



Technical Brief  
Number 33

# Treatment for Acute Pain: An Evidence Map



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# **Treatment for Acute Pain: An Evidence Map**

#### **Prepared for:**

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# Key Messages

## Purpose of review

The purpose of this evidence map is to provide a high-level overview of the current guidelines and systematic reviews on pharmacologic and nonpharmacologic treatments for acute pain. We map the evidence for several acute pain conditions including postoperative pain, dental pain, neck pain, back pain, renal colic, acute migraine, and sickle cell crisis. Improved understanding of the interventions studied for each of these acute pain conditions will provide insight on which topics are ready for comprehensive comparative effectiveness review.

## Key messages

- Few systematic reviews provide a comprehensive rigorous assessment of all potential interventions, including nondrug interventions, to treat pain attributable to each acute pain condition. Acute pain conditions that may need a comprehensive systematic review or overview of systematic reviews include postoperative postdischarge pain, acute back pain, acute neck pain, renal colic, and acute migraine.
- Certain acute pain conditions have many published systematic reviews: postoperative pain, pain associated with dental procedures and oral surgery, low back pain, acute migraine. Several acute pain conditions have sufficient new data to warrant a new systematic review: pain associated with dental procedures and oral surgery, low back pain, renal colic, acute migraine.
- Few systematic reviews of acute pain treatments examine outcomes other than very short-term outcomes. Pain during the week or month following the inciting event and persistent opioid use were rarely reported.
- Most systematic reviews report pain outcomes using scales that measure only pain intensity, while few assess function or other pain characteristics.
- Few reviews focused on specific settings or populations other than general adults or children and adolescents.
- Future research using ACTION-APS-AAPM Pain Taxonomy dimensions to characterize acute pain would be valuable.
- Additional original research and up-to-date comprehensive systematic reviews would help inform treatment decisions for a wide variety of acute pain conditions.

This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00008-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

This EPC evidence report is a Technical Brief. A Technical Brief is a rapid report, typically on an emerging medical technology, strategy or intervention. It provides an overview of key issues related to the intervention—for example, current indications, relevant patient populations and subgroups of interest, outcomes measured, and contextual factors that may affect decisions regarding the intervention. Although Technical Briefs generally focus on interventions for which there are limited published data and too few completed protocol-driven studies to support definitive conclusions, the decision to request a Technical Brief is not solely based on the availability of clinical studies. The goals of the Technical Brief are to provide an early objective description of the state of the science, a potential framework for assessing the applications and implications of the intervention, a summary of ongoing research, and information on future research needs. In particular, through the Technical Brief, AHRQ hopes to gain insight on the appropriate conceptual framework and critical issues that will inform future research.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this Technical Brief, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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## Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest. The list of Key Informants who provided input to this report follows:

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## Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

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# Treatment for Acute Pain: An Evidence Map

## Structured Abstract

**Introduction.** Acute pain is a common ailment in the U.S. often treated with opioids. This technical brief maps the current evidence on pain treatments for select acute pain conditions (postdischarge postoperative pain, musculoskeletal pain, acute migraine, dental pain, renal colic, and acute pain associated with sickle cell disease).

**Methods.** We conducted Key Informant discussions to develop the context around the acute pain conditions, settings, and current clinical practice. We then conducted a systematic literature search to identify recent systematic reviews of sufficient quality that evaluated pain treatments for select acute pain conditions. We screened results and extracted relevant data into evidence tables. We subsequently searched for original research published after systematic review search dates.

**Results.** Key Informant discussions identified important issues regarding common acute pain conditions and treatments. Certain acute pain conditions have not received sufficient attention in rigorous comprehensive systematic review; for most types of acute pain, pain etiology is critical to selecting appropriate treatment; the value of acute pain assessments in guiding treatment decisions is unclear; and regional and health system level policies play a large role in treatment decisions. Our search for systematic reviews for pain treatments for priority acute pain conditions identified 1226 potentially relevant references, of which 527 underwent full text review. After supplemental searching and full text review, 110 systematic reviews met basic eligibility criteria. Most acute pain conditions had systematic reviews that met eligibility criteria, but few reviews were sufficiently rigorous and comprehensive. Few eligible reviews focused on specific settings except emergency departments for several acute pain conditions. Eligible reviews rarely addressed specific subpopulations such as racial and ethnic groups, rural residents, pregnant women, individuals with comorbidities, or those with a history of substance use disorder, overdose, or mental illness. Comparisons addressed by many systematic reviews often included opioids.

**Discussion.** Our discussions with Key Informants and review of the literature show that additional original research and up-to-date comprehensive systematic reviews would help inform treatment decisions for a wide variety of acute pain conditions.



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# Introduction

## Nature and Burden of Acute Pain

The United States is dealing with an increased number of opioid-related deaths and other problems associated with opioid addiction. Addressing the problem will require a thorough understanding of drug and nondrug treatments for pain. Toward that end, an up-to-date overview of available research is needed. With respect to acute pain conditions, this technical brief provides an evidence map that (1) summarizes which pain treatments have been studied in trials and recent systematic reviews, and (2) prioritizes relevant identifiable research gaps. This evidence map, is not a systematic review and therefore does not synthesize the available research to determine efficacy or effectiveness of the interventions.

Pain treatment has long been a major public health issue. Over the last decade, increases in opioid misuse and overdose have highlighted the importance of acute pain treatment. While the vast majority of individuals prescribed opioids for acute pain take their medication as directed and their pain resolves after a short course, some are at risk of misuse and addiction. This is concerning given the dramatic increase in opioid-related deaths; opioids (prescription and illicit use combined) were involved in 47,600 overdose deaths in 2017.<sup>1</sup> A better understanding of how to manage acute pain with less reliance on opioids, which are highly addictive, and how to prevent misuse when opioids are prescribed is needed. Our report takes an initial step toward this understanding by mapping the current literature on pain treatment for select acute pain conditions.

The American Academy of Pain Medicine (AAPM) defines acute pain as “the physiologic response and experience to noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid actual or potential tissue injuries.”<sup>2</sup> A public-private partnership between several entities (the United States Food and Drug Administration, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks [ACTTION], American Pain Society [APS], and AAPM) developed the ACTTION-APS-AAPM pain taxonomy (AAAPT) for acute pain.<sup>3</sup> The AAAPT characterizes acute pain by duration (typically up to 7 days but sometimes as long as 30 days), determined in part by the mechanism and severity of the inciting event.<sup>3</sup> Thus, timing is a key element distinguishing acute pain from subacute or chronic pain.

The exact incidence and prevalence of acute pain is unclear given inconsistent definitions; however, the 2012 National Health Interview Survey showed that 56 percent of U.S. adults reported pain during the previous three months.<sup>4</sup> While reporting pain during the previous three months may or may not mean the pain was acute, this statistic demonstrates how widespread pain is among the U.S. population. Widespread pain leads to increased use of healthcare resources, poorer perception of health status, lower productivity, and increased antidepressant use.<sup>4, 5</sup> Our ability to understand and manage acute pain is critical to lessen duration and severity.

Acute pain arises from many conditions. The AAAPT makes a broad distinction between surgical/procedural pain and nonsurgical pain, and classifies acute pain using five dimensions: core criteria (inciting event, timing, and location of pain), common features (symptoms and other features of the acute pain), modulating features (characteristics of the individual that affect the pain response), impact/functional consequences (recovery and other implications from the acute pain episode), and putative mechanisms (neurobiological mechanisms relevant to the acute pain episode).<sup>3</sup>

Acute pain is treated in multiple settings, including urgent care clinics, hospital emergency departments, inpatient hospital settings, outpatient surgery centers, dental surgery clinics, and others. The source and timing of the acute pain largely determine the setting of treatment.

