Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Analgesics To Reduce Acute Pain in the Prehospital Setting*

Draft review available for public comment from May 1, 2019 to May 31, 2019.

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Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	Evidence summary	Evidence Summary, page x: Should be “Rationale” in the header	We have corrected this typo.
Peer reviewer #3	Evidence summary	xi line 17: “5 minutes for time to analgesia” was clinically important. This number was not used at all in any of the studies or in the paper analysis which used 15, 30, 60.	The clinically important difference of 5 minutes was used only for the outcome of “time to analgesic effect”, not for the change in pain scores. Change in pain scores were evaluated for 3 time points, including 15, 30 and 60 min.
Peer reviewer #4	Evidence Summary	Page 13 Table B: The Color coding and the plus symbols are redundant and a bit distracting Table B: Too much information in the footnotes	To be compliant with federal regulations (508 compliance) we cannot convey meaning through color alone, and a symbol is required. We believe the details in the footnotes are necessary and did not edit them further.
TEP reviewer #1	Evidence summary	-Page 11, Line 6: “Rationale” is misspelled	We have corrected this typo.
TEP reviewer #1	Evidence summary	-Pages 13-14: Table B is quite helpful for understanding the main findings	Thank you.
TEP reviewer #7	Evidence summary	Table B. The articles with low SOE and insufficient levels of evidence should not be relied upon for firm conclusions. It is much more accurate to say these sources of data cannot provide information to support a meaningful conclusion.	Articles are not graded with SOE, rather conclusions are accompanied with a SOE. The SOE qualifies the level of confidence the research team has in the conclusion statement. By definition, a low SOE means “We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.” Consistent with reported methods, if the SOE was judged to be insufficient, a conclusion was not made.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #7	Evidence summary	No conclusions should be based on this level of evidence other than adequate data are lacking.	We believe this remark is made on the conclusions for KQ3 and 4. The research team judged the evidence to be sufficient enough to permit a conclusion but graded the SOE as low, consistent with our confidence in the certainty of that conclusion. Consistent with reported methods, the SOE qualifies the level of confidence the research team has in the conclusion statement. By definition, a low SOE means "We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect."
TEP reviewer #7	Evidence summary	This review found an absence of quality data to answer these questions.	The review intends to use the best available evidence, consistent with the approved protocol, to answer the Key Questions. We agree that that evidence base had limitations but these limitations have been identified in the report and the individual study risk of bias and evidence base limitations have been accounted for in the SOE grading process.
TEP reviewer #7	Evidence summary	While there may be numerical differences, the nature and severity of the adverse events is critically important	The specific adverse events that were selected for this report, and were graded (implying a higher priority and importance to the stakeholders and research team) included hypotension, respiratory depression and mental status changes. Conclusions, when possible, are separately made for these outcomes.
Peer reviewer #2	Abstract	I found the Structured Abstracts Results section challenging to read.	We attempt to keep the abstract clear by focusing on the graded comparisons and outcomes in this review while remaining under a word count of 500 words.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	Introduction	Footnotes under the table on page xiii, Strength of evidence, should be “a priori.” In the same section under footnote “h,” it may be beneficial to clarify what depression means in that category, so that it isn’t confused with respiratory depression.	We corrected the typo associated with “a priori”. We listed (mental status change” after “depression” to make it clear this is not respiratory depression.
Peer reviewer #1	Introduction	End of the first paragraph under Background, What does “optimizing opioid exposure” intend to convey? It seems vague and euphemistic	The phrase “optimizing opioid exposure” is intended to convey the balance of selecting opioids for pain management in the appropriate patient and setting in an attempt to minimize inappropriate use and patient exposure.
Peer reviewer #3	Introduction	3 line 46: I am not sure what this means “3) assuming this level of severity for studies evaluating an opioid or ketamine in the absence of inclusion criteria or baseline pain scores.”	We re-worded this phrase to improve clarity. In the event that a study did not use inclusion criteria of moderate or severe pain and did not report mean or median baseline pain scores, we still allowed a study for opioids or ketamine in to the review, assuming the pain had to be at least moderate for a trial of such analgesics.
Peer reviewer #3	Introduction	p4 line 41: K3/4 required the comparator to be the initial drug regimen (i.e. repeat the same drug and dose). This doesn’t make sense to me. This is not how Morphine is dosed (0.1mg/kg followed by 0.05mg/kg) or ketamine which is totally weight based.	The comparator is the original analgesic regimen that the patient was found not to respond too. The Table that follows the PICOT had more clear language and thus we edited the text identified by this comment to be consistent with the table language.
Peer reviewer #4	Introduction	Page 20 Paragraph beginning Line 19: Preface this paragraph with a statement that proper pain assessment is not within the scope of this review. Table 1: Add weight-based dosing for children Table 1: Add maximum doses for all medications	Pain assessment was in part addressed as a contextual question, thus we did not add this as an area outside of the scope of this review. We have made the suggested modifications to table 1 where possible.
Peer reviewer #4	Introduction	Page 22 KQ2c: Describe in greater detail what types of harms were considered. Needle sticks? Combative/hallucinating patients and other?	The description of harms appears in the “outcomes” list of the PICOTS, and includes diversion, future risk of substance abuse or misuse and needle sticks.
Peer reviewer #4	Introduction	KQ 2c: Define these comparative harms. Risk of provider to have substance abuse/misuse OR patient. Diversion to where? Closer facility or one further away as higher acuity. What about other direct injury?	The population for KQ2c is defined as the EMS personnel, not the patient. There were no further definitions for these outcomes established for this protocol.

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Peer reviewer #4	Introduction	Page 24 The contextual questions appear here, but not well addressed in other areas of the report	We added a statement to this page letting the reader know to advance to the discussion for the findings from the Contextual Questions.
Peer reviewer #4	Introduction	Table 3: I am a bit confused about the study population relative to Sub KQ 2a. In the table, it is stated that the population had to have "acute onset" pain. How can you then evaluate the effect relative to acute vs. chronic pain? How did you handle studies that enrolled both acute and chronic pain?	The population for SubKQ2a are subgroups of interest, one of which was patients with a background of chronic pain who experience an acutely painful episode and would need treatment for acute pain. We did not include studies of patients with (only) chronic pain.
TEP reviewer #1	Introduction	Overall the introduction is well-written and summarizes the prior literature, the existing gaps in knowledge, the key questions, and the population of interest sufficiently	Thank you.
