Psilocybin

By Drug Science,
Mind Medicine Australia

With Support from
Norrsken Mind

Drug Science

Part II - Pharmacology and Therapeutic Mechanisms

norrsken mind

MIND MEDICINE AUSTRALIA

Drug Science was formed by a committee of scientists with a passionate belief that the pursuit of knowledge should remain free of all political and commercial interest.

Founded in 2010 by Professor David Nutt, following his removal from his post as Chair of the Advisory Council on the Misuse of Drugs, Drug Science is the only completely independent, science-led drugs charity, uniquely bringing together leading drugs experts from a wide range of specialisms to carry out ground-breaking research into drug harms and effects.

The Drug Science mission is to provide an evidence base free from political or commercial influence, creating the foundation for sensible and effective drug laws. Equipping the public, media and policy makers with the knowledge and resources to enact positive change.

Drug Science want to see a world where drug control is rational and evidence-based; where drug use is better informed and drug users are understood; where drugs are used to heal not harm.

@Drug_Science **/DrugScienceISCD**

Mind Medicine Australia is a registered charity working to alleviate the suffering and suicides caused by mental illness by expanding treatment options through the safe, clinical use of psychedelic-assisted therapies to treat depression, trauma, addictions and other intractable conditions. MMA's wholly clinical focus includes building a national ecosystem encompassing professional development for health practitioners through the world-leading Certificate in Psychedelic-Assisted Therapies (CPAT)™, patient access pathways, medicine supplies, regulatory and research advancements, clinical rollouts and widespread awareness and education.

MMA made global history through their successful rescheduling applications for psilocybin and MDMA making Australia the first nation in the world to reschedule these medicines for clinical use in 2023. You can learn more about our key achievements on our website.

@MindMedicineAU **/MindMedicineAU**

Norrsken Mind is a non-profit foundation dedicated to advancing psychedelic science. The foundation funds high-quality, independent research into the therapeutic potential of psychedelics for mental health disorders, along with non-profit initiatives to lay the foundation for a future integration of these treatments into healthcare.

Beyond research funding, Norrsken Mind promotes public education, stakeholder engagement, and policy dialogue. By offering grants and facilitating partnerships, Norrsken Mind aims to create the necessary conditions for psychedelic treatments to be rigorously studied, responsibly implemented, and ultimately accessible to patients in need.

Norrsken Mind actively works to mobilize philanthropic capital for psychedelic science. The foundation is funded through donations from committed benefactors and its affiliation with Norrsken Foundation.

Drug Science has received grant support from Norrsken Mind, which supported the development of this educational material.

/company/norrsken-mind

What is Psilocybin?

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is an indole alkaloid, chemically similar to the neurotransmitter **serotonin** (5-HT).

It falls within the tryptamine class of classical psychedelics.

An **indole** is an aromatic double-ring system containing a nitrogen atom in the five-membered ring, which is fused to a benzene ring.

A **tryptamine** is an indole molecule with an ethylamine group attached to carbon 3 of the 5-membered ring.

Psilocybin occurs naturally in up to 100 species of mushrooms belonging to the genus Psilocybe.

Psilocybin can also be synthesised chemically, or via biochemical synthesis, both in vivo and in vitro.

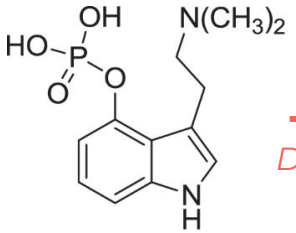
How does Psilocybin act?

Psilocybin is easily converted within the body to the similar compound, psilocin, via dephosphorylation. **Psilocybin is, therefore, a "prodrug" of psilocin.**

Psilocin acts to stimulate (is an agonist of) the **5-HT2A and 5-HT2C** receptors.

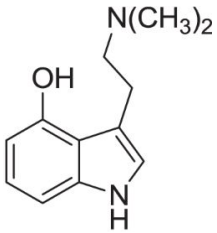
Thus, in some ways, psilocin acts to **mimic the effects of serotonin.**

However, the binding of psilocin to serotonin receptors can also elicit different effects from the binding of serotonin to the same receptors due to the phenomenon of **functional selectivity**.

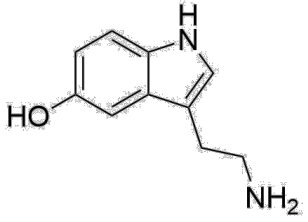


Psilocybin

Dephosphorylation



Psilocin



Serotonin

Introduction to Serotonin

Serotonin (or 5-hydroxytryptamine, 5-HT) is one of several endogenous monoamine neurotransmitters in living organisms that have very fundamental functions in basic psychological function.

In humans, serotonin is involved in sleep regulation, appetite, mood and a host of other higher-level functions.

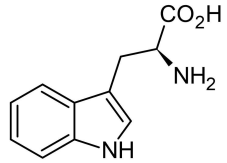
Serotonin was the first of the monoamine neurotransmitters to be discovered, as a consequence of LSD research in the 1950s. The discovery of serotonin led to the elucidation of receptors and their fundamental role in neurological function.

Serotonin Formation and Breakdown

Serotonin biosynthesis initially involves the conversion of **L-tryptophan** to **5-hydroxytryptophan** by **L-tryptophan hydroxylase (TPH)**. The subsequent metabolic step involves the decarboxylation of 5-hydroxytryptophan by the action of the cytosolic enzyme **L-aromatic amino acid decarboxylase (AADC).**

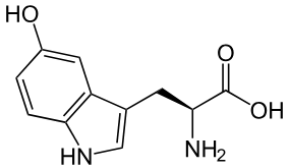
Monoamine oxidase (MAO)
Both subtypes (-A & -B) occur widely in the brain and peripheral tissues. MAO-A is more selective for serotonin oxidation by being able to metabolise serotonin with lower Km and higher affinity than MAO-B.

Interestingly, however, immunohistochemical studies have suggested that serotonin-containing neurons may themselves contain only MAO-B.



