MDMA

By Drug Science,
Mind Medicine Australia

With Support from
Norrsken Mind

Part II - Pharmacology and Therapeutic Mechanisms

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.

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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.

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What is MDMA?

MDMA (3,4-methylenedioxy methamphetamine) is a small organic compound known as a monoamine alkaloid, related chemically to **amphetamine**. Its amine group is methylated, which makes it more closely related to **methamphetamine**, although its pharmacology is significantly different.

MDMA was first synthesised around 1912 by chemists at the pharmaceutical company, Merck in Germany, and was patented at that time as an intermediate in the synthesis of compounds that Merck was hoping to develop as regulators of bleeding.

MDMA is characterised by the presence of the 3,4-methylenedioxy ring, which occurs in naturally occurring compounds including myristicin, present in nutmeg, and safrole, present in sassafras.

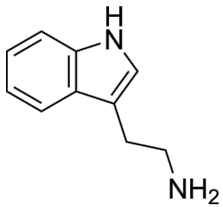
MDMA may be synthesised from natural product sources such as safrole or isosafrole, or from organic precursors used in industry and pharmaceutical manufacture.

Different Psychoactive Drugs

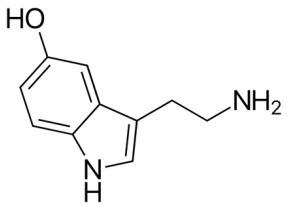
Classical Psychedelics **5HT2A Receptor Agonists** *LSD, Psilocybin, DMT, Mescaline*	**Entactogens** **Serotonin Receptor Agonists** *MDMA, MDA, MMDA, 2C-series, etc.*
Dissociative Anaesthetics **NMDA-Agonists** *Ketamine, PCP, N_2O*	**THC** **Cannabinoid Receptor Agonist**
Ibogaine **Nicotinic Receptor Antagonist**	**Salvia** **Kappa-Opioid Receptor Agonist**

What sort of drug is MDMA?

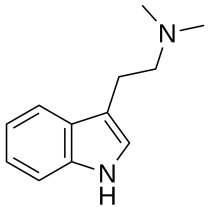
Tryptamines



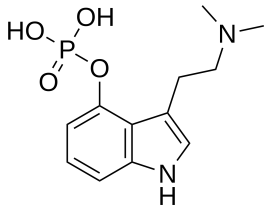
Tryptamine



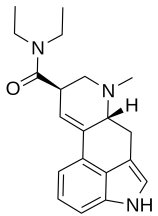
Serotonin



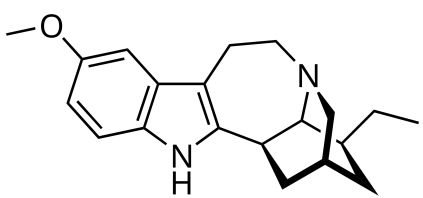
DMT



Psilocybin

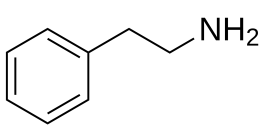


LSD

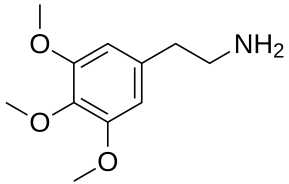


Ibogaine

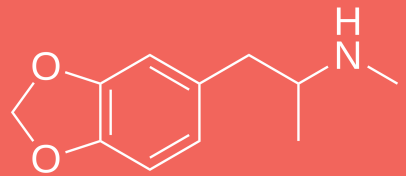
Phenethylamines



Phenethylamine



Mescaline



MDMA

While not a classical psychedelic, MDMA is a member of the larger group of ring-substituted phenethylamines.

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Drug Science

How does MDMA work?

MDMA mainly **increases the levels** of three key brain chemicals **(serotonin, noradrenaline and dopamine)** by making nerve cells **release more** of them into the synapse.

MDMA enters serotonin, noradrenaline and dopamine neurons via their transporters (SERT, NET, DAT) and briefly "reverses" these pumps, so they push monoamines **out** into the synaptic space instead of reabsorbing them. 1

MDMA also disrupts monoamine storage in synaptic vesicles via **VMAT2**, and may act at targets such as **TAARI**, further shaping release and reuptake. 2

MDMA reliably raises **oxytocin** (and often cortisol, prolactin and vasopressin), likely as a knock-on effect of serotonergic activation rather than strong direct hormone- receptor action. 3

The profile is strongly **serotonergic**, with notable **noradrenergic** activation and smaller but important **dopamine** increases (linked to stimulation and reward). 4

MDMA itself has only modest affinity at receptors like **5-HT$_2$A** and some adrenergic sites; most physical and psychological effects are **indirect**, downstream of monoamine release. 5