## **Assessment of Acute Pain**

Accurately assessing acute pain is key to diagnosis and treatment, and many unidimensional and multidimensional pain assessment scales are available, including specific scales for a variety of pain conditions<sup>6-9</sup> and sub-populations.<sup>10-13</sup> Pain scales provide a quick and simple method to assess and monitor pain intensity and are a practical tool for helping clinicians make treatment decisions.<sup>14</sup> However, our understanding of how pain is experienced has evolved, along with views about how pain should be assessed. The AAAPT lays out the dimensions of pain that assist in decision-making about treatment, and current recommendations suggest using a comprehensive, multidimensional assessment that thoroughly characterizes the pain, the individual, and the environment. Such multidimensional assessments would likely improve acute pain diagnosis and treatment,<sup>2, 15</sup> but practice remains grounded in unidimensional assessments that primarily measure pain intensity based on patient self-report. Examples include the Numerical Rating Scale, Visual Analog Scale, and the Faces Pain Scale Revised.<sup>2, 14</sup>

Focusing solely on pain intensity has several limitations. Importantly, these instruments do not capture many dimensions of pain that are essential to treatment decision-making. Some dimensions (e.g., anxiety and pain catastrophizing) are associated with longterm complications; others (e.g., instruments that assess pain with activity or movement) are equally important to pain at rest; and still other dimensions (e.g., overall health and well-being) are crucial to understanding treatment effectiveness.<sup>2</sup>

In contrast, multidimensional assessment moves beyond pain intensity to incorporate attributes such as quality and character of pain, function, pain interference, and more.<sup>2</sup> These scales, compared to unidimensional scales, better measure the characterizations about pain laid out in the AAAPT. Examples of validated multidimensional assessment instruments include the Brief Pain Inventory and the McGill Pain Questionnaire.<sup>14</sup> However, these instruments can be challenging to implement in the settings where acute pain is most often treated.<sup>14</sup>

To improve understanding of pain, effort has been directed at overcoming inconsistencies in the data collected in pain trials. Toward that end, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) developed a core set of data elements for consideration in pain trials.<sup>16</sup> They recommended that six domains of pain be considered (pain; physical functioning; emotional functioning; participant ratings of improvement/satisfaction; symptoms and adverse effects; patient disposition).<sup>16</sup> Building on this framework, attention has been given to the importance of collecting data on risk factors in order to determine how such risk factors affect the transition from postoperative pain to chronic pain.<sup>17</sup> The five core risk factor domains include demographic, pain, clinical, surgery-related, and psychological.<sup>18</sup> Also noted as important is the need to measure outcomes at multiple timepoints beyond the initial surgery.<sup>19</sup>

## **Management of Acute Pain**

Treatments for acute pain include drug and nondrug therapies. Ideally, providers customize therapy to the type and severity of pain, treatment setting, and patient characteristics. Some treatments are unique to the type of pain (e.g. triptans for migraines), or setting (regional blocks used perioperatively for postoperative pain), but most treatments are used across a wide range of

pain conditions. Treatment varies by acute pain condition and severity. Multimodal approaches for treating acute pain are becoming more common in some settings.<sup>20-22</sup> However, given the unpredictable nature and short duration of acute pain, conducting research on acute pain treatment is challenging.

Drug therapies for acute pain include drugs from several classes. Pain relieving analgesics include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. These are often used in combination. Based on putative pain mechanisms, providers may also manage acute pain with muscle relaxants, antidepressants, alpha-2 agonists, GABA analogues, corticosteroids, NMDA receptor antagonists, local anesthetics, cannabinoids, among others.<sup>23, 24</sup> Topical agents such as capsaicin and lidocaine are also used.<sup>23</sup> Many medications for pain management have serious associated harms, such as liver toxicity with acetaminophen; bleeding with NSAIDs; and the risk of misuse, abuse, addiction, respiratory distress, and overdose associated with opioids. Therefore, caution is necessary when prescribing drug treatment, especially in certain populations (older adults; individuals with comorbidities and/or polypharmacy; individuals with a history of substance use disorder; pregnant and breastfeeding women; and children and adolescents).

To avoid harms associated with drugs, a wide variety of nondrug therapies for pain are becoming more widely used, including ice, heat, acupuncture, chiropractic manipulation, physical therapy, transcutaneous electrical nerve stimulation, massage therapy, exercise, and psychological approaches (cognitive behavioral therapy, mindfulness-based stress reduction).

## Purpose of Technical Brief

This evidence map identifies and describes the current research on treatment for pain attributable to acute pain conditions selected by the Agency for Healthcare Research and Quality (AHRQ) in the statement of work:

- Postoperative pain (after discharge from hospital or surgical facility)
- Musculoskeletal pain
  - Back pain
  - Neck pain
  - Fracture
- Dental pain
- Renal colic (episodic pain)
- Migraines (episodic pain)
- Sickle cell crisis (episodic pain)

We will also attempt to map the evidence with regard to specific populations provided by AHRQ in the statement of work as relevant. These subpopulations are important because of specific vulnerabilities or access issues regarding appropriate pain treatment.

- General adult
- Children and adolescents (ages 0 to 18)
- Older populations >65 years
- People with history of substance use disorder
- People with a history of mental illness
- People with history of overdose
- Pregnant/breastfeeding women
- Rural populations

- Ethnic and racial groups
- People with comorbidities (e.g. kidney disease, sleep disordered breathing)

## Guiding Questions

1. Which acute pain conditions are most commonly treated in select settings (emergency departments; inpatient and outpatient surgical facilities; primary and specialty care clinics; and dental clinics and dental surgery centers)?
  - a. How is acute pain for these conditions assessed and monitored?
  - b. Which individual characteristics modify perceptions of pain severity, treatment options, and treatment response?
2. Which of these priority acute pain conditions have recent, high-quality guidelines that address acute pain treatments?
3. Which of these priority acute pain conditions have recent, high-quality systematic reviews evaluating acute pain treatments?
  - a. Which populations, acute pain conditions, and treatments have been sufficiently systematically reviewed?
  - b. What evidence gaps were identified in systematic reviews?
4. What original comparative effectiveness research is available evaluating acute pain treatments for priority acute pain conditions without recent high-quality systematic reviews?
  - a. Which populations and settings have been studied?

## **Methods**

We addressed Guiding Questions (GQ) 1 and 2 through narrative literature review and discussions with Key Informants (KIs). We conducted a systematic literature search to identify systematic reviews on pain treatments for specific acute pain conditions. GQ4 was informed by the findings from GQ1 through GQ3.

### **Data Collection**

#### **Discussions With Key Informants**

We identified several experts and practitioners with relevant knowledge of acute pain treatment. We sought input from individuals from a variety of backgrounds, and professions and who had an understanding of the guidance and clinical practice relevant to pain treatments and for the select acute pain conditions. We developed our initial list by searching the literature for experts on acute pain treatment; searching the internet for individuals working on acute pain issues through committees or task forces; and requesting nominations for clinicians from local investigators. We facilitated discussions with five KIs with diverse experiences and perspectives on treatments for acute pain. These included pain specialists, primary care providers, and a hospital pharmacist. We used specific questions to facilitate these discussions (Appendix A). The questions centered on types of acute pain conditions and guidelines used to identify potential treatments. In addition to the perspectives of the KIs, our Evidence-based Practice Center team brought several perspectives to the project. Investigator backgrounds covered several areas specifically relevant to acute pain treatment (dentistry, pharmacology, internal medicine, psychology, nursing, and chiropractic care).

