Ketamine

By Drug Science and Small Pharma

Part 2 - Pharmacology

Drug Science

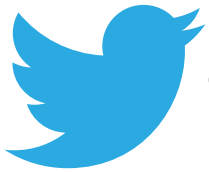
Drug Science

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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Small Pharma

Led by an experienced team committed to making a difference for people suffering from mental health conditions, Small Pharma believes that together, as a community, we can help unlock cutting edge science and bring new therapies to treat mental health disorders

Small Pharma is a virtual biopharmaceutical company on a mission to improve mental health by progressing psychedelic therapies to the clinic. At Small Pharma, they have identified the field of psychedelic medicine as an exciting and unexplored area of drug discovery, with the ability to completely transform our understanding and approach to mental health. As compounds neglected by risk averse traditional pharma, the Small Pharma team are passionate about becoming the R&D leaders of psychedelic drug discovery and development

Small Pharma funds clinical trials of DMT and related psychedelic compounds as a tool to augment psychotherapy for the treatment of depression and other mental health conditions. Their current focus is to unlock the exciting potential of DMT therapy as a treatment for Major Depressive Disorder

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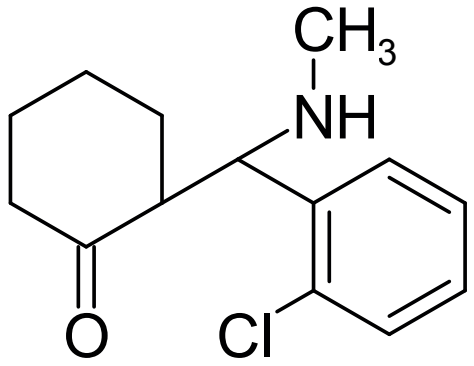
What is Ketamine?

Ketamine, **2-(2-chlorophenyl)-2-(methylamino)-cyclohexan-1-one,** is an arylcycloalkamine and is structurally related to cyclidines, such as phencyclidine (PCP).

Ketamine is a synthesised drug manufactured via a complicated multi-step process using the initial reagents of o-chlorobenzonitrile and cyclopentyl Grignard.



Ketamine primarily acts as a NMDA receptor antagonist, which affects glutamatergic transmission.

Ketamine is a racemic mixture, meaning it contains two enantiomers (optical isomers): **S-(+)-ketamine** and **R-(-)-ketamine,** which have a slightly different pharmacological profile.

Ketamine's historic and current use has been as an anaesthetic in human and veterinary medicine for short diagnostic and surgical procedures.

More recently, the proposed neuroprotective and anti-inflammatory properties of ketamine have been investigated for their potential antidepressant effects.

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Compound fact sheet

Ketamine is available as a hydrochloride salt or free base.

Ketamine hydrochloride is a water soluble, white crystalline powder (colourless aqueous solution) with a pKa of 7.5.

Ketamine is a hydrosoluble aryl-cyclo-alkylamine.

Ketamine sometimes includes benzethonium chloride or chlorobutanol as preservatives.

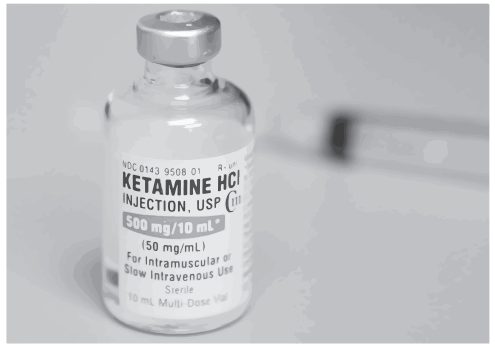
Molecular formula:
C13H16ClNO (free base)
C13H17Cl2NO (hydrochloride salt)

Molecular weight:
237.73 g/mol (free base)
274.18 g/mol (hydrochloride salt)

Melting point:
92-93°C (free base)
262-263°C (hydrochloride salt)

pH:
3.5 - 5.5

Dose	Route	Bioavailability
75 to 125 mg	Intramuscular (IM)	93%
60 to 250 mg	Insufflation (intranasal)	50%
50 to 100 mg	Intravenously (IV)	100%
200 to 300 mg	Orally (by mouth)	20%



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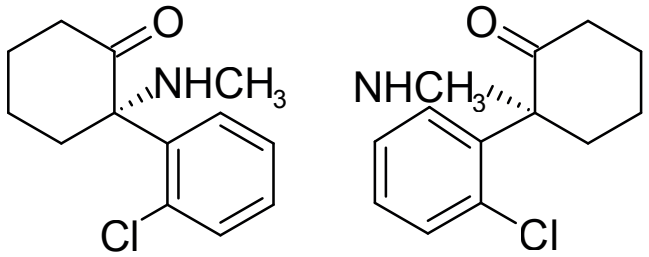
Stereoisomerism

Stereoisomers (enantiomers) are molecules made up of the **same atoms** connected by the **same bonds** but with **different 3D-orientation**.

Ketamine's stereoisomerism is due to the chirality ('handedness') of the C-2 carbon of the cyclohexanone ring.

The right-handed (R) and left-handed (S) forms of ketamine are non-superimposable mirror images.

Specific enantiomer structure determines receptor affinity, pharmacological activity, tissue uptake and metabolism.



S(+)-ketamine **R(-)-ketamine**

S-(+)-Ketamine (esketamine)

Left-handed orientation

Spravato®, Ketanest-S®/Vesierra-S®

Spravato® (esketamine hydrochloride)
An EMA and FDA approved nasal spray which is taken alongside an oral antidepressant as a medication for treatment resistant depression.

Ketanest-S®/Vesierra® (esketamine hydrochloride)
An anaesthetic drug solution administered via injection/infusion.

R-(-)-Ketamine

Right-handed orientation

Not a marketed drug product yet.

Racemic Ketamine

Equal quantities of R- and S-enantiomers

Ketlar®, Ketanest®

Marketed anaesthetic agent in human and veterinary practices.

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Ketamine enantiomers

No study has directly compared the effects of R-, S- and racemic versions of ketamine in humans.

S-(+)-ketamine

S-ketamine has a higher affinity for NMDA receptors compared to equivalent doses of R-ketamine and racemic ketamine.

Therefore, lower doses are needed to elicit similar effects, with lower incidence of side-effects such as drowsiness, lethargy, agitation and disturbed memory.

S-ketamine has been found to have a higher clearance and potency than R-ketamine *(Muller et al., 2016; Zanos et al., 2018).*

R-(-)-ketamine

R-ketamine has a lower NMDA receptor affnity and is not currently used as a clinical drug.

