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**Ketamine**, sold under the brand name **Ketalar** among others, is a [medication](/wiki/Medication) mainly used for starting and maintaining [anesthesia](/wiki/Anesthesia).<ref name=KetPres2013/> It induces a [trance](/wiki/Trance)-like state while providing [pain relief](/wiki/Analgesia), [sedation](/wiki/Sedation), and [memory loss](/wiki/Amnesia).[[1]](#cite_note-1) Other uses include for [chronic pain](/wiki/Chronic_pain) and for sedation in [intensive care](/wiki/Intensive_care).[[2]](#cite_note-2)[[3]](#cite_note-3) Heart function, breathing, and airway reflexes generally remain functional.[[1]](#cite_note-1) Effects typically begin within five minutes when given by injection with the main effects lasting up to 25 minutes.<ref name=Mary2014/><ref name=KetPres2013/>

Common side effects include psychological reactions as the medication wears off.[[4]](#cite_note-4) These reactions may include agitation, confusion, or [hallucinations](/wiki/Hallucinations).<ref name=KetPres2013>[Template:Cite web](/wiki/Template:Cite_web)</ref>[[4]](#cite_note-4)<ref name=KetSide2014/> Elevated [blood pressure](/wiki/Blood_pressure) and muscle tremors are relatively common, while [low blood pressure](/wiki/Hypotension) and a decrease in breathing is less so.<ref name=KetPres2013/><ref name=KetSide2014>[Template:Cite web](/wiki/Template:Cite_web)</ref> [Spasms of the larynx](/wiki/Laryngospasms) may rarely occur.<ref name=KetPres2013/> Ketamine has been classified as an [NMDA receptor antagonist](/wiki/NMDA_receptor_antagonist); it also acts on [opioid receptors](/wiki/Opioid_receptor) and [monoamine transporters](/wiki/Monoamine_transporter) among others.[[5]](#cite_note-5) Ketamine was discovered in 1962.<ref name=Mary2014>[Template:Cite web](/wiki/Template:Cite_web)</ref> It is on the [World Health Organization's List of Essential Medicines](/wiki/World_Health_Organization's_List_of_Essential_Medicines), of the most important medications needed in a basic [health system](/wiki/Health_system).[[6]](#cite_note-6) It is available as a [generic medication](/wiki/Generic_medication).<ref name=KetPres2013/> The wholesale cost in the [developing world](/wiki/Developing_world) is between 0.08 and 0.32 USD per dose.[[7]](#cite_note-7) Ketamine is also used as a [drug of abuse](/wiki/Drug_abuse)<ref name=KetPres2013/> and as a [recreational drug](/wiki/Recreational_drug).[[8]](#cite_note-8)[Template:TOC limit](/wiki/Template:TOC_limit)

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## Uses[[edit](/index.php?title=(none)&action=edit&section=1)]

[thumb|1000mg/10ml vial of ketamine](/wiki/Image:Home_Anesthetic.jpg)

### Medical[[edit](/index.php?title=(none)&action=edit&section=2)]

#### Anesthesia[[edit](/index.php?title=(none)&action=edit&section=3)]

Uses as an anaesthetic:

* Anesthesia in children, as the sole anesthetic for minor procedures or as an induction agent followed by [muscle relaxant](/wiki/Muscle_relaxant) and [tracheal intubation](/wiki/Tracheal_intubation)
* [Asthmatics](/wiki/Asthma) or people with [chronic obstructive airway disease](/wiki/Chronic_obstructive_airway_disease)
* As a [sedative](/wiki/Sedative) for physically painful procedures in [emergency departments](/wiki/Emergency_department)[[1]](#cite_note-1)\* Emergency surgery in field conditions in war zones
* To supplement [spinal](/wiki/Spinal_anaesthesia) or [epidural](/wiki/Epidural) anesthesia/analgesia using low doses

Since it suppresses breathing much less than most other available anaesthetics,[[9]](#cite_note-9) ketamine is used in medicine as an anesthetic; however, due to the hallucinations it may cause, it is not typically used as a primary anesthetic, although it is the anaesthetic of choice when reliable [ventilation](/wiki/Mechanical_ventilation) equipment is not available.

Ketamine is frequently used in severely injured people and appears to be safe in this group.[[10]](#cite_note-10) A 2011 [clinical practice guideline](/wiki/Medical_guideline) supports the use of ketamine as a [dissociative](/wiki/Dissociative) sedative in [emergency medicine](/wiki/Emergency_medicine).[[1]](#cite_note-1) It is the drug of choice for people in traumatic shock who are at risk of [hypotension](/wiki/Hypotension).[[11]](#cite_note-11) [Low blood pressure](/wiki/Hypotension) is harmful in people with severe head injury[[12]](#cite_note-12) and ketamine is least likely to cause low blood pressure, often even able to prevent it.[[13]](#cite_note-13)[[14]](#cite_note-14) The effect of ketamine on the [respiratory](/wiki/Respiratory_system) and [circulatory systems](/wiki/Circulatory_system) is different from that of other anesthetics. When used at anesthetic doses, it will usually stimulate rather than depress the circulatory system.[[15]](#cite_note-15) It is sometimes possible to perform ketamine anesthesia without protective measures to the airways.[Template:Citation needed](/wiki/Template:Citation_needed) Ketamine is considered relatively safe because protective airway reflexes are preserved.[[16]](#cite_note-16) Ketamine is used as a bronchodilator in the treatment of severe asthma.[[17]](#cite_note-17) However, evidence of clinical benefit is limited.[[17]](#cite_note-17)[[18]](#cite_note-18)

