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Evidence-Based Guidelines for Prehospital Pain Management: Recommendations

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ABSTRACT

This project sought to develop evidence-based guidelines for the administration of analgesics for moderate to severe pain by Emergency Medical Services (EMS) clinicians based on a separate, previously published, systematic review of the comparative effectiveness of analgesics in the prehospital setting prepared by the University of Connecticut Evidence-Based Practice Center for the Agency for Healthcare Research and Quality (AHRQ). A technical expert panel (TEP) was assembled consisting of subject matter experts in prehospital and emergency care, and the development of evidence-based guidelines and patient care guidelines. A series of nine “patient/population-intervention-comparison-outcome” (PICO) questions were developed based on the Key Questions identified in the AHRQ systematic review, and an additional PICO question was developed to specifically address analgesia in pediatric patients. The panel made a strong recommendation for the use of intranasal fentanyl over intravenous (IV) opioids for pediatric patients without intravenous access given the supporting evidence, its effectiveness, ease of administration, and acceptance by patients and providers. The panel made a conditional recommendation for the use of IV non-steroidal anti-inflammatory drugs (NSAIDs) over IV acetaminophen (APAP). The panel made conditional recommendations for the use of either IV ketamine or IV opioids; for either IV NSAIDs or IV opioids; for either IV fentanyl or IV morphine; and for either IV ketamine or IV NSAIDs. A conditional recommendation was made for IV APAP over IV opioids. The panel made a conditional recommendation against the use of weight-based IV ketamine in combination with weight-based IV opioids versus weight-based IV opioids alone. The panel considered the use of oral analgesics and a conditional recommendation was made for either oral APAP or oral NSAIDs when the oral route of administration was preferred. Given the lack of a supporting evidence base, the panel was unable to make recommendations for the use of nitrous oxide versus IV opioids, or for IV ketamine in combination with IV opioids versus IV ketamine alone. Taken together, the recommendations emphasize that EMS medical directors and EMS clinicians have a variety of effective options for the management of moderate to severe pain in addition to opioids when designing patient care guidelines and caring for patients suffering from acute pain.

ARTICLE HISTORY

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Background

The management of acute pain is an integral component of prehospital patient care. A significant proportion of patients transported by EMS agencies experience acute moderate to severe pain as part of their complaints. A review of 14.5 million patients presenting to the ED by ambulance in 1999

found that 14% reported mild pain while 20% reported moderate to severe pain (1). Another review found that 42% of prehospital patients reported acute pain, with 64% reporting their pain as intense to severe (2). Recognizing that pain management is a core component of prehospital care, achieving the goals of adequate pain assessment and subsequent administration of appropriate analgesics has been

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Table 1. Members of the technical expert panel.

Name	Primary Affiliation	Expertise
George Lindbeck Principal Investigator National Association of State EMS Officials	University of Virginia School of Medicine, Virginia State EMS & Trauma Systems Medical Director	Emergency Medicine, EMS Medical Direction
Sabina Braithwaite Co – PI American College of Emergency Physicians	Washington University School of Medicine, State of Missouri EMS Medical Director	Emergency Medicine, EMS Medical Direction
Manish I. Shah Co- PI National Association of EMS Physicians	Baylor College of Medicine	Pediatric Emergency Medicine, EMS Research
Lorin Browne	Medical College of Wisconsin, Milwaukee County EMS	Pediatric Emergency Medicine, EMS Medical Direction
Brooke Burton	Falck Ambulance Northern California	EMS Performance Improvement and System/Data Interoperability
Jeffrey Coughenour	University of Missouri Healthcare, Frank Mitchell, Jr, MD, Trauma Center	Trauma/Acute Care Surgeon
Remle Crowe	ESO	EMS Research
James J. Gasper	California Department of Health Care Services	Substance Use Disorder Pharmacology
Eddy S. Lang	Cumming School of Medicine - University of Calgary and Alberta Health Services	Evidence-Based Medicine (GRADE Methodology), Emergency Medicine
Connie J. Mattera	Northwest Community Hospital and EMS System	EMS/Trauma Education
Sandra Nasca	EMS for Children Family Advocacy Network	Patient Advocate, Clinical Forensics, Emergency Medicine
Ashish R Panchal	National Registry of EMTs, The Ohio State University Wexner Medical Center	EMS Research, Emergency Medicine, EMS Medical Direction
Peter Taillac	State of Utah EMS Medical Director University of Utah School of Medicine	Emergency Medicine, EMS Medical Direction
Mark Warth Jonathan Powell Kyle D. Guild	Colorado Springs Fire Department National Registry of EMTs Cumming School of Medicine - University of Calgary	EMS Education and Quality Assurance EMS Research Fellow Medical Student
Mary Hedges Hannah Degn Dia Gainor	National Association of State EMS Officials National Association of State EMS Officials National Association of State EMS Officials	Project Manager Project Coordinator Executive Director

recognized as a priority for improvement in prehospital care (3). A review of over 41,000 patients transported by ambulance in Denmark found that almost 28% reported severe pain, but only 8% received parenteral opioids for their pain (4). Evidence-based guidelines for pain management in trauma have been developed, stressing the need for routine assessment of pain in diverse patient populations including those with impaired ability to communicate (5). The barriers to more effective pain control in prehospital care are not entirely clear, but traditional reliance on parenteral opioids as the primary, or only, medication available may be a contributory factor.

