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Multimodal Non-Opioid Analgesia versus Opioid-First Approaches for Acute Pain in the Emergency Department: A Systematic Review of Randomized Controlled Trials

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 May 2026 and was last updated on 27 May 2026.

INTRODUCTION

Review question / Objective To evaluate the effectiveness and safety of multimodal non-opioid or opioid-sparing analgesic strategies compared with opioid-first or opioid-dominant regimens for adults presenting to emergency departments (EDs) with acute renal colic, musculoskeletal trauma, or migraine.

Rationale The role of the emergency department (ED) to effectively manage acute pain is an important one but it has some limitations; those being that emergency departments must also manage the risk associated with opioid-related harm. Opioid addiction, overdoses, and opioid related illness/morbidity are increasing at alarming levels, which has led health systems to implement alternative methods for managing acute pain in the hospital setting. To provide appropriate analgesia, emergency clinicians must weigh the speed/adequacy of pain relief against the potential risk of starting or continuing harmful opioid exposure in opioid-naive patients. Multimodal analgesia utilizes multiple classes of drugs simultaneously to achieve either additive or synergistic analgesia while reducing dependence on opioids as much as possible. Alternative-to-opioids (ALTO) pathways have been developed to address several clinical conditions and although ALTO pathways have been studied extensively in terms of comparison to traditional opioid-based treatment models; there is very little information regarding ALTO pathways as compared to traditional treatment models in the most commonly treated ED diagnoses such as renal colic, musculoskeletal trauma, and acute migraine. There are many differences among studies including demographics of the study population, dosing strategies utilized within each study and outcomes measured within each study. As a result, comparing results from previous studies is challenging. Therefore, a systematic review focusing on randomized-controlled trials in adult ED populations and utilizing standardized inclusion/exclusion criteria and outcome measurements is necessary to assess the current knowledge regarding this topic and subsequently

inform the development of ED pain management guidelines.

Condition being studied Acute pain management in adults 18 years and older presenting to the Emergency Department with musculoskeletal pain, renal colic, migraines, and trauma.

METHODS

Search strategy Electronic databases searched include PubMed/MEDLINE and Embase. PubMed Search String:
(("Emergency Service, Hospital" [Mesh] OR "emergency department"[tiab] OR "emergency room"[tiab] OR "emergency medicine"[tiab] OR "ED"[tiab] OR "ER"[tiab] OR "acute care"[tiab]) AND ("Acute Pain"[Mesh] OR "Pain Management"[Mesh] OR "acute pain" [tiab] OR "pain management"[tiab] OR "analgesia"[tiab] OR "analgesic"[tiab] OR "pain control"[tiab] OR "pain relief"[tiab]) AND ("multimodal"[tiab] OR "multi-modal"[tiab] OR "opioid-sparing" [tiab] OR "opioid sparing" [tiab] OR "nonopioid"[tiab] OR "non-opioid"[tiab] OR "opioid alternative"[tiab] OR "combination analgesia"[tiab] OR "combination therapy"[tiab])) NOT (animals[mh] NOT humans[mh]) AND ("Renal Colic" [Mesh] OR "renal colic"[tiab] OR "urolithiasis" [tiab] OR "kidney stone"[tiab] OR "ureteral stone"[tiab] OR "nephrolithiasis" [tiab] OR "Wounds and Injuries" [Mesh] OR trauma[tiab] OR fracture* [tiab] OR "musculoskeletal pain"[tiab] OR "Migraine Disorders" [Mesh] OR migraine* [tiab] OR "severe headache"[tiab] OR "acute headache"[tiab])

Embase Search Strings:

Trauma/Musculoskeletal: ('wound'/exp OR 'injury'/exp OR 'musculoskeletal injury'/exp OR 'limb injury'/exp OR trauma:ti,ab,kw OR fracture*:ti,ab,kw OR 'extremity pain':ti,ab,kw OR 'musculoskeletal pain':ti,ab,kw) AND ('emergency service'/exp OR 'emergency ward'/exp OR 'emergency care'/exp OR 'emergency department':ti,ab,kw OR 'emergency room':ti,ab,kw OR ed:ti,ab,kw) AND ('acetaminophen'/exp OR 'ibuprofen'/exp OR acetaminophen:ti,ab,kw OR ibuprofen:ti,ab,kw OR ketamine:ti,ab,kw OR 'combination drug therapy'/exp) AND ('opioid analgesic' OR opioid*:ti,ab,kw) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp)

