Ketamine

By Drug Science and Small Pharma

Part 1 - History

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

@Drug_Science

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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?

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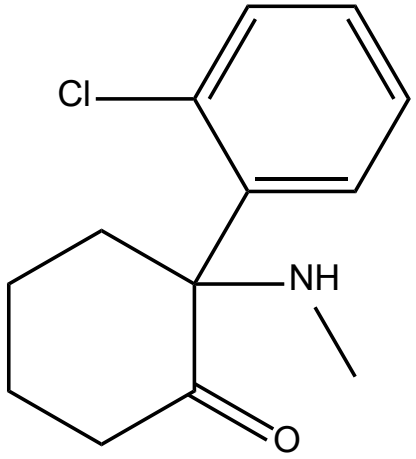
2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one (ketamine) is a cyclohexanone derivative with **analgesic** (pain killer) and **anaesthetic** properties.

Ketamine classifies as a **dissocitive sedative**.



Ketamine is a **non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist**. It acts as an inhibitor of N-methyl D-aspartate (NMDA) receptors.

Ketamine appears to **inhibit biogenic amine uptake**, by binding to opioid receptors, leading to indirect sympathomimetic activity.

It is also known to **bind with opioid mu and sigma receptors** at high doses.

Ketamine is synthesized chemically. Its appearance can be either a **clear liquid** or an **off-white powder** (Gupta et al., 2011; Kurdi et al., 2014; National Center for Biotechnology Information, 2021).

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Ketamine

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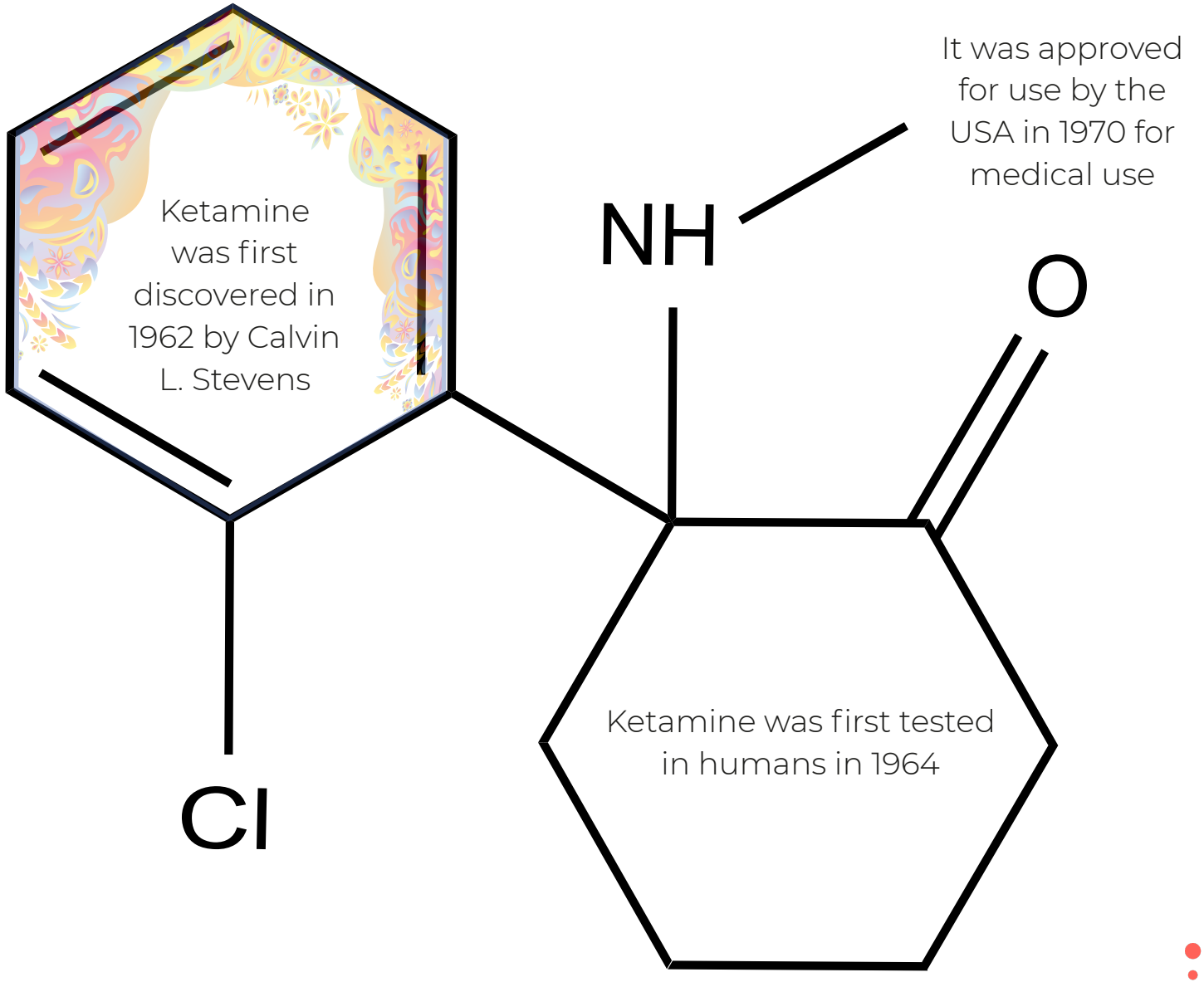

