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# Ketamine Infusion for Chronic Pain

Gabriel Barnard, MD, MS

PM&R and Interventional Pain Medicine

Health Sciences Clinical Instructor, David Geffen UCLA SOM

Associate Director

California Pain Medicine Centers

Center for the Rehabilitation of Pain Syndromes (CRPS)

Attending Physician, Greater Los Angeles VA Health System

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# Objectives

1. Define ketamine and mechanism of action
2. Discuss side effects and contraindications
3. Outline appropriate selection criteria
4. Review treatment protocols and infusion management

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# Disclosures

None

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# What is ketamine?

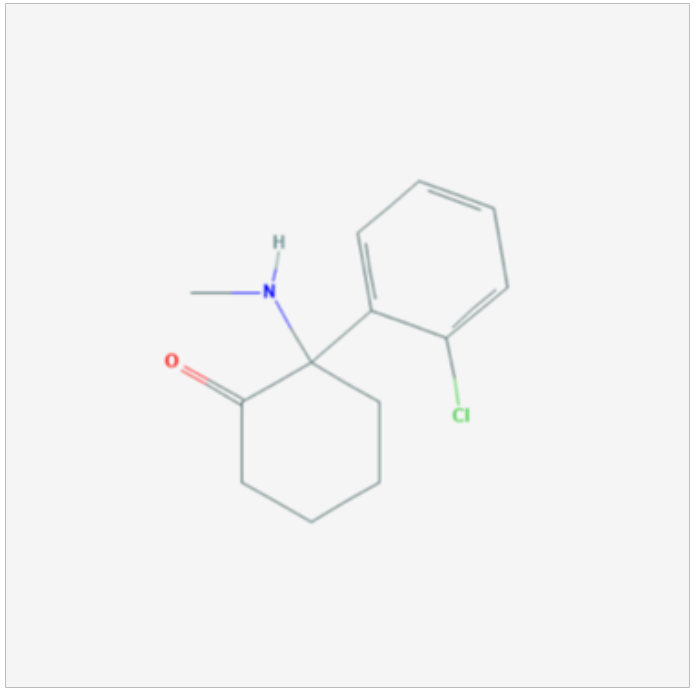
-Dissociative anesthetic

-DEA Schedule III

-Chemical derivative of phencyclidine (PCP)

-Originally synthesized in 1962 at Parke-Davis labs

-Human trials began in 1964 and it was approved by the FDA in 1970 as a general anesthetic agent




2-(2-chlorophenyl)-2-(methylamino)cyclohexan-1-one (IUPAC name)

National Center for Biotechnology Information. PubChem Compound Summary for CID 3821, Ketamine. https://pubchem.ncbi.nlm.nih.gov/compound/Ketamine. Accessed July 20, 2021.

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# What is ketamine?

## Pharmacologic effects of CI-581, a new dissociative anesthetic, in man

*Pharmacologic actions of CI-581, a chemical derivative of phencyclidine, were determined in 20 volunteers from a prison population. The results indicate that this drug is an effective analgesic and anesthetic agent in doses of 1.0 to 2.0 mg. per kilogram. With intravenous administration the onset of action is within 1 minute and the effects last for about 5 to 10 minutes, depending on dosage level and individual variation. No tachyphylaxis was evident on repeat doses. Respiratory depression was slight and transient. Hypertension,*

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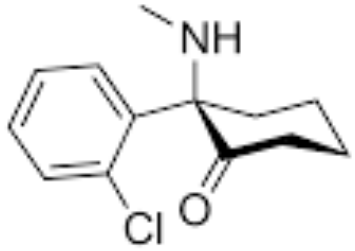
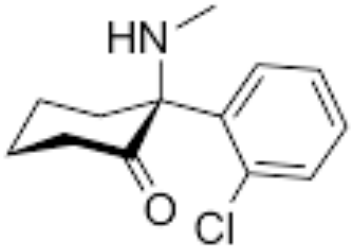
# What is ketamine?




(*R*)-(+)




(*S*)-(−)

Exists as two stereoisomers

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# Safety of Ketamine Infusion


It’s use has been evaluated in 105 studies including over 12,000 operations/diagnostic procedures

