MIND MEDICINE AUSTRALIA

MDMA

By Drug Science and Mind Medicine Australia

Part 2 - Pharmacology

Drug Science

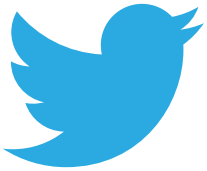
Drug Science

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 seeking to establish safe and effective psychedelic-assisted treatments for mental illness in Australia. As a registered charity (DGR-1 status), Mind Medicine Australia are supporting clinical research and working towards regulatory-approved and evidence-based psychedelic-assisted therapies. Mind medicine Australia operate as a nexus between medical practitioners, academia, government, regulatory bodies, philanthropists, and other partners.

Mind Medicine Australia is focused specifically on the clinical application of medicinal psilocybin and medicinal MDMA for certain mental illnesses. They do not advocate for recreational use of psychedelics, MDMA, or any other prohibited substances, nor do they advocate for any changes to the law with respect to recreational use. Their focus is wholly clinical.

@MindMedicineAU

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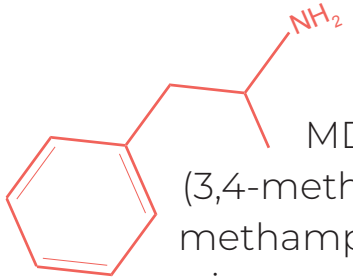
What is MDMA?

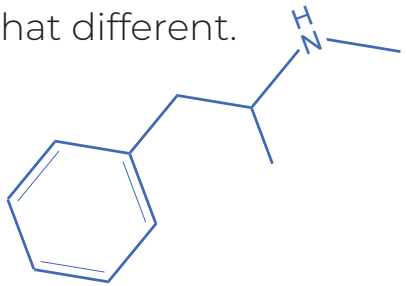


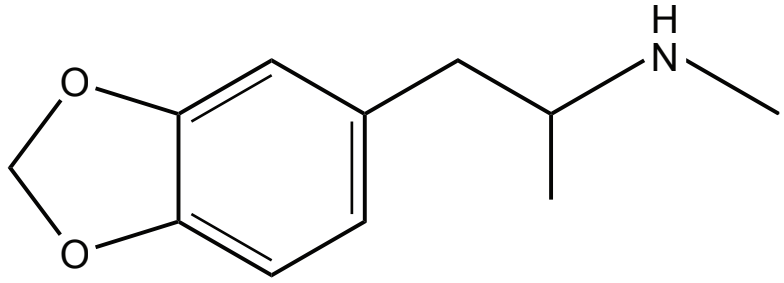
MDMA (3,4-methylenedioxy methamphetamine) is a small organic compound known as a monoamine alkaloid, related chemically to **amphetamine**. Its amine group is methylated, which makes it more closely related to **methamphetamine**, although its pharmacology is somewhat different.

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.





MDMA

Different psychoactive drugs

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Classical Psychedelics

5HT2A receptor agonists

LSD, Psilocybin, DMT, Mescaline

Entactogens

Serotonin receptor agonists

MDMA, MDA, MMDA, 2C-series etc

Dissociative anaesthetics

NMDA-antagonists

Ketamine, PCP, N2O

THC

Cannabinoid receptor agonist

Ibogaine

Nicotinic receptor antagonist

Salvia Divinorum

Kappa-Opioid receptor agonist

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What sort of drug is MDMA?

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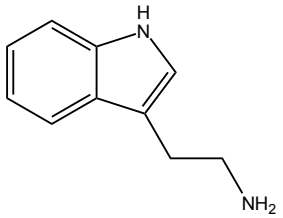
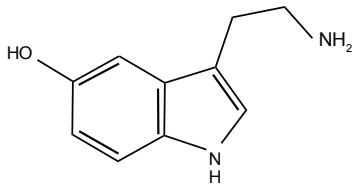
Tryptamines

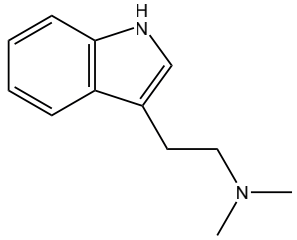
Tryptamine



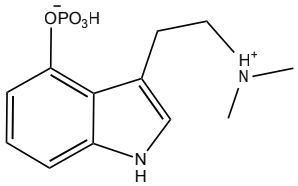
Serotonin



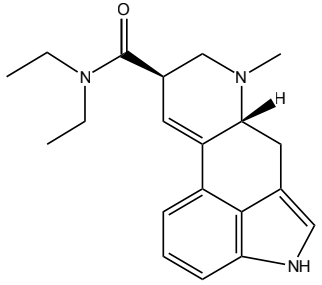
DMT



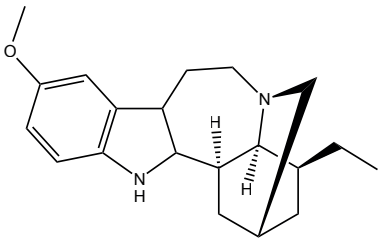
Psilocybin



LSD

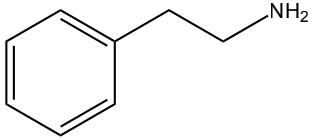


Ibogaine

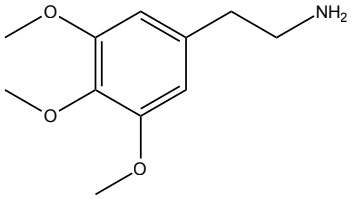


Phenethylamines

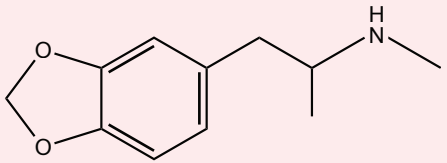
Phenethylamine



Mescaline



MDMA



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

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How does MDMA work?