MDMA's Action in the Brain

System/Target	What MDMA Does	Typical Acute Effects	Clinical Relevance
Serotonin (5-HT)	↑ 5-HT release (via SERT reversal)	Elevated mood, emotional openness, empathy/prosocial feelings	Major contributor to "entactogenic" profile
Norepinephrine (NE)	↑ NE release (via NET reversal)	Arousal/alertness; ↑ heart rate and blood pressure	Main driver of cardiovascular stimulation
Dopamine (DA)	↑ DA release (via DAT reversal)	Stimulation, motivation/reward	Generally smaller than 5-HT component
Threat/Fear Circuits (Amygdala)	↓ Threat reactivity to negative cues	Less fear/avoidance; easier access to difficult material	May support trauma processing
Oxytocin & Social Bonding	Transient ↑ oxytocin	Increased warmth, bonding, trust	May contribute to prosocial effects; not the only mechanism
Downstream 5-HT Receptors	Indirect activation (5-HT1A/2A/2C etc.)	Shapes mood/anxiety, perception/meaning	MDMA direct 5-HT2A agonism is weak; metabolite MDA is more 5-HT2A-active

Serotonin

Serotonin (or 5-hydroxytryptamine, 5-HT) is one of several **monoamine neurotransmitters** in living organisms that have very **fundamental functions** in basic physiology. In higher animals, it is also important for psychological function.

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

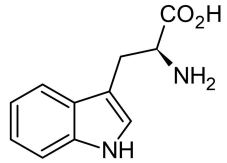
Serotonin was the **first of the monoamine neurotransmitters to be discovered**, as a consequence of LSD research in the 1950s. The discovery of serotonin led to the elucidation of receptors and their fundamental role in neurological function.

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).**

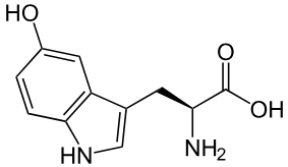
Monoamine oxidase (MAO)
Both subtypes (-A & -B) occur widely in the brain and peripheral tissues. MAO-A is more selective for serotonin oxidation by being able to metabolise serotonin with lower Km and higher affinity than MAO-B.

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



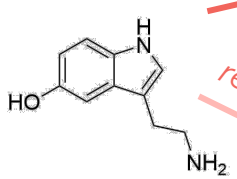
L-Tryptophan

THP



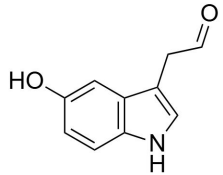
5-Hydroxytryptophan

AADC



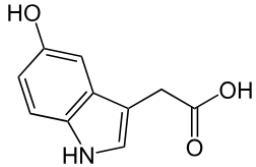
Serotonin

MAO



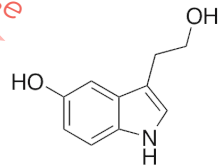
5-Hydroxyindole acetaldehyde

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.

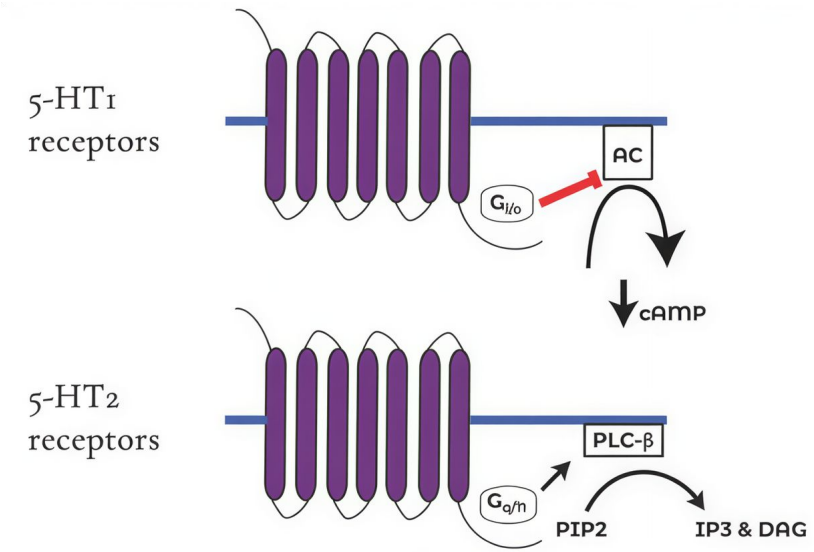
Serotonin Receptors

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:

