General:

**Generic Name:** Ketamine Hydrochloride  
**Brand name:** Ketalar  
**Legal status:** Schedule III controlled substance  
**Drug classes:** NMDA receptor antagonist, General anesthetic  
**Other drugs in same class:** Propofol, Nitrous oxide, Etomidate  
**Supplied:** Liquid form only in: 50mg/ml or 100mg/ml concentrations

Purpose:

**Pain:** Ketamine is used as an adjunct medication for opioid refractory pain or intractable side effects of opioids, particularly if the pain is neuropathic in nature or a high degree of morphine tolerance is suspected. As an adjuvant agent it can reduce the amount of narcotic required.  
**Depression:** Ketamine is used for depression, anxiety, and treatment refractory depression. It’s a rapid acting antidepressant; it is effective in hours to days versus SSRI’s which can take weeks.  
**Palliative Sedation:** Can be considered for PS in patient’s refractory to midazolam or in situations when respiratory depression or suppression of airway protective reflexes is to be considered.  
**Dyspnea:** Ketamine has also been used for terminal dyspnea as in does not cause respiratory or cardiovascular depression.  
**Seizures:** In some NICU’s ketamine has been used in cases of prolonged seizures. Some evidence indicates the NMDA-blocking effect of the drug protects neurons from glutamatergic damage during prolonged seizures.

Definition:

Ketamine is classified as a “dissociative anesthetic” meaning the patient appears to remain awake but is actually unconscious and feels no pain when given in full anesthetic doses. Ketamine is a non-competitive N-methyl-D-aspartate receptor (NMDA) antagonist that blocks the release of excitatory neurotransmitter glutamate, a calcium channel in the transmission of pain signals via dorsal horn. NMDA receptors play a role in opioid tolerance. Ketamine also interacts with cholinergic, nicotinic, muscarinic, and opiate receptors and possibly inhibits the synaptic re-uptake of monamines. It has potent multi-factorial analgesic properties when given at sub-anesthetic doses. Ketamine is useful as it does not suppress respiratory drive or decrease protective airway reflexes.

Pharmacokinetics:

Ketamine is metabolized in the liver by cytochrome P450 enzyme system. CYP3A4 is the major enzyme involved. Chronic ketamine administration increases the activity of the enzymes involved in its own metabolism and may modify the response with repeated administration. Tolerance has been reported.
Ketamine is highly lipophilic and rapidly crosses the blood-brain barrier providing quick onset of action. Its distribution half-life is approximately 7-11 minutes. Ketamine has a wide therapeutic index, so there is low chance of lethal overdose.

The main metabolite norketamine does have analgesic properties and is produced in great quantities when taking oral ketamine related to high first pass hepatic metabolism. Norketamine is 1/3 to 1/5 as potent as ketamine resulting in lower oral dosing of 25-50% than IV/SQ. Oral bioavailability is 15-20%.

The elimination half-life is 2-3 hours for ketamine and approximately 4 hours for norketamine. Less than 10% of the drug is excreted unchanged; 5% in the feces, 5% by the kidneys. Impaired renal function does not prolong the effect of the drug. Insufficient data on hepatic impairment.

**Side Effects:**

Dizziness and a dream-like feeling are reported with lower doses. There is less side effect profile when starting low and increasing slowly. These effects also tend to go away as tolerance develops.

Psychotomimetic phenomena or re-emergence syndrome such as; hallucinations, dysphoria, blunted affect, nightmares, and vivid dreams when emerging from full anesthetic doses, are rare in subanesthetic doses used with pain or depression. Full anesthetic doses are typically; 1-2mg/kg IV or 6.5-13mg/kg IM. Hallucinations and the re-emergence syndrome are usually preventable with co-administration of a benzodiazepine or haloperidol prior to or while giving ketamine.

Side effects with higher doses can also include: hyper-salivation, nausea, tachycardia, hypertension, diplopia, suprapubic pain (usually with greater than 1gm/day), and nystagmus which all resolve after lowering or cessation of the drug.