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MDMA primarily works by causing the **release of monoamine neurotransmitters** into the synaptic cleft. To a lesser extent, it also acts as **neurotransmitter reuptake inhibitor**

Thus, MDMA acts by releasing serotonin from storage vesicles into the synaptic cleft; hence it is serotonin itself which is mostly responsible for the observed physiological and psychological effects of MDMA

MDMA also has a **weak affinity for some serotonin (5-HT) receptors**; hence, some of its effects may be attributable to direct binding

The main monoamine neurotransmitter affected by MDMA is **serotonin**, although the dopamine and noradrenaline (norepinephrine) systems are also affected to a lesser degree

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How does MDMA work?

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Action in the brain		Effects
Increased Serotonin (*Positive Mood + Creative Thinking*)	5HT1A 5HT1B	↓ Depression ↓ Anxiety ↓ Fear (at the amygdala) ↓ Aggression ↑ Self-confidence
	5HT2A	Alterations in perception of meaning
Increased Dopamine & Noradrenaline (*Stimulation*)		↑ Level of altertness ↑ Arousal ↑ Conscious registeration of external stimuli
Increased alpha-2 activity (*Relaxation*)		↑ Calmness and relaxation
At the hypothalamus (*Empathy & Bonding*)		Release of oxytocin

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Serotonin

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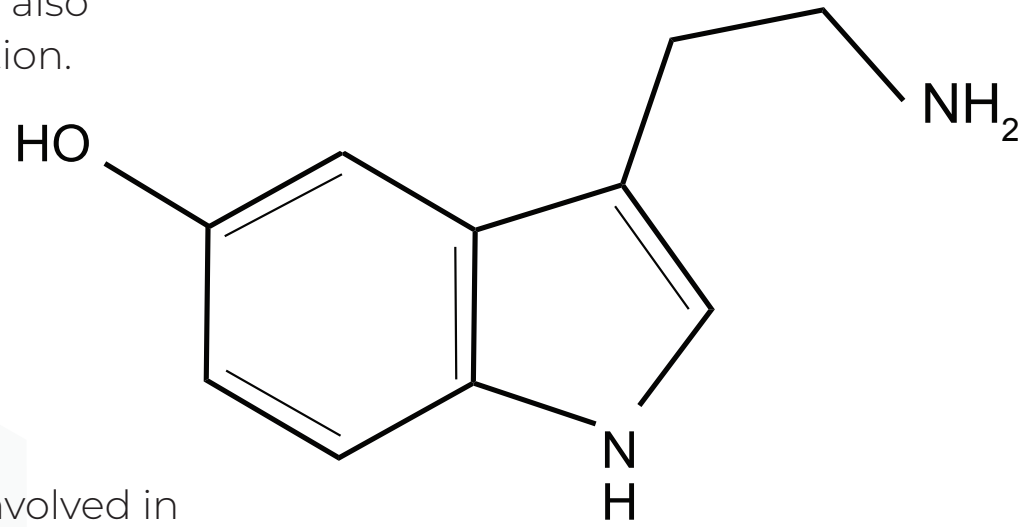
Serotonin, also known as **5-hydroxytryptamine (5-HT)**, is one of several **monoamine neurotransmitters** in living organisms that has very **fundamental functions** in basic physiology. In higher animals, it is also important for psychological function.

Serotonin was the **first monoamine neurotransmitter 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.



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

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Serotonin Formation and Breakdown

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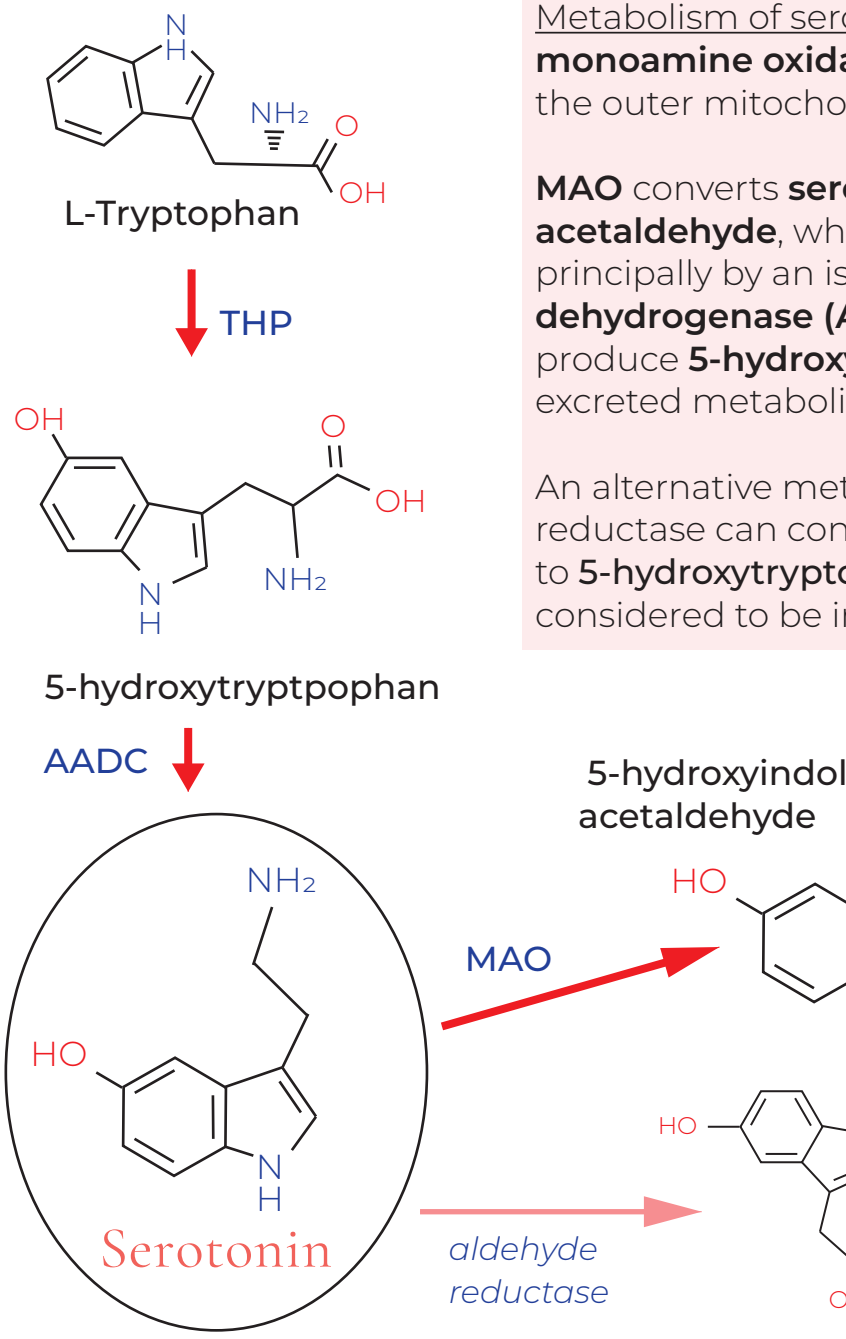
Serotonin biosynthesis initially involves the conversion of **L-tryptophan** to **5-hydroxytryptophan** by **L-tryptophan hydroxylase (TPH)**. The subsequent metabolic step involves the decarboxylation of 5-hydroxytryptophan by the action of the cytosolic enzyme **L-aromatic amino acid decarboxylase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