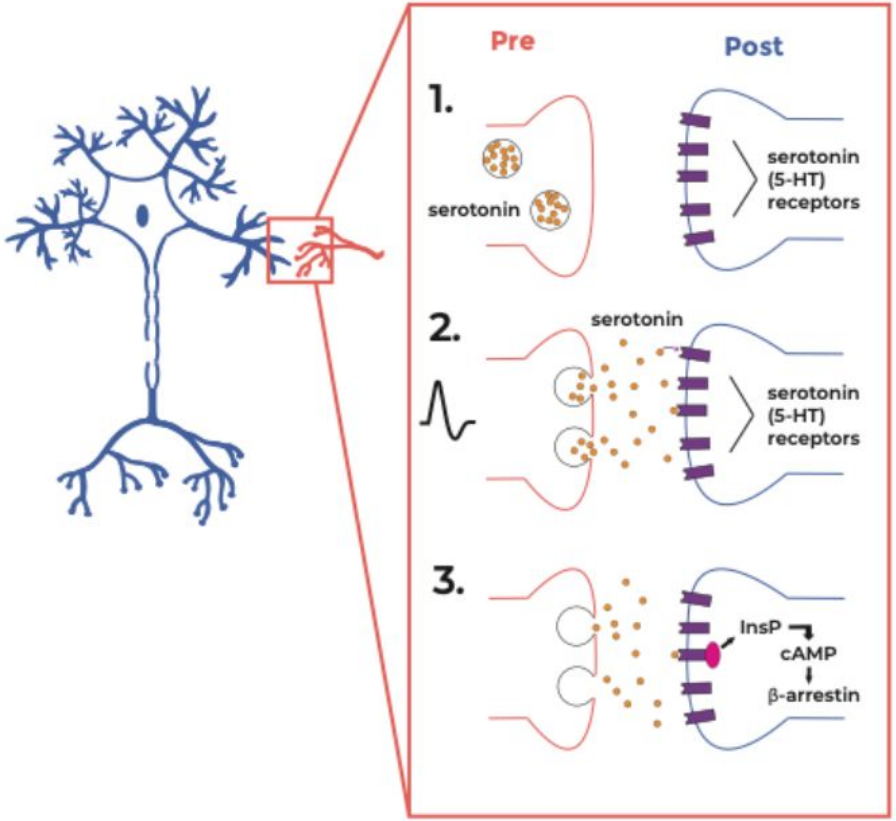
5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5A, 5-HT5B, 5-HT6, & 5-HT7

Serotonin Signalling

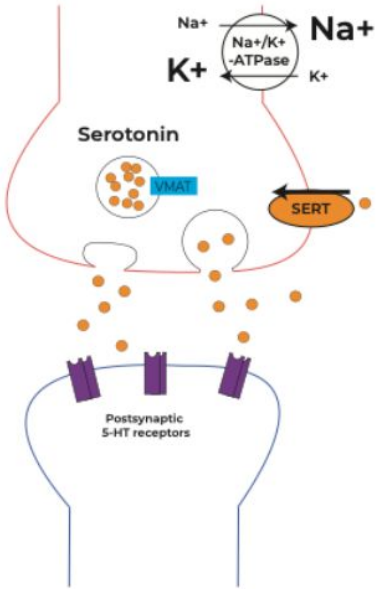
Neurotransmitters generally travel from the **presynaptic bouton** across the synaptic cleft to act on **postsynaptic receptors**. Serotonin is stored in vesicles at the bouton of the presynaptic neuron.

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.



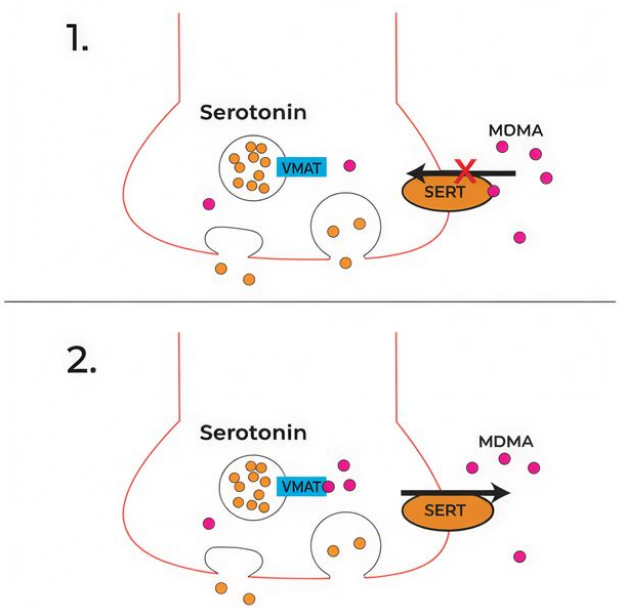
Serotonin Transporter



The serotonin transporter (SERT) is a protein embedded in the cell surface of the presynaptic neuron. Its function is to transfer 5-HT molecules back into presynaptic vesicles from the synaptic cleft, thereby preventing them from binding to the postsynaptic 5-HT receptors and exerting their neurotransmitter activity.

SERT functions in a sodium-dependent manner, meaning that a gradient of sodium concentration must exist across the membrane for the transporter to function.

SERT Modulation



SERT function may be affected by several factors, including binding by several classes of drugs, some naturally occurring and others produced by chemical synthesis.

Two major modulatory effects are:

Reuptake Inhibition

A drug binds to the transporter and interferes with the normal process of reuptake into the storage vesicles. Antidepressants of the Selective Serotonin Reuptake inhibitor (SSRI) class are examples of this type of drug. **MDMA acts as a serotonin reuptake inhibitor via a complex process of transporter withdrawal from the cell membrane of the presynaptic neuron.**

Neurotransmitter Release

A drug binds to the transporter and reverses the direction of neurotransmitter transport, resulting in efflux of the transmitter into the synaptic cleft. **MDMA acts as a serotonin releaser via its action at Vesicular Monoamine Transporter 2 and consequently reversal of the action of SERT.**

