In the setting of chronic pain low dose ketamine infusions have shown to reduce peripheral neuropathic pain, spinal cord injury, fibromyalgia symptoms, lower limb ischemic rest pain, and chronic phantom limb pain. Ketamine therapy has also shown to improve analgesia in cancer pain particularly neuropathic pain, painful bone metastases that are refractory to opioid therapy.

A. There is no restriction on the level of care for administering low dose ketamine for pain management.

B. Low dose ketamine will be administered via smart infusion pump using the locked PCA module or contained in a locked infusion box.

C. Standard concentration of 2 mg/mL of normal saline prepared by the pharmacy department.

D. Ketamine continuous infusion will be limited to low dose between 0.1-0.5 mg/kg/hr
   a. Recommended starting dose is 0.1 mg/kg/hr.
   b. An RN may not bolus Ketamine via intravenous push method or use the patient control button on the PCA pump.
   c. Do not flush or aspirate intravenous catheter once infusion has been initiated.

E. Oral Ketamine will be available as an alternative or a transition from the intravenous route with patient discharge.

F. **MONITORING PARAMETERS**
   a. Pain Procedure Suite and In-Patient: On initiation, monitor level of consciousness and pain level every 2 hours for two times then every 4 hours thereafter per unit standard.
   b. Notify physician and / or licensed provider if any adverse effect suspected such as, but not limited to:
      1. Changes in vital signs such as hypotension or decreased respiratory rate
      2. Nausea or vomiting
      3. Excess salivation
      4. Patient report of nystagmus, blurred or double vision
      5. Onset of vivid dreams or hallucinations.
      6. Decreasing oxygen saturation
      7. Excess sedation.

G. Pain assessment and vital sign monitoring per level of care

H. Notify Physician and/or licensed provider and call Rapid Response Team when clinical triggers are present.

I. **ORAL DOSE**
   a. Transition from IV Ketamine to PO as ordered by physician.
APPENDIX: UCSD Ketamine Educational Supplement: Intravenous and Oral Therapy

UCSD Ketamine Educational Supplement
Intravenous and Oral Therapy

I. Background and supporting evidence for continuous infusion therapy: Ketamine is a dissociative anesthetic that has analgesic properties in sub-anesthetic doses. Ketamine has potent NMDA antagonist properties and is being widely used to treat refractory neuropathic pain. Ketamine has other actions which may also contribute to its analgesic effect, including interactions with other calcium and sodium channels, cholinergic transmission, noradrenergic and serotonergic reuptake inhibition and μ,δ,Κ,opioid-like effects. Ketamine has a wide therapeutic range, making overdose difficult.

For anesthetic administration intravenously the range is between 1 mg/kg to 4.5 mg/kg, the average being 2 mg/kg. The dose for analgesia is 0.2 to 0.5 mg/kg intravenously.

In the setting of chronic pain low dose ketamine infusions have shown to reduce peripheral neuropathic pain, spinal cord injury, fibromyalgia symptoms, lower limb ischemic rest pain, and chronic phantom limb pain. Ketamine therapy has also shown to improve analgesia in cancer pain particularly neuropathic pain, painful bone metastases that are refractory to opioid therapy. Common side effects at these lower doses include dysphoria, hallucination, and sedation.

II. Background and supporting evidence for oral therapy:
   a. Plasma half-life: 1-3 hrs (ketamine); 12 hrs (norketamine)
   b. Onset of action: 30 min PO
   c. Duration of action: 4-12 hrs PO
   d. Metabolism: Extensive first pass metabolism to norketamine.
   e. Norketamine is one third as potent as ketamine as an anesthetic and equipotent as an analgesic (Palliative Care Formulary 2002). Serum norketamine levels after oral ketamine are 2 to 3 three times higher than after parenteral ketamine. The peak analgesic effect of oral ketamine corresponds with the peak serum level of norketamine (NK), not ketamine (K). K:NK after prolonged infusion equals 3:1. K:NK after chronic PO dosing equals 3:2-3, almost 1:1.
   f. Less than 10% of ketamine is excreted unchanged, half in the feces and half renally. Long-term use of ketamine leads to hepatic enzyme induction and enhanced ketamine metabolism.

III. Restriction in ordering medication: Ordering of ketamine intravenous infusion is restricted to the Pain/Anesthesiology, Palliative Care (Doris A. Howell) Service, and Critical Care Providers. Continuation of IV ketamine for patients who have transitioned off a critical care service will require a consult with Pain/Anesthesiology or Palliative Care.

IV. Place in therapy: Pain refractory to at least 3 analgesic regimens.

V. Intravenous dose and duration:
   a. In-patient: 0.2-0.5 mg/kg/hour continuous (No bolus due to increase in psychomimetic side effects)
   b. No dose reductions required in renal impairment. Dose reductions should be considered in elderly patients (NMDA receptor binding is decreased with age).

VI. Converting IV to oral dose
   a. Starting dose: 10-25mg q 8hrs (intervals of q 4 – 12 reported). Increase up to 0.5 - 1mg/kg q 8hrs. Maximum reported dose 200mg q 6hrs.
   b. Transition from IV to PO use 3:1 ratio
      i. Calculate total mg/24 hours of continuous IV infusion
ii. Using PO:IV ratio of 1:3, divide this total by 3 to obtain the total mg/24 hours of oral ketamine

iii. Titrate down from ketamine IV infusion by 30% daily down to zero over 3 days AND titrate up by 30% of the total mg/24 hours calculated dose of oral ketamine daily over 3 days to the full dose. For continuous analgesic effect recommended to be given 3 times per day.