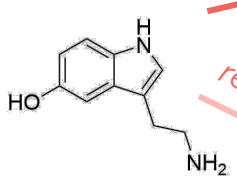
L-Tryptophan

THP



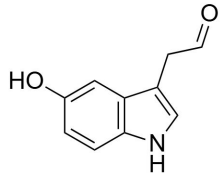
5-Hydroxytryptophan

AADC



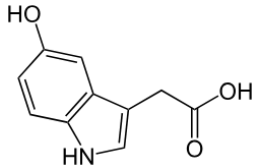
Serotonin

MAO



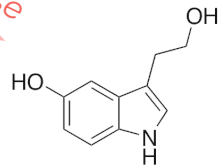
5-Hydroxyindole acetaldehyde

ALDH2



5-Hydroxyindoleacetic acid

aldehyde reductase



5-Hydroxytryptophol

Metabolism of serotonin is carried out primarily by the outer mitochondrial membrane enzyme **monoamine oxidase (MAO-A & MAO-B).**

MAO converts **serotonin** to **5-hydroxyindole acetaldehyde**, which in turn is readily metabolised, principally by an isoform of **aldehyde dehydrogenase (ALDH2)** located in mitochondria, to produce **5-hydroxyindole acetic acid** as the major excreted metabolite of serotonin.

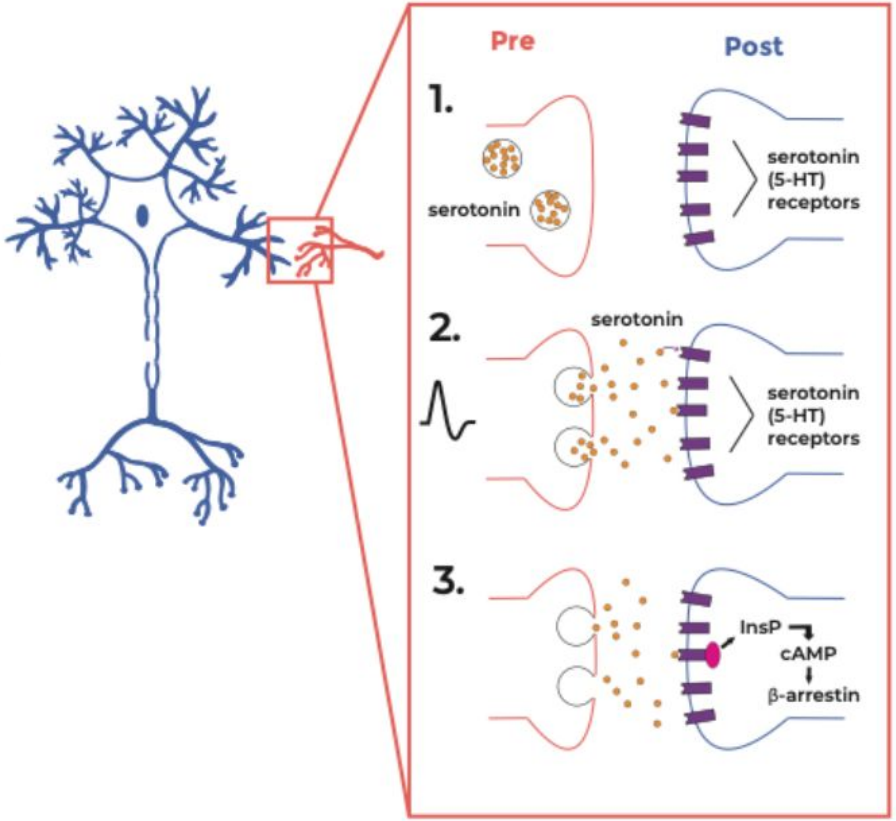
An alternative metabolic route via aldehyde reductase can convert 5-hydroxyindole acetaldehyde to **5-hydroxytryptophol,** but this pathway is normally considered to be insignificant.

Serotonin Signalling

Neurotransmitters generally travel from the **presynaptic bouton** across the synaptic cleft to act on **postsynaptic receptors**. Serotonin is stored in vesicles at the bouton of the presynaptic neuron.

In response to an action potential transmitted within the presynaptic neuron, serotonin is released from the storage vesicles into the synaptic cleft. serotonin molecules diffuse across to bind to serotonin (5-HT) receptors on the surface of the postsynaptic neuron.

Serotonin binds to its orthosteric binding site on the extracellular domain of the membrane-bound 5-HT receptor molecule, which elicits a characteristic conformational change resulting in a cascade of events related to G-protein cleavage and downstream interactions and catalysis involving second-messenger molecules such as inositol phosphate and cyclic AMP, and proteins such as β-arrestin.



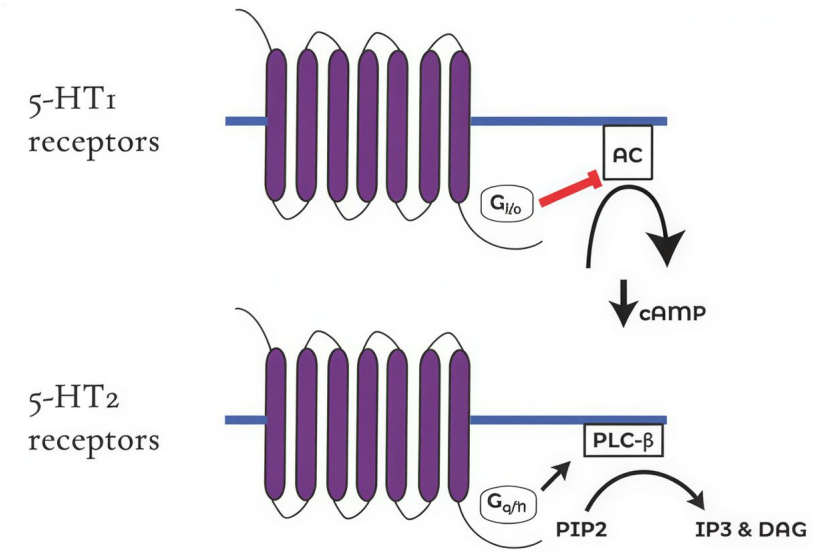
Serotonin Receptors

The **serotonin (5-HT) receptors** are postsynaptic receptors that exist as **14 subtypes** in mammals. All but one (the 5-HT3 receptor) are metabotropic, **G protein-coupled receptors**.

