD, standardised mean difference; TRD, treatment resistant depression.

treatment, going from severe PTSD to no longer meeting criteria for diagnosis.[17]

How do psychedelics work?

Biological mechanisms remain under investigation, but the 'classical' psychedelics exert their neurobiological effects via agonism at the serotonin 2_A receptor.[9] Evidence suggests that psychedelics temporarily alter communication between large-scale brain networks (eg default mode and salience networks) and can induce a period of neuroplasticity such as can allow new learning to take place.[18–20]

How is it done?

PAT treatment usually involves some time in preparation, up to three dosing sessions and a series of psychotherapeutic integration sessions, which help the patient to make sense of their experience and to preserve, protect and extend what is valuable within it. Most but not all treatment plans require two psychotherapists working together.

Importantly, the benefits of this combined psychedelic–psychotherapy approach, with the right patient mindset and a safe external setting, go far beyond what people normally experience using these drugs recreationally (eg taking ecstasy at a party).[21]

In Australia, PAT is being conducted within university and industry clinical trials and in private hospitals and clinics. Although costs vary, unfortunately the expense of the medicine and particularly psychiatrist/psychotherapist time means that a course of privately undertaken PAT is expensive, ranging widely but up to $35,000, although some limited rebates may be available. For example, one of Australia's largest private health insurers has confirmed that it will begin rebating MDMA treatment for PTSD.[22]

A substantial commitment is required of the patient, including commitment both to change and of time.

Table 2. Psychedelics in common clinical use[41]

Psychedelic	Neurotransmitter/ receptor	Poisons schedule	Acute duration (approximate)	Other information
Classical	**Serotonin 5-HT2_A agonist**			**More sensory, hallucinatory experiences**
LSD		S9	10–14 hours	
Psilocybin		S8 AP	6 hours	
Mescaline		S9	10–14 hours	
DMT		S9	30 minutes	Given with MAO inhibitor to extend duration
Ayahuasca		S9	4–6 hours	Combination of plants containing DMT and MAO inhibitor (which extends duration of DMT action)
5-MEO-DMT		S9	10 minutes	Given parenterally for short duration, intense effect
Empathogens	**Serotonin and dopamine reuptake inhibitors/releasers, noradrenaline, oxytocin**			**Increase interpersonal warmth and connection**
MDMA		S8 AP	6 hours	When used as a party drug, known as 'ecstasy'
Methylone		S9	4–6 hours	Considered gentle but similar to MDMA
Dissociatives				**Feelings of dissociation from body or senses**
Ketamine	NMDA (glutamate receptor) antagonist	S8	60 minutes	To use in PAT requires dissociative dose
Atypical	**Various**			
Ibogaine	Multiple receptor actions	S9	24–36 hours	Has been used in treating addiction
Cannabis (THC)	Cannabinoid receptors	S8	2–4 hours	

5-MEO-DMT, 5-methoxy-N,N-dimethyltryptamine; AP, authorised psychiatrist (TGA-authorised prescriber pathway only); DMT, N,N-dimethyltryptamine; LSD, lysergic acid diethylamide; MAO, monoamine oxidase; MDMA, 3,4-methylenedioxymethamphetamine; methylone, 3,4-methylenedioxy-N-methylcathinone; NMDA, N-methyl-D-aspartate; S8, Schedule 8 (controlled drug); PAT, psychedelic-assisted psychotherapy; S9, Schedule 9 (prohibited except for specified purposes, eg research); TGA, Therapeutic Goods Administration; THC, tetrahydrocannabinol.

What to expect from the treating team

You can expect the PAT treating team to be helpful in answering your questions about the treatment and whether your patient is suitable for referral. They will be proactively interested in your perspective on the patient's psychiatric and psychosocial background (including family and social supports) and physical comorbidities. The team should keep you informed of progress during treatment, perform a good handover at the end and have some helpful ideas regarding ongoing support if required (eg names of some PAT-aware psychotherapists). Refer to Box 1 and 2.

