



Effective Health Care

Ketamine for Treating Pain in Palliative Care

Results of Topic Selection Process & Next Steps

The nominator is interested in a new evidence review on the use of ketamine as an adjunct to opioids for the treatment of pain in patients in the palliative care setting.

The use of ketamine as an adjunct to opioids for treating pain in the palliative care setting has been partially addressed by a recent Cochrane Review focused on cancer pain only. Since the original research addressing ketamine for non-cancer pain in palliative care is very limited, a systematic review is not feasible at this time. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Number and Name: #823 Ketamine for Treating Pain in Palliative Care

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Background

Palliative care is a general term that includes treatment given to relieve pain and control symptoms when there is no reasonable expectation of a cure. It focuses on the whole person, encompassing body, mind, and spirit to enhance comfort and preserve dignity¹.

Pain is widely prevalent in the last weeks of life; a nationally representative longitudinal survey of community-dwelling United States residents found a prevalence of pain in the last year of life ranging from 54.3 to 60.8 percent. Another survey of hospice patients in nursing homes found that approximately 50 percent had daily pain, and for those who had pain, it was moderate or worse in approximately 85 percent.²

Opioids are endorsed as first and second line therapy by many consensus-based guidelines, and are the mainstay of pain management in terminally ill patients receiving palliative care for cancer and non-cancer related pain.³

Their usefulness in pain management is however compromised in patients who develop opioid tolerance despite escalating dosage and are at increased risk of opioid induced adverse events. Adjunctive therapies are therefore sought and may include NSAIDs, acetaminophen, antidepressants and anti-epileptics, depending on the etiology of the pain and other co-occurring conditions.⁴ The recent shortage of parenteral opioids in US hospitals largely due to manufacturing deficits, has forced many physicians to consider alternate therapies and dosing regimen to compensate for the unmet analgesic needs of their patients.^{5, 6}

The FDA has approved injectable ketamine for use as an anesthetic during surgery and as analgesic for certain diagnostic procedures.⁷ Various systematic reviews have recently published on the efficacy of ketamine in the treatment of acute and chronic pain, including cancer pain in palliative care.⁸ The results of these reviews are ambiguous with respect to ketamine's efficacy in causing significant pain relief, and their conclusions need to be considered against the results from open-label studies and case series that in majority report benefit of ketamine treatment.^{9, 10}

Recent consensus guidelines jointly issued by American Society of Regional Anesthesia & Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA) recommend best practices for administering ketamine as a therapeutic agent for the treatment of chronic and acute pain.¹¹ However, these guidelines are not applicable to terminally ill patients in palliative care.

The decisional dilemma that palliative care providers face is how to treat patients who are already on opioids in the event of refractory pain due to opioid tolerance, disease progression or acute exacerbations. Side effects of ketamine range from dizziness, somnolence, nausea, loss of appetite to severe psychomimetic effects such as hallucinations, unusual thoughts, fears and dissociative symptoms.¹² Evidence is therefore sought from recent studies, to update the state of the science on the relative effectiveness and harms of ketamine compared to other non-opioid drugs as an adjunct to opioid therapy for the treatment of refractory pain in terminally ill patients.

Nominator and Stakeholder Engagement

The American Academy of Hospice and Palliative Medicine (AAHPM) requested a systematic review (SR) on this topic. An AHRQ SR will inform evidence-based guidelines that address when and how to consider ketamine for treatment in terminally ill patients in palliative care. The initial questions included in the nomination were:

1. What is the best protocol for using parenteral ketamine for refractory pain or depression in hospice/PC patients?
2. Do ketamine infusion as compared to non-ketamine approaches, impact outcomes such as immediate and/or long-term pain scores, quality of life, anxiety or depression prevalence and/or incidence, survival, and/or length of hospitalization?

We had a conference call with the nominator to discuss and clarify the PICOTS. The nominators clarified that the patient population of interest are those that are terminally ill, in palliative care

and currently taking opioids. This includes, but is not restricted to those with cancer-related pain (including those with neuropathic pain as a side effect of chemotherapy).

Key Questions and PICOs

The key questions for this nomination are:

1a. What is the comparative effectiveness and harms of intravenous ketamine compared to other non-opioid medications as adjunct to opioids, for treatment of pain and improving the quality of life in terminally ill patients receiving palliative care?