However, there are rodent studies showing that the R-enantiomer induces synaptogenesis and longer-lasting antidepressant effects when compared to the S-version *(Fukumoto et al., 2018; Yang et al., 2015; Zhang et al., 2014).*

R-ketamine has been shown to cause fewer side effects such as dizziness, dissociation and sensory deficits *(Yang et al., 2015; Zanos et al., 2016; 2018).*

Racemic ketamine

Equal quantities of R- and S-enantiomers

Marketed all over the world as an anaesthetic agent for diagnostic and surgical procedures. It is better suited for short procedures and is administered by intravenous or intramuscular injection.

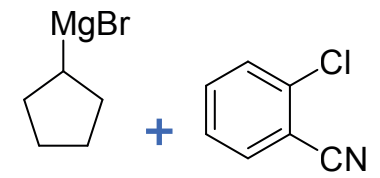
Ketamine formation and breakdown

The synthesis of ketamine starts with the reaction of
1. cyclopentyl grignard + **o-chlorobenzonitrile ---> o-chlorophenyl-cyclopentyl ketone**

2. Reaction with bromine causes alpha bromination of the ketone, leading to the formation of **Bromo ketone**

3. Reaction with methylamine forms
1-Hydroxycyclopentyl-(o-chlorophenyl)-ketone-N-methylimine

4. Application of heat facilitates a novel alpha-hydroxyimine rearangement, to form **Ketamine**



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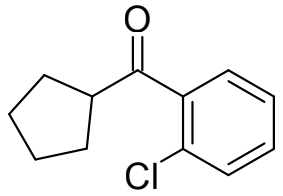

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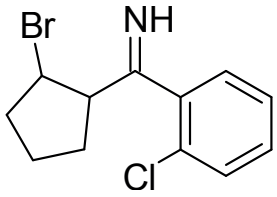

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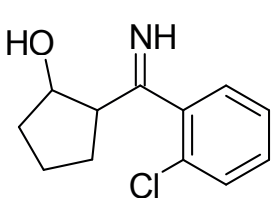

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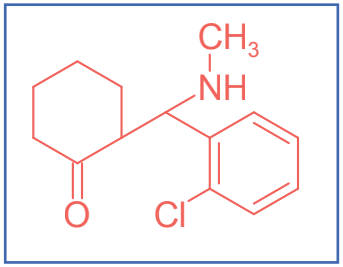

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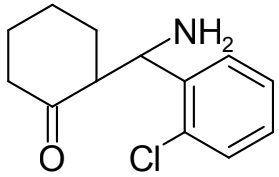

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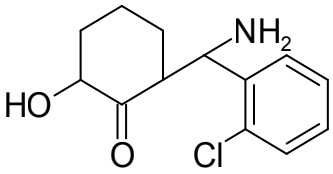

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5. **Ketamine** is primarily metabolized via **oxidative N-demethylation** of the cyclohexanone ring by the CYP450 enzyme, producing the primary and active metabolite, **norketamine** (80%)

6. Norketamine is hydroxylated to **hydroxy-norketamine (15%)**, conjugated with glucoronate and excreted in the urinE

7. Accessory pathway passes directly through the transformation of ketamine in **hydroxy-ketamine (5%)**

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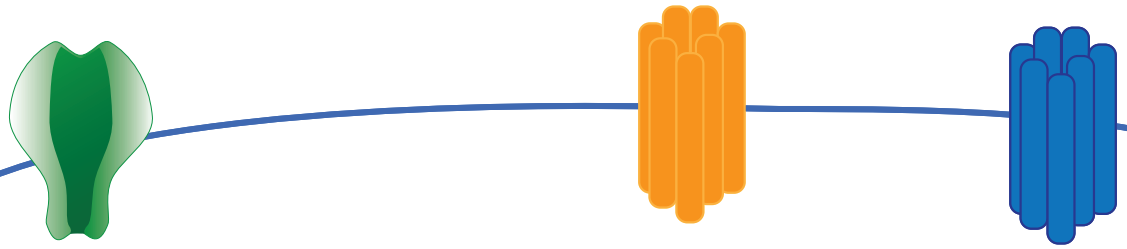
Ketamine receptor signalling

Ketamine's neuropharmacology is complex, binding to a wide range of receptors that contribute to its behavioural and physiological effects.



Catecholamine receptors
Ketamine affects catecholamine systems, in particular enhancement of dopaminergic signalling, through the inhibition of reuptake.

NMDA receptor
The main effect of ketamine is mediated through its action as a non-competitive NMDA receptor antagonist.

Ketamine blocks the PCP binding site of the NMDA receptor, thereby blocking depolarisation of the neurone.

NMDA receptor is an excitatory receptor involved in sensory input of the spinal, thalamic, limbic and cortical areas.

They play a vital role in learning and memory due to the formation of synaptic connections.

Opioid receptors
mu, delta, kappa
Several studies indicate that opioid receptors are involved in the pharmacological effects of ketamine.

This action is suggested to contribute to ketamine's antinociceptive and antidepressant effects *(Sarton et al., 2001; Hashimoto et al., 2020).*

S-ketamine has a 2-3 fold higher affinity for opioid receptor than R-ketamine.

Other neuropharmacological actions include:
- Agonistic effect on alpha- and beta-adrenergic receptors
- Antagonistic effect at muscarinic receptors of the central nervous system (CNS)
- Agonistic effect at the sigma-receptor
- Antagonist of the HCN1 receptor

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NMDA receptor structure

NMDA receptors are ionotropic glutamate receptors made up of an **extracellular N terminus**, **intracellular C terminus**, **transmembrane domain** and various **subunit families**: GluN1; GluN2; GluN3.

