KETAMINE

**Brands**  •  Ketalar
*see index for additional brand names*

**Generic?**  Yes

**Class**
•  *N*-methyl- D- aspartate (NMDA) receptor antagonist

**Commonly Prescribed for**
*bold for FDA approved*
•  Induction and maintenance of general anesthesia
•  Pain/neuropathic pain
•  Sedation
•  Treatment-resistant depression  *(experimental)*

**How the Drug Works**
•  Ketamine is a noncompetitive open channel inhibitor of the NMDA receptor; specifically, it binds to the phencyclidine site of the NMDA receptor
•  This leads to downstream glutamate release and consequent stimulation of other glutamate receptors, including AMPA receptors
•  Theoretically, ketamine may have antidepressant effects at low (subanesthetic) doses because activation of AMPA receptors leads to activation of signal transduction cascades that cause the expression of synaptic proteins and an increase in the density of dendritic spines
•  Low (subanesthetic) doses also produce analgesia and modulate central sensitization, hyperalgesia, and opioid tolerance

**How Long Until It Works**
•  For treatment-resistant depression, antidepressant effects can occur within hours
•  For neuropathic pain, effects can occur within hours but may take weeks for full effect

**If It Works**
•  For treatment-resistant depression, can immediately alleviate depressed mood and suicidal ideation, but antidepressant effects last only a few days
•  For neuropathic pain, can continue to use as long as it is beneficial

**If It Doesn’t Work**
•  Try a traditional antidepressant or electro-convulsive therapy (ECT) for treatment-resistant depression
•  Try traditional analgesics and treatments for neuropathic pain

**Best Augmenting Combos for Partial Response or Treatment Resistance**
•  For neuropathic pain, may use cautiously with opioids
•  For treatment-resistant depression, combinations have not been systematically studied

**Tests**
•  None for healthy individuals

**SIDE EFFECTS**

**How Drug Causes Side Effects**
•  Direct effect on NMDA receptors

**Notable Side Effects**
•  When used as an anesthesia induction/maintenance agent (generally at doses >2 mg/kg IV), it may produce emergent psychosis, including auditory and visual hallucinations, restlessness, disorientation, vivid dreams, and irrational behavior. Spontaneous involuntary movements, nystagmus, hypertonus, and vocalizations are also common. These adverse effects are uncommon with very low-dose therapy.
•  CSF pressure increased, erythema (transient), morbilliform rash (transient), anorexia, pain/erythema at the injection site, exanthema at the injection site, skeletal muscle tone enhanced, intraocular pressure increased, bronchial secretions increased, potential for dependence with prolonged use, emergence reactions (includes confusion, dreamlike state, excitement, irrational behavior, vivid imagery)
•  Psychotomimetic phenomena (euphoria, dysphasia, blunted affect, psychomotor retardation, vivid dreams, nightmares,
impaired attention, memory and judgment, illusions, hallucinations, altered body image, delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing, hypertension, tachycardia, hypersalivation, nausea and vomiting, erythema and pain at injection site
• Urinary tract toxicity
• When used at higher doses in anesthesia, tonic-clonic movements are very common (>10%); however, these have not been reported after oral use or with the lower parenteral doses used for analgesia

**Life-Threatening or Dangerous Side Effects**
• Syncope or cardiac arrhythmias
• Hypertension/hypotension
• Anaphylaxis
• CNS depression
• Respiratory depression/apnea
• Airway obstruction/laryngospasm

**Weight Gain**
• Reported but not expected

**Sedation**
• Many experience and/or can be significant in amount

**What to Do About Side Effects**
• Pretreatment with a benzodiazepine reduces incidence of psychosis by >50%
• For CNS side effects, discontinuation of nonessential centrally acting medications may help

**Best Augmenting Agents for Side Effects**
• Many side effects cannot be improved with an augmenting agent

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**Dosage Forms**
• Oral solution: 50 mg/mL
• Injection: 50 mg/mL

**How to Dose**
• For pain (oral): initial 10 mg; titrate up as appropriate
• For pain (IM): 2–4 mg/kg
• For pain (IV): 0.2–0.075 mg/kg
• For pain (continuous IV infusion): 2–7 μg/kg per minute