**Contraindications in Palliative Care:**
Intracranial hypertension, neurological impairment, hypertension, cardiac failure, CVA, psychosis

**Adverse drug reactions:** clonidine, anticholinergics, benzodiazepines, barbiturates, risperidone, opioids, anesthetics, alcohol

**Formulation/Administration:**

Ketamine is supplied as injection solution in 50mg/ml and 100mg/ml multi-dose vials. Ketamine is highly lipophilic; the solution can be given PO/SL/SQ/IM/IV/PR/Intranasal.

The injection solution has a bitter taste that can be disguised with flavorings when given orally. The 50mg/ml is less bitter. If giving PO/SL; give no other med/food/drink for 2 minutes following the dose.

Ketamine can be irritating to skin so SQ sites may need to be rotated daily.

<table>
<thead>
<tr>
<th>Route of Admin</th>
<th>IV</th>
<th>IM</th>
<th>SQ</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>1 min</td>
<td>5 min</td>
<td>15-30 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Duration</td>
<td>10-15 min</td>
<td>15-30 min</td>
<td>30-60 min</td>
<td>2-4 hrs</td>
</tr>
</tbody>
</table>
Dosing Guidelines for Pain Management:

Ketamine can be given in “burst” style technique similar to steroid burst until new pain threshold established and pain controlled. Ketamine is administered IV with titration upwards for 3-5 days then it is discontinued. Pain is continued on opioids only again. Effects of “burst” control may be effective for up to 6 weeks.

Continuous Infusion Sub Q or IV for Pain Management:

1. Obtain VS, 1 hr after initial dose, then Q 4 hrs x 24hrs and if stable, then prn
2. Consider reducing opioid by 25-50% at initiation of ketamine, and then every 6-12h by another 25-50% prn.
3. Below are two different protocols that are used. VCU Massey Cancer Center (20) and Comfort Care Choices by Dr. Robert Webb (11).

<table>
<thead>
<tr>
<th>VCU Massey</th>
<th>Comfort Care Choices</th>
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</thead>
<tbody>
<tr>
<td>A trial of 5-10 mg IV is considered with repeat in 15-30 min</td>
<td>Initiate at 4mg/hr (100mg/24h) (Some other reports say 50-150mg in 24h as initiation)</td>
</tr>
<tr>
<td>Starting infusion is 0.2mg/kg/hr, can increase by 0.1mg/kg/hr every 6hrs, with upward titrations to 0.5mg/kg/hr</td>
<td>If not effective in 24h go to: 12mg/hr (300mg/24h). If not effective after another 24h go to: 20mg/hr (500mg/24h)</td>
</tr>
<tr>
<td>Not to exceed 800mg in 24h</td>
<td>Continue rate at which pain control is satisfactory and stop 3 days after last increment. If no pain control at 500mg/24h for a full day, stop infusion</td>
</tr>
</tbody>
</table>

4. Comfort Care Choices also recommends addition of lorazepam 0.5 mg at HS plus every 8 hours if too “dreamy feeling”. VCU recommends that if intolerable side effects occur, ketamine should be decreased to previous dose or discontinued. Resolution of symptoms may not occur for 24 hours. Haloperidol 1mg at HS or 3x day prn is also effective for reduction in side effects.
5. A suggested conversion dose of oral ketamine would be 30-40% of the effective parenteral dose related to norketamine accumulation providing analgesia.