There have been concerns raised about bias and disparity in the management of acute pain in emergency care settings. A review of over 276,000 EMS records in the National Emergency Services Information System (NEMSIS) found that although pain was listed as a primary or associated symptom for 29.5% of patients, only 15.6% of records documented administration of pain medications, and Black patients were less likely to receive pain medications than other groups (6). A meta-analysis of ED pain management literature found that Black and Hispanic patients were less likely to receive analgesia for acute pain (7). Disparities have been identified both in the likelihood that a patient receives

an analgesic and in the analgesic administered. A review of 115 patients in a community ED found that although there were no differences in pain scores between White and non-white patients, White patients were significantly more likely to receive opioids for their long-bone fractures, and pediatric patients were less likely to receive opioids for their acute pain (8). In a group of patients suffering acute pain after a motor vehicle collision, White patients were more likely to receive an opioid analgesic in the ED or at discharge, and less likely to receive a non-steroidal medication in the ED (9). In another review of acute pain management in the ED, researchers found that, although male and female patients had similar pain scores, women were significantly less likely to receive opioid analgesics (10). It is the panel's hope that the wider inclusion of multiple non-opioid analgesics in prehospital patient care guidelines coupled with increased education of prehospital clinicians in pain management and potential biases in the management of pain will contribute to mitigating some of these disparities.

Historically prehospital pain management was based on the use of opioids, primarily morphine, for acute pain management. A review of over 270,000 records in NEMSIS showed that morphine and fentanyl were the most commonly administered analgesics in all groups (6). As the

Table 2. PICO questions for the EBG for prehospital pain management.

1. Should intranasal fentanyl vs. IV opioids be used for acute onset of moderate to severe pain in children in the prehospital setting?
2. Should IV acetaminophen (APAP) vs. IV opioids be used for treatment of moderate to severe pain in the prehospital setting?
3. Should IV non-steroidal anti-inflammatory drugs (NSAIDs) vs. IV opioids be used for treatment of moderate to severe pain in the prehospital setting?
4. Should IV APAP vs. IV NSAIDs be used for treatment of moderate to severe pain in the prehospital setting?
5. Should IV ketamine vs. IV NSAIDs be used for treatment of moderate to severe pain in the prehospital setting?
6. Should IV ketamine vs. IV opioids be used for treatment of moderate to severe pain in the prehospital setting?
7. Should IV morphine vs. IV fentanyl be used for treatment of moderate to severe pain in the prehospital setting?
8. Should a combination of weight based IV opioid plus IV ketamine vs. weight based IV opioid alone be used for treatment of moderate to severe pain in the prehospital setting?
9. Should a combination of IV opioid plus IV ketamine vs. IV ketamine alone be used for treatment of moderate to severe pain in the prehospital setting?
10. Should nitrous oxide vs. IV opioids be used for treatment of moderate to severe pain in the prehospital setting?

opioid crisis has worsened, the routine use of opioids for acute pain management has become increasingly concerning for EMS clinicians, EMS medical directors, and system managers. In addition to concerns regarding the risks of exposing opioid-naïve individuals to opioids or of enabling or reinforcing “drug seeking” behaviors in individuals activating the EMS system, the diversion of opioids by EMS clinicians has prompted increased interest in incorporating non-opioid analgesics in prehospital patient care (11). Increasing attention has been given to non-opioid analgesics and non-pharmacologic pain management strategies in emergency medicine, identifying a need for continued research (12). Although there has been a general move toward more cautious use of opioid analgesics in prehospital and emergency care, the contribution that the prehospital administration of opioids might make to the current opioid crisis is unclear (13). Higher rates of opioid prescription in the ED have been associated with an increased risk of long-term opioid use (14).

The assessment and management of acute pain in the pediatric population has been identified as particularly challenging. A recent review of the National EMS Information System (NEMSIS) found that documentation of pain symptoms and treatment of acute pain were infrequent in general in the prehospital setting, but particularly so in young children (6). A retrospective study of children transported by ambulance in Ireland found that while 41% had pain documented as a symptom, only 32% of those children had a pain assessment documented and only 26% received some form of analgesia (15). Even after publication of pediatric assessment and pain management guidelines, a retrospective study suggested no significant change in pain assessments nor the administration of opioid analgesics, suggesting additional challenges to improving pediatric prehospital pain management still existed (16). Illustrating the complexities of process and outcome measures in the pain management of pediatric patients with long bone fractures in the ED, minority children were found to be more likely to receive any analgesics and more likely to achieve 2 point or greater reduction in pain compared with non-Hispanic White children, but were less likely to receive an opioid or to ultimately achieve optimal pain reduction (17). Challenges to achieving optimum pediatric pain management include concerns about the placement of intravenous catheters,

challenges in the assessment of pediatric patients, and the concerns of parents and care-givers (18).

Project Objectives

The objectives for this project were to develop a set of EBGs for prehospital pain management building on the completed work of a previous, separately funded, systematic review recently published by the University of Connecticut Evidence-Based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) with funding support provided by the National Highway Traffic Safety Administration (NHTSA): Comparative Effectiveness of Analgesics to Reduce Acute Pain in the Prehospital Setting (19).

Methods

A technical expert panel (TEP) was assembled comprised of individuals with broad expertise in emergency medicine, prehospital care, and pharmacology (Table 1). The overall goal of the TEP was to apply established evidence evaluation methodology in addition to rigorous recommendation development techniques to generate transparent recommendations for the management of pain in the prehospital setting. The TEP identified nine PICO (population/intervention/comparison/outcome) questions arising from the Key Questions included in the AHRQ systematic review, and developed an additional question related to the intranasal (IN) administration of fentanyl for pediatric analgesia (Table 2). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was used to guide development of the questions, assessment of the certainty of the evidence, and the formulation of the recommendations of the TEP. The detailed methodology, Summary of Findings tables, and the evidence-to-decision tables, are presented in a companion paper (20).

Recommendations

Recommendation 1

We recommend in favor of intranasal (IN) fentanyl over intramuscular (IM) or intravenous (IV) opioids in the

treatment of moderate to severe pain in pediatric patients prior to IV access or without (or without indication for) IV access (strong recommendation, low certainty of evidence). The panel makes a conditional recommendation for either IN fentanyl or IV opioids once IV access is established (conditional recommendation, low certainty of evidence).