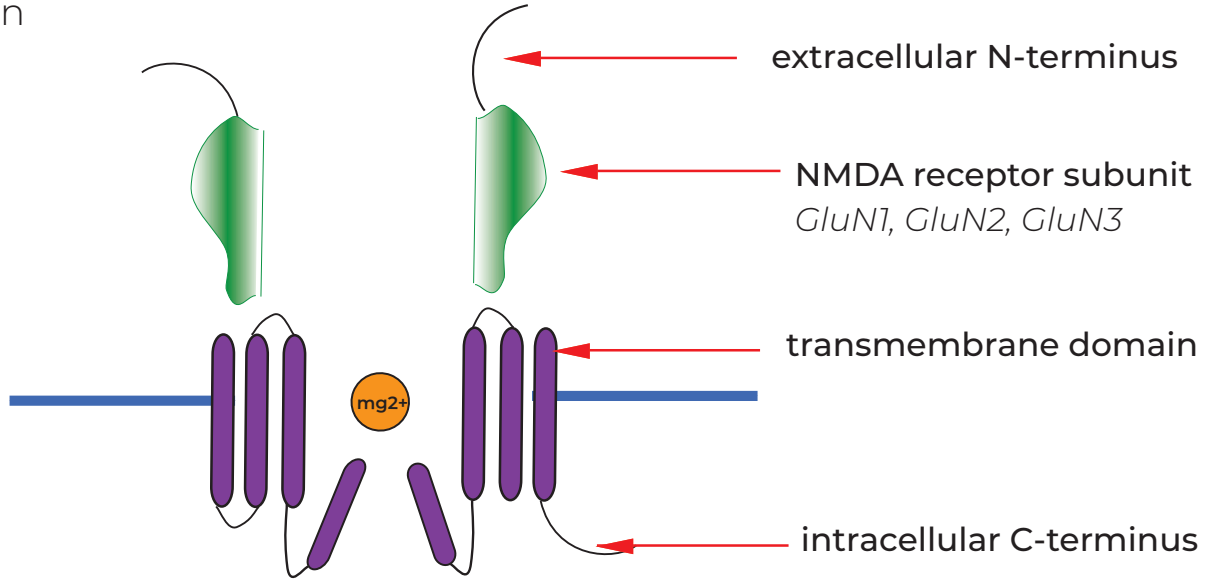
Agonists and competitive antagonists bind to the extracellular N-terminus domain.

NMDA receptor activation requires co-activation at two N-terminus binding sites:

- **Glutamate binding site** of GluN2
- **Glycine (co-agonist) binding site** of GluN1

Channel blocking agents bind to additional sites within the ion channel, also known as the PCP binding site.

Sub-unit specific binding sites also have a role in regulating NMDA receptor activity, for example GluN2B polyamine binding sites have positive allosteric modulatory action.



NMDA receptor subtypes have heterogeneous distributions in the brain:

- GluN2A - throughout the brain
- GluN2B - limbic system, thalamus, spinal cord
- GluN2C - thalamus, cerebellum
- GluN2D - brain stem, diencephalon, spinal cord

This may explain the variation in clinical effects caused by different NMDA blocking compounds.

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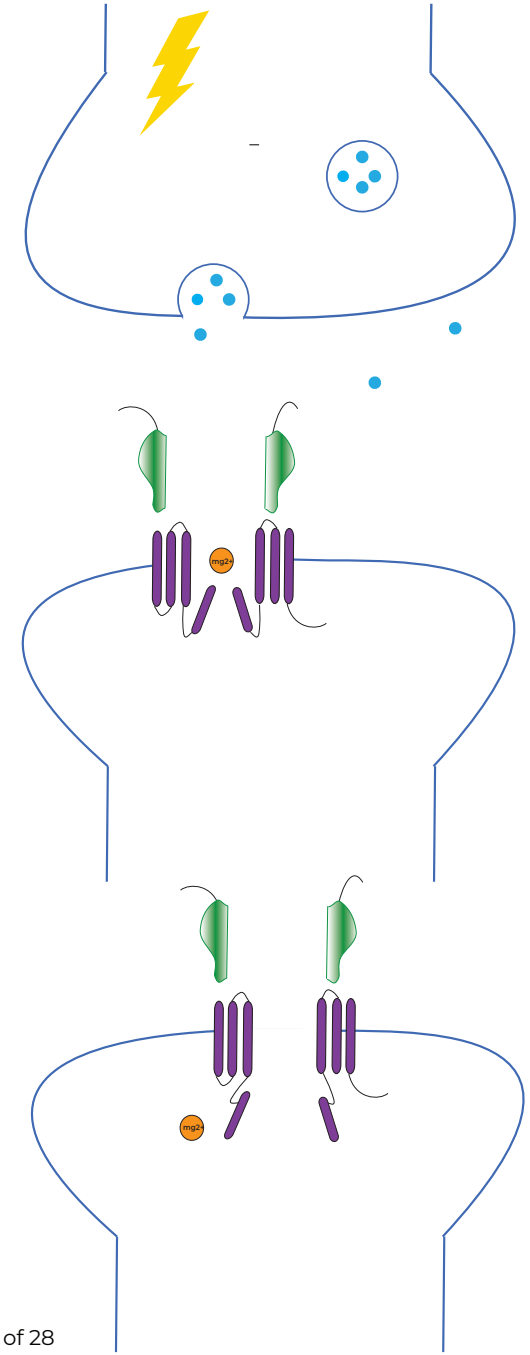
NMDA receptor action



1. **Mg2+ block at resting potential (70mV)**
   NMDA receptors are inactive at rest due to a voltage dependent block of the channel pore by magnesium ions which prevents ionic flow through the channel.

2. **Sustained pre-synaptic signalling** activates **post-synaptic** AMPA receptors and **depolarisation.**

3. Post-synaptic depolarisation **breaks the negative electrostatic forces holding the Mg2+** ion in place.

   This event, in combination with **co-agonist binding activates the NMDA receptor and channel opening**, causing a **calcium influx** into the post-synaptic cell & triggers multiple **intracellular cascades.**

4. Post-synaptic function which varies depending upon the location and distribution within the CNS.

   The activation of NMDA receptors is complex and involves multiple agonists interacting in cooperation and regulatory mechanisms.

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Ketamine action at the NMDA receptor

Ketamine's primary site of action is at the NMDA receptor, as an antagonist at concentrations of 2 - 50 MicroM.