#### Pain management[[edit](/index.php?title=(none)&action=edit&section=4)]

Ketamine may be used for postoperative pain management. Low doses of ketamine reduce [morphine](/wiki/Morphine) use and nausea and vomiting after surgery.[[19]](#cite_note-19) High quality evidence in acute pain is insufficient to determine if ketamine is useful in this situation.[[20]](#cite_note-20) It may also be used as an intravenous analgesic with opiates to manage otherwise intractable pain, particularly if this pain is neuropathic. It has the added benefit of counteracting [spinal sensitization](/wiki/Spinal_sensitization) or [wind-up phenomena](/wiki/Pain_wind-up) experienced with [chronic pain](/wiki/Chronic_pain). At these doses, the [psychotropic](/wiki/Psychoactive_drug) side effects are less apparent and well managed with [benzodiazepines](/wiki/Benzodiazepine).[[21]](#cite_note-21) Ketamine is an analgesic that is most effective when used alongside a low-dose [opioid](/wiki/Opioid); as while it does have analgesic effects by itself, the doses required for adequate pain relief when it is used as the sole analgesic agent are considerably higher and far more likely to produce disorienting side effects.[[21]](#cite_note-21) A review article in 2013 concluded, "despite limitations in the breadth and depth of data available, there is evidence that ketamine may be a viable option for treatment-refractory cancer pain".[[22]](#cite_note-22) Low-dose ketamine is sometimes used in the treatment of [complex regional pain syndrome](/wiki/Complex_regional_pain_syndrome) (CRPS).[[23]](#cite_note-23) A 2013 systematic review found only low-quality evidence to support the use of ketamine for CRPS.<ref name= OConnellWand2013>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

#### Depression[[edit](/index.php?title=(none)&action=edit&section=5)]

[Template:See also](/wiki/Template:See_also) Ketamine has been tested in treatment-resistant [bipolar disorder](/wiki/Bipolar_disorder), [major depressive disorder](/wiki/Major_depressive_disorder), and people in a suicidal crisis in emergency rooms.[[24]](#cite_note-24) Benefit is often of a short duration.<ref name=Caddy2010>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The quality of the evidence supporting benefit is generally low.<ref name=Caddy2010/>

The drug is given by a single intravenous infusion at doses less than those used in anesthesia, and preliminary data indicate it produces a rapid (within 2 hours) and relatively sustained (about 1–2 weeks long) reduction in [symptoms](/wiki/Symptoms) in some people.[[25]](#cite_note-25) Initial studies have resulted in interest due to its rapid onset,[[26]](#cite_note-26) and because it appears to work by blocking [NMDA receptors](/wiki/NMDA_receptors) for [glutamate](/wiki/Glutamate), a different mechanism from most modern antidepressants that operate on [other targets](/wiki/Biology_of_depression#Monoamines).<ref name=Caddy2010/>[[27]](#cite_note-27)

### Recreational[[edit](/index.php?title=(none)&action=edit&section=6)]

[Template:Main](/wiki/Template:Main) [thumb|right|Ketamine poured onto glass and left to dry](/wiki/Image:Ketamine_Crystals.jpg) Ketamine use as a recreational drug has been implicated in deaths globally, with more than 90 deaths in England and Wales in the years of 2005-2013.<ref name=DalyVice14/> They include accidental poisonings, drownings, traffic accidents, and suicides.<ref name=DalyVice14>See Max Daly, 2014, "The Sad Demise of Nancy Lee, One of Britain's Ketamine Casualties," at *Vice* (online), July 23, 2014, see <https://www.vice.com/en_uk/read/ketamine-slowly-ruins-your-bladder-and-kills-you-863>, accessed 7 June 2015.</ref> The majority of deaths were among young people.<ref name=TheCrownONS13>The Crown, 2013, "Drug related deaths involving ketamine in England and Wales," a report of the Mortality team, Life Events and Population Sources Division, Office for National Statistics, the Crown (U.K.), see <http://www.ons.gov.uk/ons/about-ons/business-transparency/freedom-of-information/what-can-i-request/published-ad-hoc-data/health/october-2013/drug-related-deaths-involving-ketamine-by-age-group.xls> and <https://www.ons.gov.uk/ons/rel/subnational-health3/deaths-related-to-drug-poisoning/2012/stb---deaths-related-to-drug-poisoning-2012.html>, accessed 7 June 2015.</ref> This has led to increased regulation (e.g., upgrading ketamine from a Class C to a Class B banned substance in the U.K.).<ref name=DixonTelegraph14>Hayley Dixon, 2014, "Ketamine death of public schoolgirl an 'act of stupidity which destroyed family'," at *The Telegraph* (online), February 12, 2014, see <https://www.telegraph.co.uk/news/uknews/law-and-order/10633700/Ketamine-death-of-public-schoolgirl-an-act-of-stupidity-which-destroyed-family.html>, accessed 7 Jume 2015.</ref>