The provision of adequate analgesia for pediatric patients has been recognized as particularly challenging in both the prehospital setting and in the emergency department (ED). The TEP therefore felt that this clinical issue was important enough to add this question and its evidence review to the set of PICO questions based on the AHRQ systematic review that served as the foundation for this project (19). The panel makes a strong recommendation for the use of IN fentanyl over IM opioids for the treatment of moderate to severe pain in children in the prehospital environment when pain management is indicated prior to, or in the absence of, IV access. Although the certainty of evidence was low, the potential positive impact of a rapid, easily administered, noninvasive route of analgesic administration on improving analgesia in pediatric patients prompted a strong recommendation by the TEP. Furthermore, the panel makes a conditional recommendation for either IN fentanyl or IV opioids once intravenous access is established. In some cases, IN fentanyl may be administered prior to obtaining IV access, while in other cases IN fentanyl may provide adequate analgesia alone, obviating the need for IV access. The evidence did not suggest a difference in pain severity scores at 5, 10, 15, 20, 25 and 30 minutes after IN administration versus IM or IV opioids, and no clinically significant differences in undesirable effects were noted between the two management options. The review did not find any significant difference in the therapeutic effects or adverse effects of fentanyl administered by the IN route when compared to the IV or IM route. This medication, combined with a noninvasive route of administration, provides an opportunity to greatly improve pediatric analgesia in the prehospital setting. If IV access is obtained subsequently, then either route may be used for administration of fentanyl if required.

Recommendation 2

We suggest in favor of IV acetaminophen (APAP) over IV opioids alone for the initial management of moderate to severe pain in the prehospital setting if IV APAP is available, affordable, and easy to administer. (conditional recommendation, low certainty of evidence)

The conditional recommendation for IV APAP versus IV opioids was based on equivalent pain control and improved tolerability. The panel noted that there may be significant cost and availability issues related to IV APAP which could make it more challenging to implement in some EMS systems. Acetaminophen represents a very promising analgesic that demonstrated similar analgesic efficacy to opioids in this review. The evidence did not suggest a clinically important difference in pain reduction at 15, 30, or 60 minutes or in the time to analgesic effect. Although the overall certainty

of evidence for any adverse effect was very low, the evidence did suggest that dizziness was more common in the IV opioid group with a moderate certainty of evidence. Additionally, in several studies nausea and/or vomiting was reported as an adverse event and was generally more common with IV opioids than IV APAP. The availability of an analgesic with less propensity to cause nausea would be attractive to patients, and possibly to clinicians who may encounter the need administer an antiemetic concurrently. The panel recognized that nausea and vomiting are common in EMS practice, the etiology of which is multifactorial and may include pain, anxiety, medication side effects, and motion sickness from ambulance transport. A study looking at healthy volunteers transported in an ambulance found that 43% developed nausea from ambulance transport alone (21). The panel noted that the available studies on the use of IV APAP were virtually all in the ED and in health care systems outside of the United States. Intravenous APAP is generally administered by a brief infusion which may be perceived as less desirable by prehospital clinicians than an IV push medication, which is the more common method of administration in the prehospital setting. At present, there is a significant cost difference for IV APAP over other parenteral pain medications in this review, including opioids, ketamine, and NSAIDs, which may represent a barrier to introduction in some EMS systems. Introduction of generic IV APAP in the future may help address the cost differential.

Recommendation 3

We suggest either IV NSAIDs or IV opioids for the initial management of moderate to severe pain in the prehospital setting. (conditional recommendation, moderate certainty of evidence)

There was insufficient evidence to make any conclusions regarding pain severity at 15 minutes, partial, or full relief of pain, or time to analgesic effect. The evidence did not demonstrate any clinically significant difference in pain severity at 30 or 60 minutes. The panel expressed concern that there was evidence of significant sub-therapeutic dosing of the NSAID, ketorolac, in the limited data available. There was a small difference in cost with the intervention (NSAIDs, specifically ketorolac) being more costly than opioids, but this was not examined in the evidence base. Although IV ketorolac may be more costly than morphine, at least one study suggested that pain management of limb injuries in the ED was more cost effective overall with ketorolac than morphine, and that adverse events were more common with morphine, including drowsiness/sleeping and nausea/vomiting (22). Intravenous NSAIDs, including ketorolac, may be attractive as a first line analgesic, particularly in patients who are intolerant or allergic to opioids, or for patients who, when given a choice, would prefer an analgesic with a lower risk of side effects or for those wishing to avoid opioid analgesics in any case. Speaking to feasibility and acceptance concerns, the panel noted that ketorolac is already in use in many EMS systems.

Recommendation 4

We suggest in favor of IV NSAIDs over IV APAP for the initial management of moderate to severe pain in the prehospital setting. Additionally, we recommend in favor of either PO NSAIDs or PO APAP for the initial management of pain in the prehospital setting if an oral analgesic is considered. (conditional recommendation, low certainty of evidence)

