

# THE TABLET: PALLIATIVE CARE PHARMACY TIPS



March 22, 2024

Vol. 4, No. 4

**Guest Author:**  
Kathy Wunderle, MD

**Palliative Care  
Pharmacy Team:**

**Clinical Pharmacy  
Specialist:**

**Maria Felton Lowry,  
PharmD, BCPS, BCGP**  
Assistant Professor  
University of Pittsburgh  
School of Pharmacy,  
Department of Pharmacy  
and Therapeutics  
Palliative  
Care Clinical Pharmacy  
Specialist  
UPMC Palliative and  
Supportive Institute

**Cell:** 412-627-8473  
**Office:** 412-864-2899  
**Email:** lowrymf@upmc.edu

If you have a topic you  
would like the pharmacy  
team to answer, please  
send your suggestions to:  
lowrymf@upmc.edu

## TODAY'S TOPIC:

### IV Ketamine in Palliative Care (a focus on Pain): Review of the Evidence

#### Background:

Ketamine is a dissociative anesthetic that is increasingly being used for analgesia/sedation in intensive care units. It primarily acts as an NMDA antagonist, but is also active at other receptors, including the mu opioid receptors. Because the NMDA receptor moderates central sensitization to pain, ketamine has been used as an analgesic, particularly in cases of neuropathic pain, hyperalgesia or opioid refractory pain. While the literature supporting ketamine use for post-operative pain is fairly robust, there is less evidence looking at the use of ketamine in the palliative care population.

#### Importance:

Opioid refractory pain can profoundly affect patient quality of life and is challenging for providers to treat. Palliative care providers should be aware of the potential risks and benefits of using ketamine for difficult-to-treat pain.

#### The Literature:

[Cochrane Database Syst Rev 2017 June 28;6\(6\):CD003351](#)

#### **Ketamine as an adjuvant to opioids for cancer pain.**

**Methods:** Cochrane Review 2017; Double-blind randomized controlled trials of patients with cancer pain unrelieved by opioids and  $n \geq 10$

**Results:** 3 trials met criteria, 1 of intrathecal ketamine (not further discussed here), 1 of IV bolus ketamine, 1 of subcutaneous ketamine

- *Mercandate et al:* Patients with neuropathic type cancer-related pain unrelieved by opioids
  - 0.25-0.5 mg/kg IV bolus
  - Pain intensity at 30, 60, 90, 120, 180 minutes
  - Results ( $n = 10$ ): Pain intensity improved throughout the studied period
  - Adverse Events: Hallucinations, "sense of insobriety," (both improved with 1 mg diazepam), drowsiness
- *Hardy et al:* Hospitalized patients with refractory pain related to cancer or cancer treatment
  - Subcutaneous ketamine 100 mg/24 hours with rapid escalation up to 500 mg
  - Pain improvement at day 2, 5
  - Results ( $n=180$ ): no significant difference in pain scores between groups
    - Possible increased effect in those with higher baseline pain scores
  - Adverse Events: Significantly more common overall in intervention group – confusion, cognitive disturbance. No increase in serious adverse events
  - Drop-out high in both groups – 39 in ketamine group (17 from toxicity), 55 in placebo (37 from treatment failure)

**Conclusion:** Unable to provide conclusions about efficacy of ketamine for pain at any dose based on few studies and low-quality evidence

[J Palliat Med 2012 Mar;15\(3\):287-293.](#)

#### **Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care.**

**Methods:** Randomized controlled trial of continuous ketamine infusion (0.5-1 mg/kg/day) for patients with cancer pain refractory to opioids in a palliative care unit

**Outcomes:** Primary: change in pain between baseline and 2 hours after initiation; also looked at 1 and 2 days after initiation

**Results** ( $n=20$ ): No statistically significant change in pain

- Day 1 and 2, pain scores were lower in ketamine group but this did not reach significance
- About 50% of patients in ketamine group had 30% reduction in pain scores at day 2; no statistically significant difference compared to placebo
- No significant difference in adverse events

**Conclusion:** Ketamine combined with morphine did not improve pain control more than morphine alone

- Dose used may have been too low (0.5-1mg/kg/day) & study may have been under-powered

[J Palliat Med 2019 Sept;22\(9\):1154-1161.](#)

#### **The efficacy of ketamine in the palliative care setting: a comprehensive review of the literature**

**Methods:** Case reports, clinical trials, RCTs of ketamine used for *pain or depression* in palliative care patients

**Results:** For depression: 11 articles, only 1 RCT (reviewed here)

- Fan et al: Cancer patients with depression
  - 0.5 mg/kg IV ketamine bolus vs midazolam bolus
  - Measured suicidal ideation and depression at day 1, 3, 7
  - No significant adverse effects
- Results ( $n = 42$ ): Lower SI and depression by day 1, started to fade by day 7

**Conclusion:** Studies of ketamine for depression in palliative care are favorable regardless of dose, but effects are short-lived with bolus-dosing

*"Following this review, it is apparent that ketamine may be useful in treating multiple comorbid aspects of pain in the palliative care setting...Although not established in this review, it is possible that an ideal ketamine dose exist to most effectively treat the combined symptoms of total pain in palliative care patients."*

#### **Kathy's thoughts:**

- Only a limited number of studies have explored this topic, and they have been limited by low numbers of participants and heterogeneous dosing strategies
  - No studies have looked at UPMC's recommended dosing strategy (starting at 0.1 mg/kg/hr IV infusion) or the palliative care team local practice (starting at 5 mg/hr regardless of weight)
- There are no RCTs looking at the use of ketamine to treat hyperalgesia or "reset" the opioid response
- Adverse events are primarily neuropsychiatric and generally improve with benzodiazepines
- Evidence for use in depression is better overall
- A patient's experiences of depression and pain may be closely related

#### **Bottom Line:**

- There is no clear evidence that ketamine reduces pain in patients with cancer pain refractory to opioids
- There are no high-quality studies that explore the efficacy of how we typically use and dose ketamine for our seriously ill patients at UPMC
- There are also few high-quality studies for using ketamine to treat depression in the palliative care population, but evidence overall is more favorable
- Adverse events with careful dosing are limited and generally treatable
- There is likely low risk of harm in trying ketamine for patients with pain that is truly refractory to opioids

**CLINICAL PEARL:** There is no clear evidence that ketamine offers improved analgesia for opioid-refractory cancer pain compared to opioids alone; however, the risk of serious adverse events from appropriately-dosed ketamine is low.