1b. Does the effectiveness and harms of intravenous ketamine as adjunct to opioids for the treatment of pain in palliative care vary by (1) the specific type or cause of pain (2) patient demographics (3) medical comorbidities (4) intervention characteristics

To define the inclusion criteria for the key questions, we specify the population, interventions, comparators, outcomes, timing, setting (PICOTS) of interest (Table 1).

Table 1. Key Questions and PICOTS

Key Questions	1a. What is the comparative effectiveness and harms of intravenous ketamine compared to other non-opioid medications as adjunct to opioids, for treatment of pain and improving the quality of life in terminally ill patients receiving palliative care?
	Terminally ill adults 18 years and older, in palliative care, being treated with opioids for breakthrough/refractory pain or acute exacerbations that may or may not be cancer-related.
	[IV or subcutaneous Ketamine]+opioids, [IV or subcutaneous Ketamine]+opioids +drug from another class, IV or subcutaneous ketamine
	Opioids alone Opioids+drug from another class Placebo
	<ul style="list-style-type: none"> • Pain (short and long term) • Quality of life • Anxiety • Depression • Survival • Length of stay • Harms of intervention
	All
	inpatient

Abbreviations: IV intravenous,

Methods

We assessed nomination for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix A for detailed description of the criteria.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.

4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last five years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of a New Evidence Review

We conducted a literature search in PubMed and PsycInfo from January 8, 2014 to January 8, 2019. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

We reviewed all identified titles and abstracts for inclusion and classified identified studies by key question and study design to assess the size and scope of a potential evidence review.

Results

See Appendix A for detailed results for all selection criteria.

Appropriateness and Importance

This is an appropriate and important topic.

Desirability of a New Review/Duplication

A new evidence review would be partially duplicative of an existing product. We found two systematic reviews.

The 2017 Cochrane review by Bell et al. updated a 2012 report (which updated a 2003 review) addressed the effectiveness and adverse effects of ketamine as an adjuvant to opioids for refractory cancer pain in adults in inpatient and outpatient settings (Bell et al. 2017).¹³ Although, not the primary setting of interest, it presents the best available evidence on the topic. Only three studies met inclusion criteria. The results could not be synthesized because of heterogeneity between studies; different study designs, using different doses of ketamine, different routes of administration and different durations of treatment.

A second systematic review and meta-analysis focused on non-opioid analgesics in palliative care patients with any advanced or end-stage medical disease (e.g. cancer, HIV, heart

disease, liver disease, and lung disease (Schüchen, 2018).¹⁴ This review included studies comparing treatment with non-opioid analgesics [e.g. non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and dipyrrone], to other non-opioids, placebos, opioids, or combinations of non-opioids and opioids.

See Table 2, Duplication column.

Feasibility of a New Evidence Review

A new evidence review or technical brief is not feasible. Our search did not identify any studies that evaluated ketamine as an adjunct to opioids in palliative care patients with non-cancer pain.

We identified one retrospective analysis of ketamine administered to patients in palliative care setting. The intervention included intravenous administration of ketamine with midazolam, for patients with uncontrolled cancer pain despite opioid dose escalation, and evaluated pain intensity as the outcome.

See Table 2, Feasibility column.

Table 2. Key Questions and Results for Duplication and Feasibility

Key Question	Duplication (1/2014-1/2019)	Feasibility (1/2014-1/2019)
KQ 1: What is the comparative effectiveness and harms of intravenous ketamine compared to other non-opioid medications for treatment of pain, depression and quality of life in terminally ill patients receiving palliative care, when used as an adjunct to opioids?	Total number of identified systematic reviews: 1 <ul style="list-style-type: none"> • Cochrane: 1¹³ • Other group: 1¹⁴ 	Size/scope of review Relevant Studies Identified: 1 <ul style="list-style-type: none"> • Retrospective analysis : 1¹⁵ Clinicaltrials.gov <ul style="list-style-type: none"> • Recruiting: 2 • Active: 0 • Complete: 0
KQ2: Effectiveness or harms modifiers resulting from (1) the specific type or cause of pain (2) patient demographics (3) medical comorbidities (4) intervention characteristics	Total number of identified systematic reviews: 0	Size/scope of review Relevant Studies Identified: 0 Clinicaltrials.gov <ul style="list-style-type: none"> • None

Abbreviations: KQ=Key Question

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review update would be partially duplicative of an existing product.
- Impact: A new systematic review update has high impact potential.
- Feasibility: A new review update is not feasible because of the paucity of primary studies.