Role of the GP

Referral

GPs may consider referring privately to an authorised psychiatrist a patient who has failed conventional treatment for:

- depression – psilocybin
- PTSD (including complex PTSD) – MDMA.

Clinical trials will provide free treatment, and it is worth checking trial registries to see if any are recruiting.[23,24] Other conditions that have been or are planned to be treated in Australian PAT trials include: end of life, addiction, eating disorder, obsessive–compulsive disorder, generalised anxiety disorder and autism.[3]

Referral for ketamine-assisted psychotherapy should be through a psychiatrist familiar with it.

Although PAT within proper clinical care with well-selected patients has a good safety record,[25,26] contraindications would typically include a personal or first-degree family history of psychotic illness,[25] possibly bipolar disorder and active drug addiction (although the latter two conditions have been targets of PAT trials).[25,27] PAT does not appear to itself induce addiction to the medications used.[28]

Patient education

The GP may like to provide evidence-based education about PAT to counter both unfounded fear and unrealistic expectations.

Deprescribing

As some conventional medications have potential adverse interactions with psychedelics (eg SSRIs/ serotonin–noradrenaline reuptake inhibitors for serotonin syndrome) or can interfere with the therapeutic effect (eg sedatives, alcohol),[29] patients may need to come off these before dosing. Deprescribing can be a challenge, possibly one on which the authorised psychiatrist might ask you to work with them as the doctor who has a long-term relationship with the patient. Less deprescribing is required for ketamine.

Support during treatment

Undergoing PAT can be transformative but also a vulnerable or confronting experience and, frankly, hard work at times. It is important that you, as the steward of your patient's holistic care, be open-minded about their undertaking a novel treatment so that they feel they can talk openly to you about it, even if they have some difficulty expressing the inexpressible. This helps your patient's confidence that they have a united team supporting them.[30]

The patient may experience some of the common post-dose effects; working with their PAT team, you can reassure your patient about these symptoms and help the patient cope with them. The most common symptoms can be muscle tightness or headache, as well as feelings of physical or emotional flatness or lability in the days after

Box 1. Q&A from the front line

The author interviewed a number of Australia's authorised psychiatrists active in psychedelic-assisted psychotherapy and some other prominent research leaders in this field.

What role do you think the GP has?

'A central role. The GP is the one who knows the person's psychological story in context and who will be there when they return to their life after the treatment.' (JD)

Does the GP need any special skills?

'To be able to see people as human beings, past the psychiatric diagnosis to the person with the diagnosis.' (EK)

What do GPs particularly need to be aware of?

'The psychedelic drug is the smallest part of the treatment. These drugs are revolutionising the psychotherapy process to allow the patient to get to the trauma that is otherwise hidden by shame or fear.' (TC)

'The GP really needs to understand the psychotherapeutic process that is part of therapy. Being able to screen someone to ascertain whether they are amenable to the process takes a skilled psychotherapist.' (SR)

'It's a long term process. I've seen people who came out of dosing day saying they never wanted to do that again, but 6 months later they write and say their lives have been transformed by it.' (JD)

Who does this treatment particularly suit?

'Having good social supports is important factor, it can be hard when people have profound insights where the partner is unsupportive.' (NS)

'A degree of self-reflective capacity is helpful, and being able to tolerate distress is important.' (AM)

'Response prediction is one of the least progressed scientific questions in this space. But it's a good sign if someone demonstrates readiness to change.' (PL)

Who should the GP be hesitant to refer?

'I would not accept a patient who was not psychologically minded, I would be wary of someone with poor psychosocial supports or in the midst of a crisis.' (LL)

'We don't want to treat people who lie there for 8 hrs and expect to be cured at the end of it.' (NS)

'It is like psychotherapy on rocket fuel, so the patient will need some internal and contextual stability to go the distance.' (PL)

'A lack of mentalisation skills and concepts is not an obstacle, but a lack of interest in their mental and emotional life is, where the therapist has to do all the work.' (JD)

Box continued on the next page.