Unlike the other well-known dissociative [phencyclidine](/wiki/Phencyclidine) (PCP) and [dextromethorphan](/wiki/Dextromethorphan) (DXM), ketamine is very short-acting. It takes effect within about 10 minutes,[[28]](#cite_note-28) while its [hallucinogenic](/wiki/Hallucinogenic) effects last 60 minutes when [insufflated](/wiki/Insufflation_(medicine)) or injected and up to two hours when ingested orally.[[29]](#cite_note-29) At anaesthetic doses, under-dosaged from a medical point of view, ketamine produces a [dissociative state](/wiki/Dissociation_(psychology)), characterised by a sense of detachment from one's physical body and the external world which is known as [depersonalization](/wiki/Depersonalization) and [derealization](/wiki/Derealization).[[30]](#cite_note-30) At sufficiently high doses, users may experience what is called the "[K-hole](/wiki/K-hole)", a state of extreme dissociation with visual and auditory hallucinations.[[31]](#cite_note-31) [John C. Lilly](/wiki/John_C._Lilly), [Marcia Moore](/wiki/Marcia_Moore) and [D. M. Turner](/wiki/D._M._Turner) (amongst others) have written extensively about their own [entheogenic](/wiki/Entheogen) use of, and [psychonautic](/wiki/Psychonautics) experiences with ketamine.[[32]](#cite_note-32) Both Moore and Turner died prematurely (due to hypothermia and drowning respectively) during presumed unsupervised ketamine use.[[33]](#cite_note-33)

## Side effects[[edit](/index.php?title=(none)&action=edit&section=7)]

Ketamine is generally safe for those critically ill, when administered by trained medical professionals.[[34]](#cite_note-34) Even in these cases, there are known side effects that include one or more of the following:[[35]](#cite_note-35)\* Cardiovascular: [abnormal heart rhythms](/wiki/Arrhythmia), [slow heart rate](/wiki/Bradycardia) or [fast heart rate](/wiki/Tachycardia), [high blood pressure](/wiki/Hypertension) or [low blood pressure](/wiki/Hypotension)

* Central nervous system: Ketamine is traditionally avoided in people with or at risk of [intracranial hypertension](/wiki/Intracranial_hypertension) (ICP) due to concerns about ketamine causing increased intracranial pressure. It does not increase ICP more than opioids.[[36]](#cite_note-36)\* Dermatologic: Transient [erythema](/wiki/Erythema), transient [morbilliform](/wiki/Morbilliform) rash
* Gastrointestinal: Anorexia, nausea, increased salivation, vomiting
* Local: Pain or exanthema of the injection site
* Neuromuscular and skeletal: Increased skeletal muscle tone (tonic-clonic movements)
* Ocular: [Double vision](/wiki/Diplopia), increased [intraocular pressure](/wiki/Intraocular_pressure), [nystagmus](/wiki/Nystagmus), [tunnel vision](/wiki/Tunnel_vision)
* Respiratory: Airway obstruction, apnea, increased bronchial secretions, respiratory depression, laryngospasm
* Other: Anaphylaxis, dependence, emergence reaction

In 10-20% of patients at anesthetic doses experience adverse reactions that occur during emergence from anesthesia, reactions that can manifest as seriously as hallucinations and delirium.[[4]](#cite_note-4) These reactions may be less common in some patients subpopulations, and when administered intramuscularly, and can occur up to 24 hours postoperatively; the chance of this occurring can be reduced by minimizing stimulation to the patient during recovery and pretreating with a [benzodiazepine](/wiki/Benzodiazepine), alongside a lower dose of ketamine.[[4]](#cite_note-4) Patients who experience severe reactions may require treatment with a small dose of a short- or ultrashort-acting [barbiturate](/wiki/Barbiturate).[[35]](#cite_note-35) [Tonic](/wiki/Tonic_(physiology))-[clonic](/wiki/Clonic) movements are reported at higher anesthetic doses in greater than 10% of patients.[[37]](#cite_note-37)