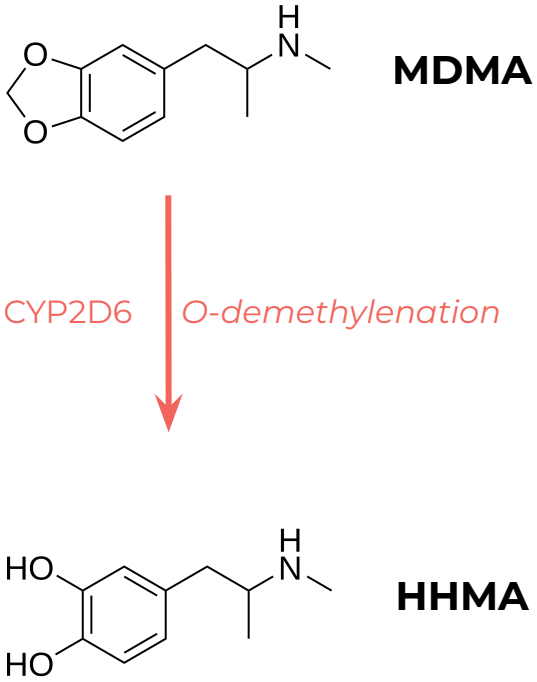
MDMA Pharmacology

MDMA is usually given as a crystalline salt (e.g. MDMA HCl), which **dissolves easily in water and is well absorbed by mouth**.

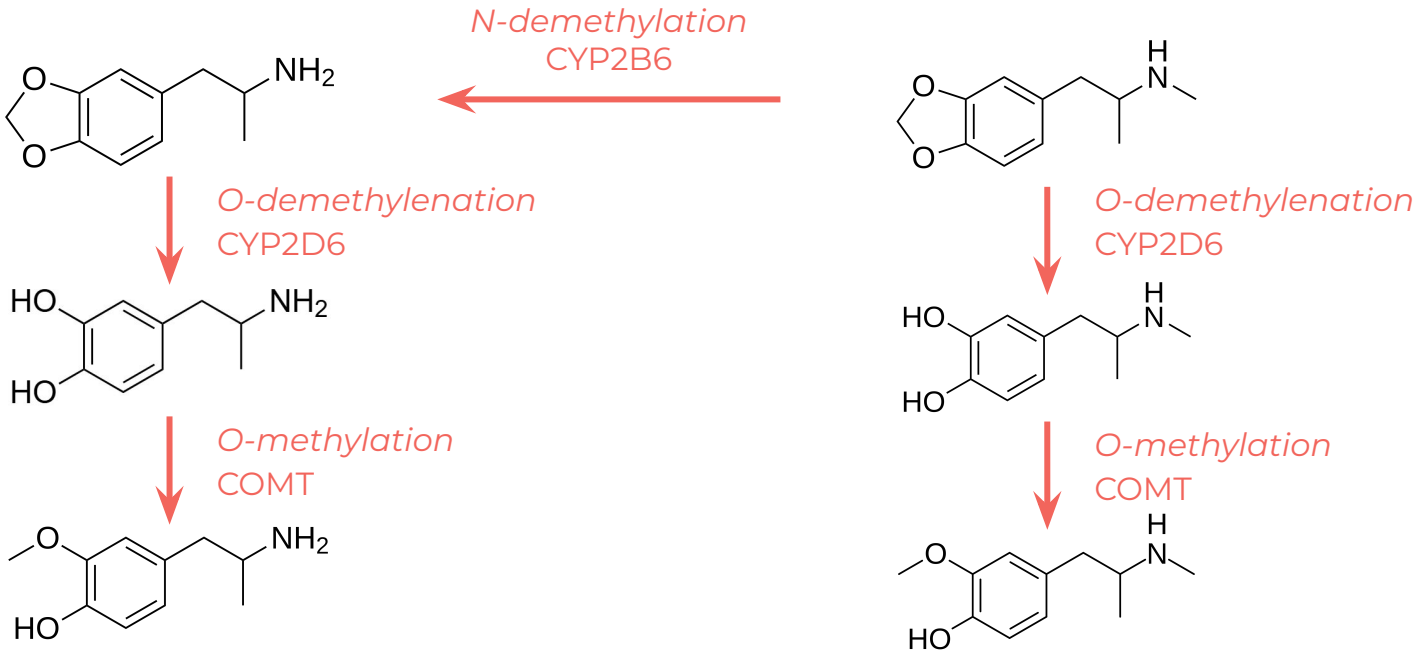
After an oral dose, **blood levels typically peak about 1-3 hours later**. Food doesn't change overall exposure much, though a heavy meal can delay the peak.

MDMA is broken down mainly in the liver. It inhibits its own main enzyme (CYP2D6), so higher doses can slow its own breakdown (non-linear kinetics). Key metabolic pathways include O-demethylenation to HHMA followed by O-methylation to HMMA, and N- demethylation to MDA. The elimination **half-life is roughly 7-9 hours**, with most of MDMA and its metabolites **excreted in urine**.

People vary in how they process MDMA, but CYP2D6 genetics usually have only a moderate impact in practice, because MDMA temporarily phenoconverts" many users toward lower CYP2D6 activity. Other genetic and physiological factors may influence who is more prone to problems like hyponatraemia or cardiovascular strain, and this remains an active research area.



MDMA Metabolism



MDMA's Psychoactive Properties

MDMA is often described as an ***entactogen*** or ***empathogen*** – a drug that tends to enhance emotional insight and connection, rather than producing the vivid perceptual changes seen with classic psychedelics.