Box 1. Q&A from the front line (cont'd)

What should the GP tell the patient when referring?

'That the medicine is not going to do all the work, they have to be willing to meet the medicine, which means to engage in deep and sometimes painful self-exploration, with the help of the psychotherapists.' (SA)

'It is not a simple thing to face your demons, your emotions and your trauma, it is a commitment over many months and patients have to be able to make that commitment.' (EK)

'That there are still some doubts and questions about the richness of the evidence base that need to be resolved with ongoing research.' (PF)

Is my patient going to be safe with you?

'Most of the side-effects and downsides are quite reversible. But the treatment can be difficult and traumatic for some, we have to be open about that.' (RG)

'Pretty good safety profile. The treatment may make them feel worse for a period of time, unearthing issues they had suppressed. It very uncommonly increases suicidal ideation, but we monitor for this carefully.' (SS)

'There may be an increased suicide risk if, after they get better, they are discharged without any close follow up and their mood suddenly drops. So our clinic only treats patients who are already linked with a psychiatrist and therapist.' (CL)

Is my patient going to get better?

'Not every patient will get a response but about 60–70% will, and the kind of responses that responders get tend to be more dramatic than in other treatments.' (TC)

'Our clinic's experience so far is that all our patients improved symptomatically, and the average improvement has been 60%, the average improvement in QOL scores was 50%.' (JL)

'My honest answer is that we don't know for sure. Putting aside the real concerns about the absence of effective placebo controls in trials to date, the evidence is that, in that high quality environment, a significant proportion of patients are likely to see significant benefit that exceeds treatment-as-usual and persists past one year.' (PF)

Interviewees: AM (AP, clinical research); CL (Professor of Psychiatry, AP, PI, PATC); EK (AP, PATC); JD (AP, PI, PATC); JL (AP, PATC); LL (public sector psychiatrist, PI, PATC); NS (AP); PF (Professor of Psychiatry, PI); PL (Head of Psychedelic research laboratory); RG (Associate Professor of Psychiatry, AP, PATC); SA (Psychiatrist, Clinical trial researcher, PATC); SR (Professor and Director of clinical trials, Neuropsychologist, PI); SS (AP, Professor of Psychiatry, PI); TC (AP, PATC)

AP, authorised psychiatrist; GP, general practitioner; PATC, private psychedelic-assisted psychotherapy clinic; PI, clinical trial principal investigator.

Box 2. In summary, what?

'It's a new field with a lot of promise which is being translated in Australia into clinics at a relatively early stage of development, so we need to embrace the possibilities but proceed cautiously.' (CL)

'For severely treatment-resistant patients this has been one of the most remarkable next step treatments that I have been involved in.' (TC)

'This is a radically unique treatment that cuts across diagnostic boundaries and has the potential to transform the lives of people living with various mental health conditions.' (AM)

'I've seen the limitations of conventional psychiatric treatments over more than 25 years, this is the first real psychiatric innovation in the 35 years since clozapine.' (RG)

The final word

'I feel like a different person with a future ahead. Something that I have not felt in a number of years. What this treatment has achieved with me in such a short period of time is something that 17 years of therapy and antidepressants failed to achieve.' (Retired policeman, treated with MDMA for PTSD)

Interviewees: AM (AP, clinical research); CL (Professor of Psychiatry, AP, PI, PATC); RG (Associate Professor of Psychiatry, AP, PATC); TC (AP, PATC)

AP, authorised psychiatrist; MDMA, 3,4-methylenedioxymethamphetamine; PATC, private psychedelic-assisted psychotherapy clinic; PI, clinical trial principal investigator; PTSD, post-traumatic stress disorder.

dosing. Challenges of adjusting to a new mindset and newly felt emotions can arise in subsequent weeks.