TEP reviewer #1	Introduction	Page 20, Line 20: The evaluation of validated pain assessment tools is important, and it is good that the authors identified this.	Thank you.
TEP reviewer #2	Introduction	Well written and complete	Thank you.
TEP reviewer #3	Introduction	Good background	Thank you.
TEP reviewer #4	Introduction	Succinctly states the problem. Review of existing guidelines could be expanded. The Title of Table 1 is somewhat of misnomer as limited PK information is actually included with that said the information is well laid out and I wouldn't change the content just the title.	We have changed Table 1 title to "Onset, duration and recommended dosing of analgesics" based on this feedback.

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TEP reviewer #5	Introduction	A minor note, but Table 1 in the Introduction lists the onset time for ketorolac IV to be about 30 minutes and for PO to be 30-60 minutes. This may be part of a deceiving myth that parenteral ketorolac works faster than oral ketorolac or ibuprofen. Although this point is not directly related to the outcomes of this paper, this summary table of analgesics is likely to be used in other settings. Turturro, et al published a comparison of IM ketorolac to oral ibuprofen that showed both to have comparable onset and analgesia at 15 minute intervals between 15 and 120 minutes. (Turturro MA, Paris PM, and Seaberg DC. Intramuscular ketorolac versus oral ibuprofen in acute musculoskeletal pain. Ann Emerg Med. 1995;26:117-120.)	Thank you for providing this citation, although we do not review IM ketorolac in the table, and the onset and duration for IM and IV are not always the same, thus we did not make changes to this section.
TEP reviewer #6	Introduction	Although nonpharmacologic pain strategies are not included with this review - consider stating that the strategies should be employed along with the current recommendations makes sense.	Former pain management guidelines for the prehospital setting (Gausche-Hill M et al. Prehospital Emergency Care 2014;18:25-34) do not address use of nonpharmacologic pain management strategies and state that the guideline panel discussed this topic but decided to focus the guideline on assessment of pain and delivery of pharmacologic agents available in the field. Thus, we did not make changes to the introduction of the report.
Public Reviewer #1, Creighton Tubb, AAOS	Introduction	The work AHRQ has done to evaluate the agents used for pain management in the prehospital setting is commendable. With the recent focus on overutilization of opioid medications, the topic is timely and valuable. The introduction section highlights the importance of this topic.	Thank you.
Public Reviewer #2, Mark Gestring	Introduction	No issues.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	Methods	The literature review and analysis are fairly expansive and the authors' study population identification was clear. The use of emergency department data as surrogates for prehospital is logical, in the absence of field data, although not necessarily a 1:1 comparison. This was well addressed through the strength of evidence grading. Table 3. Provides a detailed description of inclusion and exclusion.	Thank you.
Peer reviewer #1	Methods	Page 16, line 30, should say "...ketorolac 5mg or 15mg if pain remained elevated."	We corrected the typo.
Peer reviewer #2	Methods	No discussion of concerns regarding sympathomimetic effects of ketamine for use in ischemic chest pain. I question the inclusion of studies where the dosage form (IN, IV, etc.) is not reported. Personal opinion but the PO studies have limited relevance, though I can understand why they were used to answer some KQs.	The review did not focus on a specific type of pain (i.e. chest pain) thus our discussion and conclusions are consistently applicable to the general management of acute pain in the prehospital setting. In the discussion we report the hemodynamic side effects demonstrated by the evidence, and the reader should apply those findings in context of their clinical practice. Studies that did not report the routes clearly were not excluded as per our protocol, all routes were allowed for inclusion. These few studies were observational and did not significantly contribute to the conclusions made in the report.
Peer reviewer #3	Methods	p7 line 55: " low rating implies lack of major or minor sources of bias (add "that") are likely to influence results.	This edit has been made.
Peer reviewer #3	Methods	p8 line 20: analyzed three time points 15, 30, 60 (this is different than in initial methods summary- see above- and Table 4).	Consistent with the methods throughout, change in pain scores were evaluated at 15 min, 30 min and 60 min. Change in pain scores are not stated to be nor were they evaluated at 5 minutes. The clinically important difference in Table 4 shows a difference of 5 minutes, specific for the outcomes of time to analgesic effect, not for the outcome of change in pain scores.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #1	Methods	Page 25: The search strategy seems appropriate, and the use of a medical librarian is appropriate	No comment.
TEP reviewer #1	Methods	Page 26, Table 3: The table thoroughly summarizes the inclusion and exclusion criteria. However, the authors should consider integrating the content from Table 4 into the Outcomes section of Table 3, since the current Outcomes description of "at least one outcome listed in PICOTS" seems vague, whereas the description in Table 4 is quite clear.	Table 3 details specific inclusion and exclusion criteria for studies to be included into this systematic review. We elected to refer the reader to the list of outcomes in the PICOTS rather than typing them into the table for presentation purposes as the list is quite long. The information in Table 4 does not relate to inclusion/exclusion of citations into the systematic review. Table 4 provides details as to how the research team interpreted pooled effect estimates in making conclusions of clinical relevance.
TEP reviewer #1	Methods	Pages 27-28: The statistical methods are thoroughly described and referenced.	No comment.
TEP reviewer #1	Methods	Page 28, Line 16: The use of only 2 reviewers to grade the strength of evidence seems like a low number. What was the reason for not trying to achieve consensus among the entire technical expert panel for each recommendation?	SOE was evaluated by two independent senior researchers. The SOE grades were then shared with the research team for comments and if there were disagreements, discussion amongst the group was used to arrive at final grades. This is consistent with methods accepted in the field. Grading SOE is not a function of the Technical Expert Panel assembled for AHRQ systematic reviews.
TEP reviewer #1	Methods	Page 28, Lines 25-41: The criteria for specific language in the recommendations is clearly described	No comment.
TEP reviewer #3	Methods	Well defined search strategy. Easily interpretable. Appropriate for PICOT questions.	No comment.
TEP reviewer #4	Methods	Methods are clearly stated and appropriate.	Thank you.
TEP reviewer #6	Methods	Inclusion and exclusions were justifiable.	No comment.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #7	Methods	A change in pain score of 2 may not have any value if that means going from a 10 to an 8, but may reflect a good effect if it represents going from a 5 to a 3. There are no good data to support a 2-point difference as a clinically meaningful difference. Measures of adequate pain control have to take into account the use of additional rescue medication and whether the level of pain reduction achieved is meaningful to the patient. The former information should be collected routinely in these types of clinical trials and latter can be assessed by directly asking the patient.	During protocol development, clinically important differences were discussed with the Technical Expert Panel, the sponsor, and AHRQ. The EPC also conducted a literature search regarding clinically important differences for pain in this field. Considering all input, we applied a clinically important difference of 2 to draw conclusions for the outcome of changes in pain scores. None of the aforementioned parties disagreed with this value.