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

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.

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Serotonin Receptors (5-HTRs)

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

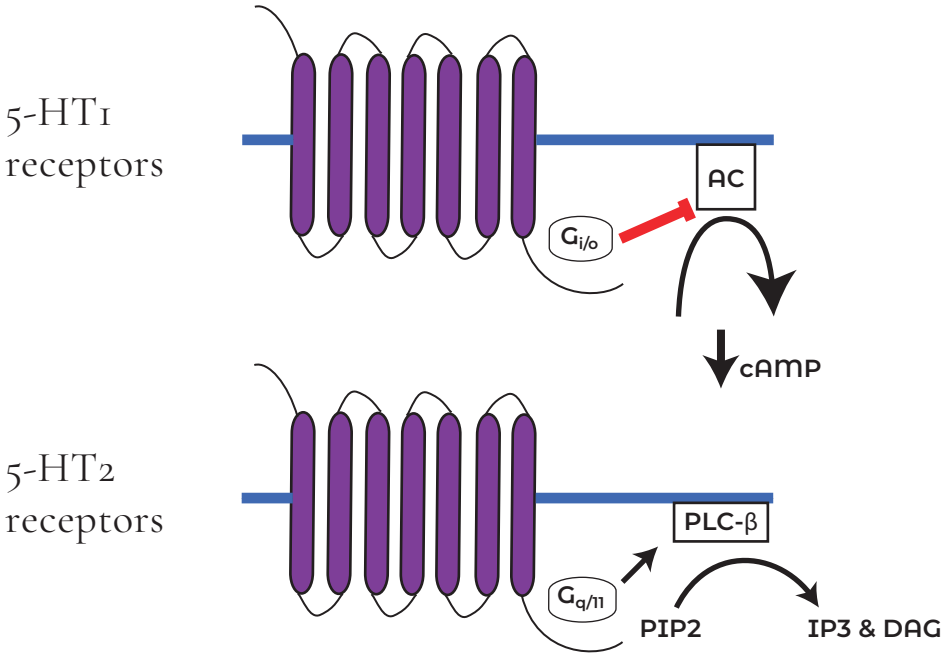
The G protein-coupled 5-HT receptors all have seven transmembrane spanning domains. They couple to different G proteins, including the **Gi/o, Gq/$_{11}$ and Gs** families of G proteins, to cause either a change in cellular cAMP levels or, in the case of 5-HT2 receptors, increase levels of inositol trisphosphate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