#### **Clinical Practice Guidelines: Search and Study Selection**

We searched MEDLINE and grey literature resources (ECRI Guideline Trust, International Guideline Library)<sup>25, 26</sup> for recent, relevant clinical practice guidelines. We conducted a supplemental search by looking for references to clinical practice guidelines in DynaMed entries for acute pain conditions.<sup>27</sup>

We included recent clinical practice guidelines of sufficient quality developed by key U.S.-based agencies and associations relevant to the select acute pain conditions. Clinical practice guidelines published prior to 2015 were considered out of date because these typically rely on systematic literature searches that are 4 to 5 years old. We required certain elements of AGREE II (systematic search of literature, recommendations linked to evidence base, and evidence grading) as a proxy for clinical practice guideline quality.<sup>28</sup>

#### **Systematic Reviews: Search and Study Selection**

We developed an overall search strategy (Appendix B) to identify systematic reviews evaluating treatments for pain attributable to the acute pain conditions. We searched MEDLINE and the Cochrane Library from January 2016 through September 2018 for all acute pain conditions. These dates were selected to identify systematic reviews with search dates less than three years old. Systematic reviews with search dates over three years old likely do not include the most recent literature and begin to be duplicative of the recently published systematic reviews. We supplemented this search with citation searches of key references.

We included systematic reviews that met our eligibility criteria:

- Full text available in English
- Published in 2016 or later
- Sufficient quality (proxy: assessed and reported risk of bias for each included study)
- Focused primarily on pain treatments attributable to selected acute pain conditions
- Included trials of any nondrug therapy or FDA-approved drugs (for any condition)

One investigator screened titles and abstracts for potential eligibility; one investigator screened full text of references identified as potentially relevant for the evidence map. To enable our team to find the most relevant references as quickly as possible for each acute pain condition within the limited timeframe for this project, we did not perform dual screening.

For acute pain conditions with only one to two systematic reviews or obviously missing interventions, we extended publication year to earlier years on a case-by-case basis. We incrementally went back until we felt we had the most relevant set of systematic reviews for the acute pain condition.

## **Original Research: Search and Study Selection**

We then conducted very precise searches for randomized controlled trials published since the search dates of the previous systematic reviews for each acute pain condition. The titles and abstracts from these references were screened to identify trials potentially relevant to pain treatments for each acute pain condition. We did not conduct full text screening of these references. We summarized the number of studies potentially available for future systematic reviews for each acute pain condition.

## **Data Organization and Presentation**

We used the reference management software, EndNote, to screen and categorize these studies.<sup>29</sup> We broadly organized relevant guidelines and eligible systematic reviews into acute pain categories as described in the ACTION-APS-AAPM pain taxonomy (AAAPT).<sup>3</sup> This broad classification separates acute pain conditions into surgical/procedural and nonsurgical. We further categorized specific pain conditions into subcategories as appropriate. We categorized interventions by drug class or class of nondrug intervention (Appendix D).

## **Information Management**

For each acute pain condition, we created evidence tables describing eligible U.S.-based clinical practice guidelines and systematic reviews. We briefly summarized relevant recommendations in eligible clinical practice guidelines. One investigator abstracted author, publication year, end search dates, and number and type of included studies, populations, interventions, comparisons, and outcomes from each eligible systematic review. One investigator also extracted data from trials from the eligible systematic reviews and new trials if they were relevant to our GQs. These data were used to create our evidence maps.

## **Data Presentation**

We mapped the evidence on pain treatment attributable to each acute pain condition in graphs that show the major comparisons studied, the number of systematic reviews and studies



included in these systematic reviews, and the number of new trials identified. These graphs show the volume of literature evaluated in previous systematic reviews and aim to identify areas not yet sufficiently addressed by systematic reviews.

# Results

## Acute Pain Conditions and Settings (GQ1)

We facilitated discussions with KIs and reviewed relevant literature for GQ1. We summarized the KI calls (Appendix C). KIs and epidemiological studies confirmed the relevance of most of the suggested acute pain conditions based on incidence in the population and/or perceived frequency of opioid prescribing. Key points from this literature and our discussions include:

- Many acute pain conditions are treated in many different settings. Postoperative pain, back and other musculoskeletal pain were most frequently mentioned. It is important to keep in mind that we did select our KIs based upon preselected acute pain conditions. Acute pain conditions mentioned during our discussions that were not among preselected acute pain conditions included pain resulting from compression fractures and neuropathic pain.
- Acute pain attributable to surgical procedures is commonly treated with opioids, and studies using administrative data have described correlations between postsurgical opioid use and persistent opioid use.<sup>30, 31</sup>
- Several KIs mentioned an observational study showing a statistically significant relationship between the number of opioid pills taken on the day before discharge (if discharge is not on the first postoperative day) and self-report of opioid pills taken during recovery at home.<sup>32</sup> Data from this study contributed new guidance regarding discharge medication, and resulted in a 40 percent decrease in opioid prescriptions.<sup>32</sup>
- Our discussions also highlighted nonsurgical acute pain conditions. Musculoskeletal pain, including back and neck pain, is frequently seen in a variety of settings. Back problems and headaches (including migraines) are two of the most common reasons people visit their healthcare providers.<sup>33</sup> Treating musculoskeletal pain appropriately requires identifying the cause (pain pathway).
- KIs agreed on the importance of the acute pain conditions in the statement of work, but mentioned other conditions not as thoroughly addressed in available research, including compression fractures, acute pain in hospital inpatients, and pain associated with shingles.
- Regarding how pain assessment informs pain treatment, our KIs suggested that formal pain assessment is fairly routine in the postoperative period, but may be less common with other acute pain conditions or in nonsurgical settings. Pain assessment tools based solely on pain intensity are commonly used, but many healthcare systems use instruments that go beyond pain intensity. KIs suggested that pain assessment is most valuable in monitoring a single patient over a period of time.
- KI discussions revealed how local policies, regulations, and health-system-level order sets guide decision-making, perhaps even more than government agency or medical society guidelines. Hospital systems and regional medical societies prepare suggested drug treatments for specific procedures often based, in part, on their healthcare system data. These are used by clinicians when ordering pain treatment.
- One KI felt that despite the frequent use of opioids for pain, their level of effectiveness for various types of pain is not well understood. Systematic reviews evaluating head-to-

head trials of opioids versus nonopioids would help identify the best medications for specific conditions and populations.

- KIs mentioned that several patient characteristics appear to influence the pain experience (e.g., fear, anxiety) and emphasized the need for improved understanding of patient risk factors associated with adverse long-term consequences from opioids.

## **Literature Search Results (GQ2 to GQ4)**

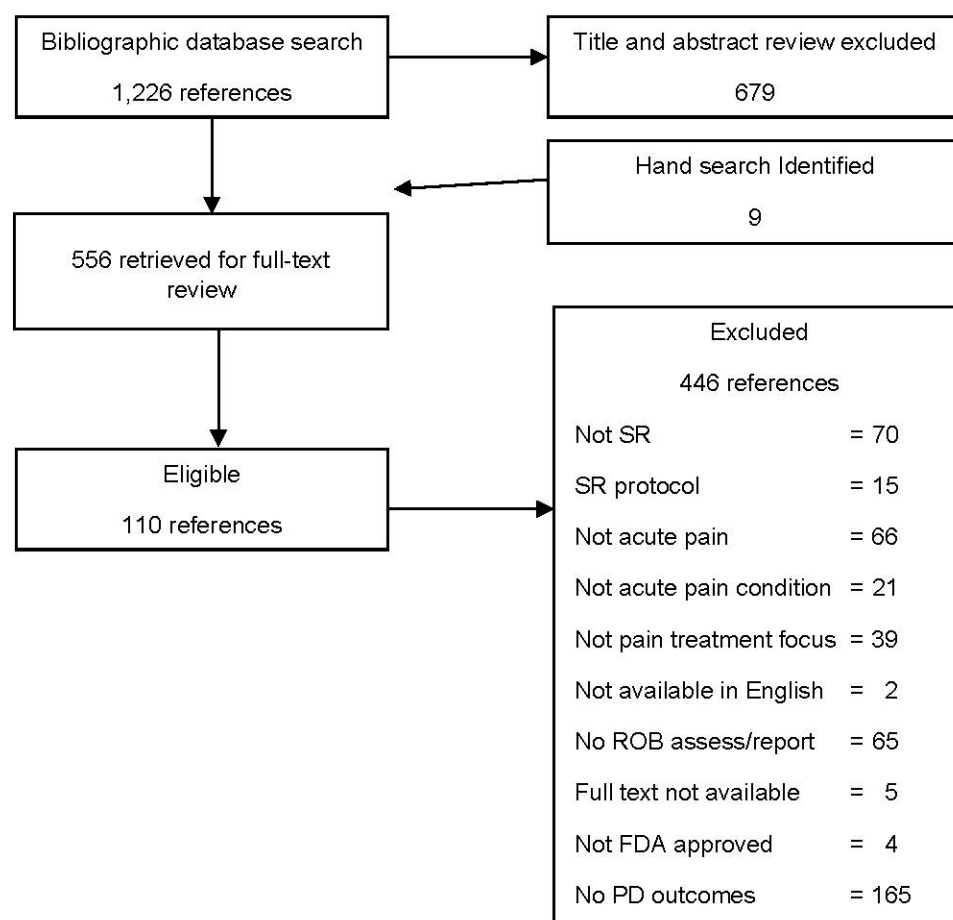
We identified several clinical practice guidelines relevant to the select acute pain conditions, and these are briefly discussed in the respective results sections.