### Neurological effects[[edit](/index.php?title=(none)&action=edit&section=8)]

In 1989, psychiatry professor [John Olney](/wiki/John_Olney) reported ketamine caused irreversible changes in two small areas of the rat brain. However, the rat brain has significant differences in metabolism from the human brain, therefore such changes may not occur in humans.[[38]](#cite_note-38) The first large-scale, longitudinal study of ketamine users found current frequent (averaging 20 days/month) ketamine users had increased depression and impaired memory by several measures, including verbal, short-term memory, and visual memory. Current infrequent (averaging 3.25 days/month) ketamine users and former ketamine users were not found to differ from controls in memory, attention, and psychological well-being tests. This suggests the infrequent use of ketamine does not cause cognitive deficits, and that any deficits that might occur may be reversible when ketamine use is discontinued. However, abstinent, frequent, and infrequent users all scored higher than controls on a test of delusional symptoms.[[39]](#cite_note-39) Short-term exposure of cultures of [GABAergic](/wiki/GABAergic) [neurons](/wiki/Neuron) to ketamine at high concentrations led to a significant loss of differentiated cells in one study, and noncell-death-inducing concentrations of ketamine (10 μg/ml) may still initiate long-term alterations of dendritic arbor in differentiated neurons. The same study also demonstrated chronic (>24 h) administration of ketamine at concentrations as low as 0.01 μg/ml can interfere with the maintenance of dendritic arbor architecture. These results raise the possibility that chronic exposure to low, subanesthetic concentrations of ketamine, while not affecting cell survival, could still impair neuronal maintenance and development.[[40]](#cite_note-40)[[41]](#cite_note-41) More recent studies of ketamine-induced neurotoxicity have focused on primates in an attempt to use a more accurate model than rodents. One such study administered daily ketamine doses consistent with typical recreational doses (1 mg/kg IV) to adolescent cynomolgus monkeys for varying periods of time.[[42]](#cite_note-42) Decreased locomotor activity and indicators of increased cell death in the [prefrontal cortex](/wiki/Prefrontal_cortex) were detected in monkeys given daily injections for six months, but not those given daily injections for one month.[[42]](#cite_note-42) A study conducted on [rhesus monkeys](/wiki/Rhesus_monkey) found a 24-hour [intravenous](/wiki/Intravenous) infusion of ketamine caused signs of brain damage in five-day-old but not 35-day-old animals.[[43]](#cite_note-43)Some neonatal experts do not recommend the use of ketamine as an anesthetic agent in human neonates because of the potential adverse effects it may have on the developing brain. These neurodegenerative changes in early development have been seen with other drugs that share the same mechanism of action of NMDA receptor antagonism as ketamine.[[44]](#cite_note-44) The acute effects of ketamine cause cognitive impairment, including reductions in vigilance, verbal fluency, short-term memory, and executive function, as well as schizophrenia-like perceptual changes.[[45]](#cite_note-45)

### Urinary tract effects[[edit](/index.php?title=(none)&action=edit&section=9)]

A 2011 systematic review examined 110 reports of irritative urinary tract symptoms from ketamine abuse.[[46]](#cite_note-46) Urinary tract symptoms have been collectively referred as "ketamine-induced ulcerative cystitis" or "ketamine-induced vesicopathy", and they include urge [incontinence](/wiki/Urinary_incontinence), decreased [bladder](/wiki/Bladder) compliance, decreased bladder volume, [detrusor](/wiki/Detrusor) overactivity, and painful [haematuria](/wiki/Haematuria) (blood in urine). [Bilateral hydronephrosis](/wiki/Hydronephrosis) and [renal papillary necrosis](/wiki/Renal_papillary_necrosis) have also been reported in some cases.[[46]](#cite_note-46)<ref name=morgan11>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The [pathogenesis](/wiki/Pathogenesis) of papillary necrosis has been investigated in mice, and mononuclear [inflammatory](/wiki/Inflammation) infiltration in the renal papilla resulting from ketamine dependence has been suggested as a possible mechanism.[[47]](#cite_note-47) The time of onset of lower urinary tract symptoms varies depending, in part, on the severity and chronicity of ketamine use; however, it is unclear whether the severity and chronicity of ketamine use corresponds linearly to the presentation of these symptoms. All reported cases where the user consumed greater than 5 g/day reported symptoms of the lower urinary tract.[[46]](#cite_note-46) Urinary tract symptoms appear to be most common in daily ketamine abusers who have abused the drug for an extended period of time.[[48]](#cite_note-48) These symptoms have presented in only one case of medical use of ketamine. However, following dose reduction, the symptoms remitted.[[48]](#cite_note-48) Management of these symptoms primarily involves ketamine cessation, for which compliance is low. Other treatments have been used, including [antibiotics](/wiki/Antibiotics), [NSAIDs](/wiki/NSAID), [steroids](/wiki/Steroid), [anticholinergics](/wiki/Anticholinergic), and cystodistension.[[46]](#cite_note-46) Both [hyaluronic acid](/wiki/Hyaluronic_acid) instillation and combined [pentosan polysulfate](/wiki/Pentosan_polysulfate) and ketamine cessation have been shown to provide relief in some patients, but in the latter case, it is unclear whether relief resulted from ketamine cessation, administration of pentosan polysulfate, or both. Further follow-up is required to fully assess the efficacy of these treatments.[[46]](#cite_note-46)

### Liver problems[[edit](/index.php?title=(none)&action=edit&section=10)]

In case reports of three patients treated with [esketamine](/wiki/Esketamine) for relief of chronic pain, liver enzyme abnormalities occurred following repeat treatment with ketamine infusions, with the liver enzyme values returning below the upper reference limit of normal range on cessation of the drug. The result suggests liver enzymes must be monitored during such treatment.[[49]](#cite_note-49)

### Interactions[[edit](/index.php?title=(none)&action=edit&section=11)]

Other drugs which increase blood pressure may interact with ketamine in having an additive effect on blood pressure including: stimulants, SNRI antidepressants, and MAOIs. Increase blood pressure and heart rate, palpitations, and arrhythmias may be potential effects.

