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Use of Oral Ketamine for Analgesia in Palliative Care

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Reviewed by: Pain Management Advisory Group and Pharmacy Workgroup

Ketamine: Background

- UPMC formulary agent for the following approved indications:
  - FDA-approved indication as an anesthetic agent
  - Off-label approval for analgesia, in sub-anesthetic doses
    - Restricted to prescribing by:
      - Acute Pain: Acute Interventional Perioperative Pain Service (AIPPS) or Anesthesiology Service
      - Opioid refractory pain: Palliative Care Service
      - Refractory complex regional pain syndrome: Chronic Pain Service

- Mechanism of action:
  - Fast-acting general anesthetic that works by **inhibiting NMDA receptors** and interacting with opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive calcium channels[1]

- 2015 UPMC Formulary Request:
  - To be used orally for analgesia in the palliative care setting

1. *Br J Anaesth*. 1996;77:441-444

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Pathophysiology of Pain

- Pain sensations begin in the periphery of the nervous system[2]
  - Pain stimuli are sensed by specialized nociceptors that are the nerve terminals of the primary afferent fibers

- Pain is categorized as being either nociceptive, neuropathic, psychogenic or muscle pain[2]
  - Nociceptive: pain from a noxious stimulus, usually due to tissue damage
  - Neuropathic: pain that arises from abnormal neural activity secondary to disease, injury, or dysfunction to the nervous system

- Ketamine binds to the phencyclidine (PCP) binding site of the NMDA receptor[3]
  - This inhibits excitatory neurotransmission producing analgesia
  - At higher doses ketamine produces general anesthesia
  - Opioid-sparing effects

2. Mayo Clin Proc. 1994 Apr;69(4):375-83.
3. Ketamine Hydrochloride [package insert]

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Current Analgesia Treatment Options for Palliative Care Patients

- Non-opioid analgesics[4]
  - acetaminophen, aspirin, NSAIDS
- There are a subset of patients that are refractory to large doses of non-opioid analgesics[4]
- Other agents studied for treatment of refractory pain[4]:
  - Barbiturates
  - Opioids
  - Neuroleptic agents (control hallucinations)
  - **Parenteral ketamine**

4. Kobierski, L et al. Hospice Palliative Care Program

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Ketamine Prescribing Restrictions

- Prescribing
  - Ketamine Package Insert Precautions[3]:
    - *"Ketamine should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration"*
    - Resuscitative equipment should be ready for use
    - "Emergence reactions have occurred in approximately 12% of patients"

3. Ketamine Hydrochloride [package insert]

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Current UPMC Policies Involving IV Ketamine

Policy	Subject	Who Can Prescribe	LIP (Other)
HS-HD-CP05*	Moderate sedation	Anesthesiologists, CCM physicians, ED physicians	If: • Current ACLS or ATLS certification • Be immediately available • Responsible for treating airway compromise, overdose, HD instability, CP distress • Cannot be actively involved in procedure • Have training and ability to rescue a patient from general anesthesia
HS-HD-CP06*	Deep sedation	Anesthesiologists, CCM physicians, ED physicians Cannot have other role in procedure aside from sedation/airway/HD monitoring and care	If: • Deep Sedation Competency completed • Current ACLS or ATLS certification • Be immediately available • Responsible for treating airway compromise, overdose, HD instability, CP distress • Cannot be actively involved in procedure • Have training and ability to rescue a patient from general anesthesia

*Policy denotes that it does not apply to medication administered for pain control, seizure control, sedation for mechanical ventilation, minimal sedation, and emergency intubation or other life/limb-saving emergencies.

LIP = licensed independent practitioner; ACLS/ACTS = Advanced Cardiac Life Support or Advanced Trauma Life Support certification; HD = hemodynamic; CP = cardiopulmonary

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Evidence: Oral Ketamine

Author, Year, Study Design	N	Patient Population (age±SD) P= 0.288	Treatment: All patients received 80-90 mg of PO Morphine QD plus:	Efficacy Outcomes (0-10 scale)		Safety Outcomes: ADEs
Lauretti et al. 1999, RCT single blinded Grade: 1B Patient population: cancer patients	60			VAS Scores before PO morphine	VAS Scores after study drug	• Patients in the nitroglycerin and ketamine group reported less somnolence ($p < 0.013$), constipation, and N/V. • There were two hallucinations reported in the ketamine group
		Control Group 60 ±14	PO 20 mg morphine BID (control group) n = 15	Control Group: 7.6 ± 1.9	Control Group: 3.9 ± 2.6	
		nitroglycerin Patch 52 ± 13	OR nitroglycerin patch 5 mg QD n = 15	nitroglycerin 7.9 ± 1.6	nitroglycerin 3.5 ± 1.7	
		ketamine 56 ± 8	OR PO .5mg/kg ketamine BID n = 15	ketamine 7.4 ± 1.5	ketamine 3.3 ± 1.6	
		dipyrone 53 ±11	OR PO dipyrone 500mg QID n = 15	dipyrone 7.6 ± 1.7	dipyrone 4 ± 1.6	
				p = 0.774	P = 0.967	

Summary: Low dose ketamine and transdermal nitroglycerin are effective as co-adjuvant analgesics.

