Ketamine Overview

History/Background

Ketamine is a dissociative anaesthetic that is primarily used for pain and depression. It's use began in the '60s and it "remains invaluable to the fields of anesthesiology and critical care medicine, in large part due to its ability to maintain cardiorespiratory stability while providing effective sedation and analgesia." (1)

The primary reason ketamine was developed was to offer a replacement for PCP (phencyclidine)— which was the primary analgesic used for surgery prior to 1970. Scientists had been searching for an alternative to PCP for a long time. While this drug worked to stop pain and suffering during surgical procedures and after severe traumatic injuries, it sometimes led to long term side effects like psychosis.

Ketamine's history begins with phencyclidine, which was first synthesized in 1956 by chemists at Parke Davis Company (Maddox et al., 1965) who discovered ketamine's unique and fascinating pharmacology. Phencyclidine was problematic and so later in 1962 ketamine (a substance 1/10th the potency) was produced by Calvin Stevens. Ketalar (1970) became the first preparation of ketamine approved by the Food and Drug Administration (FDA) for human use.

Due to its favorable sympathomimetic properties and its wide margin of safety, it was administered as a field anaesthetic to soldiers during the Vietnam War. Ketamine is on the World Health Organization's "Essential Drugs List", a list of the safest and most effective drugs needed in a modern health system. *(from the Wikipedia page)*

There are dozens of ketamine clinics located around the United States, Canada, and some parts of Europe. Most of these clinics focus on the treatment of depression. There are even virtual ketamine clinics that provide online meetings and send a dose of ketamine for the session in the mail.

Benefits

>Pain Relief
One of the safest anaesthetics, it has less chance of negative heart effects than other pain medications. Together with the ease of administration, efficacy and safety profile in children, ketamine has become one of the most commonly used drugs for

procedural sedation and analgesia for children in emergency departments. (usually via injection) K has been used as trauma medicine in conflict zones as well.

>Depression & PTSD
Over the last 50 years, there's been over 70 individual phase II clinical trials exploring the benefits of ketamine for conditions such as depression, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), bipolar disorder, drug addiction, and much more. (2)

>Harm Reduction
While ketamine is addictive, it has a much lower risk of addiction compared to other prescription medications — especially pain medications or antianxiety medications. It has been studied as a treatment for alcohol and heroin addiction.

>Ketamine & Synapse Regrowth
Studies have shown that ketamine stimulates the growth of synapses (3). This is an important finding because no other conventional antidepressant that we know of can do this.

>Circadian Rhythm Regulation
Ketamine has been shown to improve the body's ability to regulate the circadian rhythm (4).

>Blood Sugar Regulation (secondary effect)
Ketamine has been shown to regulate blood sugar levels in regions of the brain associated with depression (5).

General Effects

Ketamine is used every day by doctors performing surgery or treating people with severe traumatic injuries or burns. (sometimes by IV) It's also used as a treatment for depression in both injection and nasal spray forms.
The antidepressant effects of K seem to be transitory and last up to a week post dosing.

Possible Side Effects include

- High blood pressure (more with higher doses)
- Hypersalivation (less common compared to kids & rarely a concern)

- Nausea & vomiting (more common in early adolescence & upon leaving the dissociated state; more common via injection)
- Perceptual disturbances
- Loss of coordination
- Slurred speech
- Dissociation (out of body experiences)
- Orgasm suppression & decreased libido

Interactions/Contraindications

The K experience can cause you to lose control of your body which can be extremely terrifying. You may want to have someone you trust nearby, and above all only take the drug in a safe and comfortable environment.

Other considerations :

- Frequent use has been linked with bladder disease
- Blackmarket ketamine may be laced with other, more dangerous drugs
- Ketamine can interfere or interact with other medications or alcohol
- Ketamine stops you from feeling pain, increasing your risk of developing serious injuries
- Ketamine can increase the risk of heart attack or stroke
- Ketamine can be addictive with more frequent use
- The psychoactive effects of ketamine can be terrifying and may trigger psychosis in susceptible individuals (with higher doses)
- Being odorless and tasteless, it can be misused as a date rape drug

Ketamine is contraindicated in pregnant and lactating women, and children under 3 months.

Given its CNS modulatory activity, ketamine should be used extremely cautiously in close proximity to other drugs that alter mood and perception, including alcohol, opioids, benzodiazepines, GHB, and cannabis. Ketamine metabolism involves cytochrome P450 enzymes (Hijazi and Boulieu, 2002), and thus, concomitant use with drugs that inhibit cytochrome P450 metabolism may lead to inhibited ketamine metabolism and supratherapeutic toxicity.
Death by overdose of K is rare & overall the wide therapeutic range gives K a good safety profile.

S-ketamine vs. R-ketamine: What's The Difference?

Most drugs come in two different enantiomers.
Enantiomers are chemicals that have the exact same chemical structure but are mirror images of each other. Just like your right and left hand. Both hands have the same shape, but in order for them to share the same outline, you have to flip one of them upside down. There are two enantiomers for ketamine — the "R" and "S" enantiomers.
Typically ketamine contains both S&R at a ratio of around 1:1, but there are also R&S forms.

Esketamine (S-ketamine) contains only the "S" ketamine, which is often described as the stronger of the two molecules. S-ketamine is reported to be less prone to psychomimetic side effects, such as derealisation and hallucinations. (6) Janssen markets a product called Spravato (approved in 2019) which is grossly expensive and is often given with another SSRI. *S*-ketamine has an approximately fourfold greater affinity for the NMDA receptor than the *R*-ketamine. Furthermore, *S*-ketamine shows an approximately three-to fourfold greater anaesthetic potency and greater undesirable psychotomimetic side effects, compared with *R*-ketamine. (7)

R-ketamine is the cheaper option that Big Pharma ignores essentially. R may be better at treating depression for some people. (8) R-ketamine has also been observed to induce *synaptogenesis*—the formation of new connections between brain cells—more robustly than S-ketamine.
Kenji Hashimoto from Japan wrote in support of the R form saying it had less potential for side effects and greater efficacy for depression.

Research is still ongoing so it's hard to definitively say which form (R or S) is superior & it will depend upon your unique situation.

As a guideline users commonly report that R-ketamine is more physical and more effective for pain whereas S is more cerebral. (Keep in mind that this is a generalisation and your experience will be unique to you and dependent upon whether you're using it for pain, depression, or as a novel psychedelic.

Dosing & Administration

Ketamine is most commonly administered in the dose of 0.5 mg/kg, but some patients may respond to doses as low as 0.1 mg/kg, and others may require up to 0.75 mg/kg. The ketamine dose is conventionally administered across 40 minutes; however, safety and efficacy have been demonstrated in sessions ranging between 2 and 100 minutes in duration. (9)
If taken intranasally, you would be on the higher end of those recommendations.
Taking K orally is cost prohibitive and not wise since bioavailability is so low.
IV & intramuscular (injected) K is the most efficient mode of delivery.

Dose	Effect
0.1 – 0.3 mg/kg	Analgesia
0.2 – 0.5 mg/kg	Recreational
0.4 – 0.8 mg/kg	Partially dissociated
1-2 mg/kg	Fully dissociated

(10)

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