The G protein-coupled 5-HT receptors all have seven transmembrane spanning domains. They couple to different G proteins, including the **Gi/o, Gq/$_{11}$, and Gs** families of G proteins, to cause either a change in cellular cAMP levels, or in the case of 5-HT2 receptors, increase levels of inositol trisphosphate (IP3) and diglyceride (DAG).

5-HT receptors are located throughout the body, including on platelets in the blood. 5-HT receptors are also widespread in the brain.

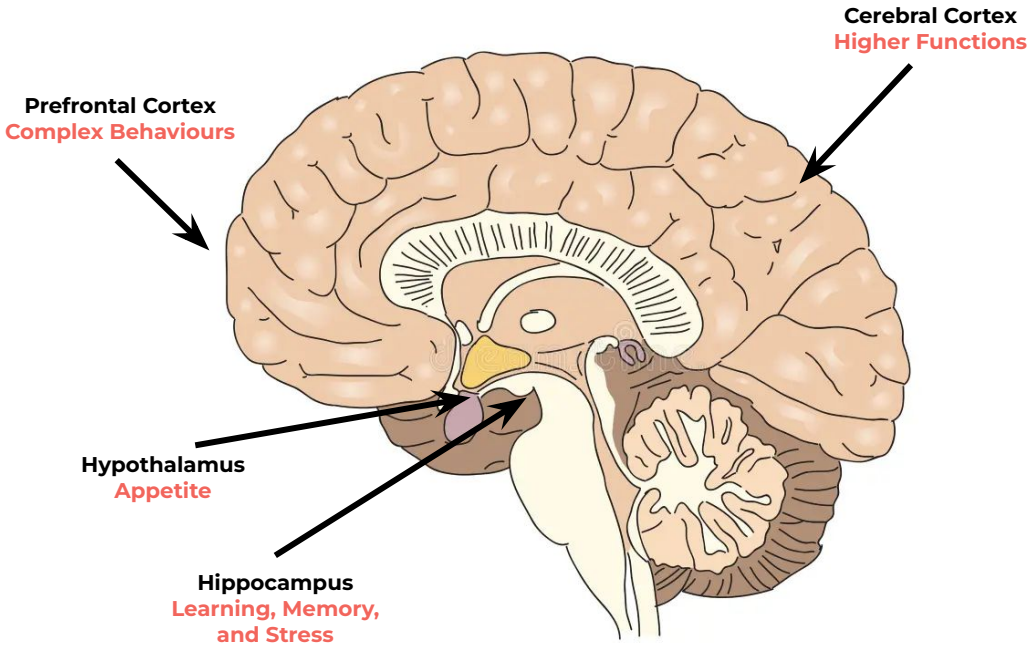
5-HT receptors have diverse functions in the brain, including regulation of sleep, mood, appetite and social functioning.



There are 14 serotonin (5-HT) receptors subtypes:

5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5A, 5-HT5B, 5-HT6, & 5-HT7

5-HT Receptors in the Brain



In the brain, 5-HT receptors are widespread although they feature particularly prominently in the **cortical regions**.

5-HT receptors have diverse functions in the brain, including regulation of **sleep, mood, appetite and social functioning**.

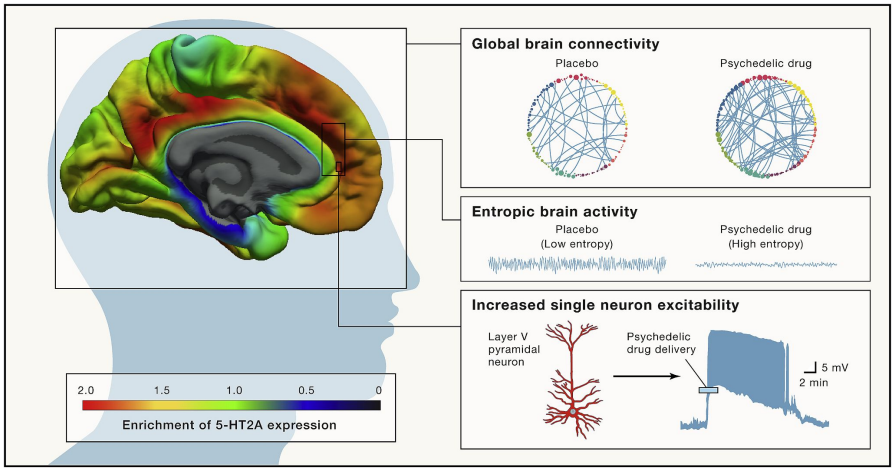
5-HT receptor expression is tightly controlled through the processes of transcription and translation, and may be up- or down-regulated in response to neurochemical influences.

5-HT2A and **5-HT2C** receptors are located predominantly in the "higher" areas, on cortical **layer V pyramidal neurons**, on cortical **glutamatergic neurons** and **GABAergic interneurons** of the prefrontal cortex.

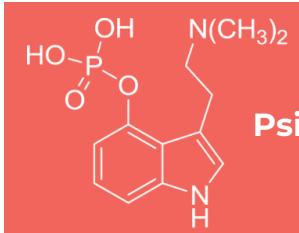
Modulating the 5-HT2A/2C Receptors

Besides being targets for the endogenous neurotransmitter, **serotonin,** the **5-HT2A** and **5-HT2C** receptors are activated by a wide range of serotonergic compounds including **psilocybin**, **mescaline** and **LSD**. Many of these compounds elicit distinctive effects on consciousness, although some (e.g. lisuride and 1-methylpsilocin) have been found to bind to the 5-HT2A/2C receptors but do not have psychoactive effects.