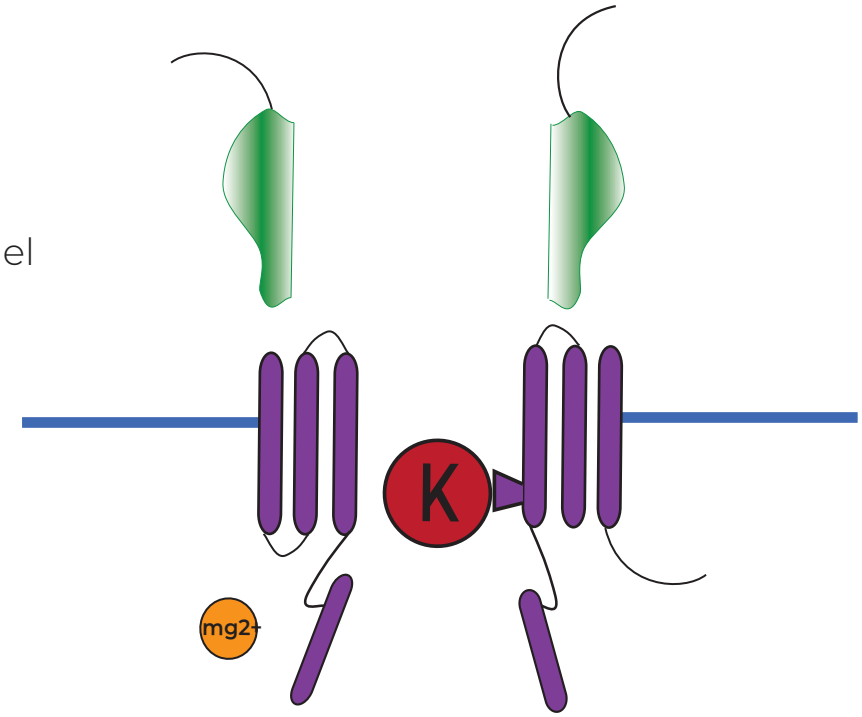
- Ketamine primarily binds to the intracellular **PCP binding site** of the open NMDA receptor as a **non-competitive, high-trapping antagonist** (with a slow off rate).

- This means that ketamine remains bound to the receptor channel in its **closed formation** after glutamate unbinds.

- This effect **prolongs the blockade of the calcium ions** through the channel and **reduces channel mean open time**.

- Causing an **inhibition of post-synaptic neuronal depolarisation** and sensory input to higher areas of the CNS, such as emotional response, learning and memory.

- Ketamine also acts as an allosteric antagonist, markedly at the hydrophobic domain of the GluN2B subunit, causing a decrease in the frequency of channel opening and is involved in changes in emotional perception and memory of pain.



S-ketamine has around 3-times higher binding affinity for the PCP binding site, compared to the R-enantiomer

Ketamine's use dependent depolarisation of the NMDA receptor can decrease the amplification of a post-synaptic response following repeated NMDA receptor stimulation. This explains why ketamine acts as an effective analgesic during situations of chronic pain, where there is a repeated stimulation of nocioceptive pathways.

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Ketamine action in the brain

Ketamine's action on a wide range of receptors generates distributed effects over multiple areas of the brain.

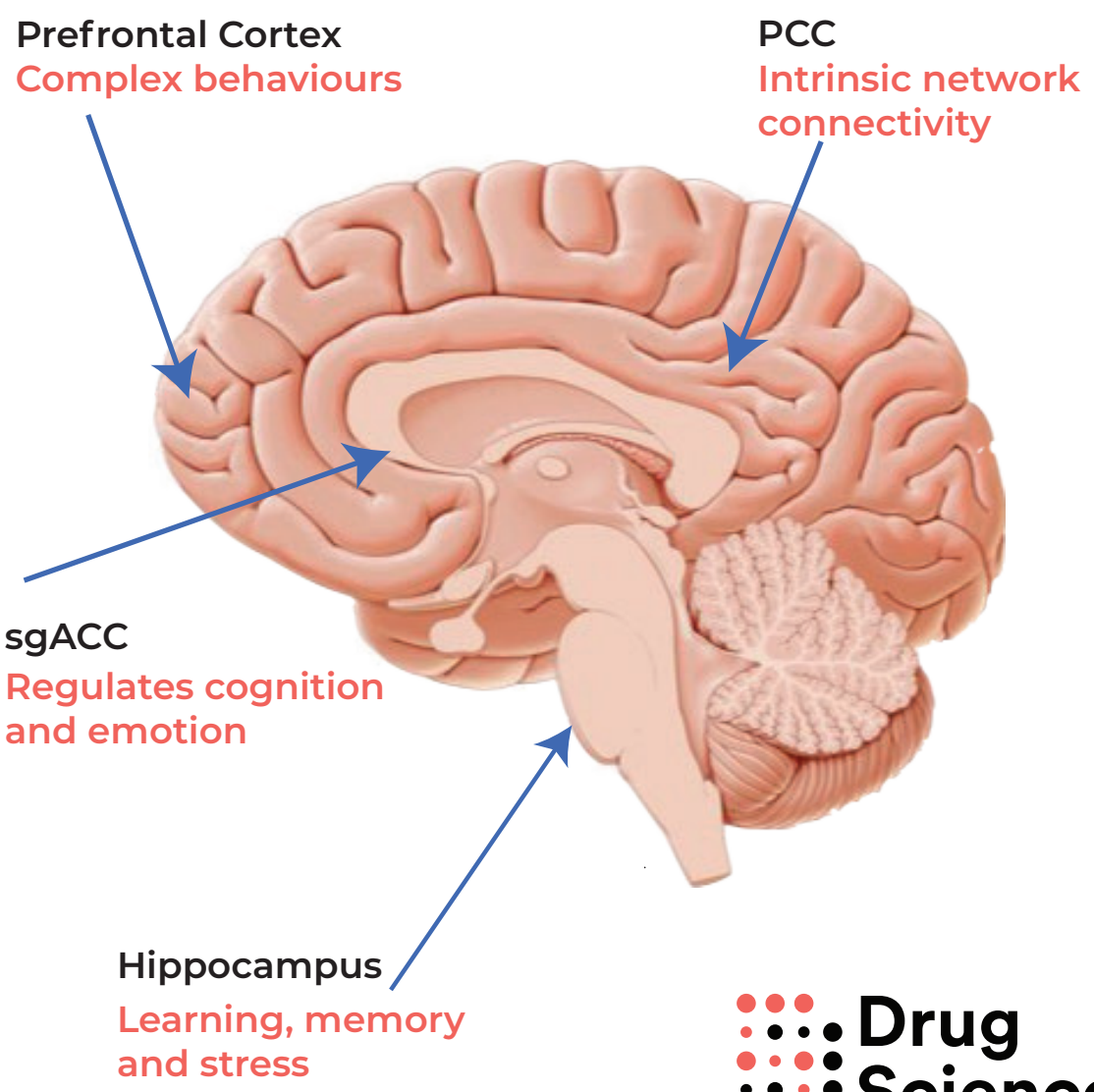
Ketamine's most notable effects occur in the **subgenual anterior cingulate cortex (sgACC)**, **posterior cingulate cortex (PCC)**, **prefrontal cortex (PFC)** and **hippocampus**.

Changes in sgACC activation may be due to ketamine's acute effects and subside a few hours post infusion.

Ketamine reduces pACC connectivity to disrupt self-monitoring behaviours.

Increased PFC connectivity is thought to enhance frontal control over limbic (emotion) areas of the brain.