TEP reviewer #7	Methods	This is not a usual standard. Much more commonly, 30% and 50% cutoffs are used as meaningful reduction in pain, and even those cutoffs are not based on good quality data.	During protocol development, clinically important differences were discussed with the Technical Expert Panel, the sponsor, and AHRQ. The EPC also conducted a literature search regarding clinically important differences for pain in this field. This value was also used in several studies included in this review as a meaningful difference in pain, used to power clinical trials. Considering all input, we decided to apply a clinically important difference of 2 to draw conclusions for the outcome of changes in pain scores. In our opinion, there was no indication that a change of 30-50% was superior to a 2-point change, nor was there any signal from our clinical expert or the studies in this field that a 30-50% change was more applicable or common versus a 2-point change.

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TEP reviewer #7	Methods	The ED is not a fair substitute for prehospital care – patients would necessarily have the same extent of injury, so may respond to milder opioids better than patients with the level of trauma that would result in transport by emergency services.	During protocol development, we sought input from the Technical Expert Panel, the sponsor, and AHRQ regarding the use of indirect evidence (studies from the ED and battlefield). There was agreement across these groups that in the absence of sufficient EMS data, ED data could provide indirect evidence of comparative effects. Considering all input, we agreed to include ED studies into the review and when EMS data did not exist or were insufficient, we based conclusions on ED data. The conclusions based on ED data were downgraded for indirectness when we graded SOE, to account for the limitation associated with setting. In our opinion, we believe the evidence report is clear in articulating when data is ED vs. EMS and that the indirectness of ED data is considered a major limitation of the evidence base.
Public Reviewer #1, Creighton Tubb, AAOS	Methods	Adequacy of analgesia was defined by a 2-point difference on Visual Analog Pain Scale of 0-10 and a 5- minute difference in time to analgesia. Understanding the scientific basis for these outcome points would be valuable. The MCID for VAS Pain is varied in the literature depending on the condition. If the MCID for adequate reduction in pain required a 3-point difference in the VAS pain score, would the results stand as presented?	During protocol development, clinically important differences were discussed with the Technical Expert Panel, the sponsor, and AHRQ. The EPC also conducted a literature search regarding clinically important differences for pain in this field. Considering all input, we decided to apply a clinically important difference of 2 to draw conclusions for the outcome of changes in pain scores. If a 3 point difference in pain score on a 0 to 10 scale was applied, the conclusions would stand as presented.
Public Reviewer #2, Mark Gestring	Methods	No issues.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	Results	The results section is detailed with easy to read tables. The key messages (driven by the data) are clear, leaving their interpretation for out of hospital treatment, subject to interpretation. The key message is that more out of hospital study is necessary.	Thank you.
Peer reviewer #2	Results	In final format, do not split tables across different pages. Statistical assessments seem appropriate. Not aware of other studies that should have been included.	AHRQ publication standards allow splitting tables across pages when the header row is repeated.
Peer reviewer #3	Results	It was very difficult to track given the volume of data . In addition, the listing of studies and their characteristics without direct link to the outcomes is not helpful. They list every dose of medication used and every route, then in a different section talk about outcomes- but it is difficult to know which trials they are referencing.	The purpose of the overview of study characteristics that begins the results section is to provide a general overview of the included studies, by analgesic comparison. We hope the reader can take away the necessary information to decide how similar or different the studies are with respect to those characteristics, and how similar or different the studies are to the reader's own practice environment. All statements are referenced, including the appendix tables, which have individual study level characteristics reported.
Peer reviewer #3	Results	p21 line 46: "Admin of a single does of the analgesic versus multiple doses of the analgesic did not appear to be associated with differing effects of opioids vs ketamine..." I am not sure how this is true that multiple doses of analgesics dont change pain scores.	This subgroup comparison separate analyzed studies only employing a single dose (i.e. a single dose of morphine vs. a single dose of ketamine) or multiple doses (morphine repeated doses vs. ketamine repeated doses). The subgroup analyses suggest that regardless if the drug frequencies are single doses or multiple doses, for both analgesics compared, there isn't a clinically important difference. The subgroup is not comparing a single dose of one analgesic to multiple doses of another analgesic. We reworded these results to clarify these points.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	Results	Despite their assertions, morphine vs. fentanyl is a relevant topic and not clearly addressed. Especially in the context of traumatic pain, the differences in prehospital monitoring (though this gap has changed dramatically), and side effects.	During protocol development, the EPC sought opinion from the TEP and sponsor to prioritize comparisons and outcomes for SOE grading. Of highest priority was the comparison of opioids vs. each non-opioid analgesic, not the comparison of morphine versus fentanyl. We revised this statement in the report to indicate that the comparison was not prioritized as a decisional dilemma for this evidence review. However, data comparing morphine vs fentanyl were analyzed and results are presented in the main report primarily in table format, with supportive text. Please refer to Tables 16 and 29.
TEP reviewer #1	Results	Overall, the evidence summaries and the inclusion of the Forest plots is helpful to understand the vast amount of literature that was reviewed.	Thank you.
TEP reviewer #1	Results	-Page 31, Table 6: It may have been stated in the Methods (and I just missed it), but if it were not, please clarify why the Strength of Evidence was not graded for some of the studies in Table 6.	The methods chapter specifies “Input from NHTSA, the TEP, AHRQ and our EPC led to a prioritized list of comparisons and outcomes for which conclusions were constructed and graded. Prioritized comparisons were opioids vs. ketamine, opioids plus ketamine vs. opioids, opioids vs. APAP, opioids vs. nitrous oxide and opioids vs. NSAIDs”
TEP reviewer #1	Results	-Pages 41-42: It seems that the conclusions drawn in Table 10 are not supported by the Forest plots in Figures 6-8. Please explain why the authors concluded that a combination of an opioid and ketamine may reduce pain more than an opioid alone if the diamonds in the Forest plots all cross 0.	The conclusion statements are made in reference to the clinically important difference, identified in Table 4, not statistical significance. The EPC used the term “may” which was reserved for instances where point estimate and confidence interval suggested a CID may exist (confidence interval included both a CID and also a smaller difference, but overall was shifted towards a CID). The conclusions are not based on statistical significance, (diamonds in the forest plot crossing 0)

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TEP reviewer #2	Results	I am not aware of any significant current studies that exist that were not included in this report. Amount of detail is appropriate, studies are well-described and key messages are clearly stated.	Thank you.