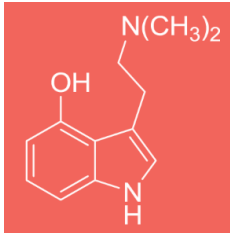
Those serotonergic compounds that exert psychedelic effects are commonly called the **"classical psychedelics"** The psychoactive effects of classical psychedelics appear to be mediated by interactions between the postsynaptic 5-HT2A and presynaptic **mGlu2 receptors** on glutamatergic neurons in the cortex. This has been supported by experiments using **5-HT2A antagonists that were shown to block the psychedelic effects** of psilocybin. However, the exact mechanisms are not yet clear, and are subject to ongoing research.



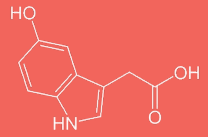
Psilocybin Pharmacology



Psilocybin



Psilocin



5-Hydroxyindoleacetic Acid

Psilocybin is relatively stable because its phenolic oxygen is “protected” as a phosphate ester. Psilocin is less stable and more easily oxidised due to its exposed 4-hydroxy group. Psilocybin is water-soluble, whereas psilocin is less so—yet both are orally active.

After oral dosing, psilocybin is rapidly dephosphorylated to psilocin. Psilocin typically peaks ~2 hours after dosing. Limited data suggest oral bioavailability around ~50-55%.

Psilocin is cleared mainly by glucuronidation (psilocin-O-glucuronide), with additional MAO-linked oxidation to 4-hydroxyindole-3- acetic acid (4-HIAA); newer metabolites include oxidized psilocin(humans) and norpsilocin (mice). Half-life: ~2–3 h in healthy adults.

Psilocin exposure varies widely between people, and common CYP2D6 variants don't seem to explain much of this; other genes (e.g., UGTs) may contribute and are still being studied.

Psilocybin's Psychoactive Properties

Psilocybin/psilocin is regarded as a prototypic classical psychedelic, and thus the main psychoactive effects of psilocin are due to binding to the 5-HT2A and 5-HT2C serotonin receptor subtypes, where it acts with high specificity as a partial agonist.

Agonism at the 5-HT2A receptor is thought to be most directly responsible for the typical psychoactive effects of changes in perception, visual patterns and discrete images, euphoria, distorted sense of time, synesthesia, emotional lability, and sometimes mystical or spiritual experiences.

Physiological Effects of Psilocybin

The physiological effects of psilocybin are primarily related to its activity at 5-HT receptors throughout the body, including the brain.

The most common physiological effects of psilocin include increased heart rate, pupil dilatation, and increased gastrointestinal motility due to the presence of 5-HT receptors throughout the gut. Nausea is also a relatively common, though not ubiquitous, effect of psilocin, and headaches are sometimes reported.

Psilocin has **no established toxicity** in humans. It is rapidly metabolised to harmless metabolites that are excreted in the urine.

Most Common Physical Effects

- Increased heart rate
- Pupil dilation
- Increased gastrointestinal motility
- Nausea

Psilocybin Risks and Adverse Effects

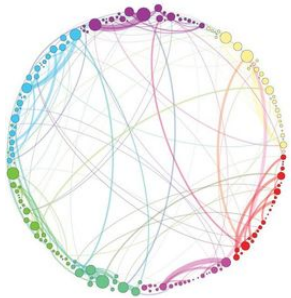
How Clinical Trials Manage Safety	Potential Psychological Risks of Psilocybin
• Common short-term effects: headache, nausea, dizziness, fatigue, and brief increased blood pressure • Challenging emotions can occur during dosing, but usually settle within 24-48 hours with preparation, support, and monitoring • Trials use strict screening, crisis plans, and follow-up after dosing • People with psychotic or bipolar disorders, unstable personality difficulties or very high suicide risk are excluded from clinical trials	• In patient groups, a small minority develop **worsening depression**, new suicidal thoughts/behaviour, or brief psychotic or manic symptoms during or in the weeks after dosing-very rare in healthy volunteers, but reported (Hinkle et al., 2024) • In non-clinical settings, many people report lasting benefits, but prospective surveys suggest ~7–11% report **persisting negative effects** in the weeks to months after psilocybin, such as mood fluctuations or depressive symptoms (Nayak et al., 2023) • A minority report short **"flashbacks"** or **re-occurring drug-like experiences**, mostly visual in nature. This occurred in up to 8.3% of healthy participants after psilocybin, and the experiences were predominantly mild and usually perceived as neutral to pleasant. Hallucinogen Persisting Perception Disorder (HPPD) appears very rare, but it has been described in case reports (Miller et al., 2022)

Structural and Neural Plasticity of Psilocybin

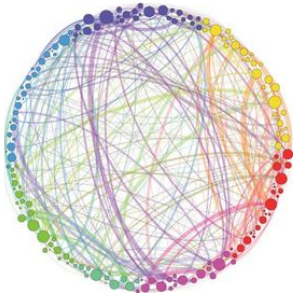
Psilocybin is increasingly described as a "psychoplastogen" — a compound that may produce rapid, lasting benefits by boosting brain plasticity after only one or a few doses.

- In mice, a single psilocybin dose increased the number and size of dendritic spines in frontal cortex by ~10% within 24 hours; many persisted at least a month and were linked to improved stress-related behaviour and stronger excitatory signalling (Shao et al., 2021).
- Psilocybin activates 5-HT2A receptors, which can engage downstream plasticity pathways (incl. BDNF/TrkB and mTOR) that support synapse growth and stabilisation. Separately, psilocin can bind TrkB directly and enhance endogenous BDNF-TrkB signalling; in mice, plasticity and antidepressant-like effects were TrkB-dependent and largely independent of 5-HT2A (Moliner et al., 2023).
- Some 5-HT2A receptors are found not only on the cell surface but also **inside neurons**. In cortical neurons, psychedelic-induced plasticity appears to require access to these **intracellular** receptors—helping explain why serotonin may not trigger the same growth programs (Vargas et al., 2023; Sonda et al., 2025).