**Dosing Tips**
• Slow titration can reduce side effects
• Food does not affect absorption
• For oral use: to prepare 100 mL of 50 mg/5 mL ketamine oral solution
• 2 x 10 mL vials of generic ketamine 50 mg/mL for injection (cheapest concentration)
• 80 mL purified water
• Store in a refrigerator with an expiry date of 1 week from manufacture
• Patients can add their own flavoring, e.g., fruit cordial, just before use to disguise the bitter taste
• For sublingual use:
  • Place under the tongue and ask patient not to swallow for 2 minutes
  • Use a high concentration to minimize dose volume; retaining >2 mL is difficult
• Start with 10 mg
• Incompatibility
  • Ketamine forms precipitates with barbiturates and diazepam (manufacturer’s data on file); do not mix
  • Mixing lorazepam with ketamine is also not recommended; compatibility data are lacking, and there is a risk of adsorption of lorazepam to the tubing

**Overdose**
• Restlessness, psychosis, hallucinations, stupor

**Long-Term Use**
• Safe

**Habit Forming**
• No

**How to Stop**
• Taper not necessary
Pharmacokinetics
• Plasma half-life: alpha: 10–15 minutes; beta: 2.5 hours; 1–3 hours IM; 2.5–3 hours orally; 12 hours norketamine
• Metabolized by CYP450 2B6, 2C9, and 3A4

Drug Interactions
• Use with caution with other drugs that are NMDA antagonists (amantadine, memantine, dextromethorphan)
• Ketamine may increase the effects of other sedatives, including benzodiazepines, barbiturates, opioids, anesthetics, and alcohol
• CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole) can increase plasma concentrations of ketamine and reduce those of norketamine, but the clinical relevance of this is unclear
• Plasma concentrations of ketamine are increased by diazepam
• Barbiturates and hydroxyzine may increase the effects of ketamine; avoid combination

Other Warnings/Precautions
• Use with caution in patients with current or past history of psychiatric disorder; epilepsy, glaucoma, hypertension, heart failure, ischemic heart disease, and a history of cerebrovascular accidents

Do Not Use
• If patient has a condition in which an increase in blood pressure would be hazardous
• If patient has schizophrenia or another psychotic disorder
• If patient has a condition in which an increase in intraocular pressure would be hazardous
• If there is a proven allergy to ketamine

Cardiac Impairment
• Use with caution

Elderly
• Some patients may tolerate lower doses better

Children and Adolescents
• Safety and efficacy have not been established

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Use only if potential benefits outweigh the potential risks to the fetus

Breast Feeding
• Unknown if ketamine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
  ✽ Recommended either to discontinue drug or bottle feed

SPECIAL POPULATIONS

Renal Impairment
• Reduce dose for moderate impairment
• Should not be used in severe impairment

Hepatic Impairment
• Dose reduction not necessary

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• For pain, may be especially useful when used in conjunction with opioids
• Severely treatment-resistant depression, suicidal ideation

Potential Disadvantages
• May produce dysphoria, nightmares, excitement (uncommon with very low-dose therapy)
• Antidepressant effects are short-lived

Primary Target Symptoms
• Pain
• Treatment-resistant depression
• Ketamine releases endogenous catecholamines (epinephrine, norepinephrine), which maintain blood pressure and heart rate, and increase myocardial oxygen demand

• Ketamine increases cerebral metabolism and cerebral blood flow while producing a noncompetitive block of the neuronal postsynaptic NMDA receptor

• Lowers seizure threshold

• Recent laboratory/clinical studies support the use of low-dose ketamine to improve postoperative analgesia/outcome

• May be especially beneficial for refractory neuropathic pain/complex regional pain syndrome

• May be especially beneficial when used in conjunction with opioids

• (S)-ketamine is available in a preservative-free solution in Europe; however, it currently is not approved by the FDA. S(+)-ketamine may be more potent and have fewer side effects when used intravenously than the racemate. Although not rigorously tested and not available in the USA; some European investigators have utilized the preservation-free solution for intrathecal/epidural use – this is not recommended

**Pearls**

- Actions in treatment-resistant depression are transient, lasting only a few days following infusion

- The use of ketamine can cause urinary tract symptoms (e.g., frequency, urgency, urge incontinence, dysuria, and hematuria); the causal agent has not been determined, but direct irritation by ketamine and/or its metabolites is a possibility. (Investigations have revealed interstitial cystitis, detrusor overactivity, decreased bladder capacity; symptoms generally settle several weeks after stopping ketamine.)

- May be used in combination with anticholinergic agents to decrease hypersalivation

- Do not mix with barbiturates or diazepam (precipitation may occur)

- Bronchodilation is beneficial in asthmatic or chronic obstructive pulmonary disease (COPD) patients. Laryngeal reflexes may remain intact or may be obtunded.

- The direct myocardial depressant action of ketamine can be seen in stressed, catecholamine-deficient patients

**Suggested Reading**