Most of MDMA's **psychoactive effects come from its ability to release large amounts of serotonin into the synapse** (along with smaller increases in noradrenaline and dopamine). MDMA itself has only modest affinity for 5-HT2A receptors, so most of its physical and psychological effects are indirect, arising downstream from this monoamine surge rather than from strong direct receptor agonism.

Typical oral session:

- Onset: ~30-60 minutes after dosing
- Peak: ~1-3 hours
- Main effects: ~4-6 hours, followed by a gradual "come-down"

The quality of the experience is highly **context-sensitive**: dose, setting, music, the therapists' stance and the person's expectations all strongly influence whether the session feels opening, challenging, or deeply meaningful.

Physiological Effects of MDMA

Typical effects during a session (usually short-lived):

- Increased heart rate and blood pressure (mild "fight-or-flight" activation)
- Jaw clenching/tight jaw, muscle tension
- Sweating, chills or feeling unusually hot or cold
- Nausea and reduced appetite
- Restlessness or feeling "wired"
- Dilated pupils and sometimes flickering eve movements or blurred vision

Short-Lived After-Effects (Hours to a Few Days)

Tiredness

Poor Sleep

Low Appetite

Psychological Effects of MDMA

MDMA reliably alters mood, perception, and social connectedness. With preparation, skilled support, and integration, most psychological effects resolve within days.

Common Acute Effects

- Euphoria / sense of well-being
- Increased sociability, empathy, and emotional openness
- Reduced fear/defensiveness (often described as anxiolysis)
- Enhanced capacity for emotional processing (especially in a supportive therapeutic setting)

Challenging experiences can also occur - Episodes of **intense anxiety, fear, grief, or emotional overwhelm**, particularly as traumatic material surfaces during therapy.

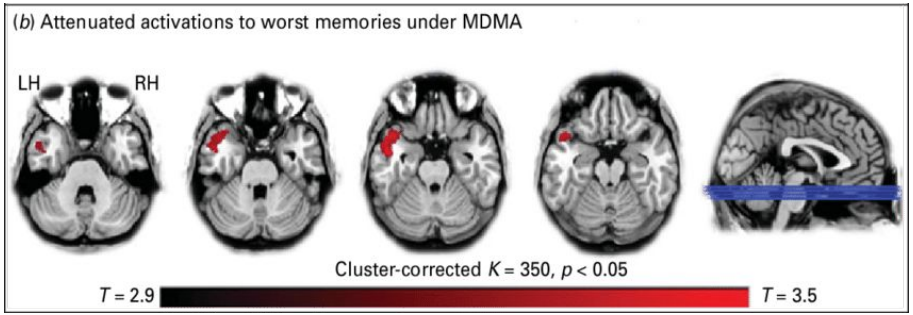
MDMA Reduces Brain Activity in the Stress Circuit

Insula

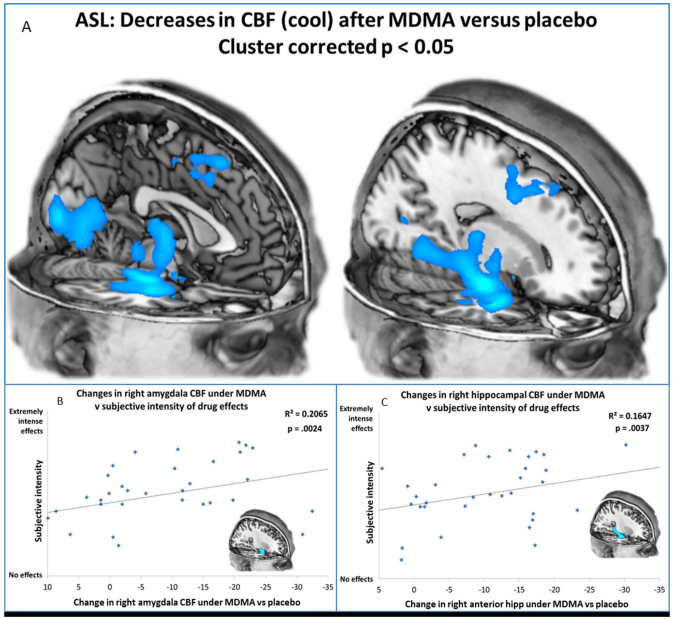
MDMA reduces activity in the insula, a region involved in interoception and the subjective sense of threat, which may explain the reduction in inner feelings of fear and bodily anxiety that patients commonly report

Hippocampus and amygdala

MDMA also reduces activity in these regions, dampening the intense emotional response to traumatic memories and allowing patients to revisit difficult experiences with greater psychological safety during therapy



Carhart-Harris et al., 2015, *Biological Psychiatry*



Carhart-Harris et al., 2014, *International Journal of Neuropsychopharmacology*

MDMA Risks and Adverse Effects

How Clinical Trials Manage Physical Safety

- Main concern: ↑ blood pressure and heart rate
- Fixed doses only after medical/cardiovascular screening (incl. ECG + baseline vitals)
- Close monitoring during the 6-8 hour session + guidance on hydration, rest, and aftercare
- Limits on total dose/sessions and no polydrug use