Functional Connectivity and Default Mode Network (DMN)



Placebo



Psilocybin

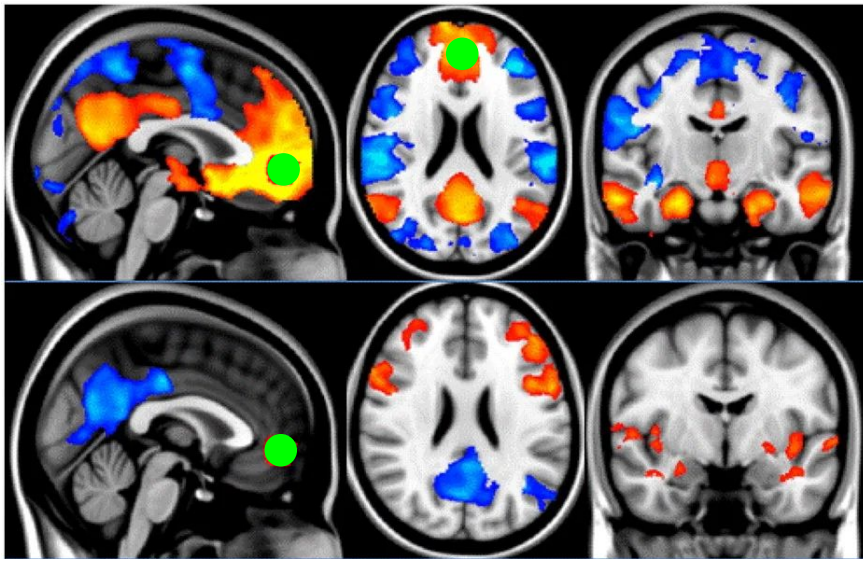
The **default mode network (DMN)** supports self-focused thought and is most active during rest (self-reflection, autobiographical memory, imagining the future). In depression and other mood disorders, this network can become overactive or rigid, and is often linked to **rumination** (repetitive, negative self-talk).

Across psychedelic imaging studies, a common acute pattern is **reduced internal coherence of the DMN** plus **stronger communication between different networks**, making brain activity look more globally "integrated" (Gattuso et al., 2022).

A **single high-dose psilocybin can strongly "desynchronise" brain networks**, producing >3x larger acute connectivity changes than methylphenidate (Siegel et al., 2024).

Some changes outlast the trip: the same study reported a weeks-long reduction in connectivity between the anterior hippocampus (involved in memory and emotion) and the DMN, candidate correlate of post-session flexibility.

Psychedelics Uncouple the DMN: Lifts Depression



Saline — strong correlations in activity in these regions

= seed region

Psilocybin — correlations lost or even negative

Carhart-Harris et al., 2012, *PNAS*

How Psilocybin Differs from SSRIs in the Brain

Both SSRIs (e.g., escitalopram) and psilocybin therapy can reduce depressive symptoms, but brain imaging suggests **different neural signatures**:

Network Reorganisation	Network reorganisation: Psilocybin therapy is linked to a **less modular (more globally connected)** brain state that can persist for weeks; comparable reorganisation is not clearly observed with escitalopram in the same datasets (Daws et al., 2022).
Different Dynamics	Different dynamics: Modelling of the psilocybin-vs-escitalopram trial suggests psilocybin may relax top-down hierarchical constraints (more flexible information flow), whereas escitalopram tends to reinforce a more directed/top-down pattern (Deco et al., 2024).
Emotion Processing	Emotion processing: SSRIs are often associated with **emotional blunting**—muted positive and negative affect (Ma et al., 2021). In an fMRI emotional-faces analysis, escitalopram reduced neural responses to emotional stimuli, while psilocybin therapy did not show the same dampening despite symptom improvement (Wall et al., 2025).

SSRIs may help by smoothing or muting emotional responses over time, whereas psilocybin may produce a **brief, high-impact reorganisation** that therapy and integration help translate into lasting change.

Psilocybin's Therapeutic Mechanisms

Network "Reset"

A high-dose psychedelic experience is like shaking up a snow globe, temporarily disrupting entrenched brain-network patterns (including DMN-related circuitry) and creating conditions for networks—and though patterns to "resettle" differently.

Plasticity "Window"

Preclinical studies show rapid increases in neural plasticity (new spines/branches, synaptic strength, plasticity- related programs). Human trials report that 1–2 psilocybin-assisted sessions can improve depression for weeks to months, beyond the drug's duration consistent with a window in which new learning and behaviour change may be easier to consolidate (Weiss et al., 2025).

What Predicts Better Outcomes:

- **Mystical-type experiences:** feelings of unity, ego-dissolution, deep connectedness or profound meaning – are associated with symptom reduction and improved quality of life across several conditions (Ko et al., 2022; Romeo et al., 2025).
- **Insight and emotional processing:** clear realisations about one's life, relationships or behaviour, together with the ability to fully feel and express emotions – are also linked to therapeutic improvement and, in some studies, show an even stronger association with positive change than mystical-type experiences (Kugel et al., 2025).

How the Psychoactive Effects May Affect Psychological Change

Mental distress is often maintained by **rigid and negative beliefs** about the self and the world (e.g. “I'm broken", "nothing will ever change”, “people can't be trusted”). It can also be driven by **repression and avoidance of traumatic or difficult memories**, feelings and thoughts, which can leave people feeling stuck.

Psychedelics can temporarily **loosen these rigid patterns** and the psychological defences that usually block difficult material, **while increasing openness and cognitive/emotional flexibility**. This allows buried or repressed material to surface, creating a window in which old beliefs, narratives and patterns can be faced and updated through therapy and integration.

Why Integration Matters:

Outcomes reflect not only pharmacology, but also context, support, and integration: how insights are interpreted and translated into daily-life change.

Life-Impact Outcomes of Psilocybin

Beyond symptom relief, psychedelic experiences can be followed by broader shifts in attitudes, values, and social/spiritual functioning.

Afterglow (Days to Weeks)

Reviews describe a short "afterglow" with improved mood, wellbeing, mindfulness and sense of connection, plus a changed perception of self, others and the environment (Evens et al., 2023).