TEP reviewer #3	Results	I am not aware of specific studies that were missed. Results have appropriate amount of detail	Thank you.
TEP reviewer #4	Results	Comprehensive	Thank you.
TEP reviewer #6	Results	Only issue would be preference for ketamine for patients who would not otherwise receive pain medication -specifically the multi-traumatized patient or patient in shock, Addressing this issue - even with poor evidence would be helpful.	Studies did not identify multitraumatized patients, most traumatic pain studies were in patients with limb fracture. Many studies required stable hemodynamics for enrollment, precluding study of shock patients. Although we attempted to conduct subgroup analysis based on pain type, etiology, and baseline hemodynamics, the dearth of evidence prohibited our ability to do so. This is identified as a limitation and in the future research needs.
TEP reviewer #7	Results	We have already seen recommendations based on Low SOEs have grave unintended consequences in pain management and it would be preferable to not draw a conclusion and acknowledge inadequate data rather than draw conclusions that may not be accurate. As stated in the introduction, “Adequate pain relief is known to minimize anxiety and cardiac complications associated with acute pain”. These conclusions could lead to worse pain management, not better.	The EPC does not create clinical recommendations. The conclusions are solely based on the evidence from included studies and what the effect estimates show relative to applied clinically important differences. As a next step, it is up to the medical community to take the synthesized evidence and provide recommendations as to how acute pain management in the prehospital setting should or should not change, based on this evidence.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #7	Results	I don't think this conclusion can be supported based on the poor quality of evidence.	We believe this comment is made in regards to the results "As initial analgesics, there is no evidence of a clinically important difference in the change of pain scores with opioids versus ketamine administered primarily intravenously (IV) (low SOE), IV acetaminophen (APAP) (low SOE), or nonsteroidal anti-inflammatory drugs (NSAIDs) administered primarily IV (moderate SOE))". We have derived these results, conclusions and SOE grading by following the approved protocol, which was designed in consultation with NHTSA, AHRQ, the TEP and our content experts. The quality of the evidence has been considered and when the research team was unable to estimate an effect (when there was no evidence at all) or had no confidence in the estimate of the effect because of significant limitations in the evidence base, we use "insufficient" and did not make a conclusion.
TEP review #7	Results	It is difficult to compare efficacy of different products without knowing if subjects received appropriate and comparable doses. We note that you listed the doses in some areas, but the dosing is not completely clear through your report. Analgesics typically have a dose-response effect on acute pain. If the dose was not described, the data are really not suitable to use for the kinds of comparisons and conclusions intended for this review. The doses used, particularly if less than labeled doses should be described for all products used for these comparisons.	The appendix provides detailed study characteristics for each study included in this review. The analgesic, route, dose and frequency is specified as completely as what is stated in the published study itself. The introductory text attempts to summarize the dose findings, to allow the reader to recognize if overall, based on the specific analgesic comparisons, the drug regimen properties are similar to clinical practice or not.

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TEP reviewer #7	Results	This is not straightforward to blind. APAP has a volume of 100 ml and should be administered over 15 minutes. Morphine will generally have a volume of less than 10 ml, and depending on the concentration, could be 5 or less and is usually given by slow push.	The report does not blind any information, regarding the analgesic regimen or otherwise. The analgesic regimen is as completely described in the appendix tables as what is stated in the published study manuscript. Most studies did not explain details as to the administration duration.
TEP reviewer #7	Results	Given the varied ages, you should report if these doses were appropriate. This is not the usual adult dosing for ketorolac.	Although the typical IV dose for ketorolac is 30mg IV, there is evidence that lower doses (10mg IV) produce similar analgesic effects to 15mg and 30mg, and thus may be appropriate in the adult population (Motov S, Yasavolian M, Likourezos A, et al. Comparison of intravenous ketorolac at three single-dose regimens for treating acute pain in the emergency department: a randomized controlled trial. Ann Emerg Med. 2017;70(2):177-184.)
Public Reviewer #1, Creighton Tubb, AAOS	Results	As noted in the review, a paucity of comparative studies specifically in the pre-hospital setting presents challenges in understanding the exact impact of these medications. Additionally, some of the prehospital work involves military personnel in a combat environment thus representing a unique population that may not translate well to the pain experience of civilians utilizing EMS. The work group addressed this by incorporating articles from the emergency department setting and downgrading strength of evidence as required.	No comment.
Public Reviewer #2, Mark Gestring	Results	Findings are not surprising.	No comment.
Peer reviewer #1	Discussion	Pg. 44, line 47 should say, “This conclusion…”	We did not change the wording because two conclusions are referred to- reduction in pain and speed in reduction if pain, as separate statements.
Peer reviewer #1	Discussion	Pg. 47, line 49-50: should it say “cannot inform individualized treatment decisions?”	We corrected the typo- it should say “and may inform…”

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Peer reviewer #1	Discussion	Further exploration for applicability of the findings may include NEMSIS data for average patient contact times (patient contact or arrival time to hospital transfer time), to determine which interval (15 min, 30 min, 60 min) is most relevant in the prehospital setting. This might be further informed by using the time of the administration of the medication to the hospital transfer time. Both would make the findings more applicable in potential EMS protocol changes.	We agree and have added timing of administration and hospital arrival time to the listed data points that would be optimal to gather.
Peer reviewer #1	Discussion	The observations about ketamine over opioids and the potential clinically relevant changes are useful considerations for EMS protocols.	No comment
Peer reviewer #1	Discussion	The findings support considering more non-narcotic options for prehospital analgesia, which have fewer operational constraints than controlled medications	No comment
Peer reviewer #1	Discussion	Stratifying patient harms based on the study's specific findings informs protocol development as well, and indications for analgesia in specific circumstances	No comment
Peer reviewer #1	Discussion	The conclusions regarding the NEMSIS database are interesting and while valid, there are myriad issues in gathering the information the study proposes, in the current state.	We recognize there may be challenges to collecting such data but still believe this is an avenue that should be explored further to fill gaps in the current literature on this topic.