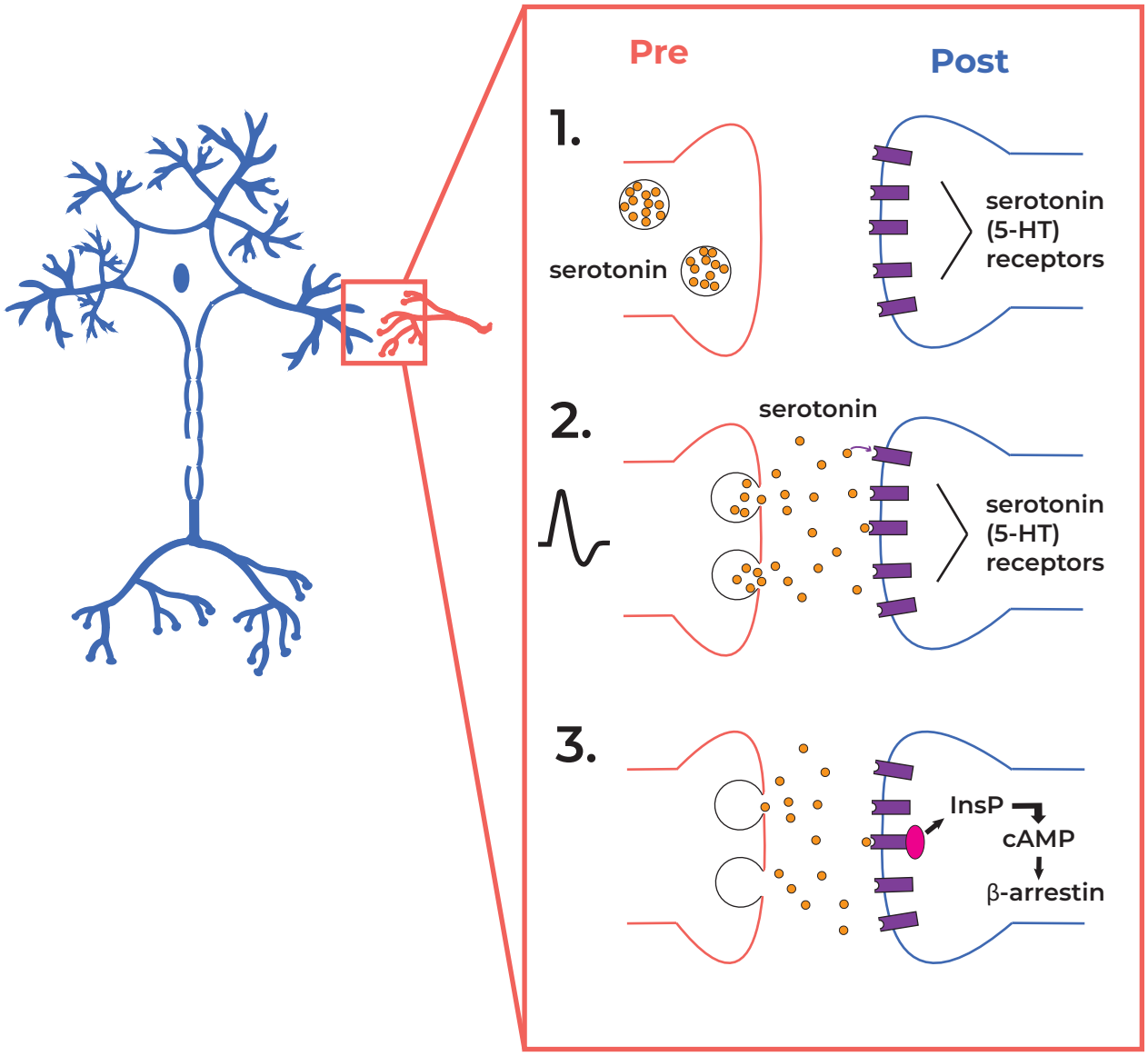
5-HT receptors have diverse functions in the brain, including regulation of sleep, mood, appetite and social functioning.

There are 14 serotonin (5-HT) receptor 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

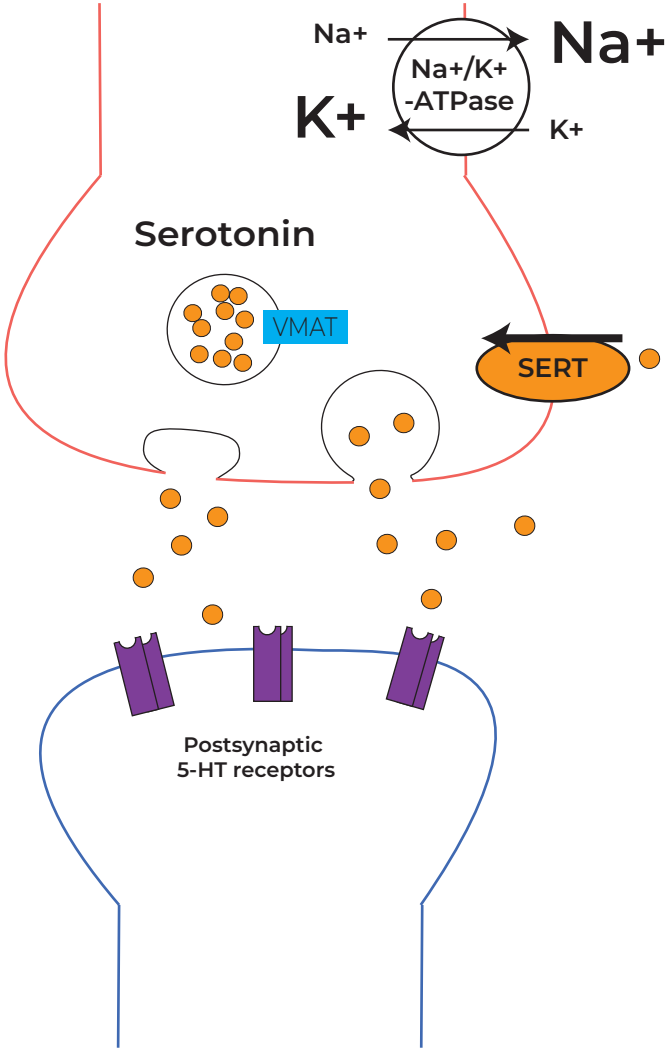


Neurotransmitters generally travel from the **presynaptic bouton** across the synaptic cleft to act on **postsynaptic receptors**. Serotonin is stored in vesicles at the bouton of the presynaptic neuron.

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 in the protein, 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.