Our search for systematic reviews identified 1,226 references published between 2016 and 2018 (Figure 1). Title and abstract review selected 527 references for full text review. Supplemental hand searching identified additional references. Overall, 110 systematic reviews met eligibility criteria. We excluded 446 references (Appendix E). We also present results of searches for original research and recently published trials to augment acute pain conditions without recent rigorous comprehensive systematic review, or when we identified specific gaps in the evidence base.

We identified a total of seven clinical practice guidelines (Table 1). The 110 eligible systematic reviews included a total of 869 studies relevant to our evidence map. Precise searching for original research not previously included in systematic reviews identified 1,659 references for all acute pain conditions combined. Title and abstract screening of those references identified 283 potentially relevant studies examining pain treatments for these acute pain conditions. In the remainder of the results section, we describe the eligible systematic reviews, trials included in those reviews, and newly identified trials for each acute pain condition.

We found no evidence specific to settings, except emergency settings for a few acute pain conditions. The systematic reviews explicitly limited their inclusion criteria to trials conducted in specific settings, except for those aimed at interventions delivered in emergency settings for renal colic and acute migraine. Often, the setting was implied by the nature of the acute pain condition or intervention. Specific subpopulations (older adults, people with history of substance use disorder, people with a history of mental illness, pregnant/breastfeeding women, rural populations, ethnic and racial groups, people with comorbidities (e.g. kidney disease, sleep disordered breathing) were rarely the focus of the systematic reviews we identified.

**Figure 1. Literature flow diagram**



**Abbreviations:** FDA = Food and Drug Administration; PD = postdischarge; ROB = risk of bias; SR = systematic review

**Table 1. Clinical practice guidelines, eligible systematic reviews and relevant studies**

<b>Acute Pain Category</b>	<b>Acute Pain Condition</b>	<b>Clinical Practice Guidelines</b>	<b>Systematic Reviews</b>	<b>Relevant Systematic Review Studies</b>	<b>Original Research: Search Results</b>	<b>Potentially Eligible After Title and Abstract Review</b>
Surgical	Postoperative Postdischarge Pain	1	36	116	362	27
	Pain Following Dental Procedures and Oral Surgery	0	17	119	315	80
Nonsurgical	Musculoskeletal Pain: Acute Back Pain	3	14	92	127	22
	Musculoskeletal Pain: Acute Neck Pain	1	8	13	34	5
	Musculoskeletal Pain: Fractures	0	6	45	108	27
	Visceral Pain: Renal Colic	0	4	88	119	40
	Orofacial Pain: Dental Pain	0	3	5	315	10
	Episodic Pain: Acute Migraine	1	22	372	578	65
	Episodic Pain: Sickle Cell Crisis	1	3	9	16	7
Total	All Acute Pain Conditions	7	110*	869	1,659	283

\*Studies/search results eligible for multiple acute pain conditions, so total is not sum of column

# **Surgical/Procedural**

## **Postoperative Pain**

A variety of pain management interventions are used before, during, immediately after, and upon discharge from surgical facilities.

### **Guidelines**

The American Pain Society (APS) developed a thorough, high-quality guideline providing recommendations on the management of postoperative pain (Table 2).<sup>21</sup> The guideline was published in 2016 and based on a comprehensive systematic literature review with literature searches conducted in December 2015. The APS guideline provides 32 recommendations: four based on high-quality evidence, 16 on moderate quality evidence, 11 on low-quality evidence, and one with insufficient evidence. The guideline addresses interventions for postoperative pain delivered during the preoperative phase through transition to the outpatient setting, and recommendations span many arenas including patient/caregiver education, patient assessment and management, organizational policies, and transitioning patients to other settings. The strongest four recommendations with high-quality evidence include using:

- Combination therapies (drug and nondrug)
- Acetaminophen and/or NSAIDs as part of the pharmacologic component
- Surgical site peripheral regional anesthetic for certain procedures with evidence of efficacy, and
- Spinal or epidural analgesia for major thoracic and abdominal procedures.

The guideline included certain perioperative pain recommendations without high-quality evidence. Among these are the adjustment of pain regimens based on efficacy and adverse events; use of validated assessment tools to monitor postoperative pain; monitoring sedation and respiratory status in patients receiving opioids; monitoring neuraxial anesthesia; and education to patient and primary care of treatment plans when patients transition to outpatient care.<sup>21</sup> The recommendation specific to discharge recommends patient education, tapering of analgesics after discharge, and an individualized approach to drug therapy and tapering.<sup>21</sup> These recommendations are logical, but challenging to research with RCTs, which likely explains the lack of high-quality evidence.

Other clinical practice guidelines relevant to specific surgeries or surgical types are available; however, their inclusion was deemed beyond the scope of this review. The focus of our report is on postoperative pain following discharge from surgical facilities. While interventions mentioned in these guidelines likely affect post-discharge pain, it is not directly emphasized.

**Table 2. Current guidelines: treatment for postoperative pain**

Clinical Practice Guideline	Population	Setting	Recommendations
American Pain Society (Chou 2016 <sup>21</sup> )	Adults and children undergoing surgery	Not specified	1. Individualized, combination therapies -Drug and nondrug 2. Patient/caregiver education 3. Organizational policies 4. Transitions to other settings

## Systematic Reviews

We identified a total of 35 systematic reviews including 116 unique trials evaluating the effectiveness of a wide variety of interventions on postdischarge postoperative pain (i.e., reporting postdischarge outcomes) (Appendix Table F1).<sup>34-69</sup> Nearly all reviews addressed adults; only two studied interventions in children and/or adolescents. All included trials conducted in surgical facilities, but they rarely restricted eligibility to a certain type of surgical facility (inpatient or outpatient). Most systematic reviews enrolled trials on postoperative pain treatment following a specific surgery type, most frequently orthopedic surgeries. Liposomal bupivacaine and dexamethasone were the most frequently studied interventions in eligible systematic reviews. Most reported pain outcomes that appeared to be measured with scales primarily assessing pain intensity.

None of the eligible systematic reviews focused on postdischarge prescribing. Therefore, we expanded our search date for systematic reviews that specifically addressed interventions prescribed at discharge from the surgical facility, and identified only one additional review.

These systematic reviews analyzed many comparisons (Figure 2), the most common being anesthetic versus placebo and different types or modes of anesthetic versus each other. In these studies, the intervention and the comparison are adjuncts to other perioperative pain interventions and may be only one component of combination therapies addressing postoperative pain control. Recent reviews also frequently addressed different drug combinations.