The panel makes two recommendations regarding the comparison of APAP and NSAIDs based on route of administration. The first is a conditional recommendation for the comparison, IV NSAIDs, against the intervention, IV APAP, for the initial treatment of moderate to severe pain in the prehospital setting. The second is a conditional recommendation for either PO NSAIDs or PO APAP. In the case of IV administration, one study found higher pain severity scores at 15 minutes with IV APAP compared to IV NSAIDs, but the remaining evidence did not demonstrate a significant difference at 30 or 60 minutes, or in partial or complete relief of pain. There were few significant differences in adverse events between APAP and NSAIDs: oral NSAIDs were found to have more gastrointestinal adverse events. All of the evidence reviewed was based on observations in the ED which contributed to very low certainty. Given the significant cost and availability difference between IV APAP and IV NSAIDs, cost effectiveness and feasibility favored IV NSAIDs. Although EMS patient care guidelines usually refer to parenteral medications, the panel felt that the consideration of oral, non-opioid, analgesic medications was appropriate. This was the only question in which an oral analgesic option was explored in addition to parenteral analgesics, and separate recommendations were made based on the route of administration. The panel noted that an oral medication may be considered rather than an IV medication based on severity of pain, resource availability, or patient preferences, particularly avoiding placement of an IV catheter. It was acknowledged that prehospital clinicians are accustomed to thinking of analgesics being administered parenterally, expecting a more rapid onset of action in acute situations and ease of administration in the ambulance. There may also be an assumption by EMS clinicians that patients with acute pain will receive analgesics promptly on arrival in the ED, possibly affecting the decision of whether or not to administer a medication that would require IV access during shorter transports. However, in reality, delays in the administration of analgesics after the patient's arrival in the ED may be significant. In a Canadian ED the mean time-to-analgesia was 129 minutes, and after a set of interventions was implemented the mean time only decreased to 100 minutes, illustrating the possibility of significant delays in analgesia after arrival in the ED (23). Another effort to improve the timeliness of analgesia in the ED found a baseline median time to analgesia of 64 minutes that paradoxically, and disappointingly, increased to 80 minutes after policy changes designed to reduce time to initial analgesia (24). The panel noted that given possible delays in administration of analgesics in the ED, any prehospital analgesia, including PO administration of analgesics, may markedly improve patient access to analgesia, and that measures to

manage pain initiated prior to arrival in the ED may extend well into the patient's ED stay.

Recommendation 5

We suggest either IV ketamine or IV NSAIDs for the initial management of moderate to severe pain in the prehospital setting (conditional recommendation, moderate certainty of evidence)

The panel discussion led to a conditional recommendation for either agent for the initial management of moderate to severe pain in the prehospital setting. A single study found a significant reduction in pain scores 30 minutes after ketorolac administration compared to ketamine, but there were no significant differences at 15 or 60 minutes, time to analgesic effect, pain relief, or memory of pain. The incidence of any adverse event was higher with ketamine, including dizziness, elevated blood pressure and heart rate, but the difference was not believed to be clinically significant.

Recommendation 6

We suggest either IV ketamine or IV opioids for the initial management of moderate to severe pain in the prehospital setting (conditional recommendation, very low certainty of evidence)

There was no difference in desirable effects and a small difference in undesirable effects with ketamine when compared to opioids. Specifically, there were no clinically significant differences in pain control at 15, 30, or 60 minutes after administration, in partial or complete pain relief, or time to analgesic effect between the two medications. It was noted that ketamine may cause more side effects than opioids, primarily dizziness, but this was based on small numbers of patients and was noted to be difficult for many patients to quantify. The use of ketamine, even at lower, "sub-dissociative", doses as an analgesic, has been associated with dysphoric reactions in some patients, but these phenomena were not assessed in this evidence base. A systematic review of ketamine found that it provided somewhat inconsistent, but potentially rapid, onset of pain relief, although there was a fairly wide range of dosing strategies, and a moderate number of patients experienced mild-to-moderate side effects such as dizziness, dysphoria, and confusion (25). A series of 500 patients treated with low dose ketamine (0.1-0.3 mg/kg) in the ED for acute pain found that 3.5% suffered a psychomimetic or dysphoric reaction (26). In comparison, opioid administration was suggested to increase respiratory depression, but this was not clinically significant. Additionally, during panel discussion it was noted that the inclusion of either medication in patient care guidelines would likely be acceptable to all key stakeholders. Therefore, the panel made a conditional recommendation for either IV ketamine or IV opioids for the management of acute pain in a prehospital setting. One important consideration is that opioids have been included in prehospital care guidelines for decades, resulting in high existing clinician acceptance,

although ketamine is increasingly included in clinician training and accepted by EMS clinicians (27,28). Although there could be costs involved in introducing ketamine into an EMS agency's patient care guidelines resulting from initial training, and the purchase and stocking of medications, those expenses would be similar to the costs of introducing other new medications. The expense of purchasing and of administering ketamine compared to that of opioids is not addressed in the evidence base, but seems comparable. Ketamine may be an attractive alternative for patients who are allergic to, intolerant of, or have otherwise experienced adverse events with opioids, or who wish to avoid opioid analgesics altogether. Having a non-opioid analgesic alternative may increase health equity, but this question was not addressed in the evidence base.

Recommendation 7

If opioids are selected for pain management, we suggest either IV morphine or IV fentanyl for the treatment of moderate to severe pain in the prehospital setting (conditional recommendation, low certainty of evidence)

The evidence from randomized, controlled trials did not suggest a significant difference in improvement of pain severity scores, resolution of pain, or time to analgesic effect between the two opioid medications. Although there were conflicting results from trials in the prehospital setting versus the ED, morphine was associated with an increase in nausea and/or vomiting when compared with fentanyl. However, there was insufficient certainty in the evidence to warrant favoring one opioid over another. Although there did seem to be a small increase in undesirable effects with morphine, particularly nausea and/or vomiting, the significance of the adverse effects did not clearly differentiate between the two agents. Use of morphine may be associated with increased need for administration of a second medication for control of nausea, but that was not examined in the evidence base. Morphine has a long history of use for prehospital analgesia and EMS clinicians tend to be comfortable with it, but the use of fentanyl is growing steadily. Again, EMS clinicians may tailor their selection of analgesic based on the clinical situation. Multiple routes of administration for fentanyl may increase opportunities for analgesia in some patients, particularly pediatric patients.