Ketamine can induce hyperconnectivity in hippocampal networks.



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Pharmacokinetics and Pharmacodynamics

Pharmacokinetics (PK)

What the body does to the drug

Ketamine is **highly liposoluble** with **low protein binding ability**, which enables rapid transfer across the blood-brain barrier.

Concentrations of ketamine in the brain are often 4-5 times higher than that in the blood plasma.

It takes between 7 - 11 minutes, for the plasma concentration of ketamine to reduce by 50%.

Pharmacodynamics (PD)

What the drug does to the body

Central Nervous System (CNS): analgesic and sedation. At higher doses is can cause unease, hallucinations, vivid dreams, floating sensations and delirium.

Cardiovascular: sympathetic nervous system stimulator which causes increased cardiac output, tachycardia and increased blood pressure.

Respiratory: presevered airway tone and both pharyngeal and laryngeal reflexes. Ketamine has been shown to cause bronchodilation.

Other: Increased muscle tone, blood glucose, cortisol and prolactin levels.

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Ketamine's anaesthetic effects

Ketamine was first discovered as an anaesthetic drug in 1956.

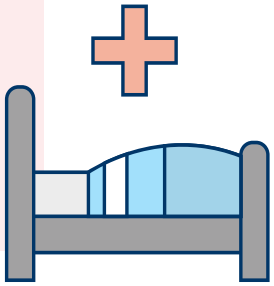
In the 1960s, ketamine was developed as an anaesthetic agent in human and veterinary medicine and continues to be used all over the world today.

In the UK, Ketamine is delivered via intravenous and intramuscular administration in anaesthesia.

Ketamine can also be administered orally, nasally, rectally and via epidural, depending on specific international licences.

The dose depends on the route of administration and the desired clinical effect.

Patients experience a loss of response to their external environment at ~ 2000ng/ml



Route	Analgesic dose	Anaesthetic dose	Advantages	Disadvantages
Intramuscular (i.m.)	4-5 mg/kg	8-10 mg/kg	Safe, predictable	Painful on injection
Intravenous (i.v.)	0.25-1 mg/kg	1–2 mg/kg	Optimal route	Longer recovery time, higher rate of vomiting
Intranasal (in)	0.25-4 mg/kg	3-9 mg/kg	Rapid systemic absorption, ease of access	Transient feelings of dizziness and dissociation
Intraosseous (io)	0.5-1 mg/kg	1-2 mg/kg	Useful in emergencies, obese and children	Long recovery time
oral	3-15 mg/kg (children) 500mg max (adults)	n/a	Ease of administration	Low bioavailability

Ketamine is a safe and versatile anaesthetic as it does not cause a significant depression of breathing and blood pressure, meaning patient monitoring equipment is not required during clinical procedures.

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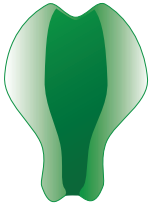
Ketamine's anaesthetic action

Ketamine acts upon the central nervous system and local areas to produce a range of global and local anaesthetic effects.

Ketamine's anaesthetic effects are largely attributed to the depressant activity of NDMA antagonism, which causes a transient decrease in glutamate release.

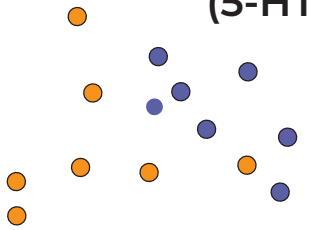


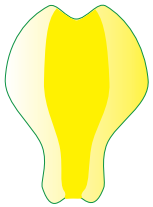
Non-competitive NMDA receptor antagonist

- blocks calcium channel pore
- loss of excitatory synaptic activity

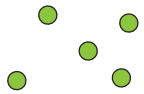
Ketamine also binds to a wide range of additional receptors which exerts a paradoxical stimulatory action on the CNS:

Increased amines (5-HT, NA)





Modified response of opioid receptors



Inhibited nitric oxide production

HCN1 channel inhibition

These conflicting effects make it difficult to achieve full anaesthesia in many species, meaning it is often co-administered with an alpha-2 adrenergic agonist to achieve surgical anaesthesia.

However, ketamine's ability to induce a range of dissociative symptoms and half-life of ~3 hours has limited its widespread use as an anaesthetic and analgesic medicine.

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Ketamine analgesic action

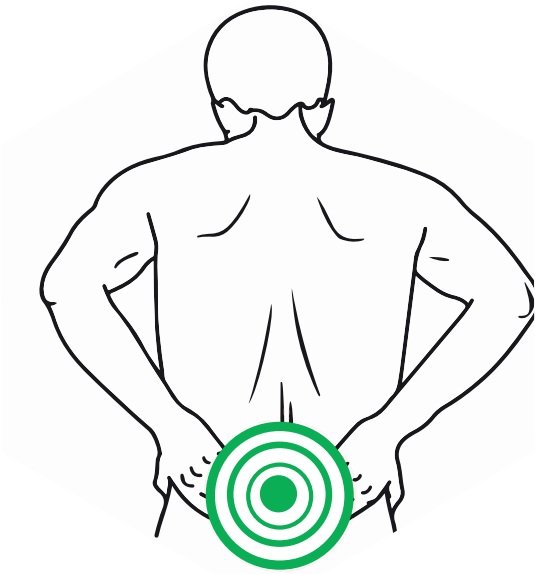
Ketamine will **reduce pain scores at ~200 ng/ml concentrations**, similar to its dissociative concentrations.

Ketamine produces a complex mixture of **anti- and pro-nociceptive** effects in acute and chronic pain attributed to a broad range of direct and downstream receptor effects.

Chronic pain

Ketamine regulates a number of gene expression and cell signalling cascades which are thought to interrupt the gradual propagation of pathological changes associated with chronic pain development including:

- Changes to NMDA receptor expression
- Increased concentration of amines (5HT, NA, DA)
- Modified opioid receptors responsivity
- Inhibition of nitric-oxide synthase
- Astrocytic activation
- Changes to synaptic structure and function



Chronic pain and depression are often closely linked, although the direction of the relationship is unclear. One potential explanation describes ketamine's antidepressant effects to precede an enduring reduction in neuropathic pain (Wang et al., 2011).