## Original Research

We searched for recent RCTs published since previous systematic reviews. We screened the titles and abstracts from 362 references, 27 of which appeared to be RCTs published primarily since 2017, of treatments for postoperative pain and reporting outcomes postdischarge. These RCTs offer new data on the effectiveness and comparative effectiveness of NSAIDs, opioids, anticonvulsants, and combination treatments.

## Research Gaps

Despite many systematic reviews of treatments for perioperative pain, few focused on specific populations such as individuals with substance misuse issues, rural residents, pregnant women, and older adults. Yet, better understanding is needed of how to best treat postoperative pain in individuals with comorbidities, because of the average age of surgical patients and the likelihood of comorbidities in that age-group.

Additionally, systematic reviews often failed to clarify the type of surgical facility involved. A review focused specifically on postdischarge pain control after outpatient surgery would provide valuable information.

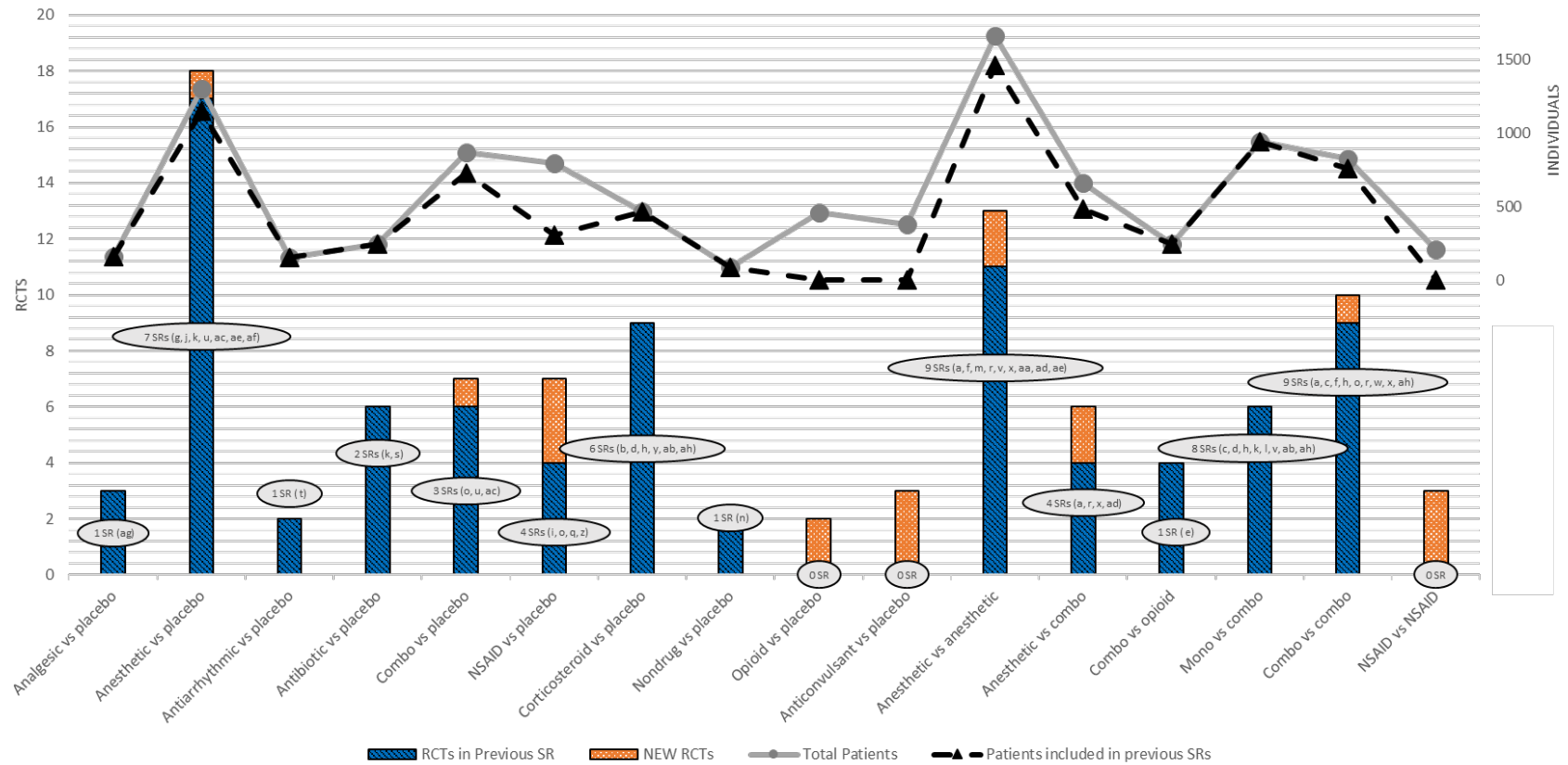
While pain is consistently reported in previous systematic reviews, most of these analyze scales that measure primarily pain intensity. Scales that better characterize pain and include elements assessing function would provide richer data. Also lacking are systematic reviews that

analyze longer-term pain and opioid use; focusing on these outcomes might improve understanding of the transition from acute to subacute and chronic pain.

Systematic reviews infrequently reported harms other than nausea and vomiting. Other harms associated with opioids, such as falls, should be examined.



**Figure 2. Comparisons addressed in systematic reviews and new trials: postoperative postdischarge pain**



a = Cao 2017; b = Chen 2017; c = Fan 2018a; d = Fan 2018b; e = Jia 2017; f = Li 2018a; g = Li 2018b; h = Li 2018c; i = Liang 2017; j = Liu 2018; k = Lyons 2017; l = Ma 2016; m = Ma 2017; n = Powell 2016; o = Qiu 2017; p = Sproat 2016; q = Sun 2018; r = Wang 2017; s = Wanis 2017; t = Weibel 2018; u = Wilson-Smith 2018; v = Wu 2016; w = Xing 2017; x = Yan 2017; y = Yang 2017a; z = Yang 2017b; aa = Yu 2018; ab = Yue 2017; ac = Zhang 2017a; ad = Zhang 2017b; ae = Zhang 2017c; af = Zhao 2018a; ag = Zhao 2018b; ah = Zhou 2018

## **Dental Procedures and Oral Surgery**

Dental procedures and oral surgery commonly result in acute pain and involve treatments with analgesics, often opioids. A recent observational study examining administrative data highlighted a correlation between opioid prescriptions for opioid naïve patients from dental clinics and subsequent opioid misuse or abuse in adolescents and young adults compared to a cohort of opioid-naïve counterparts.<sup>70</sup> This is especially alarming given the large proportion of adolescents and young adults undergoing third molar extraction.

## **Guidelines**

We found no recent high-quality U.S.-based guidelines on treatments for pain associated with dental procedures and oral surgery. The American Dental Association and the American Association of Oral and Maxillofacial Surgeons have issued statements regarding opioid use that support NSAIDs as a first-line drug for pain relief, published in 2018 and 2017.<sup>71, 72</sup> Regarding opioids, the statements recommend screening for history of substance use disorder and then starting at the lowest possible dose and shortest duration.

## **Systematic Reviews**

We identified 17 recent systematic reviews, sixteen of which<sup>73-88</sup> analyzed data from 119 RCTs evaluating drug interventions for pain management, and one analyzed data from five RCTs on hilotherapy.<sup>77</sup> Among the interventions addressed in eligible systematic reviews included acetaminophen, NSAIDs, corticosteroids, and opioids (Appendix Table G1). Only one systematic review addressed children, while the rest focused on adults. Most RCTs focused on adults undergoing oral surgery or other dental procedures in dental clinics and oral surgery facilities. Procedures most commonly studied included third molar extraction and root canals. All reviews of drug interventions analyzed only short-term pain (<48 hours). Several comparisons were studied in previous systematic reviews (Figure 3).