Oral dosing (or Sublingual) for Pain Management:

<table>
<thead>
<tr>
<th>VCU Massey</th>
<th>Comfort Care Choices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mask taste with cola or cherry syrup</td>
<td>Mix in fruit cordial to mask taste</td>
</tr>
<tr>
<td>Consider decreasing opioid by 25-50%</td>
<td>Consider decreasing opioid by 25-50%</td>
</tr>
<tr>
<td>Starting dose is 10-15 mg PO every 6hrs</td>
<td>Test dose of 25mg is given</td>
</tr>
<tr>
<td>Dosing may be increased daily by 10mg every 6 hrs until pain is relieved or side effects occur. Do not increase doses more frequently than every 24hrs</td>
<td>If no adverse reaction and/or pain is reduced, continue 25mg 4x/day and prn. MAX dose is 200mg 4x/day</td>
</tr>
<tr>
<td>Doses as high as 1000mg/day have been reported with average doses of 200mg per day in divided doses.</td>
<td>Give smaller dose more often if drowsiness occurs and doesn’t improve with reduction of opioid.</td>
</tr>
</tbody>
</table>
Ketamine Administration Guidelines for Depression:

Ketamine in use for therapeutic effects in major depressive disorder (MDD) has been reported to be effective for more than a decade. The most recent RCT (Rot, et al) provides evidence that a single IV subanesthetic dose of ketamine (0.5mg/kg over 40 minutes) may relieve depressive and anxiety symptoms within hours and may last for weeks for some patients. Studies have shown that patients who also receive daily oral and IM ketamine experienced a robust antidepressant and anxiolytic response with few adverse events. This is especially useful in the setting of end of life care where treatment needs to be rapid and effective.

Ketamine targets the excitatory glutamate neurotransmitter. Methylphenidate is also used for antidepressant effects but mechanistically the psychostimulant blocks reuptake of dopamine and inhibits reuptake of serotonin or norepinephrine as does SSRI’s, it can also cause anxiety.

<table>
<thead>
<tr>
<th>Dosing of oral ketamine for depression</th>
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<tbody>
<tr>
<td>0.5mg/kg of IV solution mixed in flavoring once daily at HS</td>
</tr>
<tr>
<td>If you see a decrease in benefit increase dose by 20%</td>
</tr>
<tr>
<td>If side effects occur, administer lorazepam or haloperidol at HS. May also adjust dose lower or decrease frequency to 3-4x/week.</td>
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</table>

Topical Administration of ketamine in painful wounds:

There is currently no available RCT or clinical trials for review, only data from hospice and palliative care websites and compounding pharmacies. There is a RCT done on topical amitriptyline, ketamine, and lidocaine for neuropathic pain caused by radiation dermatitis. This showed a significant reduction in intensity, sharpness, burning, and sensitivity to the area with very minimal central absorption. From studies of ketamine gels over intact skin there are promising results for reducing neuropathic pain.

Samaritan Evergreen Hospice has used this formulation for fungating wounds and severe decubitus ulcerations with reported significant pain relief from patients. There can be mild stinging on application that abates shortly.

<table>
<thead>
<tr>
<th>Topical Spray for Wound Care</th>
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<tbody>
<tr>
<td>Ketamine 5% or 10%</td>
</tr>
<tr>
<td>Lidocaine 1%</td>
</tr>
<tr>
<td>Morphine 1% or 5%</td>
</tr>
<tr>
<td>May follow with metronidazole 500 mg paste for odor control</td>
</tr>
<tr>
<td>Compound all 3 with normal saline in a 30 or 60 ml atomizer spray bottle. Apply compound to entire wound bed prior to dressing changes and up to 3x daily for pain relief.</td>
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</tbody>
</table>
Ketamine use for dyspnea

Evaluation is ongoing for dyspnea control with ketamine; it shows promise in that there are bronchodilation effects, along with analgesic and anesthetic effects without respiratory or cardiovascular depression.

There is one study by Abhijit (1) that trialed ketamine 0.2mg/kg and midazolam 0.02mg/kg (mainly for negation of undesirable side effects of ketamine) to evaluate the efficacy of low dose ketamine in relieving terminal dyspnea. The study showed excellent symptomatic relief of dyspnea but it was short lived (36.7 min on average). This study was done in India where they report consistent shortages of opioids thus attempting to find an alternative.

Compiled by Katrina Hoffman FNP, September 2013
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REFERENCES