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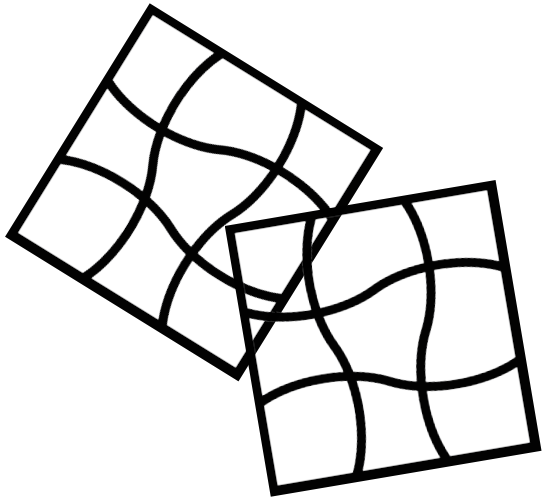
Ketamine's dissociative properties

50-100 ng/ml (sub-anaesthetic) doses of ketamine can induce a dissociative state characterized by hallucinations, distortion of visual and auditory stimuli, feelings of detachment from the environment and self, delirium and agitation.

These effects are associated with the blocking of NMDA channel activity which dysregulate excitatory neuronal activity.

Sensory inputs reach the cerebral cortex but fail to be perceived in some association (information processing) areas.



Other dissociative actions include:

- Disrupted synaptic homoeostasis
- Excess glutamate release
- Increased dopaminergic activity
- Decreased acetylcholinergic activity

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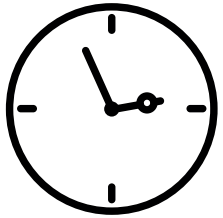
Ketamine's antidepressant effects

In the early 2000s research began into ketamine's use as an antidepressant treatment.

At low doses, ketamine's activity has been shown to rebalance the brain's glutamate and GABA levels via a downstream cascade of events elicited from its activity at the NMDA receptor.

High levels of glutamate and low GABA can lead to anxiety, whilst depleted glutamate and GABA levels contribute to depression.

Immediate changes (hours)

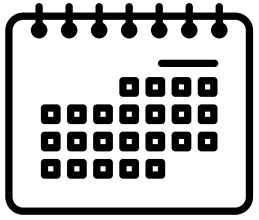


Blockade of NMDA receptors at the brain's inhibitory interneurones, causing a decrease in the release of GABA.

Disinhibition of glutamatergic neurones leads to increases presynaptic release of glutmate.

Patients may feel relaxed, or experience feelings of invulnerability during this time.

Lasting changes (days / weeks)



AMPA receptors are activated at the postsynaptic cell, causing calcium influx.

Stimulating BDNF and mTOR pathways eliciting synaptic plasticity and increase in synaptic strength, particularly in the prefrontal cortex.

This promotion of synaptic growth can help to 'undo' or 'reset' the stress induced structural changes of depressed brains, such as the emotional processing and memory areas of the prefrontal cortex and hippocampus.

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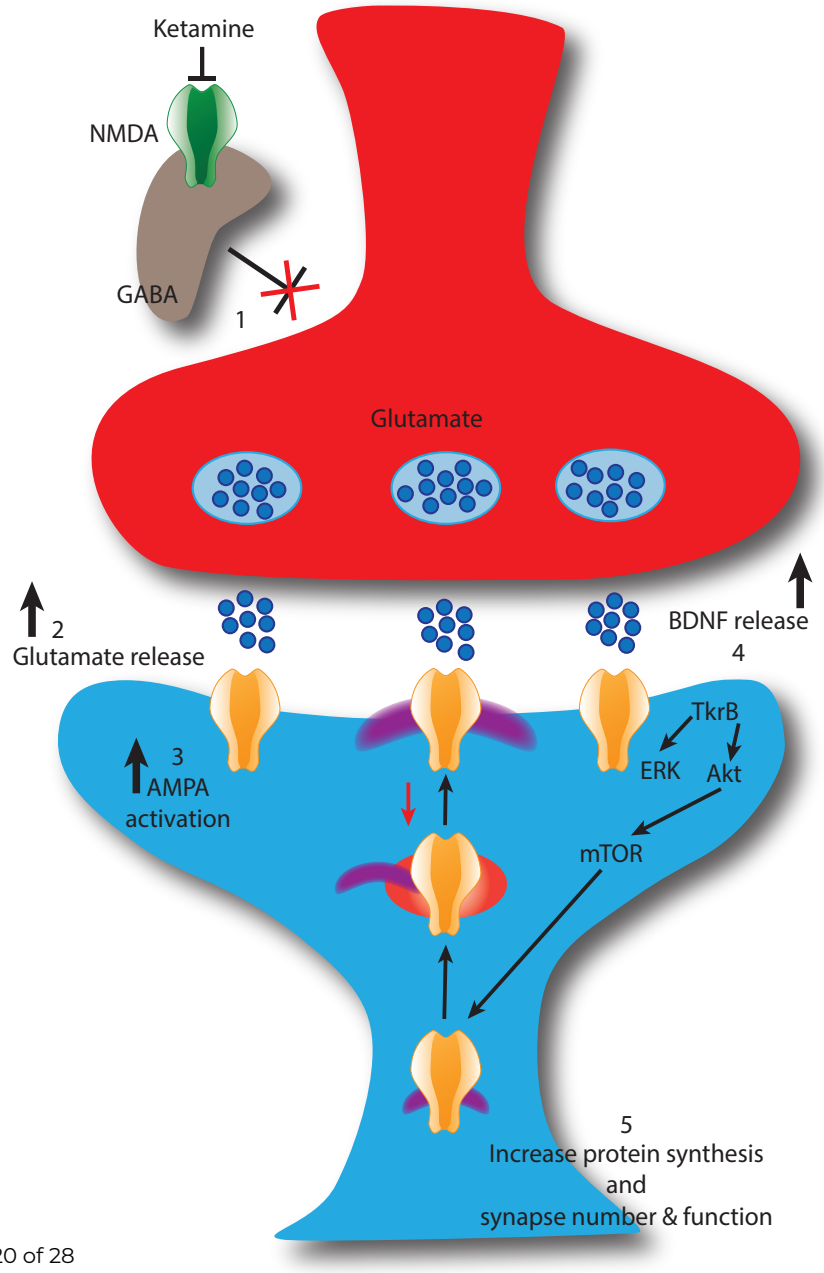
Potential antidepressant action



Ketamine's proposed antidepressant action is believed to be largely **glutamatergic.**

1. Ketamine binds to NMDA receptors on inhibitory interneurones which inhibits GABA release.

2. Blockade of tonic GABAergic inhibition and thereby dis-inhibition of the pre-synaptic cell.

Depolarisation of pre-synaptic cell causes mobilisation of glutamate vesicles.