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Appendix A. Selection Criteria Assessment

Selection Criteria	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents interventions available in the U.S
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible and is consistent with what is known about the topic.
2a. Represents a significant disease burden; large proportion of the population	Yes. This topic represents a significant disease burden. The prevalence of pain in the last year of life ranges from 54.3 to 60.8%. In hospice patients in nursing homes 50% experience daily pain which is moderate or worse in approximately 85%
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects health care decisions for a large proportion of the US population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of adjunctive ketamine treatment for patients in palliative care
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, Since reimbursement for hospice care has limited dollars to manage the needs of the dying (in whom pain is common) cost-effective prescribing options would be valuable.
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	Yes, a new systematic review would not be redundant. We did not find any systematic reviews that fully address the KQs.
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear. There is no standard protocol for ketamine use for refractory pain in palliative care.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. Due to lack of guidelines people are currently either making their own protocols or experimenting with different treatment combinations.
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Primary studies are very limited

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed below are the sources searched, hierarchically.

Primary Search
AHRQ: Evidence reports and technology assessments https://effectivehealthcare.ahrq.gov/ ; https://www.ahrq.gov/research/findings/ta/index.html ; https://www.ahrq.gov/research/findings/evidence-based-reports/search.html
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program https://www.hsr.d.research.va.gov/publications/esp/
Cochrane Systematic Reviews http://www.cochranelibrary.com/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
Secondary Search
AHRQ Products in development https://effectivehealthcare.ahrq.gov/
VA Products in development https://www.hsr.d.research.va.gov/publications/esp/
Cochrane Protocols http://www.cochranelibrary.com/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospéro/
Tertiary Search
PubMed https://www.ncbi.nlm.nih.gov/pubmed/

Appendix C. Search Strategy & Results (Feasibility)

Feasibility	
MEDLINE(PubMed) searched on: January 15, 2019	
Concept	Search String
Ketamine (Subject headings and trade names)	(((((("Ketamine"[Mesh] OR "N-methylketamine"[Supplementary Concept] OR "2-Oxo-PCE"[Supplementary Concept]) OR (((((((((Anesject[Title] OR Brevinaze[Title])) OR 2- AND (2-Chlorophenyl) AND -2- AND (methylamino) AND cyclohexanone[Title]) OR (Calipsol[Title] OR Calypsol[Title])) OR CI 581[Title] OR (CI581[Title] OR CI-581[Title] OR Etamine)) OR (Ivanex[Title] OR Kanox[Title] OR Kalipsol[Title] OR Keiran[Title] OR Ketacor[Title] OR Keta[Title] OR ketaject[Title] OR Ketalar[Title])) OR Ketamine[Title]) OR (Ketanest[Title] OR Ketaset[Title] OR Ketava[Title] OR Ketaved[Title] OR Ketazol[Title] OR Ketolar[Title])) OR (Narkamon[Title] OR Quetanex[Title] OR Velonarcon[Title] OR vetalar[Title])))
AND	
Palliative Care	((((((((((("Palliative Medicine"[Mesh] OR "Palliative Care"[Mesh] OR "Hospice and Palliative Care Nursing"[Mesh])) OR ((palliative[Title/Abstract] OR hospice[Title/Abstract])) OR end of life[Title/Abstract])))
Limits: English	Filters activated: English
Total N=75	
SR N=4	Systematic[sb]
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/57534557/public/	
RCT N=51	((((((((groups[tiab]) OR (trial[tiab]) OR (randomly[tiab]) OR (drug therapy[sh]) OR (placebo[tiab]) OR (randomized[tiab]) OR (controlled clinical trial[pt]) OR (randomized controlled trial[pt])
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/57534578/public/	
Other N=20	
https://www.ncbi.nlm.nih.gov/sites/myncbi/r.relevo.1/collections/57534609/public/	
clinicalTrials.gov searched on January 8, 2019	

ClinicalTrials.gov

4 Studies found for: palliative OR hospice | Recruiting, Active, not recruiting, Completed, Enrolling by invitation Studies | Ketamine | First posted from 01/08/2014 to 01/08/2019

https://clinicaltrials.gov/ct2/results?cond=&term=palliative+OR+hospice&type=&rslt=&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&gndr=&intr=Ketamine&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&

[dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=01%2F08%2F2014&sfpd_e=01%2F08%2F2019&lupd_s=&lupd_e=&sort=](#)

Recruiting: 2 studies on ketamine for pain management (1 for refractory cancer pain, 1 for refractory pain)
Recruiting: 2 studies on ketamine for the management of depression in palliative care.