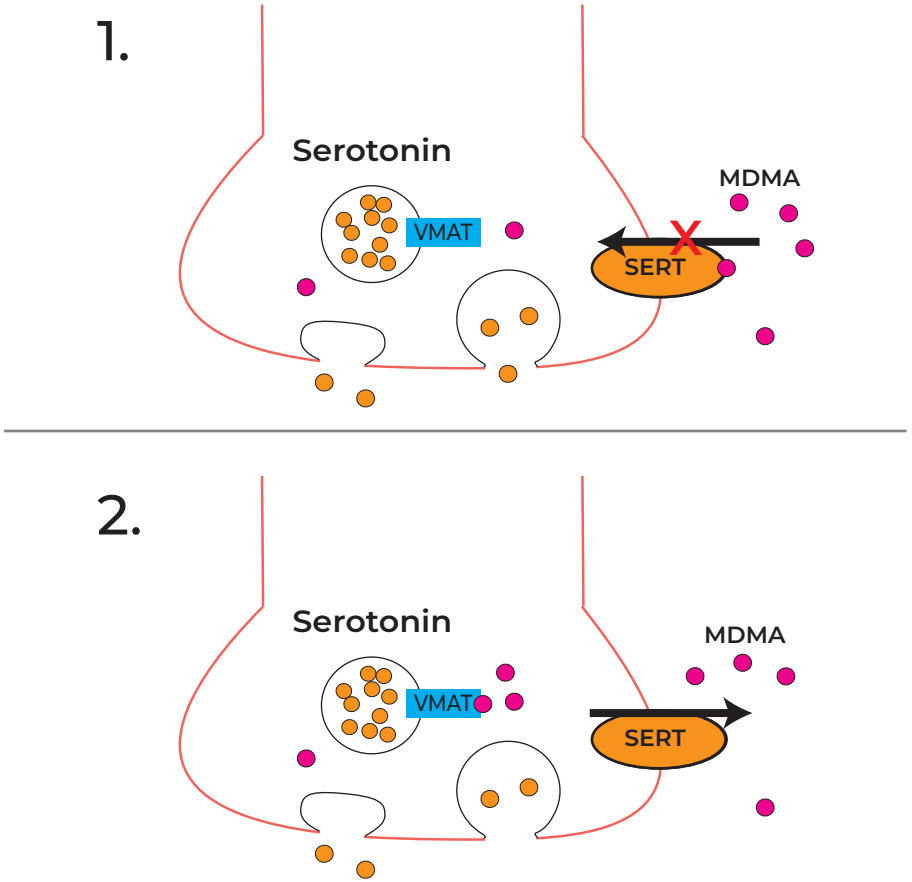
SERT functions in a sodium-dependent manner, meaning that a gradient of sodium concentration must exist across the membrane for the transporter to function.

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:

1. 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.**



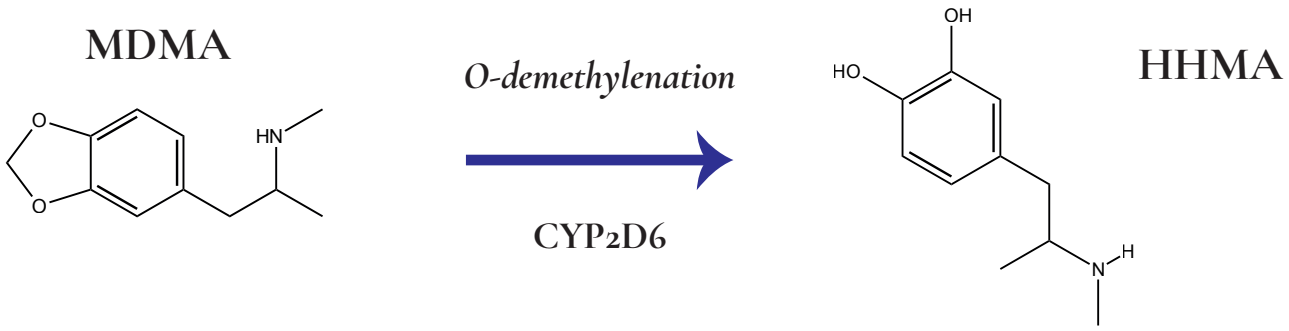
2. Neurotransmitter release: a drug binds to the transporter and reverses the direction of neurotransmitter transport, resulting in efflux of the transmitter into the synaptic cleft. **MDMA acts as a serotonin releaser via its action at Vesicular Monoamine Transporter 2 and consequently reversal of the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

MDMA Distribution & Metabolism

MDMA is **orally available** and is **quickly absorbed** into the bloodstream through mucus membranes and the stomach wall.

MDMA is both a **high-affinity substrate** and a potent **mechanism-based inhibitor (MBI)** of the **cytochrome P450 (CYP) 2D6** system in the liver. In healthy humans who are classified as "extensive CYP450 metabolisers", MDMA has a half-life of 6-7 hours.

CYP2D6 regulates MDMA O-demethylenation leading to the formation of **3,4-dihydroxymethamphetamine (HHMA)**, which undergoes disposal from the body via the kidneys.