Ketamine may increase the effects of other [sedatives](/wiki/Sedative) in a dose dependent manner, including, but not limited to: [alcohols](/wiki/Alcohol),[[50]](#cite_note-50) [benzodiazepines](/wiki/Benzodiazepines),[[51]](#cite_note-51) [opioids](/wiki/Opioids),[[52]](#cite_note-52) [quinazolinones](/wiki/Quinazolinones), [phenothiazines](/wiki/Phenothiazines), [anticholinergics](/wiki/Anticholinergic) and [barbiturates](/wiki/Barbiturates).[[53]](#cite_note-53)

## Pharmacology[[edit](/index.php?title=(none)&action=edit&section=12)]

### Pharmacodynamics[[edit](/index.php?title=(none)&action=edit&section=13)]

Ketamine acts primarily as an antagonist of the NMDA receptor, and this action accounts for most of its effects.[[5]](#cite_note-5) However, the complete pharmacology of ketamine is more complex, and it is known to directly interact with a variety of other sites to varying degrees.[[5]](#cite_note-5) A study conducted in mice that published in [*Nature*](/wiki/Nature_(journal)) in 2016 found that ketamine's antidepressant activity in mice is not caused by ketamine inhibiting NMDAR, but rather by sustained activation of a different glutamate receptor, the [AMPA receptor](/wiki/AMPA_receptor), by a metabolite, (2R,6R)-[hydroxynorketamine](/wiki/Hydroxynorketamine).[[54]](#cite_note-54)[[55]](#cite_note-55) Known actions of ketamine include:

* [Non-competitive antagonist](/wiki/Receptor_antagonist#Non-competitive) of the [NMDA receptor](/wiki/NMDA_receptor) (NMDAR)[[5]](#cite_note-5)[[56]](#cite_note-56)\* [Negative allosteric modulator](/wiki/Negative_allosteric_modulator) of the [nACh receptor](/wiki/Nicotinic_acetylcholine_receptor)[[5]](#cite_note-5)\* Weak [agonist](/wiki/Agonist) of the [μ-opioid](/wiki/Mu_opioid_receptor) and [κ-opioid receptors](/wiki/Kappa-opioid_receptor) (10- and 20-fold less affinity relative to NMDAR, respectively),[[5]](#cite_note-5) and very weak agonist of the [δ-opioid receptor](/wiki/Delta-opioid_receptor)[[5]](#cite_note-5)\* Agonist of the [D2 receptor](/wiki/D2_receptor)[[57]](#cite_note-57)\* Weak [mACh receptor](/wiki/Muscarinic_acetylcholine_receptor) antagonist (10- to 20-fold less affinity relative to NMDAR)[[5]](#cite_note-5)\* [Inhibitor](/wiki/Reuptake_inhibitor) of the [reuptake](/wiki/Reuptake) of [serotonin](/wiki/Serotonin), [dopamine](/wiki/Dopamine), and [norepinephrine](/wiki/Norepinephrine)[[5]](#cite_note-5)\* [Voltage-gated sodium channel](/wiki/Voltage-gated_sodium_channel) and [L-type calcium channel](/wiki/L-type_calcium_channel) [blocker](/wiki/Channel_blocker),[[5]](#cite_note-5)[[58]](#cite_note-58) and [HCN1 cation channel](/wiki/HCN1) blocker[[59]](#cite_note-59)\* [Inhibitor](/wiki/Enzyme_inhibitor) of [nitric oxide synthase](/wiki/Nitric_oxide_synthase)[[5]](#cite_note-5)[[60]](#cite_note-60)\* [σ receptor 1 and 2](/wiki/Sigma_receptor) agonist (μM affinities).[[5]](#cite_note-5)[[60]](#cite_note-60)[[61]](#cite_note-61)\* Activation of AMPA receptors[[62]](#cite_note-62)

Ketamine appears to inhibit the NMDAR by binding both in the open channel and at an allosteric site.<ref name=Orser>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The S(+) and R(-) [stereoisomers](/wiki/Stereoisomer) bind with different affinities: Ki = 3200 and 1100 nM, respectively.<ref name=hirota>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

The significance of these additional mechanisms in the therapeutic effects of ketamine is poorly understood due to its relatively complex pharmacological profile.