Recommendation 8

We suggest against the combination of weight-based IV opioid plus weight-based IV ketamine versus weight-based IV opioid alone for the initial management of moderate to severe pain in the prehospital setting. (conditional recommendation, very low certainty of evidence)

The panel's conditional recommendation against combination therapy was based on very low certainty of evidence, lack of a clinically demonstrable improvement in pain control, slight increase in undesirable side effects, and the desire to avoid increased complexity in administration. The panel found no clinically significant differences in pain control at

15, 30, or 60 minutes after administration, in partial or complete pain relief, or time to analgesic effect between the two medications. Dizziness was noted to be more common in the combination therapy group, otherwise there was insufficient evidence related to other reported adverse events including hypotension or sedation. There was no increase in respiratory depression in the combination therapy group versus the opioid monotherapy group. It is possible that the use of multiple analgesics may allow for lower, and possibly safer, dosages of the analgesics (29). The cost of the two medications are similar, as are the costs of administration, but this was not addressed specifically in the studies reviewed. The panel was concerned that the complexity and risk of preparing and administering two medications with different dosing regimens might represent a barrier to EMS clinicians who would prefer using a single medication, particularly when monotherapy offered similar benefits. Weight based dosing regimens have been recognized as challenging for prehospital providers, particularly when dealing with pediatric patients, and multiple medications and dose calculations could represent another barrier to a two medication strategy.

Recommendation 9

No recommendation was made at this time on the comparison between the combination of an IV opioid plus IV ketamine, versus IV ketamine alone for the initial management of moderate to severe pain in the prehospital setting due to significant uncertainty of the evidence and incomplete information concerning the comparison.

Although the benefits of multi-modal analgesia have been discussed, the panel found that the evidence was insufficient to make a recommendation regarding this question. The panel did not make a recommendation for this question based on an inadequate, rather than equivocal, evidence base.

Recommendation 10

No recommendation was made regarding the comparison between nitrous oxide versus IV opioids for the initial management of moderate to severe pain in the prehospital setting.

The panel finds that there is insufficient evidence to make a recommendation regarding this question. Nitrous oxide has been used in the prehospital setting for decades so there is experiential evidence supporting feasibility. A retrospective study and review described its use in prehospital care, and suggested that it might be safe enough for use by non-certified or lay responders (30). The equipment required for administration is somewhat complex and does involve significant acquisition cost relative to opioid administration, which could present a barrier to its introduction for some EMS agencies. Administration of nitrous oxide is limited to patients who can understand instructions and cooperate with self-administration. Nitrous oxide is inappropriate in some clinical settings, (e.g. bowel obstruction, pneumothorax). As with other interventions, the availability

Table 3. Summary of judgements and recommendations for each PICO question identified by the TEP.

	Intranasal fentanyl vs IV opioids in children	IV APAP vs IV opioids	IV NSAIDs vs IV opioids	APAP vs NSAIDs	IV ketamine vs IV NSAID
Problem	Yes	Yes	Yes	Yes	Yes
Desirable effects	Trivial	Trivial	Don't know	Trivial	Trivial
Undesirable effects	Trivial	Moderate	Trivial	Trivial	Moderate
Certainty of evidence	Very low	Low	Moderate	Very low	Moderate
Values	Possibly important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Probably no important uncertainty or variability
Balance of effects	Probably favors the intervention	Probably favors the intervention	Does not favor either the intervention or the comparison	Does not favor either the intervention or the comparison	Don't know
Resources required	Negligible costs and savings	Don't know	Negligible costs and savings	Moderate costs	Negligible costs and savings
Certainty of evidence of required resources	No included studies	No included studies	No included studies	No included studies	No included studies
Cost effectiveness	No included Studies	No included studies	Does not favor either the intervention or the comparison	No included studies	No included studies
Equity	Probably increased	Don't know	Don't know	Don't know	Don't know
Acceptability	Yes	Probably yes	Yes	Probably yes	Probably yes
Feasibility	Probably yes	Probably yes	Yes	Varies	Probably yes
Type of recommendation	Strong recommendation for the intervention (fentanyl prior to or without IV access)	Conditional recommendation for the intervention (APAP) if acceptable cost and ease of administration	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the comparator (NSAID) when IV, either when PO.	Conditional recommendation for either the intervention or the comparison
	IV ketamine vs IV opioids	IV morphine vs IV fentanyl	Combination weight based IV opioid plus IV ketamine vs weight based IV opioid	IV opioid plus iv ketamine vs iv ketamine	Inhaled nitrous oxide inhaled vs IV opioid
Problem	Yes	Yes	Yes	Yes	Yes
Desirable effects	Trivial	Trivial	Trivial	Don't know	Don't know
Undesirable effects	Small	Small	Small	Don't know	Don't know
Certainty of evidence	Very low	Low	Very low	Very low	Very low
Values	Probably no important uncertainty or variability	Probably no important uncertainty or variability	Possibly important uncertainty or variability	No important uncertainty or variability	Possibly important uncertainty or variability
Balance of effects	Does not favor either the intervention or the comparison	Does not favor either the intervention or the comparison	Does not favor either the intervention or the comparison	Don't know	Don't know
Resources required	Negligible costs and savings	Negligible costs and savings	Negligible costs and savings	Don't know	Don't know
Certainty of evidence of required resources	No included studies	No included studies	No included studies	No included studies	No included studies
Cost effectiveness	No included studies	No included studies	No included studies	No included studies	No included studies
Equity	Don't know	Don't know	Don't know	Don't know	Don't know
Acceptability	Probably yes	Probably yes	Probably no	Probably yes	Yes
Feasibility	Probably yes	Yes	Probably yes	Probably yes	Yes
Type of recommendation	Conditional recommendation for either the intervention or the comparison	N/A, two recommendations listed	Conditional recommendation against the intervention (combination)	No recommendation due to significant uncertainty	No recommendation

of a non-opioid analgesic option may be perceived as beneficial for patients who are intolerant or allergic to available opioids, or who would prefer to avoid opioid analgesics. The panel did not make a recommendation for this question based on an inadequate, rather than equivocal, evidence base.