Peer reviewer #2	Discussion	I think the future research section is well done. I like the idea of using nationwide NEMSIS data for prehospital research of this type.	Thank you.
Peer reviewer #3	Discussion	Decently organized discussion that helps clarify the other 45 pages of information.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	Discussion	All side effects are not created equal. This isn't really addressed until the discussion. At multiple points it is noted that ketamine has more side effects, but not until the discussion do they hint at severe vs. clinically insignificant side effects.	The specific adverse events that were selected for this report, and were graded (implying a higher priority and importance to the stakeholders and research team) included hypotension, respiratory depression and mental status changes. Conclusions, when possible, are separately made for these outcomes. In the discussion, we emphasize clinically important changes for graded outcomes. For outcomes that were not graded, clinically important differences were not established for this review. However, if in the opinion of the EPC the changes found for harms outcomes could exceed thresholds the reader may consider to be clinically important, we point them out. Examples include the hemodynamic changes with ketamine.
Peer reviewer #3	Discussion	p49 line: 14: "Our conclusions support the efficacy of ketamine, in comparison to opioids, without evidence of clinically important differences in reducing pain". What does this mean? That ketamine and morphine work the same? Clarify	We re-worded the statement to clarify that there is no evidence of a clinically important difference in pain reduction between ketamine and opioids. “Our conclusions support the efficacy of ketamine, and when compared to opioids there was no evidence of a clinically important differences in reducing pain.”
Peer reviewer #4	Discussion	Page 66 Line 27: I believe that the FDA has approved Intranasal Ketamine in the U.S., but perhaps not for this indication.	The FDA approved ketamine product is for treatment of resistant depression. This product is not currently approved for pain management, as is stated in the discussion.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Discussion	Page 69/70 Line54-14: Regarding discussion of Nitrous Oxide: Nitrous is an FDA approved product, but perhaps not for this indication. It is also worth mentioning the risk of equipment failure/malfunction particularly relative to blending with oxygen, when administered via face versus nasal mask.	We corrected the statement regarding FDA status of nitrous oxide. The Contextual Question posed the question about contraindications to the analgesics in this review. We focused the writing on the types of patients excluded from the studies that were included in this review as well as labeled contraindications to each product. The comment regarding oxygen blending does not apply to contraindications or study inclusion/exclusions and thus no changes were made.
Peer reviewer #4	Discussion	Page 71 Line 34-36: Same issue as above under Page 26. If only acute pain studies were considered, how can you make a comparison to treatment of chronic pain?	Studies of chronic pain were not included in this review. The subgroup refers to patients who have a history of chronic pain as a comorbidity and experience superimposed acute pain.
TEP reviewer #1	Discussion	The subheadings throughout the Discussion make it easier for the reader to follow the main points that are presented. The implications of the findings are clearly stated. The suggested areas for future research are well-defined, and the conclusions summarize the main findings succinctly.	Thank you.
TEP reviewer #1	Discussion	-Page 71, Line 17: It is appropriate that the authors acknowledge the major limitation of the indirectness of the evidence to the prehospital setting. Despite that, the results still seem applicable, since most of the evidence is from the emergency department setting.	No comment.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #1	Discussion	-Page 71: The authors should also include the following limitations: the lack of evaluation of non-pharmacologic methods to address pain and the lack of PO routes compared for medications	We added comments about lack of oral route studies in the future research needs section of the discussion. We felt this was the most appropriate spot given the existing discussion of the need for future research on routes other than IV. We appreciate this reviewer's opinion that because the scope of the review was specific to pharmacologic analgesics, this was perceived as a limitation. We have added a statement in the applicability section of the discussion, intervention and comparator subheading, regarding this.
TEP reviewer #2	Discussion	The findings are well-summarized and clearly stated. Limitations are well stated. Lots of opportunity for future study in this specifically in the prehospital setting. This is well-stated in the document.	Thank you.
TEP reviewer #3	Discussion	I would include more of the limitations in the final conclusions. The authors avoided explicit recommendations but don't explain why in the final conclusions.	We did not add further limitations to the conclusion statement so as not to crowd the information presented. We encourage readers to at least consult the evidence summary (or main report, discussion chapter, limitations subsection) where major limitations are addressed more thoroughly.
TEP reviewer #6	Discussion	Yes well done overall - only one comment; add need for studies beyond pain assessments of relative dosing and efficacy in special populations, pediatrics, geriatrics, patients in shock...	We have revised our statement about the need for future research in subgroups of interest to be more specific, as recommended.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #7	Discussion	We recommend you describe if opioids or ketamine have more severe adverse events.	The specific adverse events that were selected for this report, and were graded (implying a higher priority and importance to the stakeholders and research team) included hypotension, respiratory depression and mental status changes. Conclusions, when possible, are separately made for these outcomes. The protocol for this review does not include the outcome "severe adverse events", similar to total adverse events but those reported to be severe by the individual trials.
Public Reviewer #1, Creighton Tubb, AAOS	Discussion	The discussion section highlights the limitations of the review given available literature but is impactful in clearly stating the lack of current available evidence to suggest that there is any clear analgesic benefit of opioid medications over IV Tylenol, NSAIDs, or Ketamine. Additionally, the discussion presents the potential adverse events associated with opioids and ketamine. Though mentioned, there would be value on clearly defining what resources would be required to ensure proper training and safe use of Ketamine in civilian EMS units.	In the Key Areas for Future Research section of the discussion, we state that there currently is no evidence regarding how the level of EMS personnel training may impact outcomes. Following, we cite recent guidance on suggested provider qualifications and monitoring, when administering ketamine for acute pain.
Public Reviewer #2, Mark Gestring	Discussion	Well written. Would be interested in cost differences (generic) between medications tested.	Thank you. Economic outcomes were outside of the scope of this report.
Peer reviewer #1	Conclusion	Conclusions supporting the sub-dissociative use of ketamine for analgesia both alone and in combination with opioids is a potentially relevant set of findings for prehospital protocols	No comment
TEP reviewer #5	Conclusion	Conclusions are concise and usable. Conclusions are not overstated.	Thank you.