Migraine/Headache: ('migraine'/exp OR migraine*:ti,ab,kw OR 'acute headache':ti,ab,kw OR headache:ti,ab,kw) AND ('emergency service'/exp OR 'emergency ward'/exp OR 'emergency care'/exp OR 'emergency department':ti,ab,kw OR 'emergency room':ti,ab,kw OR ed:ti,ab,kw) AND (prochlorperazine:ti,ab,kw OR metoclopramide:ti,ab,kw OR ketorolac:ti,ab,kw OR diphenhydramine:ti,ab,kw OR antiemetic*:ti,ab,kw OR 'non opioid':ti,ab,kw OR nonopioid:ti,ab,kw OR 'non opioid analgesic') AND ('opioid analgesic' OR opioid*:ti,ab,kw OR morphine:ti,ab,kw OR hydromorphone:ti,ab,kw) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ti,ab,kw OR trial*:ti,ab,kw OR comparative:ti,ab,kw)

Renal Colic: ('renal colic'/exp OR 'urolithiasis'/exp OR nephrolithiasis:ti,ab,kw OR 'kidney stone':ti,ab,kw OR 'kidney stones':ti,ab,kw OR 'ureteral stone':ti,ab,kw OR 'ureteral stones':ti,ab,kw) AND ('emergency service'/exp OR 'emergency ward'/exp OR 'emergency care'/exp OR 'emergency department':ti,ab,kw OR 'emergency room':ti,ab,kw OR ed:ti,ab,kw) AND (ibuprofen:ti,ab,kw OR ketorolac:ti,ab,kw OR diclofenac:ti,ab,kw OR nsaid*:ti,ab,kw OR 'nonsteroidal anti inflammatory':ti,ab,kw OR 'non opioid':ti,ab,kw OR nonopioid:ti,ab,kw OR 'non opioid analgesic') AND ('opioid analgesic' OR morphine:ti,ab,kw OR hydromorphone:ti,ab,kw OR fentanyl:ti,ab,kw) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp OR 'comparative study'/exp OR random*:ti,ab,kw OR trial*:ti,ab,kw OR comparative:ti,ab,kw).

Participant or population Adults (≥18 years, or mixed-age samples where the mean or median age was ≥18 and more than 80% of participants were adults) presenting to a hospital-based ED or closely affiliated acute care area with acute pain (≤7 days' duration or clearly described as an acute ED presentation) from one of three conditions: renal colic or urolithiasis, trauma or musculoskeletal injury (including traumatic limb injury, limb fractures, and musculoskeletal pain), or migraine, cluster headache, or tension headache. Baseline pain severity was required to be documented using a validated scale (Numeric Rating Scale [NRS] or Visual Analogue Scale [VAS]).

Intervention Multimodal or opioid-sparing acute pain management strategies, defined as: (a) use of two or more analgesic modalities (pharmacologic and/or regional/non-pharmacologic), with at least one non-opioid component; (b) non-opioid-dominant regimens in which a non-opioid agent was used as the primary analgesic and compared directly with an opioid-dominant regimen; or (c) protocolized "alternative to opioids" (ALTO) pathways prioritizing non-opioid agents with

opioids reserved for rescue only. Specific interventions of interest included peripheral nerve blocks, systemic intravenous non-opioid analgesia (e.g., acetaminophen, ibuprofen, ketorolac), subdissociative-dose ketamine, and inhaled agents (e.g., methoxyflurane, sufentanil).

Comparator Opioid-only or opioid-dominant regimens, including single-agent opioids (morphine, hydromorphone, fentanyl, tramadol, oxycodone), oral opioid combinations (e.g., oxycodone, hydrocodone, codeine), fixed-dose opioid–acetaminophen combinations, or standard ED care protocols (e.g., weight-based intravenous morphine titration) where opioid therapy constituted the primary analgesic strategy.