## **Original Research**

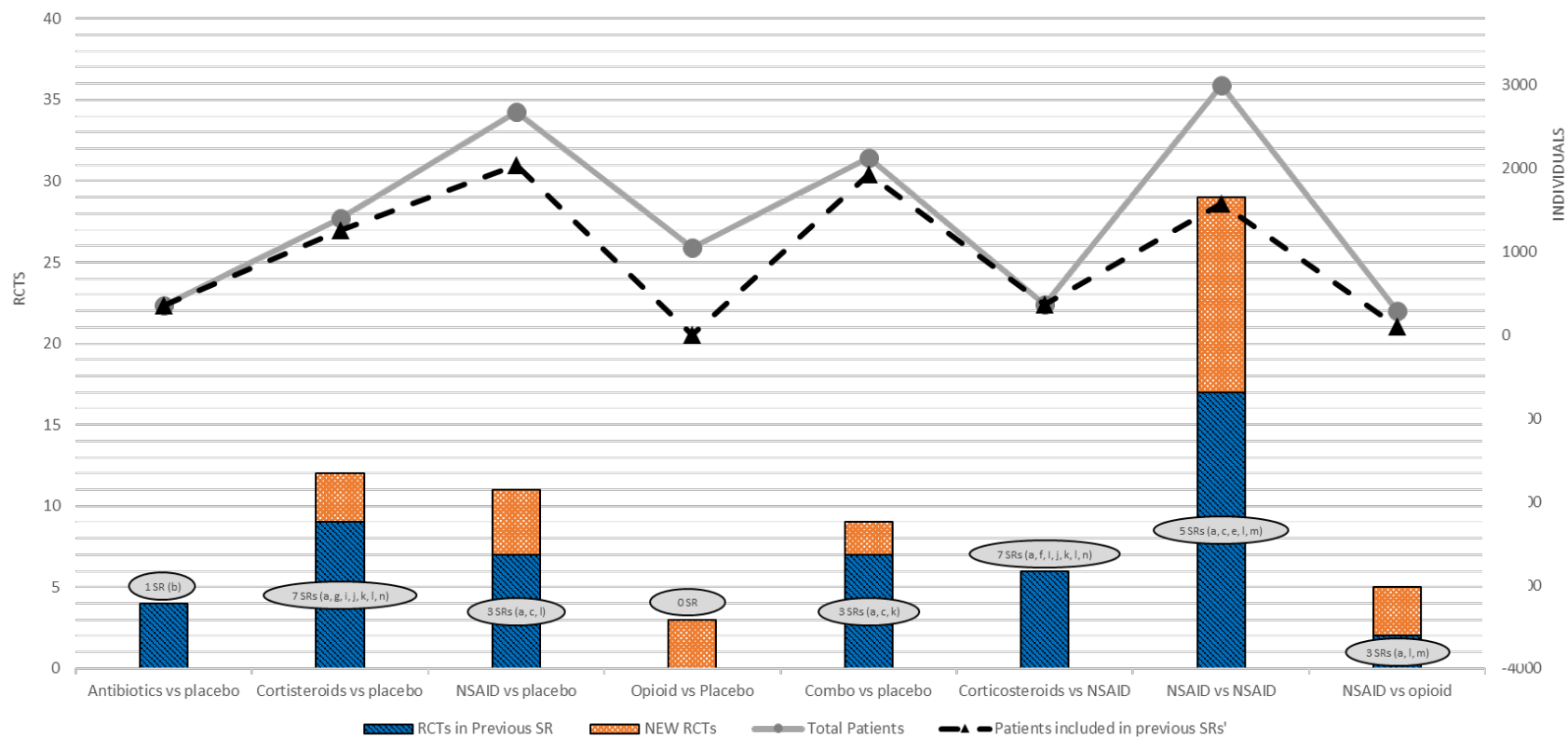
We searched for published RCTs not included in previous eligible systematic reviews. We screened the titles and abstracts from 315 references and identified 80 references that appeared to be RCTs of pain treatments following dental procedures or oral surgery. Several additional RCTs on opioids were available and not included in previous systematic reviews. The most frequently studied comparisons involved NSAIDs. Approximately half of the RCTs that compared one NSAID to another have been reported in a systematic review. The next most frequently studied comparisons were NSAIDs versus placebo, glucocorticoids versus placebo, and analgesic and antipyretics versus placebo (Figure 3).

## **Research Gaps**

We identified several research gaps. Research was limited regarding pain treatment following dental procedures and oral surgery in children and adolescents. A rigorous and comprehensive review of postoperative pain treatments for adolescents and young adults after third molar extractions would be informative given how frequent this procedure is in this population. Additionally, very few systematic reviews analyzed outcomes beyond 48 hours following dental procedures and oral surgeries. Trials that follow patients to determine their pain control and opioid usage in the week after the procedure would add value to the field. Improving

understanding of the circumstances that lead to opioid misuse after oral surgery, and identifying the most effective therapies for this type of pain and better opioid stewardship practices, could lead to better clinical decisions.

**Figure 3. Comparisons addressed in systematic reviews and new trials: dental procedures and oral surgery**



a = Amin 2016 (anal); b = Amin 2016 (anti); c = Bailly 2014; d = Chen 2017; e = Costa 2015; f = Falci 2017; g = Fernandez 2018; h = Larsen 2018; i = Nath 2018; j = Noreugia 2018; k = Shamszadeh 2018; l = Shirvani 2017; m = Smith 2017; n = Suneel 2018

# Nonsurgical

## Musculoskeletal Pain

Musculoskeletal pain is a common reason for opioid prescriptions. Effectively treating acute musculoskeletal pain has the potential to decrease transitions to chronic pain and long-term reliance on opioids. We mapped the evidence on pain treatment for two common types of musculoskeletal pain, acute back and neck pain. We aggregated interventions into broad treatment classes (Appendix Table D2). Nondrug interventions were classified as exercise (any), spinal manipulative therapy (any provider), muscle therapy (e.g. massage, trigger point), physiotherapy modalities (e.g. ultrasound, hot packs, traction, low-level laser), acupuncture, brace/support, or combination therapies (two or more nondrug interventions, or drug plus nondrug intervention).

## Acute Back Pain

### Guidelines

We identified two eligible clinical practice guidelines relevant to treating acute back pain (Table 3). Most systematic reviews and randomized controlled trials on back pain focus on low back pain. The 2017 American College of Physicians developed a comprehensive high-quality guideline on the management of acute, subacute, and chronic low back pain (Table 3).<sup>89</sup> The first line recommendation for acute low back pain includes nondrug approaches such as heat, acupuncture, spinal manipulation, and massage. NSAIDs and muscle relaxants may also be used. Exercise is weakly recommended for radicular back pain.<sup>89</sup> The VA-DOD 2017 guideline recommended self-care (stay active, superficial heat) and nonopioids (NSAIDs, muscle relaxants) for acute low back pain of less than 4 weeks' duration.<sup>90 91</sup>

**Table 3. Current guidelines: treatments for acute back pain**

Clinical Practice Guideline	Population	Setting	Interventions Addressed	Recommendations
American College of Physicians 2017 <sup>89</sup>	Adults with acute, subacute, or chronic LBP	Not specified	Any noninvasive (pharmacologic & nonpharmacologic)	1. Use nondrug approaches 1st: superficial heat, massage, acupuncture, spinal manipulation. 2. If desired, NSAIDs or skeletal muscle relaxants  <u>Radicular back pain:</u> 1. Exercise
Department of Veterans Affairs and Department of Defense 2017 <sup>90</sup>	Adults with acute, subacute, or chronic LBP	Any setting	Pharmacologic Nonpharmacologic Self-care (ex., heat, books) Other (i.e. interdisciplinary rehabilitation)	1. Start with self-care and NSAIDs or nonbenzodiazepine muscle relaxants. 2. Reassess after 4 weeks. 3. Opioids should be prescribed at the lowest dose for the shortest duration possible.