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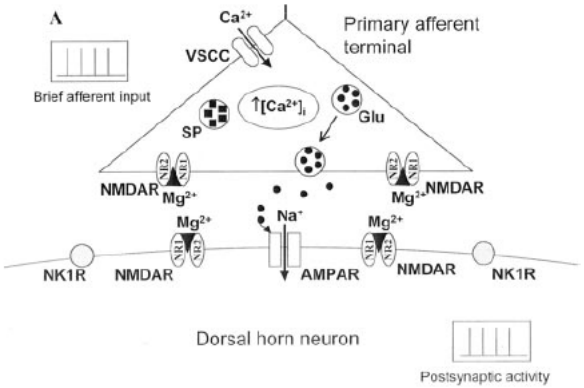
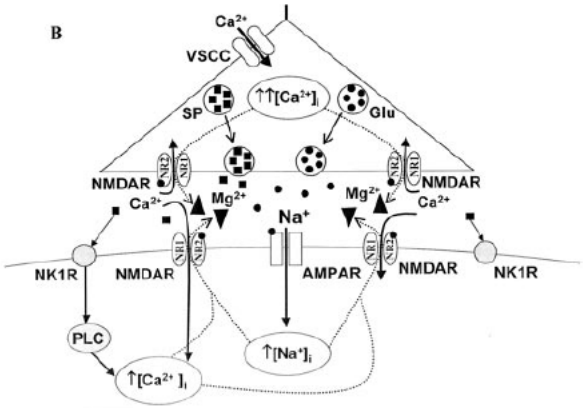
# Mechanism of Action

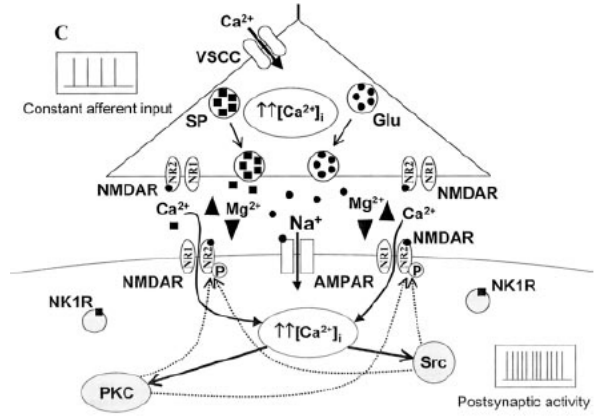
- Non-competitive NMDA antagonist in the central nervous system mainly at the prefrontal cortex and hippocampus (major)
- NMDA receptor have also been demonstrated in the peripheral nervous system and the spinal cord
- NMDA receptors have been shown to have lower activation thresholds in primary allodynia associated with peripheral tissue damage. This hyperexcitability then translates to the dorsal root ganglion and spinal cord leading to central sensitization.




Normal NMDA function




Acute injury NMDA function




Posttranslational modification

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# Mechanism of Action

- Ketamine also acts at opioid receptors  mu > kappa > sigma

- Other mechanisms that have been shown are nicotinic and muscarinic cholinergic antagonism, Na+/K+ blockade, activation of D2 dopamine receptors, enhancing descending modulatory pain pathways

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# Pharmaco- dynamics & kinetics

-S ketamine isomer has 3-4 times the affinity for the PCP binding site on NMDA receptors

-route of administration can vary widely; IV, IM, intranasal, inhalation, oral, topical, and rectal

- Rapid absorption and bioavailable at around 93%, but after first pass metabolism only 17%
- 85-95% is eliminated via the kidneys
- Ketamine has a large volume of distribution, rapid clearance, and low protein binding; making it good for continuous infusion.

-It crosses the blood-brain barrier and is mostly metabolized by the liver CYP450 system

-plasma half life is approximately 2.3 +/- 0.5 hours

-it is rapidly metabolized to norketamine, hydroxyketamine, and dehydronorketamine

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# Pharmaco- dynamics & kinetics

| Route of Administration | Typical Dosing | Bioavailability, % | Time of Onset | Duration of Action After Dosing |
|---|---|---|---|---|
| Intravenous | 1–4.5 mg/kg for general anesthesia induction; 1–6 mg/kg per hour for anesthesia maintenance; 0.5–2 mg/kg for 1-d outpatient or 3- to 5-d inpatient awake ketamine infusions in chronic pain (higher dosages titrated to effect from lower doses); 0.2–0.75 mg/kg for procedural analgesia, can be repeated; 0.1 mg/kg for IV infusion test; 5- to 35-mg/h continuous infusion for acute traumatic or postoperative pain, 1–7 mg/demand dose mixed with opioids in patient-controlled analgesia | N/A | 30 s | 5–10 min for bolus doses |
| Intramuscular | 2–4 times IV dosing; 5–10 mg/ kg for surgical anesthesia; 0.4–2 mg/kg for procedural analgesia; bolus and treatment dosing 0.10–0.5 mg/kg for chronic pain | 75–95 | 2–5 min | 30–75 min |
| Intranasal | 0.2–1 mg/kg for chronic pain and sedation; 3–6 mg/kg for procedural analgesia and anesthetic premedication | 25–50 | 5–10 min | 45–120 min |
| Subcutaneous | 0.1–1.2 mg/kg per hour for chronic pain; bolus and treatment dosing 0.10–0.6 mg/kg | 75–95 | 10–30 min | 45–120 min |
| Oral | 0.3–1.25 mg/kg for chronic pain; up to 3 mg/kg for procedural analgesia and anesthetic premedication | 10–20 | 5–20 min | 2–4 h |
| Rectal | 5–10 mg/kg for anesthesia premedication and procedural analgesia | 25–30 | 5–15 min | 2–3 h |
| Topical | 1%–10% cream for chronic pain | <5 | <2 d | NA |