Study designs to be included Randomized Controlled Trials.

Eligibility criteria Inclusion Criteria: RCTs published between 2010 and 2025; conducted in ED settings; reporting validated pain scores (NRS/VAS); published in English.

Exclusion Criteria: Enrolled pediatric populations; focused on chronic pain, cancer pain, or conditions outside the predefined scope (e.g., sickle cell pain, rheumatoid arthritis); conducted outside acute care settings; lacked quantifiable pain data. Studies from clinical trial registries or unpublished grey literature were excluded.

Information sources Electronic database searches were limited to PubMed/MEDLINE and Embase. Manual screening of the reference lists of retrieved articles was also performed. Trials from clinical trial registries or grey literature sources were not included.

Main outcome(s) The primary outcome was change in pain intensity during the emergency department stay, quantified using a validated clinical measurement tool such as the Numeric Rating Scale (NRS, 0–10) or Visual Analogue Scale (VAS, 0–100 mm).

Additional outcome(s) Secondary outcomes included total opioid dose administered during the ED stay (quantified in morphine milligram equivalents [MME]), need for rescue analgesia, time to initial pain relief, adverse events (e.g., nausea, vomiting, dizziness, euphoria, disorientation, dysgeusia, respiratory depression), emergency department or hospital length of stay, short-term return visits, and patient-reported satisfaction.

Data management After obtaining a list of articles, studies were deduplicated and screened by title and abstract by two independent reviewers, and disagreements were resolved by a third reviewer. This followed a full-text evaluation of possible eligible studies. Data was extracted using a synthesis matrix that included author, study site country, intervention description, comparator description, study population, population size, baseline pain scores, mean pain score reduction from 5 minutes to 60 minutes, difference in pain score, patient satisfaction, adverse events, need for additional analgesia, time to obtain pain relief, total opioid exposure, length of stay, and conclusion.

Quality assessment / Risk of bias analysis Risk of bias in the primary included studies was assessed based on several core domains of methodology quality with a validated instrument that has been independently verified to be valid. The two main core domains were the risk of bias for deviation from intended intervention design (e.g., open-label or unblinded) and the risk of bias for the measurement of subjective pain outcomes. Studies were categorized overall as having low risk of bias, some concerns, or high risk of bias.

Strategy of data synthesis A quantitative meta-analysis was not possible due to significant differences across the studies, particularly in their intervention designs, comparator dosing schedules, and evaluation timelines. To assess the clinical significance of pain reduction beyond statistical p-values, we used the established minimal clinically important difference (MCID). The MCID is recognized as 13 mm on a 100-mm visual analogue scale (VAS) or 1.3 points on a 0–10 numeric rating scale (NRS). Mean differences between groups falling below these thresholds were interpreted as clinically equivalent.

Subgroup analysis No formal quantitative subgroup analyses were planned or performed due to clinical heterogeneity. Data were qualitatively extracted and analyzed by the distinct underlying clinical etiologies (trauma/musculoskeletal, migraine, or renal colic).

Sensitivity analysis Sensitivity analyses were not performed because a quantitative meta-analysis was not conducted due to the clinical heterogeneity of the included trials.

Language restriction Search was restricted to show only english published articles.

Country(ies) involved United States (Ponce Health Sciences University).

Keywords multimodal analgesia; opioid-sparing; emergency department; acute pain; renal colic; musculoskeletal trauma; migraine.

Contributions of each author

Author 1 - Winifred Chijioke - Created study question, designed the PICO framework, contributed to creating search string for PUBMED and Embase, screened articles, extracted data from articles, drafted the manuscript.
Author 2 - Lucas Troche - Screened articles, created the synthesis matrix, extracted data from articles, and drafted manuscript.
Author 3 - Kodinakachukwu Ojukwu - Article screening and proofreading.
Author 4 - Mathew Kunjappy - Proofread, managed the overall direction of the study, and approved the final manuscript.