Longer-Term Shifts

Some studies suggest enduring changes in personality, attitudes and spirituality, often linked to intense connectedness, emotional breakthroughs or "mystical-type" experiences (Aday et al., 2020; Schutt et al., 2024). Qualitative work has similarly documented themes of increased acceptance and reconnection with self and others (Watts et al., 2017).

Empathy and Prosocial Feelings

Meta-analytic data indicate that classic psychedelics can increase emotional empathy (feeling with others), while effects on perspective-taking are less consistent (Olami &Peled-Avron, 2024).

Nature, Values, and Wellbeing

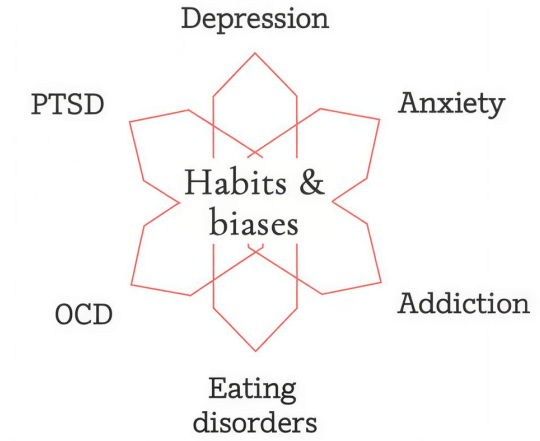
In psilocybin studies, people sometimes report stronger connection to nature (Forstman et al. 2023), modest shifts away from rigid or authoritarian attitudes (Lyons & Carhart-Harris, 2018), along with movement away from strictly materialist beliefs toward more spiritual or non-materialist worldviews in some participants (Timmermann et al., 2021).

Therapeutic Applications

Psilocybin is increasingly studied as a "transdiagnostic" treatment for **conditions linked to cognitive rigidity** (stuck thoughts, habits, avoidance). Early clinical and mechanistic work suggests psilocybin-assisted therapy may increase psychological flexibility, which could be relevant across multiple disorders.

The strongest clinical evidence is for major depressive disorder (MDD) and treatment-resistant depression (TRD).

Read more about emerging therapeutic targets in "Psilocybin History & Law"



Other emerging therapeutic targets include:

- Depression & anxiety, including existential distress in life-threatening illness
- Obsessive-Compulsive Disorder (OCD)
- Eating disorders (e.g., anorexia nervosa)
- Addictions (e.g., alcohol and nicotine use disorders)
- Headache disorders (e.g., cluster headache; evidence remains preliminary)

Psychedelic-Assisted Psychotherapy

Preparation

Day -14 to -1
1-4 Sessions

Dosing

Day 0
5-8 Hour Session

Integration

Day 0 to 6 Months
Multiple Sessions + Follow-Up

Psilocybin in modern trials is delivered as **psychedelic-assisted psychotherapy (PAP)**—a structured treatment that combines medication with psychological support **before, during, and after** the psychedelic session.

Preparation and integration are considered just as crucial as the dosing day itself. Preparation usually begins a few weeks before the psychedelic session, with integration meetings held repeatedly over the following months (often for up to six months).

Preparation: Safety and Consent

Listen to Drug Science Podcast featuring Dr Edward Jacobs and Sam Bloomfield on psychedelic ethics

Preparation is designed to make the dosing day safer, more predictable and more therapeutic, especially for people who have never taken psilocybin before. Key elements typically include:

Screenings & Exclusions	Careful medical and psychiatric risk assessment, medication review, and clear decisions about who is (and is not) suitable, excluding people at high risk of psychosis
Therapeutic Alliance	Building rapport, trust and a supportive “container" where difficult emotions can be explored without panic or judgement
Psychoeducation & Expectations	Explaining session logistics (length, setting, music, eyeshades), the range of possible experiences and how to respond if fear or resistance arises — emphasizing the principle of leaning in rather than pulling away
Skills for Navigating the Session	Practising acceptance, staying present, noticing thoughts without getting caught in them, and reconnecting with personal values and goals
Advanced Consent & Boundaries	Clear discussion of touch, privacy, recording, emergency procedures and the right to pause or stop at any point, with consent revisited over time

Dosing Session: Set and Setting

The dosing day brings together set and setting:

- **Set** - the emotional, cognitive and behavioural mindset and expectations shaped during the preparation phase.
- **Setting** - the physical environment in which the psychedelic session takes place.

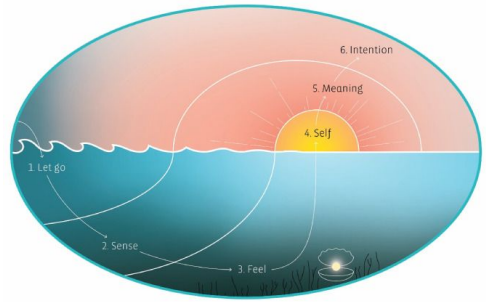
An example of the room at Imperial College London

Common Features Across Clinical Manuals:

- **Supportive environment**: A quiet, comfortable, confidential room with careful attention to lighting, temperature and privacy, and minimal interruptions.
- **Non-directive therapeutic stance**: Two trained therapists are present throughout, offering calm, empathic support. They “support, not steer”, encouraging an inward focus rather than talk-heavy therapy during peak effects.
- **Music and eyeshades**: Curated music and optional eyeshades are used to facilitate inward attention and emotional processing, with the patient free to adjust as needed.
- **Caring presence as an active ingredient**: Steady, compassionate human presence and a strong sense of relational safety are treated as central parts of the therapeutic effect, not just background conditions.

Integration: Meaning-Making & Sustained Change

Integration is the phase where people unpack their psilocybin experience and process it in depth, turning insights into meaningful, lasting behaviour changes in daily life—work that is difficult to do during the acute psychedelic state.



