



## What is Psychedelic-Assisted Therapy?

### The therapeutic process

Psychedelic-assisted therapy typically involves ‘talk-therapy’ alongside the ingestion of a classical psychedelic such as psilocybin, LSD, or ayahuasca. Researchers and clinicians often describe three distinct therapy phases: preparation, the acute psychedelic experience, and integration. The non-psychedelic elements of this approach are essential for both effectiveness and safety.

Various approaches to **preparation** have been developed, from diet to psychotherapy. In clinical trials, participants will typically attend a number of talk-therapy sessions with a trained therapist who will be in attendance during the psychedelic session. A therapeutic alliance is developed during this time, and the nature of the individual’s struggle is explored.

The therapist will prepare the patient for the psychedelic session in a number of ways, with a particular emphasis on curiosity, and ways to remain open to challenging experiences (“If you see a door, go through it”; “If you meet something scary, walk towards it and ask, ‘what do you have to teach me?’”). While challenging experiences are considered by many who work in the field to be integral to the therapeutic and personal benefits that follow, the so called ‘bad trip’ is borne out of an attempt to avoid the experience, and can be mitigated by an open and trusting approach.

During the **psychedelic session**, ‘set’ and ‘setting’ are considered paramount. ‘Set’ refers to mind-set, a complex mix of more transient phenomena like expectation and mood, and more enduring phenomena like personality and past experience. ‘Setting’ refers to the context or environment in which the session takes place, including basic factors like the comfort and aesthetic quality of the room, and more complex factors like the quality of the relationship with the clinicians and the mood they help to set. Whilst many modern clinical trials occur within hospitals or research institutes, the session rooms are made to appear as comfortable living rooms (see image 1). There are typically two therapists in attendance. The patient can sit or lie on a couch, is often encouraged to wear eyeshades, and sometimes listen to a carefully selected playlist of music. Oral ingestion of a capsule of synthesised psychedelic compound (e.g., psilocybin) is the most common route of administration, and the session will typically last for about 8 hours.

A common therapeutic approach during psychedelic sessions is to be non-directive: attentive but usually silent, supporting the emerging process, offering assistance and guidance if needed, listening and responding to the patient when they speak, with little analysis of the material. In some trials, a single high-dose psychedelic session occurs (usually 20-30 mg per 70 kg body weight); in others, there are two or three high-dose sessions. Many trials are also placebo-controlled, wherein the patient will usually have one placebo session – sometimes a very low dose of the psychedelic, sometimes a ‘active placebo’ that produces some noticeable somatic effects – in addition to their high-dose session(s).

Immediately after the psychedelic session and in the following days, a process of **integration** is facilitated by the therapist. During these conversations, the patient has the opportunity to process, make sense of, and give meaningful expression to their psychedelic experience.



Image 1: A psilocybin-assisted therapy session, Johns Hopkins University.

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## The psychedelic experience

Classical psychedelics appear to produce many of their effects through the activation of a specific Serotonin receptor (5HT2A) in the brain. Numerous complex changes in brain activity occur following ingestion of a psychedelic, from reductions in activity in some areas (like the Default Mode Network, which is associated with mind-wandering, thinking about the past or future, and thinking about yourself), to alterations to the way different areas connect to each other (for example, areas of the brain that typically don't interact much begin to work together). Much of what psychedelics do to brain activity remains to be investigated. What psychedelics do to the mind is also of central relevance to clinical research.

The 'psychedelic experience' is certainly not consistent across different people and the range of experiences and responses is wide. However, with specific constraints on 'set' and 'setting' – as is the case within modern clinical trials – certain subjective features occur for many people in a surprisingly reliable way. These include increased empathy for others; increased compassion for oneself; profound and novel insights about one's character or life or the world; feelings of deep connectedness with other people or other things; a sense of meaningfulness; a reduced sense of one's Self, its permanence, and its boundaries; and in some cases, a completely other-worldly experience often referred to as 'mystical'. Psychedelic experiences entail an 'altered state of consciousness', a shift in the fundamental nature of one's experience that is often startling, and difficult to imagine, much less describe. A common feature of these experiences is that the accompanying insights and perspectives are felt to be more reliable, more 'true' or 'wise', than one's usual understanding. Further, the 'authority' of these novel perspectives tends to endure well beyond the acute stages of the psychedelic session.