TEP reviewer #7	Conclusion	These conclusions are not based on comparable patient populations nor settings. Patients presenting to an ED include those who arrived on their own and by ambulance. Many of the opioid studies were pre hospital battlefield injuries. A patient with a broken ankle can rate their pain as 8/10 but that is not qualitatively the same as someone with major injuries – crushed pelvis, extensive burns, etc. For some of the studies, there is selection bias regarding patients considered appropriate to receive acetaminophen and those considered appropriate to get an opioid. So patients getting enrolled in an acetaminophen vs. opioids have to be suitable for acetaminophen. Patients with pain that is not suitable for acetaminophen because of more extensive injuries and more severe pain would not be appropriate to study. With this in mind, it appears that the APAP vs opioid studies conducted were in post traumatic headache, fractures, acute limb trauma, renal colic and sciatic nerve pain. These are not the same as patients that would be transported via ambulance after a major trauma.	During protocol development, we sought input from the Technical Expert Panel, the sponsor, and AHRQ regarding the use of indirect evidence (studies from the ED and battlefield). There was agreement across these stakeholders that in the absence of sufficient EMS data, ED data could provide indirect evidence of comparative effects. Considering all input, we agreed to include ED studies into the review and when EMS data did not exist or were insufficient, we based conclusions on ED data. The conclusions based on ED data were downgraded for indirectness when we graded SOE, to account for the differences in the ED and EMS settings. As stated in the methods chapter, meta-analysis was never done across settings (i.e. combining EMS and ED data into one effect estimate), only within each distinct setting (i.e. only EMS, only ED). For inclusion into this review, it was decided to require subjects to have moderate to severe pain, regardless of the analgesics studied. Baseline pain scores (mean or median) ranged from 7.4 to 9.14 on a 0 to 10 scale for the included studies comparing opioids to APAP, and for almost all of the analgesic comparisons. Source or cause of pain was not used for inclusion/exclusion rather for subgroup analyses. For the subgroup of traumatic pain, for the comparison of opioid versus APAP, change in pain scores at 15, 30 and 60 min were similar to the main conclusion suggesting no evidence of a clinically important difference between opioid and APAP. The most common patient population to be included in studies identifying as “traumatic pain”, regardless of the analgesics studied, was limb fracture. This was not specific to opioid vs. APAP studies, it applies broadly to all analgesic

Commentator & Affiliation	Section	Comment	Response
			comparisons in this report. We have added this point to the discussion of applicability in the discussion chapter. We have added a statement that patients with multiple major traumas, crushed pelvis or major burns are not represented in this evidence base.
TEP reviewer #7	Conclusion	The biggest problem from drawing these analyses based on cross study comparisons of different populations and types of studies is that there is a high level of uncertainty about the validity of the conclusions, and this will not be taken into account when the report is used to support policy or other actions. The result could be substantially under treated pain. You point out that the quality of the data are not good. Rather than making conclusions based on inadequate data, with potential unintended consequences, perhaps it is preferable to conclude that the data cannot support a particular recommendation or outcome.	We believe the conclusions made in the report are consistent with what the evidence shows and derived from applying the process outlined in the approved protocol, developed by our EPC with input from AHRQ, NHTSA, the Technical Expert Panel and our content experts from the research team. We point out the indirectness of data in the key messages, abstract results and conclusion, evidence summary results and conclusion and the main report so that the reader knows this limitation of the evidence. Each conclusion is accompanied with a SOE grade to further qualify our certainty of the conclusion. The report does not make clinical recommendations.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #1	General	I appreciated the effort to study out of hospital analgesia options. This type of information is great for crafting both patient care and operational standards in EMS, as many of the considerations in hospitals are different. In EMS, accountability for controlled substances has a particular set of challenges, as does deploying EMS personnel across state lines. More evidence for non-narcotic analgesics has operational benefits, particularly when there is not a negative tradeoff clinically. Thank you for your efforts. The limitations of pain assessment across all populations of patients in the prehospital setting is a valid and important observation of the report. More work needs to occur in this area. It was unclear that ketamine was the focus of the inquiry in the beginning of the manuscript, but was part of the conclusions. Was this intentional?	Thank you. Opioid vs. each non- opioid analgesic (APAP, NSAIDs, ketamine, nitrous oxide) were the focus of this report as these were graded comparisons. Results that had a graded conclusion, regardless of which specific opioid vs. nonopioid) were the focus of the abstract, evidence summary and conclusion.
Peer reviewer #2	General	Yes, it is clinically meaningful. Unfortunately, as the report mentions, it raises more questions than it answers.	No comment.
Peer reviewer #2	General	There is inconsistency in the document on a major abbreviation/spacing format: e.g., KQ1 vs. KQ 1.	We have reviewed the report for consistency within the report and with AHRQ publishing guidelines.
Peer reviewer #3	General	Not particularly clinically meaningful. The report is very thorough, almost to the point of distraction. The only relevant clinical point is that adding ketamine to opioids may provide superior pain control. It does a very comprehensive job of detailing the insufficiency of analgesic data.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	General	The evidentiary summary is helpful at the beginning as is the table of contents. First, thanks to the agencies for supporting this and to the authors and technical experts for putting together this mountain of data. What a potentially frustrating exercise to review thousands of pages to conclude, we need to do better research. Thanks for doing the work. Personally, the pdf version had mixed fonts that made it difficult to track the information flow between KQs given the volume and similarity of data presented. The large volume of data in the results section prior to actually getting to the KQ also was distracting. Not sure you can get around it, except to consider moving the characteristics of the studies to the Methods section (though not sure if this makes sense topically) The point of this paper was to say there is a ton of data, it is very dirty and inconclusive and we need more research. I think it becomes an effective reference for policy decisions to fund future research. It does not change any clinical practice.	We apologize if the pdf file had discrepancies in font and editorial style. These will be resolved through the process of finalizing the report and will be consistent with the AHRQ style guide.
Peer reviewer #4	General	In the methods, it is stated that the project aims were to compare opioid v. non-opioid. From the manuscript, it appears that the review started off more broadly and entertained non-opioid to non-opioid and opioid to opioid comparisons to determine best practice. Which was it? If it as stated, opioid to non-opioid as the focus, the sections discussing the latter are distracting and make the report very cumbersome to read. Perhaps consider that as a second technical report or as a supplement, and focus this one strictly on the aims introduced at the beginning of the methods.	The analgesics of interest overall included both opioids and nonopioids and comparisons across these groups or within these groups. However, the priority was opioid vs. nonopioid comparisons. This creates the focus of the report, particularly the key messages, abstract and evidence summary. Opioid vs. opioid and nonopioid vs. nonopioid were still of interest to the stakeholders, but of lower priority to opioid vs. nonopioid comparisons. Thus we limit presentation of findings to the report results chapter and briefly discuss these findings in the discussion. These comparisons do not appear in the key messages, the abstract or evidence summary, since they are not the focus of the report.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	General	One concern I have is using opioids as the gold standard. If non-inferiority/equipoise is already established, then contemporary RCTs may not compare to opioids. Example: Prehospital Analgesia with Intranasal Ketamine (PAIN-K): A Randomized Double-Blind Trial in Adults. Andolfatto, Gary et al. Annals of Emergency Medicine.	This review was focused on direct analgesic comparisons and comparative effectiveness and harms. Per the protocol, nonopioid comparisons were of interest and were included in this review. The specific nonopioid comparisons of interest were decided upon after input from the sponsor, TEP and AHRQ. The provided citation compares ketamine to placebo, added to nitrous oxide. This did not meet inclusion criteria for the comparators of interest.