#### Effects in central nervous system[[edit](/index.php?title=(none)&action=edit&section=14)]

NMDAR antagonism is responsible for the anesthetic, [amnesic](/wiki/Amnesic), dissociative, and hallucinogenic effects of ketamine, although activation of κ-opioid receptors and possibly sigma and mACh receptors may also contribute to its [hallucinogenic](/wiki/Hallucinogenic) properties.[[5]](#cite_note-5) [Dopamine reuptake inhibition](/wiki/Dopamine_reuptake_inhibitor) is likely to underlie the [euphoria](/wiki/Euphoria) the drug produces, although an additional involvement of μ-opioid receptor activation cannot be excluded.[[5]](#cite_note-5) The mechanism of actions for the possible [antidepressant](/wiki/Antidepressant) effects of ketamine at lower doses have yet to be elucidated.[[63]](#cite_note-63) NMDAR antagonism results in [analgesia](/wiki/Analgesia) by preventing central sensitization in [dorsal horn](/wiki/Posterior_horn_of_spinal_cord) neurons; in other words, ketamine's actions interfere with pain transmission in the spinal cord.[[37]](#cite_note-37) Inhibition of nitric oxide synthase lowers the production of [nitric oxide](/wiki/Nitric_oxide) – a neurotransmitter involved in pain perception, hence further contributing to analgesia.<ref name=aroni>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> The action of ketamine at sigma and μ-opioid receptors is relatively weak, and evidence is mixed as to whether the latter is of significance to its analgesic effects.[[5]](#cite_note-5)<ref name=rowland>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

Ketamine also interacts with a host of other targets to cause analgesia. In particular, it blocks voltage-dependent calcium channels and sodium channels, attenuating [hyperalgesia](/wiki/Hyperalgesia); it alters [cholinergic](/wiki/Cholinergic) neurotransmission, which is implicated in pain mechanisms; and it inhibits the reuptake of serotonin and norepinephrine, which are involved in descending [antinociceptive](/wiki/Antinociceptive) pathways.[[37]](#cite_note-37)<ref name=meller>[Template:Cite journal](/wiki/Template:Cite_journal)</ref>

#### Effects in peripheral systems[[edit](/index.php?title=(none)&action=edit&section=15)]

Ketamine affects [catecholaminergic](/wiki/Catecholamines) transmission as noted above, producing measurable changes in peripheral organ systems, including the [cardiovascular](/wiki/Cardiovascular), [gastrointestinal](/wiki/Gastrointestinal_system), and [respiratory systems](/wiki/Respiratory_system):[[64]](#cite_note-64)\* Cardiovascular: Ketamine inhibits the reuptake of catecholamines, stimulating the [sympathetic nervous system](/wiki/Sympathetic_nervous_system), resulting in cardiovascular symptoms.

* Gastrointestinal: [Serotonin reuptake inhibition](/wiki/Serotonin_reuptake_inhibitor) is thought to underlie nausea and vomiting.[[5]](#cite_note-5)\* Respiratory: Catecholamine elevation and stimulation of β2 [adrenergic receptors](/wiki/Adrenergic_receptor) probably causes [bronchodilation](/wiki/Bronchodilation), although other processes may also be involved. The exact mechanism is not fully understood.

### Pharmacokinetics[[edit](/index.php?title=(none)&action=edit&section=16)]

Ketamine is absorbable by [intravenous](/wiki/Intravenous), [intramuscular](/wiki/Intramuscular), [oral](/wiki/Oral_administration), and [topical](/wiki/Topical) routes due to both its water and lipid solubilities.[[64]](#cite_note-64) When administered orally, it undergoes [first-pass metabolism](/wiki/First-pass_metabolism), where it is [biotransformed](/wiki/Biotransformation) in the liver by [CYP3A4](/wiki/CYP3A4) (major), [CYP2B6](/wiki/CYP2B6) (minor), and [CYP2C9](/wiki/CYP2C9) (minor) isoenzymes into [norketamine](/wiki/Norketamine) (through N-demethylation) and finally [dehydronorketamine](/wiki/Dehydronorketamine).[[65]](#cite_note-65) Intermediate in the biotransformation of norketamine into dehydronorketamine is the [hydroxylation](/wiki/Hydroxylation) of norketamine into [hydroxynorketamine](/wiki/Hydroxynorketamine) by CYP2B6 and [CYP2A6](/wiki/CYP2A6). Dehydronorketamine, followed by norketamine, is the most prevalent metabolite detected in urine.<ref name=heng2011>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> As the major metabolite of ketamine, norketamine is one-third to one-fifth as potent anesthetically, and plasma levels of this metabolite are three times higher than ketamine following oral administration.[[64]](#cite_note-64)[[66]](#cite_note-66) Bioavailability through the oral route reaches 17–20%; bioavailability through other routes are: 93% intramuscularly, 25–50% intranasally, 30% sublingually, and 30% rectally.[[37]](#cite_note-37)<ref name=sinner>[Template:Cite book](/wiki/Template:Cite_book) [Template:Doi](/wiki/Template:Doi). PMID 18175098.</ref> Peak plasma concentrations are reached within a minute intravenously, 5–15 min intramuscularly, and 30 min orally.<ref name=haas>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> Ketamine's duration of action in a clinical setting is 30 min to 2 h intramuscularly and 4–6 h orally.[[37]](#cite_note-37) Plasma concentrations of ketamine are increased by [diazepam](/wiki/Diazepam) and other [CYP3A4 inhibitors](/wiki/CYP3A4#CYP3A4_ligands) due to inhibition of conversion to norketamine.[[37]](#cite_note-37)