Rare But Important Psychological Risks

- A minority experience worsening PTSD symptoms, low mood, suicidal thoughts or brief dissociative episodes during or after dosing
- Trials typically exclude people with psychotic or bipolar disorders, use close in-session monitoring, and provide structured follow- up and integration support

Higher-Risk Factors Outside Clinical Settings

- Risk rises with unknown pill purity/adulterants, high or repeated doses, mixing with other drugs or medications, heat/crowds/exertion and severe sleep los
- Serious complications, although uncommon, can include hyperthermia, hyponatraemia, abnormal heart rhythms, serotonin syndrome and hepatitis with multi-organ failure
- Longer-term concerns mainly relate to heavy or frequent "ecstasy" use (often with other drugs): more anxiety/depressive symptoms and small cognitive changes
- Repeated high-dose use can also lead to tolerance, cravings and "come-down" withdrawal-like symptoms (fatigue, low mood, poor concentration)

MDMA Therapeutic Mechanisms: Emotional Safety

MDMA may support therapy by **reducing fear** and **increasing connection**, so people can stay with difficult memories instead of shutting down or avoiding them.

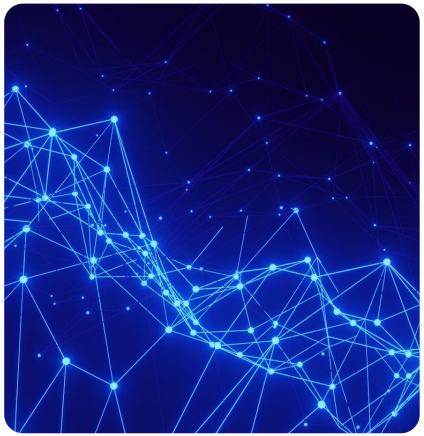
1. **It softens threat responses and is associated with reduced fear, shame and emotional "numbing" during sessions, which can make trauma processing more tolerable (Mitchell et al., 2023).**

2. **It often increases feelings of openness, closeness and trust. This can strengthen the therapeutic relationship and make it easier to talk honestly about painful experiences (Lewis & Byrne, 2023).**

3. **It reliably causes a short-lived rise in oxytocin (sometimes called the "bonding hormone"), which may support these prosocial effects. However, oxytocin is only one part of a wider pattern of changes in mood, social cognition and threat processing (Vaslavski et al., 2025).**

MDMA Therapeutic Mechanisms: Memory Processes

One leading idea is that MDMA helps update traumatic memories by influencing learning and memory processes:



- In animal and early human work, MDMA seems to support **"extinction learning"** – forming new, safer associations that compete with old fear responses, similar to what exposure therapy aims to do (Sottile & Vida, 2022).
- MDMA allows for **memory reconsolidation**. When traumatic memories are re-activated under MDMA in a safer emotional state, they may be "re-stored" in a less overwhelming form, allowing new meaning and context to be attached (Luoma et al., 2021).

- These mechanisms are strongly supported by preclinical studies and are widely discussed as plausible in humans, but direct proof that they drive clinical outcomes is still emerging (Sarmanlu et al., 2024).
- During the acute MDMA state, while memory is the most affected cognitive domain, **attention and executive function are largely preserved**, which allows many people to engage in talk therapy during MDMA sessions (Basedow et al., 2024).

MDMA Therapeutic Mechanisms: Plasticity “Window”

Listen to Drug Science Podcast on critical periods and the famous MDMA octopus study

MDMA is increasingly described as a modest psychoplastogen - a drug that may open a temporary window of heightened learning and neural plasticity.

- Preclinical work suggests MDMA may reopen a critical period for social reward learning, pointing to a time-limited state of social neuroplasticity where supportive relationships and therapy may reshape patterns more deeply (Schmid & Bershad, 2024).
- Contemporary models suggest MDMA may increase psychological and neural malleability, implying that psychotherapy and the surrounding context may be especially influential in shaping what is learned or unlearned (Agnorelli et al., 2025).
- Human studies have not yet shown a clear, consistent increase in markers like blood BDNF after MDMA. This doesn't rule out plasticity effects, but it means we still need better tools to measure them in people (Calder et al., 2024).

MDMA Therapeutic Mechanisms: Summary

Mechanism	MDMA Shift	Therapeutic Relevance
Threat/Fear Circuitry	↓ Fear/threat reactivity	Easier to face traumatic material with less avoidance
Social Connection/Bonding	↑ Trust, closeness, openness (incl. oxytocin-related effects)	Stronger therapeutic alliance; more willingness to engage
Emotional Learning	↑ Fear extinction learning	New "safe" learning can replace old fear responses
Memory Updating	↑ Reconsolidation/reprocessing potential (proposed)	Traumatic memories may be updated in a safer state
Neuroplastic “Window”	↑ Short-term plasticity (modest psychoplastogen; proposed)	Therapy may have more leverage for lasting change
Communication / Engagement	↑ Ability to talk and process in-session	Supports active therapeutic work during dosing (not only after)