**Abbreviations:** LBP=low back pain; NR: not reported; NSAIDs=nonsteroidal anti-inflammatory drugs

## Systematic Reviews

We identified 14 eligible systematic reviews (Appendix Table H1). The American College of Physicians guideline was based on two systematic reviews.<sup>92, 93</sup> We identified 12 other eligible reviews published from 2016 to 2018.<sup>94-105</sup> All included systematic reviews and new randomized trials focused on low back pain; no studies reported mid-back pain. Most studies included in the systematic reviews enrolled mixed samples of adults with acute, subacute, or chronic back pain. Only two focused exclusively on acute back pain.<sup>97, 102</sup> Most studies examined central (nonradicular) low back pain; several addressed adults with radicular (nerve root) pain into the leg(s). Treatment setting was not often specified, but most involved interventions delivered in primary and specialty care settings. One review examined nonchronic low back pain seen in emergency departments.<sup>94</sup> Many reviews focused on specific interventions such as epidural steroid injections<sup>100, 103</sup> or NSAIDs.<sup>96</sup>

The 14 systematic reviews included 92 trials that enrolled some or all participants with acute low back pain. Reviews addressed numerous comparisons, (Figure 4) but mostly nonopioid treatment of acute low back pain, versus another nonopioid, or an inactive comparator. Spinal manipulation was the most common nondrug approach reviewed. The majority of participants were adults with nonspecific acute low back pain; fewer included adults with low back and sciatica or radicular pain.

## Original Research

We identified 127 references published since the search dates of the eligible systematic reviews, after 2016. Title and abstract screening of these identified 22 potentially relevant RCTs that reported intervention outcomes for acute low back pain. More than half of new RCTs examined drug interventions delivered by various modes. Five RCTs examined drug combinations versus a single nonopioid drug, placebo, or another drug combination. Nine nondrug new RCTs examined six types of approaches, including spinal manipulation, muscle therapy, physiotherapy modalities, acupuncture, and education/advice.

## Research Gaps

Among the reviews we identified from the past three years, we found no single, high-quality systematic review on acute back pain interventions that clearly summarized the evidence from the past 20 years. Systematic reviews that analyzed data from mixed samples with acute and chronic pain are not easily interpretable when translating evidence into practice.

Recent systematic reviews are primarily focused on nonopioid therapies for acute low back pain. Nondrug approaches, alone or in combination with other treatments, are less commonly studied. A combination of therapies early in the course of back pain may better reduce acute pain and enable earlier transition from passive (i.e., muscle work) to active therapies (i.e., exercise). We found no studies of sequencing from drug to nondrug or from passive to active treatments, although these approaches are common in practice.

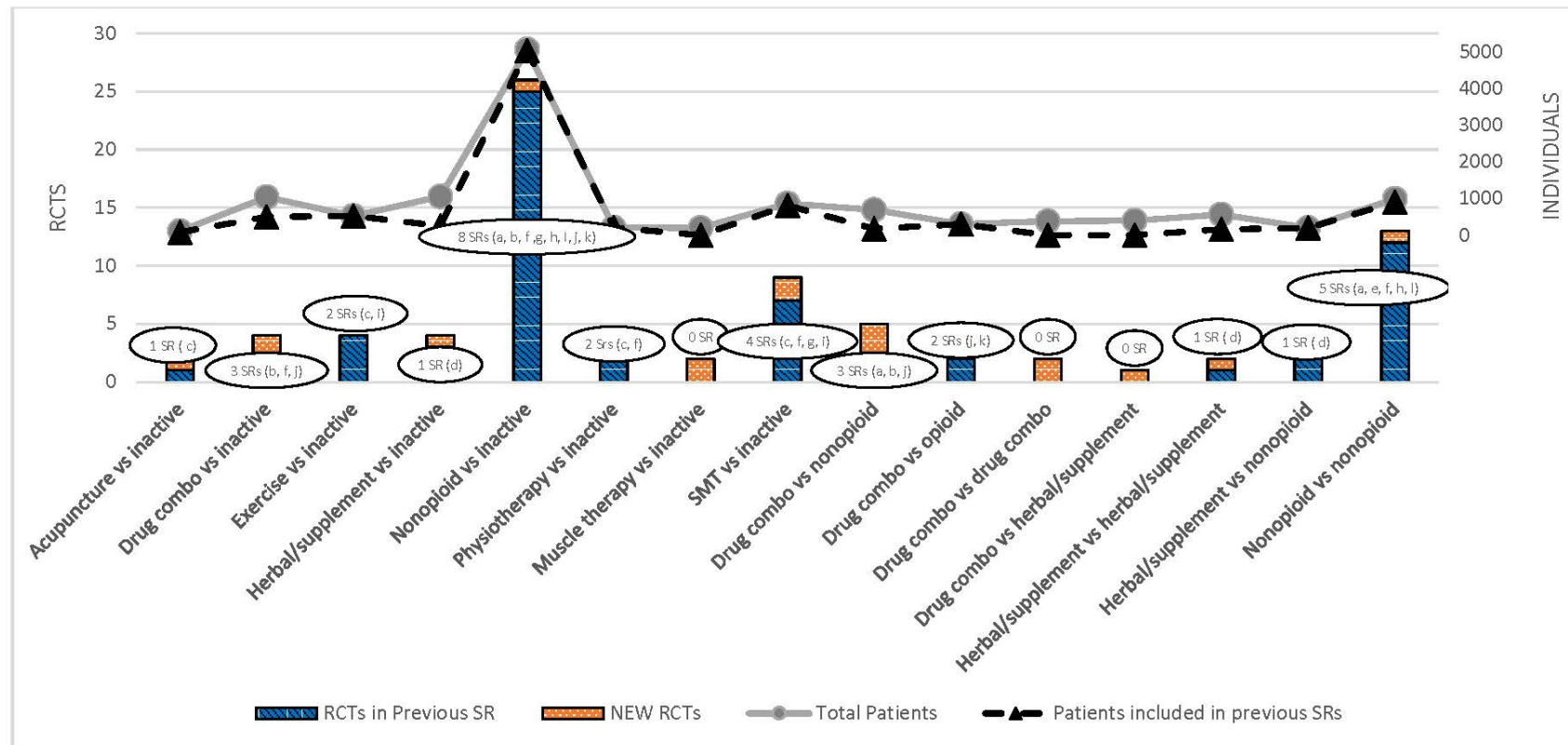
Many current reviews failed to report potential underlying causes that may impact treatment selection, such as spinal stenosis or disc herniation. Back pain arises from many different sources. While the most offending or causative factor is often indeterminable, identifying subgroups of patients that may necessitate treatment modifications, such as those with a history of spine surgery, prior significant low back pain episodes, radicular pain, and/or spinal stenosis may better guide treatment selections.

Systematic reviews failed to address episodic back pain, a fairly common complaint among adults. Eligible reviews did not differentiate between initial versus recurrent low back pain episodes. Nor did they specify whether recurrent episodes, which may grow more severe over time, benefit from different treatments or treatment combinations than do initial back pain episodes.

Systematic reviews primarily addressed young to middle-aged adults. Evidence is lacking on which interventions are suitable for older adults with or without stenosis and radicular pain, and any necessary treatment modifications appropriate for this age group, many of whom have mobility-limiting osteoarthritis and comorbid conditions.

The incremental benefits of combining interventions is poorly understood. More research is needed on these approaches for acute back pain. This research should aim to identify the optimal sequencing, intensity, and duration of component therapies.