MDMA Metabolism

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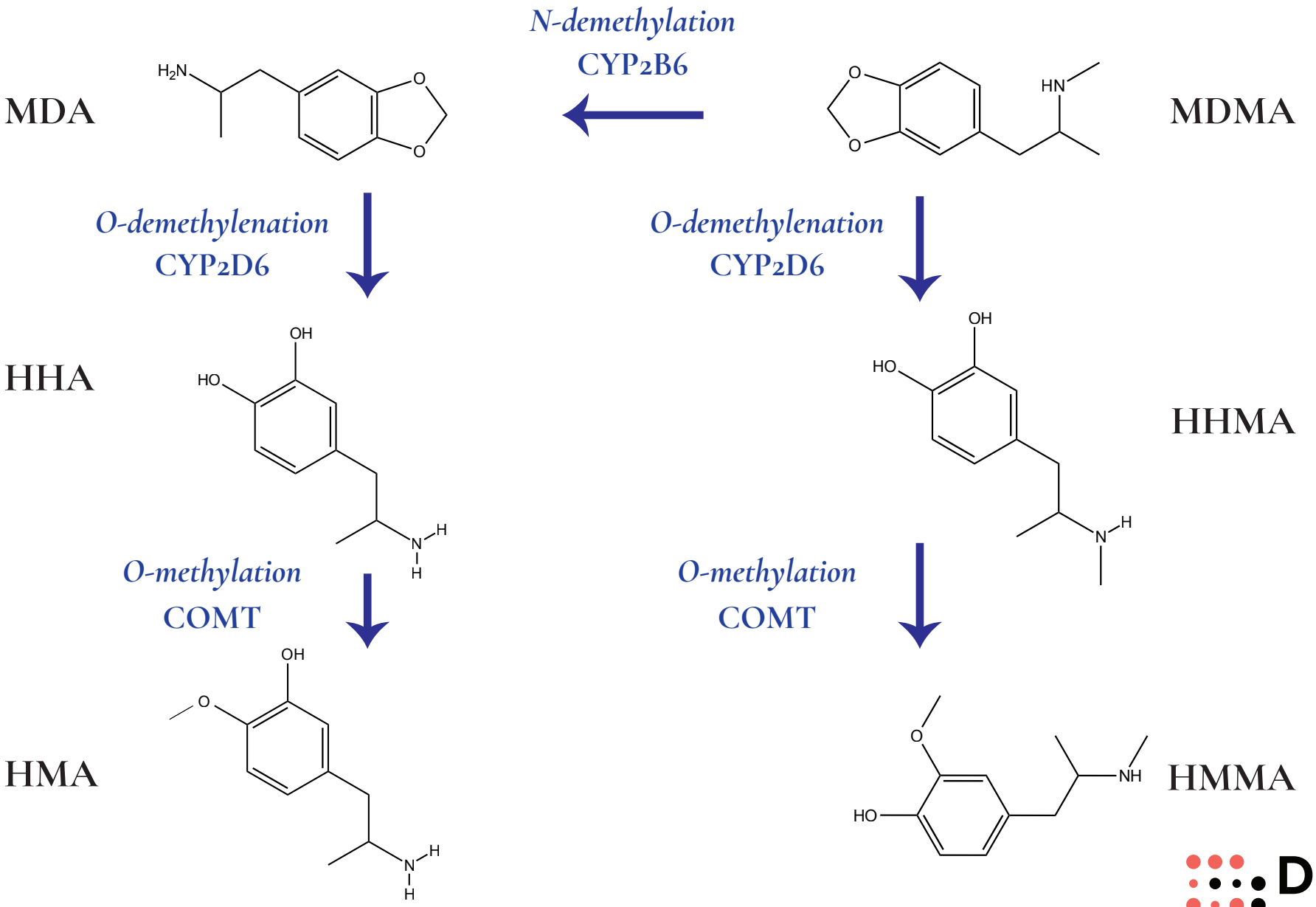

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MDMA - Psychoactive Properties

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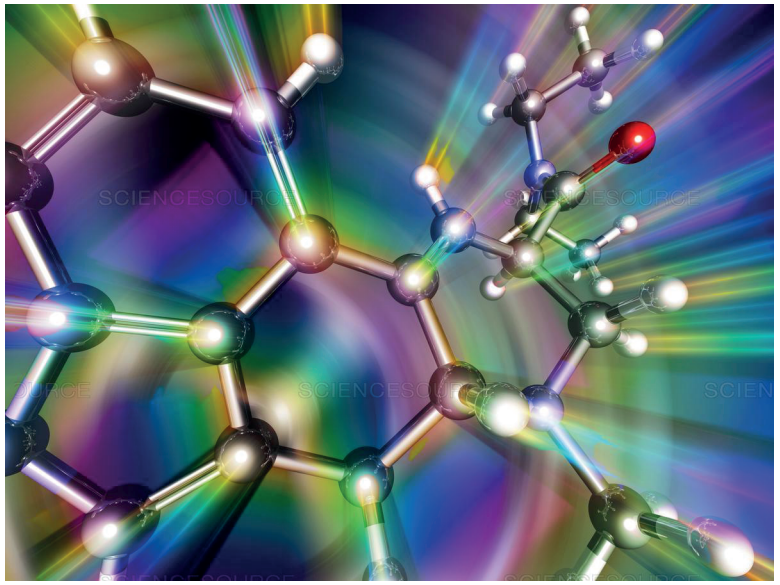
The main psychoactive effects of MDMA are due to SERT binding, causing pronounced release and reuptake inhibition of serotonin



High concentrations of serotonin in the synaptic cleft result in the typical effects of serotonin binding 5-HT receptors

MDMA may have psychoactive effects in its own right through its modest affinity for 5-HT and other receptors, but these are far less significant than the effects of high synaptic concentrations of serotonin due to MDMA effects on the SERT

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MDMA Physiological Effects

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The most common **physiological effects** of MDMA include:

Tachycardia

Increased blood pressure

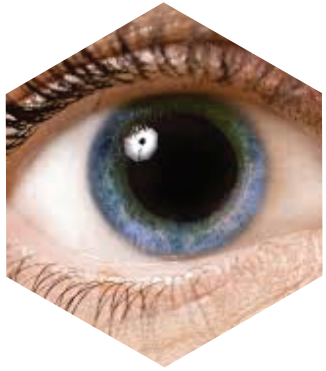
Hyperthermia

Sleep disturbances

Reduced appetite

Nystagmus (eye wobble)

Mydriasis (dilated pupils)