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# Clinical Effects

*Analgesia and sedation*, at high doses…general anesthesia

*Cardiovascular*- hypertension, tachycardia, rarely arrhythmias or hypotension

*Respiratory*-bronchodilation and little effect on airway reflexes, increased tracheobronchial and salivary secretions

*Psychomimetic*-dysphoria, hallucinations, visual disturbances, unpleasant dreams. There is conflicting evidence about whether ketamine causes psychomimetic side effects, especially at subanesthetic doses. Bell *et al* performed a review of 37 RCTs and found that there was no difference in psychomimetic effects between ketamine and placebo. In contrast, Laskowski *et al* found in a cohort of 70 studies analyzing postoperative ketamine that there was an increase in psychomimetic effects.

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# Clinical Effects

*Hepatic/GI/GU*- hepatotoxicity and cystitis have been shown in high dosing and with chronic abusers.  Elevated liver enzymes in patients undergoing normal treatment have shown to return to normal after the drug is discontinued

Nausea is quite common with vomiting also occurring during treatment, but subsides after discontinuation

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# Contraindications: absolute/relative

| Category | Contraindication/Precaution |
|---|---|
| Cardiovascular | • Unstable angina<br>• Poorly controlled hypertension<br>• High-risk coronary vascular disease |
| Neurological and ophthalmic | • Elevated intracranial pressure, including secondary traumatic brain injury or tumor<br>• Elevated intraocular pressure, acute globe injury, or glaucoma |
| Endocrinological (due to possible potentiation of sympathomimetic effects) | • Hyperthyroidism<br>• Pheochromocytoma |
| Metabolic | • Severe liver disease |
| Gastrointestinal | • Full stomach aspiration risk |
| Pregnancy | • Lack of data on safety |
| Psychiatric | • Intoxication with alcohol or other substances<br>• Active substance abuse<br>• Delirium<br>• Psychosis<br>• Refusal or inability to consent |

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# Treatment Selection Criteria

Chronic uncontrolled neuropathic pain conditions: CRPS, neuropathies, postherpetic neuralgia, fibromyalgia, chronic ischemic limb pain, phantom limb pain, cluster headaches

TABLE 2. Randomized Placebo-Controlled Trials Evaluating Intravenous Ketamine for Chronic Pain With a Minimum of 48 Hours of Follow-Up

| First Author, Year | Patients | Ketamine Regimen | Follow-Up | Results | Comments |
|---|---|---|---|---|---|
| Amr,[155] 2010 | 40 patients with neuropathic pain after spinal cord injury | 80 mg over 5 h per day × 1 wk | 4 wk | Ketamine better than placebo for 2 wk | All patients also received gabapentin |
| Eichenberger,[117] 2008 | 20 patients with PLP | 0.4 mg/kg over 1 h with 48 h minimum interval between infusions | 48 h | Ketamine better than placebo and calcitonin. No difference between ketamine alone and combination for worst pain reduction, but combination superior for mean pain reduction. Mixed results for QST | Crossover study comparing ketamine to calcitonin to combination of both to placebo |
| Schwartzman,[123] 2009 | 19 patients with CRPS types 1 and 2 | Up to 100 mg over 4 h for 10 consecutive weekdays | 9–12 wk | Ketamine better than placebo for pain, but no improvement in QST and no correlation between response and serum levels | Study halted at midpoint because of lack of improvement in ketamine group |
| Sigtermans,[161] 2009 | 60 patients with CRPS type 1 | 0.43 mg/kg per hour continuously over 4.2 d | 12 wk | Ketamine better than placebo, but results were not statistically significant beyond 11 wk | Blinding ineffective |
| Noppers,[160] 2011 | 24 patients with fibromyalgia | 0.5 mg/kg over 30 min | 8 wk | Ketamine better than placebo only up to 3 h | Blinding ineffective |
| Mitchell,[162] 2002 | 35 patients with ischemic limb pain | 0.6 mg/kg over 4 h | 2–9 d (mean, 5 d) | Ketamine better than placebo | All patients also received opioids |
| Salas,[164] 2012 | 20 patients with cancer pain | 0.5 mg/kg per day increased to 1 mg/kg per day × 2 d for persistent pain | 48 h | No difference between treatment groups | All patients received morphine |

QST indicates quantitative sensory testing.

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# Treatment Protocols

Monitoring: cardiac, pulse ox, blood pressure, nursing, ACLS capability, drug reversal

Pretreatment: antiemetics, antihypertensives, antipsychotics, benzodiazepines

During Treatment: benzodiazepines, antihypertensives

Post Treatment: antiemetics, benzodiazepines

Dosing: Subanesthetic approximately 1mg/kg/hr or less

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# THANK YOU!

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gbarnard@crpscenter.com

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