Watts & Luoma (2020)
J. Context. Behav. Sci. 15:92-102

Typical integration work includes:

- **Early debriefing:** A first check-in soon after dosing (often within hours), followed by additional integration sessions over the next weeks or months.
- **Narrative & meaning-making:** Revisiting key images, emotions and moments; normalising challenging content; linking the experience to current symptoms, history and life context.
- **Values-based action:** Using insights to clarify what really matters (values) and to plan concrete steps the last step in ACE (Accept, Connect, Embody) translates insights into everyday, value-guided behaviour change.
- **Safety & continuity of care:** Monitoring mood, anxiety, sleep and functioning; addressing any adverse effects; and coordinating with other clinicians (e.g. GP, psychiatrist, therapist) to keep care joined-up and stable.

PAP: Clinical & Therapeutic Frameworks

Acceptance and Commitment Therapy

ACT is a mindfulness-based therapy that helps people build psychological flexibility:

- Noticing and accepting difficult thoughts and feelings rather than fighting them,
- Committing to actions aligned with their core values, so they can live a meaningful life even when distress is present.

Accept, Connect, and Embody

ACE is a psilocybin-focused integration framework that supports people to:

- Accept painful or difficult experiences that arise,
- Connect with emotions, bodily sensations and personal values with curiosity and compassion,
- Embody insights by translating them into concrete, value-guided changes in everyday life.

Cognitive Behavioural Therapy & Motivational Enhancement Therapy

CBT and MET are structured talking therapies that help people:

- Understand triggers
- Build new coping skills
- Strengthen motivation to change

Used alongside psilocybin in trials for smoking and alcohol use disorders.

Psychedelic Harm Reduction

Psychedelic harm reduction is a non-clinical approach used in naturalistic settings (festivals, retreats) to support people having difficult psychedelic experiences.

Read the Yale ACT Manual for Psilocybin in Depression

Watch Dr Rosalind Watts Introduce the ACE Model

Read More About Harm Reduction & Peer Support Principles in “Psilocybin History and Law”

Psilocybin Suggestibility & Vulnerability

Although psilocybin can support therapeutic insight, the resulting increase in psychological openness can also **heighten suggestibility and interpersonal vulnerability:**

- During psychedelic states people may have reduced usual decision-making capacity, feel in a state of high uncertainty, and **become more susceptible to external framing** and guidance, which can amplify a facilitator's or therapist's influence (Villiger, 2024).
- Insights can feel powerful without guaranteeing accuracy: recent models suggest that psychedelics can boost the number and intensity of insights – including false ones – sometimes **strengthening confident but mistaken beliefs**, especially when set, setting and integration are not carefully managed (McGovern et al., 2024).
- Powerful psychedelic experiences can **reshape self-beliefs**. Survey data suggest they often evoke awe and connectedness, which is linked to lower maladaptive narcissism (van Mulukom et al., 2020), but other naturalistic work shows a more mixed picture, with mystical experiences sometimes associated with **higher "narcissistic admiration"** even as antagonistic “rivalry” is lower (Ruban et al., 2025).

Microdosing Psilocybin

Microdosing refers to taking very low, sub-perceptual amounts of a psychedelic (often ~1/10-1/20 of a full dose) on a regular schedule, e.g. every 2–3 days, with the aim of subtle benefits rather than a full psychedelic experience.

Overall, **psilocybin microdosing remains an experimental practice:** popular in culture, but with benefits and risks that are not yet well established in rigorous clinical research.

Studies on Microdosing

Although naturalistic and online surveys report **self-perceived benefits** of psilocybin microdosing, double-blind, placebo- controlled **studies have found no reliable advantages:** microdosing did not improve emotion processing or reduce anxiety/depression symptoms (Marschall et al., 2021), and a separate trial found no improvements in well-being, creativity, or cognition and suggested that expectancy/unblinding may account for at least some anecdotal benefits (Cavanna et al., 2022).

Key Findings

Recent systematic review/meta analysis of controlled microdosing studies found (Pinhas et al., 2025):

- No robust evidence that low doses of psilocybin (or other psychedelics) reliably improves memory, attention or executive functions. Reported cognitive or mood benefits tend to be small, inconsistent and often disappear when placebo and expectancy are carefully controlled.
- Low doses are generally well tolerated, but there is very little data on long-term safety, cumulative cardiovascular effects, or use in people with significant mental health problems or on complex medication regimens.

Drug-Drug Interactions

Drug-drug interactions happen when one medicine changes how another works or affects its safety. Because psilocybin and many psychiatric medications act on serotonin, combinations need careful planning.

SSRIs/SNRIs	• Examples:, sertraline, escitalopram, fluxoetine • Chronic SSRI/SNRI use can “blunt” psilocybin effects in many people, and survey data suggest this dampening can persist for up to several months after stopping in some cases (Gukasyan et al., 2023). • In clinical trials, participants are usually tapered off SSRIs/SNRIs for at least a few weeks before psilocybin. • In a small crossover RCT, 14-day escitalopram pretreatment did not reduce psilocybin's positive mood effects and reduced adverse (anxiety/cardiovascular) effects (Becker et al., 2021).
Tricyclic Antidepressants (TCA)	• Examples: desipramine, imipramine, clomipramine • Limited evidence suggests some TCAs may amplify or unpredictably alter classic psychedelic effects (Halman et al., 2023).
Antipsychotics	• Examples: chlorpromazine, risperidone • Tend to attenuate psilocybin's subjective effects, while D2-only blockade (haloperidol) does not reduce perceptual effects and may increase anxiety (Sarparast et al., 2022).
MAOIs	• Examples: moclobemide, higher-dose selegiline • May potentiate/prolong psilocybin by reducing MAO-A metabolism of psilocin; serotonin-toxicity risk appears theoretical with limited evidence, but hypertensive reactions have been reported with mushrooms +MAOI combinations (Tap et al., 2025).
Other 5-HT2A Receptors Antagonists	• Examples: ketanserin, mirtazapine, trazodone • Expected to cause a blocking or loss of psychedelic effects (Wall et al., 2024).