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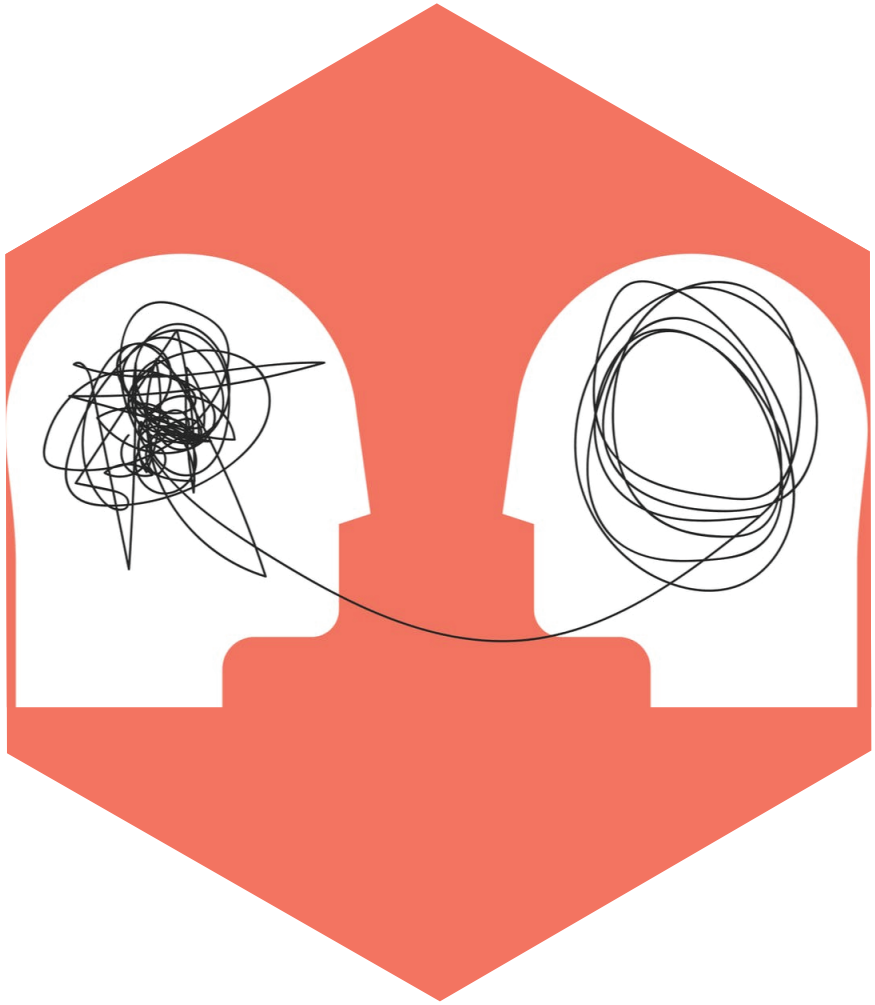
MDMA Psychological Effects

The most common **psychological effects** of MDMA include:



Euphoria

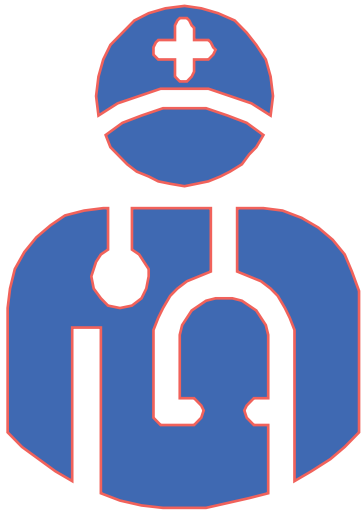
Sense of well-being

Increased sociability

Empathy for others

Anxiolysis

MDMA Risks and Adverse Effects



Acute risk of cardiac events (**tachycardia** and **arrhythmias**), **hyperthermia** and **hyponatremia**, almost exclusively at high (non-therapeutic) doses in non-clinical contexts

Acute risk of **serotonin syndrome**

- resulting from excessive MDMA misuse with an increased risk through polydrug use

Short-term **negative mood** 24-48 hours after use due to serotonin depletion

Possible risk of **chronic serotonin and dopamine neurotransmitter depletion** and/or **changes in receptor expression** associated with excessive/chronic non-clinical use

- unclear if due to polydrug use patterns in non-clinical context

MDMA Therapeutic Applications

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MDMA-assisted psychotherapy has shown great promise in a variety of disorders, including:

- Post-Traumatic Stress Disorder
- Social anxiety
- Conditions comorbid with trauma, e.g. substance use disorder

CLICK HERE TO FIND OUT MORE ABOUT THE THERAPEUTIC APPLICATION OF MDMA ON THE DRUG SCIENCE PODCAST

> "MDMA could be a very effective treatment for alcoholism and other chronic mental health conditions, because it allows us to provide an emotional platform, which is containing and safe, for patients to address traumatic issues"
>
> *Dr Ben Sessa, Bristol University*

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MDMA-assisted therapy
Therapeutic Mechanisms

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How does MDMA work as a therapeutic?

Essentially a form of **Exposure Therapy** with reduced negative behavioural responses such as anxiety and avoidance

Amygdala activity ↓	=	↓	**Hypervigilance**
Oxytocin and prolactin level ↑	=	↑	**Trust & therapeutic alliance**
Lack of inebriation for most of experience	=		**Unimpaired memory recall/processing**

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MDMA Therapeutic Practicalities