A rare condition, hallucinogen persisting perception disorder, involves sensory distortions continuing well after the psychedelic drug has left the system. This has mostly been seen with lysergic acid diethylamide (LSD) and in recreational rather than clinical settings.[31]

Handing back

Open-mindedness is also needed after the patient completes PAT. They may well want to talk to you about what has happened or seek a referral to a psychotherapist who understands PAT, especially if they have come from a clinical trial where the psychotherapy has a definite end date. Although the field is too young to have standardised credentialling, the team that has been providing PAT may well know a locally based, qualified colleague.

Getting involved

For any GP interested in participating in PAT, there are a number of organisations and common interest groups offering peer support, membership and training. But, as stated above, the field does not yet have standardised training or credentialling. The Royal Australian and New Zealand College of Psychiatrists has published a training guideline with a syllabus for psychiatrists.[32] Getting involved in a university clinical trial is one option, and Table 3 contains some others.

Conclusion

The TGA rescheduling of two psychedelic medications for use with psychotherapy in Australia has brought what had been cutting-edge treatment with much potential but still under investigation into the reach of GPs who may wish to refer their patients to a TGA-authorised psychiatrist.

The current place for PAT is for patients who have failed conventional treatments, such as for PTSD or depression. The clinical evidence so far shows good results for the majority of such patients, with effect sizes well above those of conventional treatments.

However, PAT does not work for everyone and can be challenging even for those for whom it does. Not every patient who

Table 3. Some Australian training resources for psychedelic-assisted psychotherapy[A]

Organisation	Training	Contact	Comment
Monash Clinical Psychedelic Lab	Psychedelic Education Program	www.monash.edu/medicine/scs/clinical-psychedelic-lab/education-program	University accredited units
Multidisciplinary Association for Psychedelic Studies (MAPS)	MDMA Therapy Training Program	www.monash.edu/psychedelics	
Mind Medicine Australia	Certificate in Psychedelic-Assisted Therapies	https://cpat.mindmedicineaustralia.org.au	
Empax Centre	Psychedelic Assisted Therapy Foundations	https://empaxcentre.com	Option for mentorship in private psychedelic-assisted psychotherapy dosing
Anam Cara Centre	Certificate in Psychedelic and Contemplative Therapies	www.anamcaracentre.com.au	
Integrated Psychology and Medicine	Psychedelic integration	https://integrativepsychology.net.au/training/training-home	
Psychedelic Institute Australia	Essential Skills for Psychedelic-Assisted Therapy	www.psychedelicinstitute.com.au	
Wild Mind Institute	Foundations of psychedelic-assisted psychotherapy	www.wild-mind.com/wild-mind-institute	
Indigenous Psychedelic-Assisted Therapies		www.ipat.au	Culturally informed
Australian Multidisciplinary Association for Psychedelic Practitioners		www.amapp.org.au	Education, peer support
Psychedelic Perspectives		www.psychedelicperspectives.com	Peer discussion

[A]This list is neither comprehensive nor implies approval by the author.

may be technically eligible will be suited. Appropriate psychological or psychiatric support after a course of PAT is essential.

The GP, working with the authorised psychiatrist and their team, can make a significant contribution to the ongoing evaluation of this treatment in Australian patients.

Key points

- Psychedelic medicines as part of a course of psychotherapy represent an exciting new development in psychiatric medicine that offers hope for patients with treatment-resistant conditions such as depression and PTSD.
- This is still cutting-edge psychiatry very much under clinical trial study, but results so far show effect sizes well above that of many conventional psychiatric treatments.
- Not every patient is suited to, safe for, can afford or will respond to this treatment; careful patient selection is required.
- When done with appropriate patients by experienced clinicians, PAT is a safe treatment. However, it can be quite hard work for the patient psychologically as it can bring up uncomfortable emotions and memories, challenge existing mindsets and involve significantly out-of-ordinary experiences.
- GPs have a role to play in selecting appropriate patients for referral, informing patients but also tempering unrealistic expectations and supporting them during and after treatment as part of their mental health team.

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