MDMA Therapeutic Applications

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

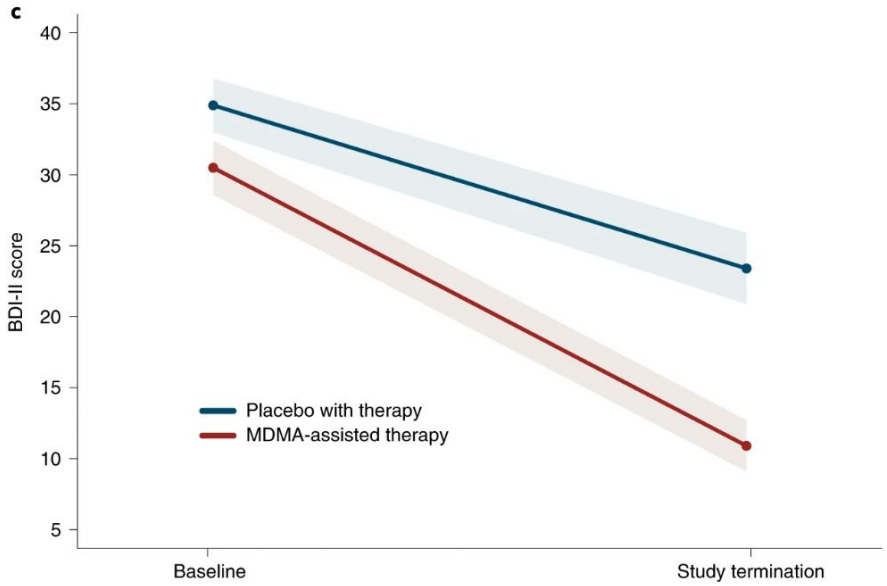
MDMA-assisted psychotherapy is most advanced as a trauma-focused intervention, where its acute effects may reduce fear and defensiveness while increasing emotional engagement and trust—potentially making it easier to process painful memories and strengthen therapeutic connection.

The strongest clinical evidence is for post-traumatic stress disorder (PTSD).

Other emerging therapeutic targets include:

- Alcohol use disorder (AUD)
- Social anxiety in autistic adults
- Couples / relational distress
- Eating disorders (especially with comorbid PTSD)

MAPS-Sponsored MDMA-Assisted Psychotherapy for PTSD trials



MAPP1 — Phase 3 clinical trial for severe PTSD

- Symptom severity roughly halved in the MDMA group compared to therapy alone, a large effect by clinical standards
- 67% no longer met diagnostic criteria for PTSD at 18 weeks, vs 32% in the placebo group
- No signals for abuse potential, suicidality, or dangerous heart rhythm changes

Mitchell et al., 2021, *Nature Medicine*

MAPP2 — Confirmatory trial for moderate-to-severe PTSD

- 86.5% of MDMA-treated participants showed clinically meaningful improvement; 71.2% no longer met diagnostic criteria for PTSD
- 46.2% met full remission criteria
- No deaths or serious treatment-emergent adverse events

Mitchell et al., 2023, *Nature Medicine*

MDMA-Assisted Therapy (MDMA-AT)

Preparation

~3 sessions in the weeks before dosing

Dosing Session

~2-3 sessions, ~6-8 hours each, ~1 month apart

Integration

Multiple sessions + follow-ups (weeks-months)

MDMA in modern trials is delivered as **MDMA-assisted therapy (MDMA-AT)**—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 dosing session, with integration meetings held repeatedly over the following months (often for up to six months).

Preparation: Safety and Consent

Watch MAPS overview of what MDMA therapy really involves

Preparation ensures that the MDMA dosing days are emotionally safe, clinically appropriate, and grounded in a strong therapeutic relationship. Key elements typically include:

Screenings & Exclusions	Comprehensive medical and psychiatric evaluation, medication review (especially serotonergic drugs), and decisions about suitability and dosing safety.
Therapeutic Alliance	Building deep trust and rapport with two trained therapists who will also be present during dosing sessions.
Psychoeducation & Expectations	Orientation to session structure (length, environment, music, support style), potential emotional intensity, and the range of possible experiences.
Coping & Grounding Skills	Learning to notice and stay with sensations, emotions, and memories as they arise, using grounding, breathing, and mindful acceptance.
Informed Consent & Boundaries	Clear discussion of touch, confidentiality, emergency protocols, and the participant's right to pause or stop at any 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.

MAPS MDMA session

Common Features Across Clinical Manuals:

- **Set & Setting:** A comfortable, private room with soft lighting, eyeshades, and music to support inward focus; both therapists remain present throughout.
- **Therapeutic Stance:** Empathic and non-directive, yet responsive-therapists invite participants to speak when helpful and engage in dialogue that supports processing, grounding, or meaning-making as emotions or memories arise.
- **Relational Safety:** The co-therapy model (typically one male and one female therapist) provides a secure, attuned relational base for exploring fear, grief, or trauma without avoidance.
- **Session Flow:** Each dosing session lasts --6-8 hours; participants usually have 2-3 sessions spaced ~1 month apart. A supplemental ("booster") dose is often given -1.5-2 hours after the initial dose.
- **Aftercare:** Participants remain on site until fully oriented and emotionally stable, with overnight contact or next-day check-in to ensure safety and continuity of support.

Integration: Meaning-Making & Sustained Change

Integration sessions help participants understand and apply insights from the MDMA experience to daily life, relationships, and long- term healing.