### Administration[[edit](/index.php?title=(none)&action=edit&section=17)]

In medical settings, ketamine is usually injected [intravenously](/wiki/Intravenous_therapy) or [intramuscularly](/wiki/Intramuscular_injection).[[67]](#cite_note-67) Ketamine can be started using the [oral route](/wiki/Oral_administration), or people may be changed from a [subcutaneous infusion](/wiki/Hypodermoclysis) once pain is controlled. [Bioavailability](/wiki/Bioavailability) of oral ketamine hydrochloride is around 20%

* Oral ketamine is easily broken down by [bile acids](/wiki/Bile), thus has a low bioavailability (about 20%). Often, lozenges or "gummies" for [sublingual](/wiki/Sublingual_administration) or [buccal](/wiki/Buccal_administration) absorption prepared by a compounding pharmacy are used to combat this issue.
* Some specialists stop the subcutaneous infusion when the first dose of oral ketamine is given. Others gradually reduce the infusion dose as the oral dose is increased.[[68]](#cite_note-68)

## Chemistry[[edit](/index.php?title=(none)&action=edit&section=18)]

### Structure[[edit](/index.php?title=(none)&action=edit&section=19)]

In chemical structure, ketamine is an [arylcyclohexylamine](/wiki/Arylcyclohexylamine) derivative. Ketamine is a [chiral](/wiki/Chirality_(chemistry)) compound. Most pharmaceutical preparations of ketamine are [racemic](/wiki/Racemic); however, some brands reportedly have (mostly undocumented) differences in their [enantiomeric](/wiki/Enantiomer) proportions. The more active enantiomer, [esketamine](/wiki/Esketamine) (*S*-ketamine), is also available for medical use under the brand name Ketanest S,[[69]](#cite_note-69) while the less active enantiomer, [arketamine](/wiki/Arketamine) (*R*-ketamine), has never been marketed as an [enantiopure drug](/wiki/Enantiopure_drug) for clinical use.

<gallery> Image:R-ketamine-2D-skeletal.png|

[Skeletal formula](/wiki/Skeletal_formula) of *(R)*-ketamine

Image:R-ketamine-3D-balls.png|

[Ball-and-stick model](/wiki/Ball-and-stick_model) of *(R)*-ketamine

Image:S-ketamine-2D-skeletal.png|

Skeletal formula of *(S)*-ketamine

Image:S-ketamine-3D-balls.png|

Ball-and-stick model of *(S)*-ketamine

</gallery>

The [optical rotation](/wiki/Optical_rotation) of a given enantiomer of ketamine can vary between its [salts](/wiki/Salt_(chemistry)) and [free base](/wiki/Free_base) form. The free base form of (*S*)‑ketamine exhibits [dextrorotation](/wiki/Dextrorotation_and_levorotation) and is therefore labelled (*S*)‑(+)‑ketamine. However, its [hydrochloride](/wiki/Hydrochloride) salt shows [levorotation](/wiki/Dextrorotation_and_levorotation) and is thus labelled (*S*)‑(−)‑ketamine hydrochloride. The difference originates from the [conformation of the cyclohexanone ring](/wiki/Cyclohexane_conformation). In both the free base and the hydrochloride, the cyclohexanone ring adopts a [chair conformation](/wiki/Cyclohexane_conformation#Chair_conformation), but the orientation of the substituents varies. In the free base, the *o*-chlorophenyl group adopts an equatorial position and the methylamino group adopts an axial position.[[70]](#cite_note-70) In the hydrochloride salt, the positions are reversed, with the *o*-chlorophenyl group axial and the methylamino group equatorial.[[71]](#cite_note-71) Not all salts of ketamine show different optical rotation to the free base: (*S*)-ketamine (*R*,*R*)-[tartrate](/wiki/Tartrate) is levorotatory, like (*S*)‑ketamine.[[72]](#cite_note-72)

<gallery> File:S-ketamine-2D-skeletal.png|

*(S)*-(−)-ketamine

File:S-(+)-ketamine-hydrochloride-2D-skeletal.png|

*(S)*-(+)-ketamine hydrochloride

File:S-ketamine-3D-balls.png|

*(S)*-(−)-ketamine in the crystal structure of the free base

File:S-(+)-ketamine-from-xtal-3D-balls.png|

*(S)*-(+)-ketamine in the crystal structure of the hydrochloride

</gallery>

## History[[edit](/index.php?title=(none)&action=edit&section=20)]

### Medical use[[edit](/index.php?title=(none)&action=edit&section=21)]

[thumb|Ketamine vials](/wiki/File:Ketamine_Vials.jpg) Ketamine was first synthesized in 1962 by [Calvin L. Stevens](/wiki/Calvin_L._Stevens), a professor of Chemistry in [Wayne State University](/wiki/Wayne_State_University) and a [Parke Davis](/wiki/Parke_Davis) consultant conducting research on alpha-hydroxyimine rearrangements.<ref name=Clark>[Template:Cite book](/wiki/Template:Cite_book)</ref> After promising preclinical research in animals, ketamine was introduced to testing in [human prisoners](/wiki/Experimentation_on_prisoners) in 1964.<ref name=Morris>[Template:Cite journal](/wiki/Template:Cite_journal)</ref><ref name=domino>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> These investigations demonstrated ketamine's short duration of action and reduced behavioral toxicity made it a favorable choice over [phencyclidine](/wiki/Phencyclidine) (PCP) as a dissociative anesthetic.[[73]](#cite_note-73) Following FDA approval in 1970, ketamine anesthesia was first given to American soldiers during the [Vietnam War](/wiki/Vietnam_War).[[74]](#cite_note-74)