## What is the clinical evidence?

In rigorous and well-controlled clinical trials over the past decade, psychedelic-assisted psychotherapy (using classical psychedelics such as psilocybin, and related compounds such as MDMA<sup>[i]</sup>) has produced some remarkable clinical outcomes for individuals suffering with addiction<sup>[iii]</sup>, depression<sup>[iii]</sup>, end-of-life distress<sup>[iv][v]</sup>, and Post-Traumatic Stress Disorder<sup>[vi]</sup>. Preliminary and currently active trials are investigating additional applications, for example for obsessive-compulsive disorder and autism.

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About one hundred psychedelic and MDMA research trials have recently been completed or are currently active. In many cases, the results have been remarkable in terms of the strength, speed, and enduring nature of the treatment effect. For example, reductions in psychopathology symptoms within the modern trials has been substantially larger than what is typically found for other effective treatments (for the scientists: Cohen's  $d$  ranging from 0.8 to 3.1; i.e., a 'large effect'). While it remains to be seen how well these results will stand up to the larger studies planned (Phase 3 clinical trials), results from clinical trials to date have been so compelling that the US Food and Drug Administration (FDA) recently designated both psilocybin- and MDMA-assisted psychotherapies as 'breakthrough therapies', expediting their research and development.

In addition, some trials have found that treatment effects can be sustained at least up to 6 months. For example, in a recent well-controlled study using psilocybin-assisted psychotherapy, 51 terminally ill patients suffering with depression and anxiety symptoms received two high-dose sessions: following the first psilocybin session, 60% reported a drop in depression symptoms into the normal range, with sustained and improved outcomes 6-months later (71% reporting remission into normal range)<sup>[iv]</sup>.

### What research is still to be done?

While psychedelic-assisted therapies have shown some strong clinical results, considerable research is still required to ensure appropriate levels of safety and to optimise clinical effectiveness. A number of large multi-site international 'Phase 3' trials of both psilocybin and MDMA are set to commence in the next 2 to 3 years. These trials are essential to determine whether the promising results seen to date will hold up in larger and more realistic clinical settings.

While classical psychedelics pose only negligible toxicity or dependence risks, psychological risks need to be better understood and mitigated. To date, research trials have done well to select appropriate participants and conduct trials in such a way as to produce impressive levels of safety. However, in order to offer these therapies to a much larger proportion of the population, more work is needed to understand the psychological risks and how to maintain the currently low levels of adverse events.

A number of theories have been put forward to explain why psychedelic-assisted therapies may be clinically effective. However, many of these theories are not clinically useful, and none that are have been directly tested. More research into the 'therapeutic mechanisms' of this approach is essential in order to: optimise the effective aspects while reducing any

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unhelpful aspects of the therapy; understand why some people do not respond clinically; determine what works best for different clinical issues; and so on. There is much work to be done, and very good reason to do it – both in terms of the substantial unmet need in mental ill-health, and the impressive results of this approach. Indeed, we are seeing a surge of interest around the world, and large investments in further exploration of psychedelic-assisted research and therapy. This is an historic moment in mental health research and treatment. And it is time for Australia to join in this exploration.

## Footnotes

- i. MDMA is not a classical psychedelic, but is associated with various ‘psychedelic effects’ and often discussed among the classical psychedelics.
- ii. Johnson, M et al. (2014). 5-HT<sub>2A</sub>R agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology*, 28-11:983-992.
- iii. Carhart-Harris et al. (2016). Psilocybin with psychological support for treatment-resistant depression. *The Lancet*, 3-7:619-627.
- iv. Griffiths, R. R. et al. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology*, 30(12), 1181-1197.
- v. Ross et al. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology*, 30-12:1165-1180.
- vi. M.C. Mithoefer, T.M. Wagner, A.T. Mithoefer, L. Jerome, R. Doblin, The safety and efficacy of  $\pm$ 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study, *J. Psychopharmacol.* 25 (4) (2011) 439–452.

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