Discussion

The panel's recommendations as a whole represent an opportunity to increase the recognition among prehospital clinicians and EMS medical directors that there is a wider variety of analgesics available for prehospital pain

management than may have been traditionally considered. The general approach of the panel, given the evidence base available, was to add "tools in the toolbox" for EMS medical directors to select when designing patient care guidelines, and for prehospital clinicians to choose from when faced with a patient experiencing moderate to severe pain. Rather than having a single medication, or "tool", in the drug box for the management of acute pain, traditionally an opioid, there could be a variety of options available including multiple non-opioid medications. The prehospital clinician could then tailor the medication and route of administration to the clinical situation, for example the use of ketamine for the rapid management of severe pain, an oral NSAID for

less severe pain, or IN fentanyl for an anxious child suffering acute pain. There is also the obvious benefit of having more choices available if the patient has an allergy or intolerance to a specific medication or class of medications, or desires to avoid opioid medication altogether because of choice or previous negative experience with opioids. As noted earlier, the panel acknowledges the significant impact of the opioid crisis on patients and the EMS clinicians caring for them, and the advantages of having equally efficacious, non-opioid options to address acute pain in the prehospital environment. The panel also discussed the opportunity that multiple analgesic options provide for a conversation between the prehospital clinician and the patient regarding choices for pain management, i.e. the opportunity for “shared decision-making” in the choice of analgesic and the route of administration. It is recognized that there are some cost, availability, and administration issues, particularly with IV APAP, but these do not seem to be prohibitive and may become less significant in the future. The concept of replacing opioids in the prehospital formulary of a given EMS agency or system is quite viable, taking into account EMS agency medical direction and any local or regional challenges with medication availability and cost.

The panel’s recommendations refer to IV administration of analgesics with the exception of intranasal administration of fentanyl to pediatric patients and the PO administration of NSAIDs and APAP. The majority of analgesics evaluated in the AHRQ review were administered intravenously, although a limited number of studies addressed intramuscular or intranasal administration, or administration by nebulization (19). No studies addressed the intraosseous administration of analgesics, even though use of that route of medication administration is increasing in EMS practice (19). The panel limited its recommendations, with the exception of IN fentanyl in pediatric patients and PO administration of NSAIDs and APAP, to the IV route of administration as the panel did not feel that the evidence base was sufficient to allow the panel to produce recommendations for other routes of administration. The panel felt that the evidence base for the intranasal administration of fentanyl in children was robust enough, and the issue of pediatric analgesia important enough, to support the development of an additional PICO question for that intervention.

The GRADE system has been described as a transparent framework for developing and presenting summaries of evidence and providing a systematic approach for making clinical practice guidelines (31). The accompanying Methods paper provides an in depth description of how the PICO questions for this project were developed, how the evidence base was selected and reviewed, and how the quality of the evidence was evaluated (20). The GRADE process has also been described as subjective, both in terms of the evaluation of the quality of the evidence and the strength and direction of the recommendations produced, but reproducible and transparent (31). In addition to considering the quality of the evidence, the TEP may consider factors such as the priority of the problem, the balance of desirable versus

undesirable effects, patient values and preferences, resource requirements and cost effectiveness, equity, acceptability, and feasibility, when producing their recommendations (32,33). A summary of the factors that the TEP considered for each recommendation is presented in Table 3.

The recommendations do not specify or differentiate the etiology of the pain presented in the evidence base. The AHRQ review found that the most common type of traumatic pain included in the evidence base was limb fracture pain; patients with severe injuries, multi-trauma or burns were not represented in the evidence base, and the most common type of non-traumatic pain was renal colic (19). The AHRQ review did not further sub-divide the etiology of the pain given the wide variation across comparisons and no further efforts were made to do so in this project.

Limitations

The development of these EBGs was limited by several factors. In general, the evidence base for prehospital care is limited and the evidence base for prehospital pain management shared this limitation. Many of the studies included both in the systematic review and the evidence tables developed from the review were set in the ED rather than the prehospital environment. Although patients in the emergency department suffering from acute pain share similarities with the patients that EMS clinicians assess and treat, the lack of studies conducted in the prehospital setting contributed to significant concerns regarding the indirectness of the evidence base. An example of a study with serious concerns for indirectness was a prospective, randomized study comparing IV paracetamol versus IV morphine for acute limb trauma; although the study dealt with a painful condition commonly encountered by prehospital clinicians, it was set in an emergency department and excluded patients who had any previous analgesia, including any prehospital pain management (34). Additionally, the studies included in the systematic review were conducted in a variety of health care systems that were organized differently and may have had different approaches to pain management and differing availability and cost of analgesics.

The authors readily acknowledge that pain arises from a wide variety of causes and the experience of pain by an individual is variable and contextual. This project illustrated that there was a limited body of literature of high quality that directly addressed the prehospital questions evaluated by the TEP. As noted above, the AHRQ systematic review that this project was based on described pain as “moderate to severe” and did not further sub-divide the etiology of the pain, or describe further inclusion or exclusion criteria, so no further efforts in that respect were made in this project. Clearly there are opportunities for future research in prehospital pain assessment, pain management, and prehospital clinician training. As noted in the discussion, it is our hope that the recommendations provide EMS medical directors and EMS clinicians increased flexibility in tailoring their approach to pain control for the individual patient and clinical situation.

The authors acknowledge the degree of subjectivity inherent in the GRADE process, as discussed above, and recognize that a different TEP, or the readers of this paper, might have reached some different conclusions in the development of the recommendations presented above. It is our hope that a similarly constituted technical expert panel, using the same evidence base, and rigorously applying the GRADE process, would reach substantially similar conclusions and recommendations.

Finally, the age of 18 was used as a cutoff for the pediatric age range, which may fail to capture the nuances present in the assessment and management of acute pain across the full range of pediatric populations. Given the limitations of the evidence base in general as discussed above, and for pediatrics specifically, we did not further differentiate this population. Again, the opportunity for future clinical research in acute pain management is illustrated.