Next-Generation Psilocybin Medicines

Natural psilocybin mushrooms vary widely in alkaloid content. Pharmaceutical psilocybin is designed to provide consistent dosing, high purity and better stability for clinical use.

Standardised Psilocybin Products	More Innovations
• **COMP360 (COMPASS Pathways):** a stabilised crystalline synthetic psilocybin formulation. A Phase 3 trial in treatment-resistant depression (COMP005) has reported a positive primary outcome, and a second pivotal Phase 3 (COMP006) is underway to support regulatory submissions. • **25 mg synthetic psilocybin (Usona):** being tested in the Phase 3 uAspire trial for major depressive disorder, with extended follow- up to assess durability and longer-term safety. • **MSP-1014 (Mindset / Otsuka):** an oral "psilocybin-like" prodrug of psilocin being tested in an adaptive Phase 2a/2b programme for major depressive disorder.	• **Toward More Predictable Session Length:** IV psilocin benzoate (ELE-101) is an investigational intravenous psilocin formulation aimed at producing a more controllable, ~2-hour psychedelic session in early proof-of-concept studies. • **Neuroplasticity Without the "Trip":** Experimental "psychoplastogens" seek to harness neuroplasticity with weaker or absent psychedelic effects, but it is still unclear whether full clinical benefits can be separated from the subjective experience. • **Formulation Intellectual Property:** Many patents now focus on crystalline forms, stabilised psilocybin/psilocin mixtures and novel delivery routes (e.g. rapid-onset or sublingual approaches), which may influence both clinical use and market access.

Emerging Frontiers Beyond Psychiatry

Beyond mood and perception, newer lab and preclinical work is exploring how psilocybin might interact with the immune system, the gut-brain axis and biological aging.

Immunity and Inflammation

A recent systematic review of animal and cell studies finds that classic psychedelics can alter immune signalling. They often reduce inflammation in already inflamed models, but may have neutral or even pro-inflammatory effects under normal baseline conditions, suggesting context-dependent immunomodulation (Low et al., 2024).

Gut-Brain Axis & the “Psilocybiome”

Reviews propose that the gut microbiome and microbiota-gut-brain axis could shape how people respond to psychedelic therapy across preparation, dosing and integration, but direct human data are still very limited (Kelly et al., 2022).

Aging Biology

A 2025 mouse study reported that psilocybin/psilocin influenced several “hallmarks of aging" (e.g. cellular senescence, DNA stability) and improved survival in aged animals, raising interest in longevity research (Kato et al., 2025).

MIND MEDICINE AUSTRALIA

Drug Science

Why We Need More Research

1	Clinical research is fundamental to government approval of new drugs and medical interventions.
2	Regulatory authorities require large, well-designed trials showing not just efficacy, but also safety, consistent manufacturing and clear standards for the therapy component.
3	We still need longer follow-up to understand how long benefits last, how often people relapse, and how often rare or delayed adverse events occur in real-world use.
4	More data are needed in diverse groups (e.g. multiple diagnoses, trauma histories, different socio-cultural backgrounds) and on interactions with common medications.
5	Research is still clarifying how 5-HT2A signalling, brain-network changes, plasticity and the quality of the experience and psychotherapy combine to drive outcomes.
6	Key open questions include how to handle blinding/placebo issues, which psychotherapy models work best, how to train and supervise therapists, and how to make any future services affordable and accessible.

MIND MEDICINE AUSTRALIA

Drug Science

Into the Future

Check the Psychedelic Perception Tracker

Public Attitudes to Psilocybin-Assisted Therapy in the UK

- **Global research is accelerating:** Psilocybin has moved from small pilot studies to large, multicentre Phase 2 and Phase 3 trials, with active engagement from regulators in North America, Europe, Australia and beyond.
- **Public perceptions are shifting, but cautiously:** UK polling suggests a majority support easing restrictions for psilocybin research (55%) and many would consider psilocybin-assisted therapy if evidence-based (59%).
- **Limited access models are emerging internationally:** U.S. states Oregon and Colorado allow for regulated, supervised psilocybin access, while countries like Australia and Germany permit regulated clinical access under national scheduling frameworks, and others, including Switzerland and Canada, maintain narrower medical/special-access pathways.
- **Implementation will be the next challenge:** As psilocybin medicines move from approval to scaled delivery, health systems face ongoing challenges around trained staff, clear care pathways, suitable facilities, long-term monitoring for relapse, rare adverse events, and equitable access — with early implementation lessons already emerging from Australia, Oregon, and Colorado.
- **Payment and reimbursement remain uncertain:** Although insurers and health systems are watching the field, major questions remain about delivery models, staffing/time costs, and reimbursement.

References

Becker AM, et al. (2022). Acute effects of psilocybin after escitalopram or placebo pretreatment in a randomized, double-blind, placebo-controlled. crossover study in healthy subjects. Clinical Pharmacology & Therapeutics. 111(4):886–895.

Carhart-Harris RL, & Friston KJ. (2019). REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics. Pharmacological Reviews, 71(3):316–344.

Daws RE, et al. (2022). Increased global integration in the brain after psilocybin therapy for depression. Nature Medicine, 28(4):844-851.

Gattuso JJ, et al. (2023). Default mode network modulation by psychedelics: A systematic review, International Journal of Neuropsychopharmacology. 26(3):155-188.

Moliner R, et al. (2023). Psychedelics promote plasticity by directly binding to BDNF receptor TrkB, Nature Neuroscience, 26(6):1032-1041.

Nutt, D. (2024). Psychedelics: The revolutionary drugs that could change your life—A guide from the expert, Balance,

Pollan, M. (2018). How to change your mind: the new science of psychedelics. Penguin Books.

Shao L-X, et al. (2021). Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo. Neuron. 109(16):2535-2544.e4.
Vargas MV, et al. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. Science. 379(6633):700-706.

Watts R, & Luoma JB. (2020). The use of the psychological flexibility model to support psychedelic assisted therapy. Journal of Contextual Behavioral Science. 15:92-102.

drugscience.org.uk