Peer reviewer #4	General	Does the "any adverse event" category include events other than hypotension, mental status changes and respiratory depression OR hypotension, mental status changes, respiratory depression and other adverse events? There were inconsistencies throughout the document on how these were defined/described.	"Any adverse event" was what the individual studies would report as the number of subjects who experienced an adverse event in the trial, regardless of what that adverse event was. The outcomes are defined (including "any adverse event" in the methods chapter).
Peer reviewer #4	General	In background and discussion sections, it is worth emphasizing that children are particularly understudied and that their pain goes untreated- far less than the 43% cited in the introduction. Browne LR, Studnek JR, Shah MI, Brousseau DC, Guse CE, Lerner EB. Prehospital Opioid Administration in the Emergency Care of Injured Children. Prehosp Emerg Care. 2016;20(1):59-65. doi: 10.3109/10903127.2015.1056897. PubMed PMID: 26727339. Browne LR, Shah MI, Studnek JR, Ostermayer DG, Reynolds S, Guse CE, Brousseau DC, Lerner EB. Multicenter Evaluation of Prehospital Opioid Pain Management in Injured Children. Prehosp Emerg Care. 2016 Nov-Dec;20(6):759-767. doi: 10.1080/10903127.2016.1194931. Epub 2016 Jul 13. PubMed PMID: 27411064.	Thank you for these citations, we have added reference to higher rates of untreated pain in the pediatric population in the introduction.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	General	Page 59 Table 24: Capitalize Indirect in Row 3, Column 4	We corrected this typo.
Peer reviewer #4	General	Page 61 Table 27: Add definition for OBS to footnote	We added this abbreviation.
Peer reviewer #4	General	Page 62 Line 18: Change “less” to “lower” oxygen saturation and “more” to “higher” systolic blood pressure Line 35: Ketamine misspelled	We corrected the wording in this section.
Peer reviewer #4	General	Page 69 Line 8: Change “predisposed” to “predispose” Line 43/44: Change “warning” to “warnings”	We corrected these typos.
TEP reviewer #1	General	The stated objective of this report is very relevant to the population of patients transported by emergency medical services, since many of them are transported for painful conditions. The inclusion of opioids, ketamine, acetaminophen, non-steroid anti-inflammatory drugs, and the attempt to include nitrous oxide is thorough. The inclusion of mainly randomized controlled trials is rigorous. The population of prehospital patients (with inclusion of emergency department and battlefield data due to limited prehospital research) is well-defined. The key questions are well-stated in the table of contents; it may be helpful to add these questions to Figure A (analytic framework).	Consistent with AHRQ format, the analytic framework is a visual representation of the Key Questions and the full Key Questions are not included.
TEP reviewer #1	General	The report is well-organized. There is new information presented that challenges current practice.	Thank you.
TEP reviewer #2	General	The report is very good as a summary of what we currently know and what we don’t know about pain control in the pre-hospital setting. It is as complete as it can be, given the available evidence. The report is clinically meaningful, target population and audience are defined and the key questions are appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #2	General	This is an excellent summary of what is currently understood about pain management in the prehospital setting. The document stresses that more work is needed in the prehospital setting (compared to working backwards from ED setting) Additional factors, such as cost, may also influence future policy or practice decisions.	Thank you.
TEP reviewer #3	General	Well done, clinically meaningful but given the weakness of the evidence not sure a change in practice is appropriate target population understood. Question is clear and well defined. Very well written. Concise. May not change practice due to limitations of evidence.	Thank you.
TEP reviewer #4	General	Given the limited research available for the comparisons the author's did an exceptional job and deriving clinically meaningful conclusions while at the same time highlighting the many limitations.	Thank you.
TEP reviewer #4	General	Identified limitations of existing evidence. Conclusions are relevant. As a whole outcomes are balanced. The author's did not clearly state the limited risks of addiction and diversion for the brief and limited administration of opioids in the prehospital setting.	Although diversion and future risk of substance abuse or misuse for EMS personnel were outcomes of interest, there was no evidence found for these outcomes. We added a statement to future research needs to make it clear there was no evidence found for these outcomes thus they are a potential future research need.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #5	General	This paper is comprehensive and excellent. I have two general comments for consideration. It is difficult to suggest a specific location/page/line number for these because each occurs in various locations: Dosing of ketamine - although the dosing of ketamine points out the quantity dose when discussing studies, it does not point out the rate of administration or other nuances. Many that use subdissociative doses of ketamine for analgesia have suggested that the side effects occur more often if given IV bolus and less often if given as an infusion within 100mL NSS over 10-15 minutes. This review does not consider the effect of different rates or dilutions when giving ketamine. I doubt this would affect the analgesic effectiveness, but it is quite possible that statements related to side effects of ketamine may be affected by these administration differences. On page 21, line 11, it states that typical dosing for ketamine IV is "...over 10-15 minutes...". I think this is consistent with many who have started to give the dose diluted in 100mL of NSS over 10-15 minutes, but some still give it as an IV bolus that may be given faster than this time. Since the references to the section on side effects with ketamine list the dosing amounts, but not the rate, would it be helpful to consider whether the higher side effects were seen in studies where the dose was given by bolus rather than slow bolus or infusion within NSS? This could be important in several areas - e.g. section starting with Page 33, line 29.	We have reviewed the trials evaluating ketamine for information regarding the administration time. Half of the ketamine IV trials do not specify more about the IV dosing or administration. Of those that do, 2 provided a bolus and 3 used a slower administration over 10-15 minutes. However, the majority of trials contributing data to the outcomes of "total adverse events" or "dizziness", where opioids were concluded to cause less events, ketamine was studied IN, not IV. We revised the key messages, abstract, evidence summary, main report results to reflect this detail specific to certain harms outcomes for the comparison of opioids versus ketamine.