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Evidence: Oral Ketamine

Time (days)	Control Group (Daily PO morphine consumption)	Morphine + Ketamine group (Daily PO morphine consumption)	P-value
1	81 mg	81 mg	NS
5	81 mg	81 mg	NS
10	85 mg	77 mg	NS
15	120 mg	77 mg	P=0.036
20	130 mg	73 mg	P= 0.004
30	132 mg	74 mg	P=0.003

These data were extrapolated from a graph: it shows the daily consumption of PO morphine on days 1, 5, 10, 15, 20 and 30 after the test drug was introduced. Overall, patients treated with ketamine required less morphine than the control group.

5. Lauretti GR Oral ketamine and transdermal nitroglycerin. *Anesthesiology*.

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Evidence: Oral Ketamine

Author, Year, Study Design	N	Patient Population (age±SD)	Treatment	Safety Outcomes
Ishizuki et al 2007, RCT double blinded Grade: 1B Patient population: cancer patients	30	G1: 59.3 ± 14.6	G1: n=15, PO morphine 10 mg q6h + PO ketamine 10 mg q8h	The majority of patients in both groups reported side effects in every appointment (somnolence, N/V, constipation)
		G2: 59.2 ± 12.9	G2: n=15, PO morphine 10 mg q6h + PO placebo q8h	

Summary: There was no statistical difference between both arms in terms of pain relief, number of times the morphine needed to be adjusted and side effects. Dosing of ketamine was noted to be less than what is required for analgesic effect.

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Evidence: Oral Ketamine

Pain Relief in G1 and G2	Week 1	Week 2	Week 3	Week 4
G1 (% of patients who experienced moderate to complete pain relief)	33.4%	44.4%	66.6%	55.6%
G2 (% of patients who experienced moderate to complete pain relief	53.9%	69.2%	69.2%	53.9%

Severity of Pain as evaluated by the Verbal Pain Scale	Week 1	Week 2	Week 3	Week 4
G1 (% of patients with moderate to severe pain)	100%	77.8%	77.8%	55.4%
G2(% of patients with moderate to severe pain)	100%	46.2%	38.5%	38.5%

These differences were not statistically significant

7. ISHIZUKA, Pedro et al. Assessment of oral S(+) ketamine. *Rev. Bras. Anestesiol.*

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Meta Analysis: Findings

- "Based on our experience with oral ketamine, this drug should be administered after an intravenous trial to monitor response and side effects in patients with an adequate functional status. However, patients in the palliative care and hospice setting, especially the one at the end of their lives, may also benefit from oral ketamine even if an intravenous trial is not feasible."

- In patients with cancer pain, oral ketamine has been used as an adjuvant therapy in a wide variety of scenarios from patients with refractory pain syndromes with permanent intrathecal devices to patients at the end of their lives

- Most of the studies have failed to demonstrate statistically significant pain relief. However, a study conducted by Lauretti et al did show a significant decrease in opiate consumption on the ketamine group when compared to oral morphine, which is consistent with the previously reported opiate-sparing effect

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Soto E, Stewart Oral ketamine in the palliative care setting *Am J Hosp Palliat Care*. 2012; 29:308-17

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Dosing and Preparation

- Recommendation: To be used orally for analgesia in the palliative care setting only

- Dosing
  - Recommend an initial starting dose of either PO 0.25mg/kg or 0.5mg/kg adjunctively with an opioid[6,7,8]
  - For a patient already on ketamine use 25-50% of the IV dose when converting to oral[9]

- Preparation
  - Dissolving ketamine in water or juice is appropriate[10]
  - Use a 10 mg/mL injectable solution to prepare the dose
  - Dispense in a clearly labeled oral syringe

6. Lauretti GR Oral ketamine and transdermal nitroglycerin. *Anesthesiology*
7. Pain Physician. 2007 May;10(3):493-500.
8. ISHIZUKA, Pedro et al. Assessment of oral S(+) ketamine. *Rev. Bras. Anestesiol.*
9. a strategy for conversion from parenteral to oral ketamine.*Fitzgibbon EJ, Hall P*
10 . Kotlinska-Lemieszek A, Luczak J. Subanesthetic Ketamine

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2. Cross, S A. *Mayo Clinic Proceedings* Volume: 69 Issue: 4 (1994-04-01) p. 375-383. ISSN: 0025-6196
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5. Soto E, Stewart DR, Mannes AJ, Ruppert SL, Baker K, Zlott D et al.. Oral ketamine in the palliative care setting: a review of the literature and case report of a patient with neurofibromatosis type 1 and glomus tumor-associated complex regional pain syndrome. *Am J Hosp Palliat Care*. 2012; 29:308-17
6. *Lauretti GR, Lima IC, Reis MP, Prado WA, Pereira NL*
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10. Kotlinska-Lemieszek A, Luczak J. Subanesthetic Ketamine: an essential adjuvant for intractable cancer pain. *J Pain Symptom Manage* 2004; 28:100-102.

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