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PCP and what led to discover ketamine

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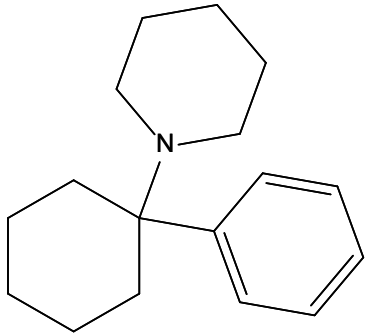
Ketamine research was initiated by an interest in finding an alternative to phencyclidine (PCP).

PCP was first synthesized in 1956 by chemists at Parke Davis Company.



PCP was proved to be a powerful anaesthesia in both animals and humans. However, research progressively revealed some **serious side effects of PCP**, including:

- Poor muscle relaxation
- Prolongued delirium
- Breathing problems

After some clinical trials, it was determined that PCP was **not suitable for human anaesthesia** (Domino & Luby, 2012).

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The discovery of ketamine

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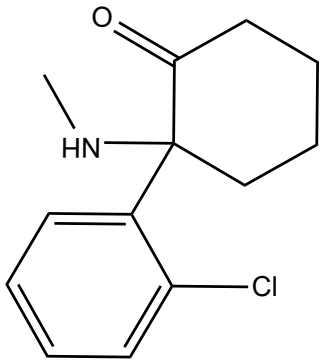
Efforts were subsequently redirected towards synthesizing analogs of PCP that would have similar anaesthetic potential but cause less emergence delirium and other side effects.

In the early 1960s, research continued and in **1962**, ketamine was discovered by merging a ketone with an amine:



Ketamine, then identified as CI-581, was originally developed by Calvin Stevens, a Parke Davis consultant and organic chemist.

Ketamine was a **structural analog at one-tenth the potency** of its parent drug PCP.

Research confirmed that ketamine presented **minimal side effects** and a lack of delirium compared to PCP. Moreover, ketamine offered a **limited duration of effects** which could be safely prolonged with repeated administation.

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Ketamine research for anesthesia

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1962

Ketamine is synthesized for the first time

1964
Domino & Corseen

First human anaesthetic dose administered

Evidence that the drug could be safe and effective for clinical anesthetic use

After 1966

Following the first clinical use of ketamine for anaesthesia and analgesia, it quickly became a popular induction agent among anesthesiologists

1970

U.S. FDA approval of ketamine as anaesthetics and analgesics

Ketalar became the first preparation of ketamine approved by the food and drug administration (FDA) for human use

1985

Ketamine listed as an essential medicine by the WHO for intravenous anaesthesia

Today

Ketamine is now used widely throughout the world for anaesthesia and pain relief in both humans and animals

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An emergency medicine

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Ketamine was first discovered in the midst of the Vietnam War. During the war, the combat conditions often made it difficult for doctors and nurses to have access to proper equipment for breathing support.