Conclusions

The panel viewed the recommendations as an opportunity to increase the awareness of the number and variety of medications available for the management of pain in the prehospital setting. Non-opioid analgesics, including NSAIDs, APAP, and ketamine offer options for pain management with comparable efficacy to opioids and with more favorable adverse effect profiles. Rather than having a single option in the medication kit, well trained EMS clinicians who have multiple “tools in the toolbox” can tailor analgesic selections based on the patient’s history, the clinical situation, and a discussion of patient values and goals of therapy when the situation allows. Increased analgesic options and routes of administration may help to increase the proportion of patients treated appropriately for their pain, and also help to address disparities in pain assessment and pain management. Increased options also present opportunities for “shared decision-making” in which prehospital clinicians can present options for pain management to the patient and select an analgesic based on the patient’s desires, for example avoiding opioid medications as a class or avoiding potential adverse effects such as nausea, dizziness, or dysphoria. Increased availability of IN fentanyl for pediatric patients may help to increase the number of children treated for acute pain by overcoming clinician barriers to providing analgesia, such as challenges in obtaining IV access to children, and acceptance by pediatric patients and their caregivers.

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Author Contributions

GL, MIS, SB, JRP, ARP, LRB, and ESL directed the design of the project, discussion of the data, grading of the evidence, and development of the recommendations. GL, MIS, SB, ARP, and ESL drafted the manuscript. All authors contributed substantially to the discussion and development of the recommendations. GL takes responsibility for the manuscript as a whole.

Disclosure statement

Brooke Burton, Sabina Braithwaite, Lorin Browne, Jeffrey Coughenour, James Gasper, Kyle Guild, Mary Hedges, Eddy Lang, Sandra Nasca, Ashish Panchal, Jonathan Powell, Manish Shah, Peter Taillac, and Mark Werth report no conflicts of interest. George Lindbeck reports receiving an honorarium from NASEMSO for his work on the project.

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References

- McLean SA, Maio RF, Domeier RM. The epidemiology of pain in the prehospital setting. *Prehosp Emerg Care*. 2002;6(4):402–5. doi:10.1080/10903120290938021.
- Galinski M, Ruscev M, Gonzalez G, Kavas J, Ameer L, Biens D, Lapostolle F, Adnet F. Prevalence and management of acute pain in prehospital emergency medicine. *Prehosp Emerg Care*. 2010;14(3):334–9. doi:10.3109/10903121003760218.
- Alonso-Serra H, Wesley K. Prehospital pain management. *Prehosp Emerg Care*. 2003;7(4):482–8. doi:10.1080/312703002260.
- Friesgaard K, Riddervold I, Kirkegaard H, Christensen E, Nikolajsen L. Acute pain in the prehospital setting: a register-based study of 41.241 patients. *Scand J Trauma Resusc Emerg Med*. 2018;26(1):53 doi:10.1186/s13049-018-0521-2.
- Gausche-Hill M, Brown K, Oliver Z, Sasson C, Dayan P, Eschmann N, Weik T, Lawner B, Sahni R, Falck-Ytter Y, Wright J, et al. An evidence-based guideline for prehospital analgesia in trauma. *Prehosp Emerg Care*. 2014;18(Suppl 1):25–34. Epub 2013/11/26. doi:10.3109/10903127.2013.844873.
- Hewes HA, Dai M, Mann NC, Baca T, Taillac P. Prehospital pain management: disparity by age and race. *Prehosp Emerg Care*. 2018;22(2):189–97. Epub 2017/09/28. doi:10.1186/154.1080/10903127.2017.1367444.
- Lee P, Le Saux M, Siegel R, Goyal M, Chen C, Ma Y, Meltzer AC. Racial and ethnic disparities in the management of acute pain in US emergency departments: meta-analysis and systematic review. *Am J Emerg Med*. 2019;37(9):1770–7. Epub 2019/06/05. doi:10.1016/j.ajem.2019.06.014.
- Benzing AC, Bell C, Derazin M, Mack R, MacIntosh T. Disparities in opioid pain management for long bone fractures. *J Racial Ethn Health Disparities*. 2020;7(4):740–5. Epub 2020/05/07. doi:10.1007/s40615-020-00701-1.
- Beaudoin FL, Gutman R, Zhai W, Merchant RC, Clark MA, Bollen KA, Hendry P, Kurz MC, Lewandowski C, Pearson C, et al. Racial differences in presentations and predictors of acute pain after motor vehicle collision. *Pain*. 2018;159(6):1056–63. doi:10.1097/j.pain.0000000000001186.