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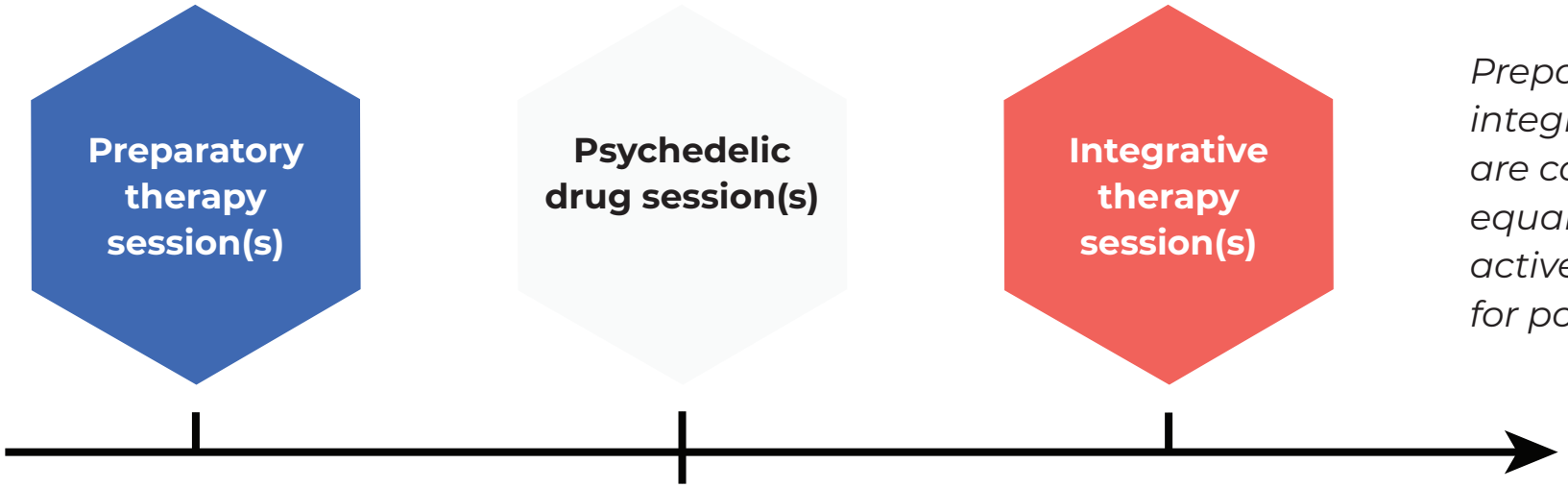
MDMA is generally utilised therapeutically in conjunction with a form of psychotherapy commonly termed **Psychedelic-Assisted Psychotherapy (PAP)**

Just as with other Psychedelic-Assisted Psychotherapy, MDMA is used with a standardised protocol involving:



Preparatory and integrative therapy are considered equally crucial to the active drug session for positive outcomes

In total, the whole process can take up to 6 months

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Preparatory Psychotherapy

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Preparatory psychotherapy:

- **prepares the participant/patient for the overall process**, particularly the psychedelic experience to come. This is especially important for MDMA-naïve patients

- it establishes a **therapeutic alliance** between the patients and therapists

- it allows for discussion of the **participant's condition and broader context**

- makes participants aware of possible **mind-states, transient anxiety, breakthroughs** etc. that can occur during the active drug session

Typically, patients will attend multiple preparation sesssions before beginning the active dosing sessions. Each preparation session usually lasts around 90 minutes.

CLICK HERE FOR AN INTRODUCTION INTO MDMA-ASSISTED THERAPY IN PTSD

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Active MDMA Session

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SET: the patient's emotional/cognitive/behavioral mindset and expectations

SETTING: the physical environment in which the exposure occurs

The importance of Set and Setting

Set is optimised through preparatory session(s), so that the patients feel comfortable with their therapists and familiar with the location, so they are able to relax. The therapists present are there to "support, not guide" the experience.

Setting is optimised by creating a comfortable space, using muted lighting, calming décor and elements of ceremony/ritual. The importance of music has also been established in creating the right set and setting.

MAPS MDMA session

The active MDMA session takes place over 6 to 8 hours, following the time course (pharmacodynamics) of MDMA action.

Participants are encouraged to speak to the therapists to enable processing of the material being uncovered. Support is particularly important when difficult psychological material is being recalled and processed.

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Integrative Psychotherapy

Integration sessions are considered critical for optimal therapuetic outcomes with regards to MDMA therapy because:

- analysis can be difficult during the acute phase of the MDMA experience, although initial work can be done, due to the lucidity maintained during an MDMA experience

- this helps participants to make sense of what they experienced

- therapists can help frame the experience in broader perspective of the participant's condition

Why We Need More Research

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- **Clinical research** is fundamental to government approval of new drugs and medical interventions
- Research into therapeutic applications was **interrupted by global War on Drugs,** but many research questions were left unanswered
- **Mechanisms of action** still need to be elucidated
- Exploration of the **scope of MDMA-assisted psychotherapy**, e.g. beyond treatment of PTSD and social anxiety to other mental health conditions, e.g. potential
- Exploration of **applicability beyond the adult population**
- Research is an effective means to **promote awareness and acceptance** of new approaches within the medical, and broader, community
- There is the potential to shed light on **mechanisms of mental illness, and brain function more broadly**

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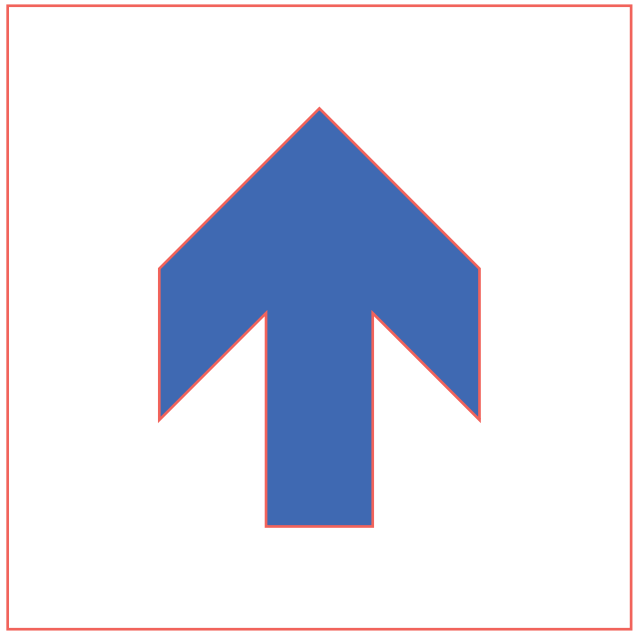
Into the Future

The future of psychedelic medicine is looking promising, although there is a need for mid- to long-term strategic planning to manage the process

1. MDMA research is now blossoming globally
2. There are realistic prospects of regulatory approval
3. There is potential for widespread application within public health models
4. The health insurance industry is already paying attention to the field



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