Before the discovery of ketamine, typical anaesthetics would regularly cause breathing difficulties.

Ketamine – having a **good safety profile** on that level compared to other anaesthetics - offered a revolutionary alternative for anaesthesia on the battlefield.

In the US, the FDA approved its use as a **field anaesthetic** for soldiers during the war.

Ketamine was therefore extensively used during the Vietnam War, both as an **emergency medicine for anaesthesia and for pain management in amputees and wounded soldiers**.

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Veterinary use

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Since its discovery, ketamine is commonly used across the globe in veterinary medicine.

It produces **sedation and anaesthesia** in animals. Veterinarians widely use ketamine in **domestic animals, small animals and horses**.

It is particularly useful thanks to its **rapid onset** and short duration of action.

It is often used for **surgery, transportation, pain management and research**.

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Recreational Use

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Clinical trials on ketamine demonstrated significant anaesthetic and analgesic effects. Moreover, one of the main side effects were **potent hallucinations and dissociative effects.**

Soon after the discovery of the molecule and its medical properties, ketamine started drawing the attention of the public when many realised ketamine could be used recreationally.

Ketamine quickly became popular among clubbing and rave culture, being appreciated for its **euphoriant properties and mild stimulant effects** when taken in small amounts. At higher doses, ketamine can also create **hallucinogenic and dissociative effects**, such as the distortion of sights, colours, sounds, sense of self and the environment.

Following reports of misusages and incidents caused by ketamine, it became a **Class III substance** of the US Controlled Substances Act in the US in 1999. Whilst previously only controlled under the Medicine's Act in the UK, ketamine was classified in 2006 (class C). Since 2014, ketamine has been classified as class B.

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Mental Health Use

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Today, the molecule is still being used in dentistry, veterinary medicine, and is a popular recreational drug. In recent years, scientific research has developed an interest for the **potential of ketamine to treat mental health conditions.** These investigations have been offering promising results and created a surge in research and drug development activities.

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Research into ketamine's psychological effects (Domino & Warner, 2010; Lil & Vlisides, 2016; Wei et al., 2020)

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1964-1966

During the first clinical experiences with ketamine, participants report a unique state of altered consciousness

Participants describe feelings of dissocation and disconnectedness from their bodies

Ketamine is first characterized as a dissociative anaesthetic

1970s

Early accounts of the recreational use of ketamine begin to spread

1978

Ketamine recreational use popularized by John Lilly and Marcia Moore

1983

Confirmation of ketamine as NMDAR antagonist

2000

First double-blind placebo control study of (R,S)-ketamine

Evidence for the rapid anti-depressant effects of ketamine on treatment resistant patients

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Ketamine research for mental health

(Grady et al., 2017; Ivan Ezquerra-Romano, 2018; Taylor et al., 2018; Wei et al., 2020)

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2014

The rapid improvement in suicidal ideation after ketamine administration are put forward for the first time

Ketamine shows proven efficacy for the treatment of PTSD

2015

Ketamine is shown to induce large-scale persistent network reconfiguration

2017

Ketamine shows promise in quickly reducing symptoms in patients with bipolar depression

2018

Preliminary evidence suggests that ketamine may be effective in addiction

A proof-of-concept trial provides initial evidence that ketamine may be effective in reducing anxiety

2019

U.S. FDA and European Commission approval of (S)-ketamine nasal spray for treatment-resistant depression

(R)-ketamine in Phase 1 clinical trial

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Ketamine-assisted psychotherapy

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As a result from this wave of research, ketamine was deemed "**breakthrough therapy**" for mental health and "the most important discovery in 50 years".

In 2019, the FDA approved **Spravato** (esketamine) nasal spray, in conjunction with an oral antidepressant, for the treatment of depression in adults who have tried other antidepressant medicines but have not benefited from them (treatment-resistant depression).

Drug Science

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