10. Chen EH, Shofer FS, Dean AJ, Hollander JE, Baxt WG, Robey JL, Sease KL, Mills AM. Gender disparity in analgesic treatment of emergency department patients with acute abdominal pain. *Acad Emerg Med*. 2008;15(5):414–8. doi:10.1111/j.1553-2712.2008.00100.x.
11. Roy E. DEA investigating drug thefts at Lynchburg hospital. *The Lynchburg News and Advance*. 2014 Dec 18 [accessed 2021 Apr 11]. https://roanoke.com/news/virginia/dea-investigating-drug-thefts-at-lynchburg-hospital/article_dcb83025-f5b3-59d7-b0b4-206692baefec.html
12. Todd K. A review of current and emerging approaches to pain management in the emergency department. *Pain Ther*. 2017;6(2):193–202. Epub 2017/11/10. doi:10.1007/s40122-017-0090-5.
13. Strayer R, Motov S, Nelson L. Something for pain: responsible opioid use in emergency medicine. *Am J Emerg Med*. 2017;35(2):337–41. Epub 2016/10/24. doi:10.1016/j.ajem.2016.10.043.
14. Barnett M, Olenski A, Jena A. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *N Engl J Med*. 2017;376(7):663–73. doi:10.1056/NEJMsa1610524.
15. Murphy A, McCoy S, O'Reilly K, Fogarty E, Dietz J, Crispino G, Wakai A, O'Sullivan R. A prevalence and management study of acute pain in children attending emergency departments by ambulance. *Prehosp Emerg Care*. 2016;20(1):52–8. doi:10.3109/10903127.2015.1037478.
16. Browne L, Shah M, Studnek J, Ostermayer D, Reynolds S, Guse C, Brousseau D, Lerner EB. Multicenter evaluation of prehospital opioid pain management in injured children. *Prehosp Emerg Care*. 2016;20(6):759–67. Epub 2016/07/13. doi:10.1080/10903127.2016.1194931.
17. Goyal MK, Johnson TJ, Chamberlain JM, Cook L, Webb M, Drendel AL, Alessandrini E, Bajaj L, Lorch S, Grundmeier RW, et al. Racial and ethnic differences in emergency department pain management of children with fractures. *Pediatrics*. 2020;145(5):e20193370. Epub 2020/04/20. doi:10.1542/peds.2019-3370.
18. Whitley DE, Li T, Jones CMC, Cushman JT, Williams DM, Shah MN. An assessment of newly identified barriers to and enablers for prehospital pediatric pain management. *Pediatr Emerg Care*. 2017;33(6):381–7. doi:10.1097/PEC.0000000000000514.
19. Sobieraj DM, Baker WL, Martinez BK, Miao B, Hernandez AV, Coleman CI, Cicero MX, and, Kamin RA. Comparative effectiveness of analgesics to reduce acute pain in the prehospital setting. Comparative Effectiveness Review No. 220. (Prepared by the University of Connecticut Evidence-based Practice Center under Contract No. 290-2015-00012-I.) AHRQ Publication No. 19-EHC021-EF. Rockville, MD: Agency for Healthcare Research and Quality; 2019 Aug. doi:10.23970/AHRQEPCCER220.
20. Powell JP, Browne LR, Guild K, Shah MI, Crowe RP, Lindbeck G, Sabina BS, Lang ES, Panchal AR, & On behalf of the Technical Expert Panel. Evidence-based guidelines for prehospital pain management: literature and methods. *Prehosp Emerg Care*. 2021. doi:10.1080/10903127.2021.2018074.
21. Weichenthal L, Soliz T. The incidence and treatment of prehospital motion sickness. *Prehosp Emerg Care*. 2003;7(4):474–6. doi:10.1080/312703002247.
22. Rainer TH, Jacobs P, Ng YC, Cheung MT, Tam M, Lam PKW, Wong R, Cocks R. Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial. *BMJ*. 2000;321(7271):1247–51. doi:10.1136/bmj.321.7271.1247.
23. Woolner V, Ahluwalia R, Lum H, Beane K, Avelino J, Chartier LB. Improving timely analgesia administration for musculoskeletal pain in the emergency department. *BMJ Open Qual*. 2020;9(1):e000797. doi:10.1136/bmjopen-2019-000797.
24. Patrick PA, Rosenthal BM, Iezzi CA, Brand DA. Timely pain management in the emergency department. *J Emerg Med*. 2015;48(3):267–73. Epub 2014/11/07. doi:10.1016/j.jemermed.2014.09.009.
25. Ghate G, Clark E, Vaillancourt C. Systematic review of the use of low-dose ketamine for analgesia in the emergency department. *Can J Emergency Med*. 2018;20(1):36–45. Epub 2017/06/28. doi:10.1017/cem.2017.48.
26. Ahern TL, Herring AA, Anderson ES, Madia VA, Fahimi J, Frazee BW. The first 500: initial experience with widespread use of low-dose ketamine for acute pain management in the ED. *Am J Emerg Med*. 2015;33(2):197–201. Epub 2014/11/15. doi:10.1016/j.ajem.2014.11.010.
27. Aroni F, Iacovidou N, Dontas I, Pourzitaki C, Xanthos T. Pharmacological aspects and potential new clinical applications of ketamine: reevaluation of an old drug. *J Clin Pharmacol*. 2009;49(8):957–64. Epub 2009/06/22. doi:10.1177/0091270009337941.
28. Buckland D, Crowe R, Cash R, Gondek S, Maluso P, Sirajuddin S, Smith ER, Dangerfield P, Shapiro G, Wanka C, et al. Ketamine in the prehospital environment: a national survey of paramedics in the United States. *Prehosp Disaster Med*. 2018;33(1):23–8. Epub 2017/12/21. doi:10.1017/S1049023X17007142.
29. Helander EM, Menard BL, Harmon CM, Homra BK, Allain AV, Bordelon GJ, Wyche MQ, Padnos IW, Lavrova A, Kaye AD. Multimodal analgesia, current concepts, and acute pain considerations. *Curr Pain Headache Rep*. 2017;21(1):3 doi:10.1007/s11916-017-0607-y.
30. Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? *Emerg Med J*. 2005;22(12):901–8. doi:10.1136/emj.2004.020891.
31. Siemieniuk R, Guyatt G. What is grade? *BMJ Best Practice*. <https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/> [accessed 2021 Oct 9].
32. Goldet G, Howick J. Understanding GRADE: an introduction. *J Evid Based Med*. 2013;6(1):50–4. doi:10.1111/jebm.12018.
33. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, Rind D, Montori VM, Brito JP, Norris S, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726–35. doi:10.1016/j.jclinepi.2013.02.003. Epub 2013 Apr 6.
34. Jalili M, Mozaffarpour Noori A, Sedaghat M, Safaie A. Efficacy of intravenous paracetamol versus intravenous morphine in acute limb trauma. *Trauma Mon*. 2016;21(1):e19649. doi:10.5812/traumamon.19649.