VII. Undesirable effects: (side effects are route and dose dependent) At lower doses the side effects include: psychotomimetic phenomena (euphoria, dysphoria, blunted affect, psychomotor retardation, vivid dreams, nightmares, poor concentration, illusions, hallucinations, altered body image), delirium, dizziness, diplopia, blurred vision, nystagmus, altered hearing. Erythema and pain at injection site. Side effects less frequent with PO use.

VIII. Standard concentration:
   a. IV: 100 mg/50 mL of normal saline (made by the pharmacy department) delivered in locked pump.

IX. Managing Side Effects with Pharmacotherapy: Low doses of benzodiazepines may be necessary to control excessive secretions and dysphoric feeling. Haloperidol may be used for hallucinations and delirium. Doses and routes will be incorporated in the order sets. Use of oral route will be encouraged.

X. Relative contraindications: Listed as relative contraindications because derived from anesthesia literature which uses ~10 – 20 times higher dosing. (Adapted from San Diego Hospice Ketamine Infusion Protocol)
   • Unstable cardiovascular disease, such as angina, heart failure or malignant hypertension
   • Intraocular hypertension including glaucoma (↑ IOP reported in animals, not reproducible in subsequent human studies)
   • Active psychosis
   • Porphyria (no clinical evidence of worsening porphyria, but does elevate serum porphyrin markers)
   • History cerebrovascular disease CVA (small case series of patients with known intracranial CSF obstruction experienced ↑ ICP)

XI. References
22. San Diego Hospice Ketamine protocol.

ATTACHMENT A

Table 1 Various Uses of Injectable Ketamine for Pain Control

<table>
<thead>
<tr>
<th>Reference</th>
<th>Route</th>
<th>Dose Range</th>
<th>Type of Pain</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seddon et al. 2005</td>
<td>IV</td>
<td>0.5-1 mg/kg</td>
<td>Postoperative pain or incisional wounds</td>
<td></td>
</tr>
<tr>
<td>Merckmiller et al. 1995</td>
<td>SQ</td>
<td>0.25 mg/kg IV</td>
<td>Neuralgic</td>
<td></td>
</tr>
<tr>
<td>Mathias, 1995</td>
<td>IV</td>
<td>0.5 mg/kg</td>
<td>Chronic orofacial pain</td>
<td></td>
</tr>
<tr>
<td>Lasten et al. 1995</td>
<td>IV</td>
<td>0.5 mg/kg</td>
<td>Nociceptive pain</td>
<td></td>
</tr>
<tr>
<td>O′Nolan et al. 1995</td>
<td>IV/SQ</td>
<td>0.25 mg/kg IV, then 0.1 mg/kg SQ</td>
<td>Acute trauma pain</td>
<td></td>
</tr>
<tr>
<td>Falby et al. 1995</td>
<td>IV</td>
<td>0.2 mg/kg bolus then 0.5 mg/kg infusion</td>
<td>Peripheral neuropathic pain, in 3/10 related to CQ</td>
<td></td>
</tr>
<tr>
<td>Eto, 1994</td>
<td>IV</td>
<td>0.15 mg/kg</td>
<td>Postherpetic Neuralgia</td>
<td></td>
</tr>
<tr>
<td>Eto et al., 1995</td>
<td>SQ</td>
<td>0.05-0.1 mg/kg</td>
<td>Postherpetic Neuralgia</td>
<td></td>
</tr>
<tr>
<td>O′Nolan &amp; Bhatia, 1995</td>
<td>IV</td>
<td>0.5 mg/kg</td>
<td>Head and neck cancer</td>
<td></td>
</tr>
<tr>
<td>Boden et al. 1994</td>
<td>IV</td>
<td>0.25 mg/kg bolus</td>
<td>Miscellaneous type</td>
<td></td>
</tr>
<tr>
<td>Yang et al., 1995</td>
<td>IV</td>
<td>0.5 mg/kg bolus</td>
<td>Most common cancer-related pain</td>
<td></td>
</tr>
<tr>
<td>Caster et al. 1993</td>
<td>IV</td>
<td>0.04-0.2 mg/kg</td>
<td>Local anesthetics</td>
<td></td>
</tr>
<tr>
<td>Steen et al. 1995</td>
<td>IV/SQ</td>
<td>0.125-0.5 mg/kg</td>
<td>Moderate pain</td>
<td></td>
</tr>
<tr>
<td>Pessina et al. 1995</td>
<td>IV bolus</td>
<td>0.2-0.5 mg/kg</td>
<td>Clinical wound dilution</td>
<td></td>
</tr>
<tr>
<td>Onuma et al. 1998</td>
<td>SQ</td>
<td>0.25-0.5 mg/kg</td>
<td>Cancer pain</td>
<td></td>
</tr>
<tr>
<td>Scannell et al. 1997</td>
<td>IV</td>
<td>0.5 mg/kg over 60 min</td>
<td>Phlebitis</td>
<td></td>
</tr>
<tr>
<td>Walker &amp; Cottam, 1997</td>
<td>IV</td>
<td>0.14-0.38 mg/kg</td>
<td>Lumbar radiculopathy</td>
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</tr>
</tbody>
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