### Nonmedical use[[edit](/index.php?title=(none)&action=edit&section=22)]

[Template:Main](/wiki/Template:Main) See the foregoing discussion and citations regarding the increasing stringency of governmental regulation that has resulted from a significant number of deaths of youth and young adults by overdose, accident, and suicide in which nonmedical/recreational ketamine use is implicated (in the Recreational use section, above).

Nonmedical use of ketamine began on the West Coast of the United States in the early 1970s.[[74]](#cite_note-74) Early use was documented in underground literature such as [*The Fabulous Furry Freak Brothers*](/wiki/The_Fabulous_Furry_Freak_Brothers). It was used in [psychiatric](/wiki/Psychiatry) and other academic research through the 1970s, culminating in 1978 with the publishing of [psychonaut](/wiki/Psychonautics) [John Lilly's](/wiki/John_C._Lilly) *The Scientist*, and [Marcia Moore](/wiki/Marcia_Moore) and Howard Alltounian's *Journeys into the Bright World*, which documented the unusual phenomenology of ketamine intoxication.[[75]](#cite_note-75) The incidence of nonmedical ketamine use increased through the end of the century, especially in the context of [raves](/wiki/Rave_party) and other parties.[[76]](#cite_note-76) However, its emergence as a [club drug](/wiki/Club_drug) differs from other club drugs (e.g. [MDMA](/wiki/MDMA)) due to its [anesthetic](/wiki/Anesthetic) properties (*e.g.*, slurred speech, immobilization) at higher doses;<ref name=hongkong>[Template:Cite journal](/wiki/Template:Cite_journal)</ref> in addition, there are reports of ketamine being sold as "ecstasy".[[77]](#cite_note-77) The use of ketamine as part of a "postclubbing experience" has also been documented.[[78]](#cite_note-78) Ketamine's rise in the dance culture was rapid in [Hong Kong](/wiki/Hong_Kong) by the end of the 1990s.[[79]](#cite_note-79) Before becoming a federally controlled substance in the United States in 1999, ketamine was available as diverted pharmaceutical preparations and as a pure powder sold in bulk quantities from domestic chemical supply companies.<ref name=Morris/> Much of the current ketamine diverted for nonmedical use originates in China and India.<ref name=Morris/>

In addition to its ability to cause confusion and [amnesia](/wiki/Anterograde_amnesia), ketamine can leave users vulnerable to [date rape](/wiki/Date_rape) (i.e., because of the associated confusion and amnesia).[[28]](#cite_note-28)[[74]](#cite_note-74)

## Society and culture[[edit](/index.php?title=(none)&action=edit&section=23)]

### Legal status[[edit](/index.php?title=(none)&action=edit&section=24)]

Ketamine is a "core" medicine in the [World Health Organization's](/wiki/World_Health_Organization) [Essential Drugs List](/wiki/WHO_Model_List_of_Essential_Medicines), a list of minimum medical needs for a basic healthcare system.[[80]](#cite_note-80) The increase in illicit use prompted ketamine's placement in Schedule III of the [United States](/wiki/United_States) [Controlled Substance Act](/wiki/Controlled_Substance_Act) in August 1999.[[81]](#cite_note-81) In the [United Kingdom](/wiki/United_Kingdom), it became labeled a [Class C drug](/wiki/Misuse_of_Drugs_Act_1971) on 1 January 2006.[[82]](#cite_note-82)[[83]](#cite_note-83) On 10 December 2013 the UK [Advisory Council on the Misuse of Drugs](/wiki/Advisory_Council_on_the_Misuse_of_Drugs) (ACMD) recommended that the government reclassify ketamine to become a Class B drug,[[84]](#cite_note-84) and on 12 February 2014 the Home Office announced they would follow this advice "in light of the evidence of chronic harms associated with ketamine use, including chronic bladder and other urinary tract damage".[[85]](#cite_note-85)[[86]](#cite_note-86) The UK Minister of State for Crime Prevention, [Norman Baker](/wiki/Norman_Baker), responding to the ACMD's advice, said the issue of its recheduling for medical and veterinary would be addressed "separately to allow for a period of consultation."[[85]](#cite_note-85) In [Australia](/wiki/Australia) Ketamine is listed as a schedule 8 controlled drug under the [Poisons Standard](/wiki/Standard_for_the_Uniform_Scheduling_of_Medicines_and_Poisons) (October 2015).[[87]](#cite_note-87)