3. Increase in glutamate release and cycling, which binds to AMPA receptors.

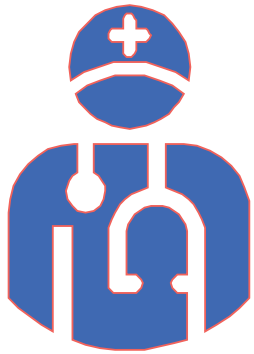
4. AMPA receptor activation.

Surface expression may also be independently upregulated due to supression of spontaneous NMDA receptor-mediated neurotransmission.

5. Increased synaptogenesis, leading to rapid and sustained antidepressant effects.

Drug Science

Ketamine - Risks and adverse effects



Ketamine is considered to have a good safety profile when administered in a clinical setting.

Moderate-to-high doses can produce a number of transient side-effects such as nausea, dizziness, double vision, drowsiness, dysphoria and confusion which can be distressing for patients.

Recreational use of ketamine has a greater risk profile due to the taking of unmonitored doses, concurrent drug use and unsafe environmental settings.

Chronic and extended abuse of ketamine may elicit withdrawal symptoms including chills, sweats, excitation, hallucinations, teary eyes and drug cravings.

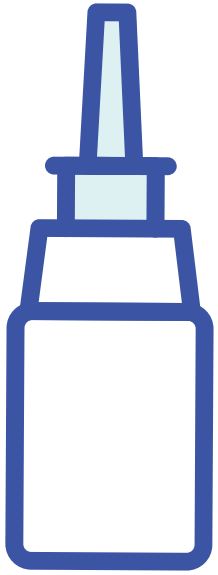
Example effects of recreational use of ketamine:

Short-term effects	Long-term effects
· Disrupted attention, learning and memory	· Uropathy
· Dreamlike states and hallucinations	· Kidney problems
· Confusion	· Stomach pain
· Unconsciousness and sedation	· Depression
· Raised blood pressure	· Deteriorated memory
· Dangerously slowed breathing	

The risk of fatal intoxication is very low, although it is increased with extreme alcohol intoxication or when taken alongside other CNS depressants.

Drug Science

Esketamine nasal spray



- In March 2019, a nasal spray formulation of esketamine became an FDA (U.S. Food and Drug Administration) approved prescription treatment for depressive symptoms in combination with an oral antidepressant under the trade name of SPRAVATO®.

- SPRAVATO® is a nasal spray which is self-administered under the supervision of a healthcare provider in a healthcare setting using a tailored dose prescribed by a healthcare professional.

- In December 2019, the Medicines and Healthcare Products Regulatory Agency (MHRA) also approved the use of SPRAVATO® for treatment resistant major depressive disorder (MDD) in Europe.

- In January 2020, the National Institute for Health and Care Excellence (NICE) rejected the use of SPRAVATO® within the NHS due to uncertainties over its clinical and cost effectiveness.

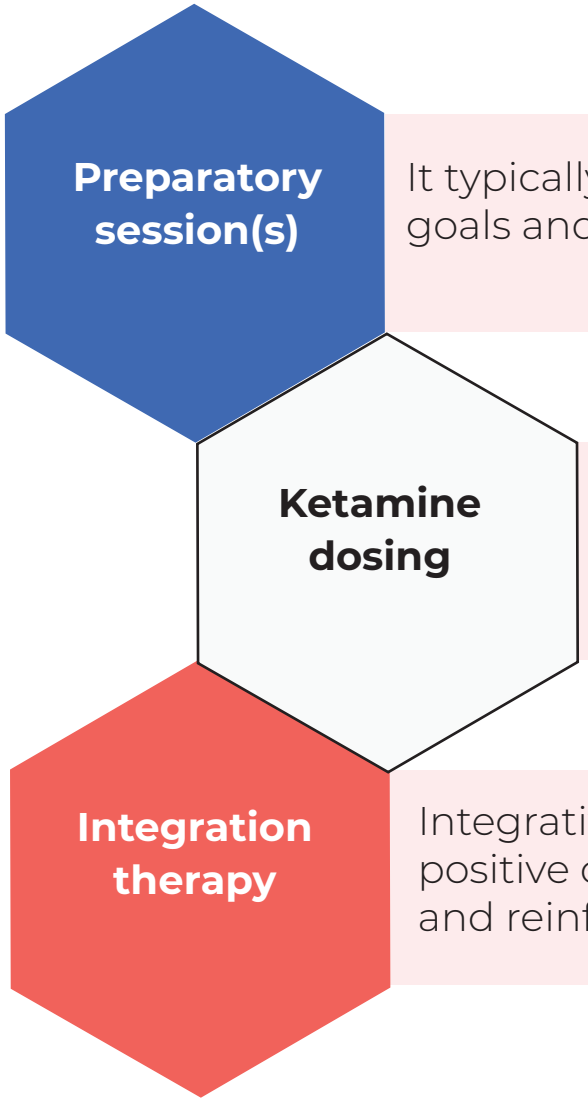
- In August 2020, the FDA extended its approval for the clinical use SPRAVATO® to include treatment of MDD with suicidal thoughts or actions when take in combination with a oral antidepressant.

- There are currently 37 studies listed on clinicaltrials.gov for the use of esketamine for the treatment of depression.

Drug Science

Ketamine-assisted psychotherapy

Ketamine-assisted psychotherapy is an off-label approach which combines ketamine and psychotherapy and is used to enhance the therapeutic efficacy of psychotherapy as an integrative form.



It typically begins with an eligibility session to identify a patient's treatment goals and to determine whether the form of therapy is a suitable fit.

45 minutes - 3 hours in length
Patients are often given multiple separate dosing and therapeutic sessions.

Integrative therapy is considered equally crucial to the active drug session for positive outcomes and focuses on support, integrating insights, and identifying and reinforcing change that may also be a part of the treatment process.