Typical integration work includes:

- **Early debriefing:** First integration within 24 hours, followed by multiple sessions in the following weeks.
- **Processing memories & emotions:** Revisiting experiences that surfaced, linking them to personal history, and reinforcing new perspectives or self-compassion.
- **Values-based action:** Translating insights into concrete life changes, improved relationships, and healthier coping patterns.
- **Safety & continuity:** Monitoring for post-session anxiety, sleep changes, or mood shifts; maintaining communication with participants' broader care teams.
- **Long-term follow-up:** Scheduled check-ins for up to 6 months post-therapy in most research protocols.

MDMA Suggestibility & Vulnerability

Although the "prosocial" state produced by MDMA can enhance the therapeutic process, it can also increase interpersonal vulnerability:

- Less fear and more trust can **amplify a therapist's influence**, so subtle cues (tone, framing, and suggestions) may carry extra weight.
- Because MDMA can heighten empathy, some patients may **start attending to therapists' wellbeing** if they sense fatigue or burnout, pulling focus away from their own process (Perivoliotis et al., 2025).
- MDMA can heighten sensitivity and increase the perceived pleasantness of touch, which can **impair some people's ability to clearly provide or withdraw consent** during dosing sessions.
- Lab data suggest MDMA produces a complex memory profile, but does not clearly increase vulnerability to external suggestion in misinformation tasks (Kloft et al., 2022).
- However ethics authors still highlight **risks** of coercion, boundary violations, and even sexual misconduct if safeguards are weak.

Common practical safeguards, apart from a clear discussion of touch and consent, also include having two trained therapists during dosing and video-recording where appropriate to strengthen safeguarding.

Drug-Drug Interactions

Drug-drug interactions happen when one medicine changes how another works or affects its safety. Because MDMA acts on serotonin, norepinephrine and dopamine, and is metabolised by CYP2D6, mixing it with psychiatric drugs can significantly alter both effects and risks. Summary based on Sarparast et al., 2022.

SSRIs/SNRIs	• Examples:, sertraline, escitalopram, fluxoetine • Markedly blunt MDMA's subjective and emotional effects, reducing feelings of well-being, empathy, and closeness by 30-80%. Heart rate and blood pressure are only modestly reduced.
Tricyclic Antidepressants (TCA)	• Examples: desipramine, imipramine, clomipramine • Direct MDMA-TCA data are sparse, but TCAs also boost serotonin and noradrenaline. Combination is considered theoretically high-risk for serotonin toxicity and exaggerated cardiovascular responses.
Antipsychotics	• Examples: chlorpromazine, risperidone • 5-HT2A/D2 blockade can strip away MDMA's positive mood/empathogenic profile and increase dysphoria or anxiety.
MAOIs	• Examples: moclobemide, higher-dose selegiline • Because MDMA increases monoamine release and MAOIs block monoamine metabolism, the combination poses a high risk of severe serotonin syndrome and hypertensive crisis and is regarded as contraindicated.
Other 5-HT2A Receptors Antagonists	• Examples: ketanserin, mirtazapine, trazodone • Expected to attenuate or block many of MDMA's serotonergic/empathogenic effects, similar to antipsychotics.

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 consistent efficacy, strong safety data, and standardized drug + therapy delivery.
3	FDA reviewers explicitly note concerns about selection bias (who was enrolled versus who did not), as well as functional unblinding/expectancy effects and how these can bias outcomes (including durability follow-up).
4	More data are needed in diverse groups (e.g.multiple diagnoses, trauma histories, different socio-cultural backgrounds) and clearer guidance for people on common psychiatric medications.
5	Research also needs to clarify mechanisms of change and define best-practice therapy models, therapist training/supervision, safeguards, and scalable access without compromising safety or quality.

Into the Future

- **Global research is accelerating:** MDMA-AT has progressed from small Phase 2 studies to large, multi-site Phase 3 PTSD trials, with active regulator engagement in North America, Europe, Australia and beyond.
- **Medicinal chemistry is also moving fast:** researchers are developing next-generation MDMA analogues designed to keep prosocial/therapeutic effects while aiming for a cleaner safety profile. Notably, methylone, a close chemical relative of MDMA, has shown rapid and durable reductions of PTSD symptoms in clinical trials. It remains a controlled substance outside clinical research
- **Approval still hinges on stronger safety evidence:** The FDA's August 8, 2024 Complete Response Letter requested new trials with longer follow-up, improved bias controls, and more complete safety data (including baseline/post-dose labs and stronger cardiac assessment).
- **Limited access models are emerging internationally:** Through the advocacy efforts of MMA, Australia is the first country in the world to allow authorised psychiatrists to prescribe MDMA for PTSD via a controlled pathway (from 1 July 2023), and special-access programs exist in countries such as Canada and Switzerland.
- **Implementation will be the next challenge:** Even if approved, health systems will need trained staff, clear pathways, suitable facilities, and long-term monitoring for relapse, rare adverse events, and equitable access. Australia's authorised prescriber pathway is already offering emerging evidence on how these challenges can be met.
- **Payment and reimbursement remain uncertain:** Delivery models and staffing costs are becoming clearer through Australia's operational experience, but coverage and reimbursement, in Australia and globally, remain unresolved and will shape how equitably these therapies can scale.

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