Commentator & Affiliation	Section	Comment	Response
TEP reviewer #5	General	Use of these medications in older individuals - this issue occurs in many locations. While there is an effort to discuss the differences in outcomes in groups < 18 years of age getting various analgesics compared with those 18 y/o and greater, there is not similar attention to considering some of these questions (particularly related to side effect rates like depressed respiratory rate or hypotension) in older age groups. In fact, some of the studies seem to exclude older patients. It may be worth mentioning this limitation or considering whether some of these can be sub analyzed in ages > 65 or other older age groups. The importance of this is seen in several sections - e.g. Page 35, lines 3-4 and Page 40, lines 14-18.	We sought to conduct subgroup analysis based on age stratifications, although studies did not present data to evaluate older aged persons, like was done for younger aged persons. Where we present evidence regarding age subgroups, we have added language to make it clear that the age subgroups were <19 and 18y and older, so as not to confuse this with older aged subgroups. We have also added the geriatric population as a subgroup of interest for future research needs. The applicability section in the discussion provided commentary regarding applicability as it related to age.
TEP reviewer #5	General	This is a difficult and comprehensive comparison to describe. I think that the format is clear and usable, despite the length and the significant sections that show no difference.	Thank you.
TEP reviewer #6	General	The target population is defined - although all persons with pain are specified perhaps further clarification that the population includes pediatric and adult patients without age limits.	We added “without restrictions on age” to the inclusion criteria text in the PICOTS, as the accompanying table specified “any age” for inclusion. .
TEP reviewer #6	General	Conclusions are relevant to the questions asked. Overall they validate current practice in pain management even though treatment of pain may be neglected in prehospital environment there are clear directives that it should be treated.	No comment.
Public reviewer #1, Creighton Tubb, AAOS	General	Well presented	Thank you.
Public Reviewer #2, Mark Gestring	General	Seems thorough and inclusive	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	This is a systematic review to assess the effectiveness of a few different pain medications to treat acute pain. The data is derived from studies that report on ER patients predominantly – some confounding factors to consider – the etiology of pain compared to post-surgical patients may be different, the expectations of the patients presenting to the ER vs those who are post-op may be different.	We did not specifically include post-operative patient groups, as that population was not felt to reflect the prehospital population.
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	Most of the RCTs and observational studies included were performed outside the US – there are some biases that need to be considered based on the societal expectations and norms for dealing with pain.	We have added this as a consideration in the Applicability section of the discussion, subheading of Outcomes, Timing and Setting.
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	All drugs were IV administrations – oral medications may not have the same risk profile and may have different time duration for effectiveness (oral arguably longer and lower rates of respiratory depression, which were cited as some of the downsides of opioids)	As mentioned by another reviewer above, little evidence exists in regards to the oral route, and we have added this to the future research needs section of the report.
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	Acetaminophen was only administered IV – costly, many US centers limit the use of it IV and often only allow 2-3 doses.	No comment.
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	Ketamine discussed as an alternative to morphine but orthopedic providers don't have much experience with using it – it's mostly used by ER physicians and anesthesiologists. Also, it would be difficult to administer the drug on the floor where a majority of orthopedic patients are given that administration usually requires airway and cardiac monitoring	No comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3, Kalpit Shah, AAOS - EBVQ Committee	General	We have to be careful in interpreting these results because of the limitations – ER patients, IV only administration, lack of oral medication evaluation, low strength of evidence, use of medications that aren't routinely used on the wards or are cost-prohibitive to be used widely, lack of RCTs from the US. These must be considered before designing recommendations for all populations of patients. Also, these findings only apply for the initial pain control needs – for orthopedics, this would likely be applicable post-operatively on day 0 after the surgery – that should be emphasized	We agree that these limitation apply, which have all been articulated throughout the discussion of the report. We have added the term "acute" to pain in the conclusion statement and also "in the prehospital setting". We did not evaluate this evidence in the contect of any other settings, including the post-operative orthopedic patient.

Public Reviewer #4, Julie Samora, Nationwide Children Hospital	General	The AHRQ has performed a robust systematic review of 48 RCT and 12 observational studies to assess the comparative effectiveness and harms of opioid vs non-opioid analgesics administered in emergency department settings. They found that there are no clinically important differences in pain scores with opioids vs. ketamine, IV acetaminophen, or IV NSAIDs. Opioids were found to have fewer side effects than ketamine, but more than IV Tylenol and IV NSAIDs. The AHRQ is to be commended for their work on this timely and important issue. There are a couple items to consider when evaluating this research. One of the difficulties in assessing pain is that there is a wide range of pain thresholds and tolerances. Although VAS is a standard assessment of pain, no two patients will experience the same pain in similar scenarios. Certainly there are cultural differences in pain tolerances as well, and there were several international studies included in this review. Furthermore, patients presenting to an emergency department may not reflect those patients requiring opioids secondary to surgery or an invasive procedure, so care should be taken in extrapolating these data to other scenarios/settings. In addition, in this report, only IV medications were evaluated, many of which are unavailable in other healthcare settings (e.g. ketamine is not routinely used on a non-critical care inpatient unit, or in an outpatient setting; IV acetaminophen is quite costly, etc). Perhaps oral opioid analgesics vs oral acetaminophen or oral NSAIDs may have a different comparative effectiveness and harm profile, and we must be careful not to extrapolate these data to the oral medicines, which will have a distinctive bioavailability and effectiveness profile. Generally, the strength of evidence was low, but this is a great starting point for future research in this area. The conclusion states that opioids are no	Thank you.

Commentator & Affiliation	Section	Comment	Response
		different in reducing pain than ketamine, APAP and NSAIDS when administered in IV form. The authors openly acknowledge the low strength of evidence. Clearly, more research is needed. This report does provide a nice foundation from which to evaluate various pain regimens.	
Public Reviewer #5, Kirstem Aquino, AANS/CNS Joint Sections on Pain and Disorders of the Spine and Peripheral Nerves	General	The AANS/CNS Joint Sections on Pain and Disorders of the Spine and Peripheral Nerves have reviewed the draft report for the systematic review on Comparative Effectiveness of Analgesics to Reduce Acute Pain in the Prehospital Setting provided by The Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ), and they affirm the educational benefit of this document.	Thank you.