Drug Science

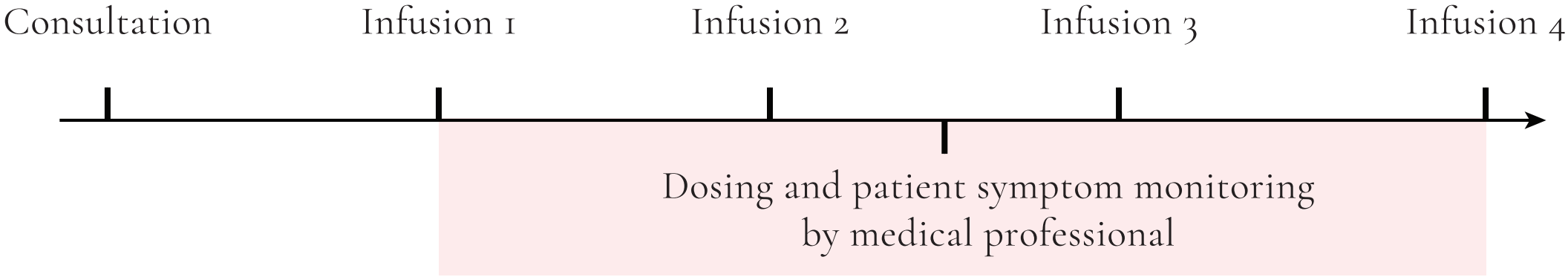
Off-label ketamine treatment

- Ketamine is used as an off-label and legal treatment for a variety of health conditions including depression, PTSD, addiction, anxiety and chronic pain.

- The emergence of off-label ketamine clinics has risen in recent years, particularly in the UK and US.

- Dosing and therapeutic regimes differ depending on healthcare professional preferences and specific patient needs. Most commonly, these clinics consist of multiple infusion dosing sessions which are monitored by an experienced doctor.

- An estimated 70 - 80% of patients respond to ketamine treatment, after a 3rd or 4th dose.



Example off-label ketamine clinic schedule

Drug Science

Nomenclature

Trade names

Anaket®, Anasket®, Anesketin®, Brevinase® Brevinaze®, Calypsol®, Calypsovet®, Chlorketam®, Ereska®, Imalgene®, Inducmina®, Kalipsol®, Katalar®, Keta®, Keta-Hameln®, Ketaject®, Ketalar®, Ketalin®, Ketalor®, Ketamav®, Ketamax®, Ketamil®, Ketamin®-ratiopharm, Ketaminol Vet®, Ketanarkon®, Ketanest®, Ketanest-S®, Ketaset®, Ketasol®, Ketava®, Ketaved®, Ketavet®, Ketmine HCl®, Ketolar®, Ktmin®, Narkamon®, Narketan®, Pan-Ketamine®, Ralatek®, Spravato®, S-Ketamin®, Tekam®, Velonarcon® Vetaket®, Vetalar®, Vetus Ketha-Thesia®.

Chemical names

2-(2-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride; 2-(o-chlorophenyl)-2-(methylamino)cyclohexanone hydrochloride; 2-(methylamino)-2-(2-chlorophenyl)cyclohexanone hydrochloride; 2-(methylamino)-2-(o-chlorophenyl)cyclohexanone hydrochloride; cyclohexanone, 2-(2-chlorophenyl)- 2-(methylamino) hydrochloride; cyclohexanone, 2-(o-chlorophenyl)-2-(methylamino) hydrochloride.

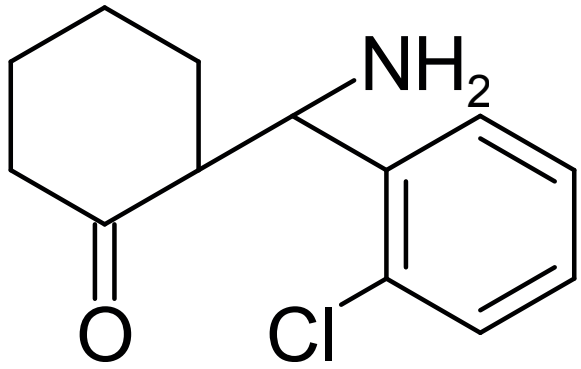
Street names

“Cat valium”, “Flatliners”, “Jet”, “K”, “Kaddy”, “Kate”, “Ket”, “Kéta K”, “Ketamine”, “Kit Kat”, “Liquid E”, “Liquid G”, “Mauve and Green”, “1980 acid”, “Purple”, “Special K”, “Special LA coke”, “Super acid”, “Super C”, “Super K”, “Tac et Tic”, “Vitamin K”

Drug Science

Norketamine

- Norketamine is ketamine's primary and active metabolite, which exerts a range of effects, similar to that of ketamine.
- Preclinical research has been conducted to investigate its clinical potential.
- It is a noncompetitive NMDA receptor antagonist, with a binding affinity 1/3 of that for ketamine. (S)-isomer (Ki = 1.7 μM) is higher than its (R)-isomer (Ki =13 μM).
- Norketamine concentration peaks at around 30 minutes after IV injection and has a half life of approximately 6 hours.
- Norketamine has around 30% of ketamine's anaesthetic activity.



- Animal models indicate that (S)-norketamine may provide antidepressant activity which is independent and equivalent to that of racemic ketamine, but lower than (R)-ketamine (Yang et al., 2018; Hashimoto & Yang., 2019).
- (S)-norketamine does not cause psychotomimetic effects or has the potential to be abused, unlike racemic and (R)-ketamine.
- Norketamine is not known to be used for recreational purposes.

Drug Science

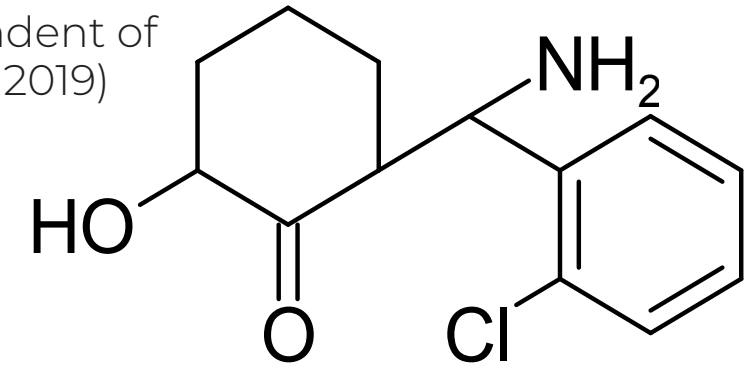
Hydroxynorketamine (HNK)

- HNK or 6-HNK is a minor metabolite of ketamine, predominantly formed via the hydroxylation of norketamine.

- HNK does not have analgesic or psychoactive properties and does not have a strong affinity for the NMDA receptor.

- HNK has been shown to exert antidepressant activity independent of its parent, ketamine, in non-clinical studies (Zanos et al., 2016; 2019)

- Exerts effects at the a7-nicotinic acetylcholine receptor and mTOR function, however, its main molecular target is unknown.



- A phase 1 clinical trial to evaluate the effects of (2R,6R)-Hydroxynorketamine hydrochloride for the treatment of major depressive disorder is currently underway in the USA (NCT number: NCT04711005).

- HNK is not known to be used for recreational purposes.

Drug Science

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