**Figure 4. Comparisons addressed in systematic reviews and new trials: acute low back pain**



a = Abdel 2017; b = Chou 2017 (pharm); c = Chou 2017 (nonpharm); d = Gagnier 2016; e = Liu 2016; f = Machado 2017; g = Paige 2017; h = Rasmussen-Bar 2017; i = Rothberg 2017; j = Song 2018; k = Strudwick 2018; l = Wei 2016

**Abbreviations:** SMT=spinal manipulative therapy

**Note:** Inactive comparisons included placebo, sham procedures, and usual care.



## Acute Neck Pain

### Guidelines

We identified one eligible clinical practice guideline on the treatment of neck pain (Table 4). The 2017 American Physical Therapy Association guideline distinguished between neck pain with and without mobility deficits, recommending manipulation, exercise, and mobilization when mobility deficits are present, and instead advising education, exercise, and combined approaches, with minimal use of cervical collars, when mobility deficits are absent.

**Table 4. Current guidelines: treatments for acute neck pain**

Clinical Practice Guideline	Population	Setting	Recommendations	Not Recommended
Blanpied 2017 <sup>106</sup>	Patients with acute neck pain with mobility deficits;	Clinics	Thoracic manipulation, exercises, strengthening; cervical manipulation and/or mobilization	NR
Blanpied 2017 <sup>106</sup>	Patients with acute neck pain and no mobility deficits	Clinics	Education, exercises, reassurance; combined interventions;	Minimize use of cervical collar

Abbreviations: NR = not reported

### Systematic Reviews

We identified eight eligible systematic reviews addressing treatments for acute neck pain (Appendix Table I1).<sup>107-114</sup> All included studies of acute neck pain treatment enrolled samples of individuals with acute, subacute, and chronic neck pain. Studies of adults with acute neck pain were typically a small proportion of the those eligible for each review. Few reviews restricted the settings in which eligible studies were conducted. Most either did not specify setting or reported that trials in any setting were eligible.

The eight systematic reviews included thirteen unique trials analyzing treatments for acute neck pain (Figure 5). Major comparisons addressed in these reviews include muscle therapy versus sham therapy; physiotherapy versus sham therapy; and comparison of different spinal manipulation techniques.

### Original Research

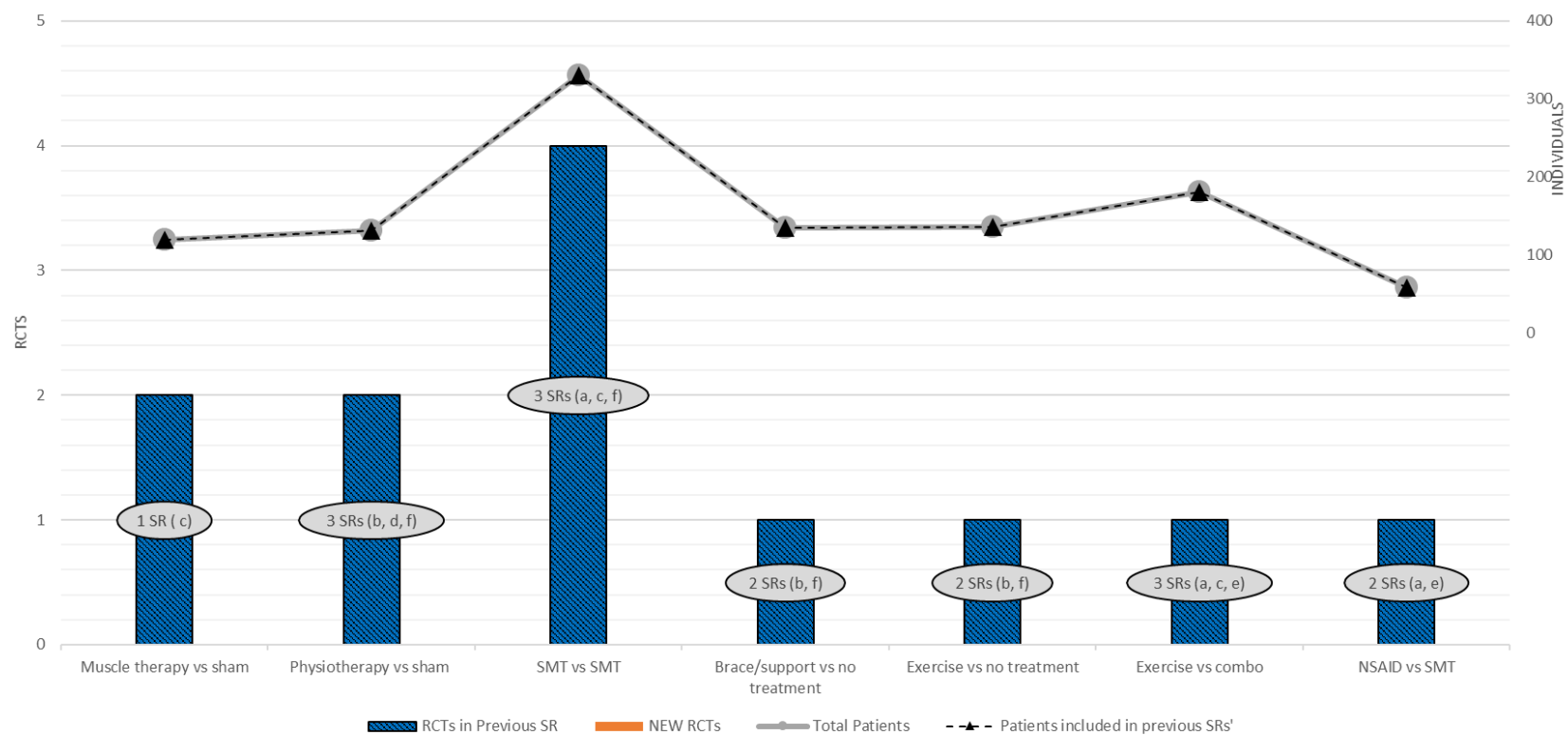
We searched for new RCTs published since the search dates of eligible systematic reviews and identified 34 references, of which five were potentially relevant RCTs of acute neck pain treatments. The new RCTs analyzed a variety of interventions including dry needling and drug therapies (benztropine, NSAIDs, local anesthetics, and glucocorticoids). New RCTs were relatively small and addressed comparisons not previously addressed in systematic reviews of acute neck pain treatments.

## **Research Gaps**

Few eligible systematic reviews examined drug interventions for acute neck pain. A rigorous comprehensive systematic review evaluating all treatments for acute neck pain by underlying cause would provide necessary information for decision-making. However, available research appears limited for such a review. The research on neck and back pain appears to use slightly different definitions of acute and subacute pain.

In order for a new review of treatments for initial or episodic neck pain to provide valuable evidence to prevent transition to chronic pain, experts should first be solicited to determine the appropriate timeframes to include in such a review.

**Figure 5. Comparisons addressed in systematic reviews: acute neck pain**



a = Bussieres 2016; b = Gross 2013; c = Hidalgo 2017; d = Kadhimi-Saleh 2013; e = Sutton 2016; f = Wong 2016

**Abbreviations:** NSAID = nonsteroidal anti-inflammatory drug; SMT = spinal manipulation therapy

## **Acute Pain Associated With Fractures**

### **Guidelines**

We identified no eligible recent U.S.-based guideline addressing the management of acute pain associated with fractures.

### **Systematic Reviews**

We identified six eligible systematic reviews evaluating treatments for acute pain associated with fracture (Appendix Table J1).<sup>115-120</sup> Two evaluated treatments delivered specifically in emergency settings,<sup>118, 119</sup> and all six focused on older adults and evaluated acute pain treatments for fractures common in this population (hip fracture, femoral neck fracture, and osteoporotic compression fracture). The six systematic reviews included 45 unique trials.

Interventions evaluated in systematic reviews evaluating pain treatment attributable to osteoporotic compression fracture included procedures (vertebroplasty, kyphoplasty), taping, and bracing (Figure 6). Few trials studied analgesics or anesthetics. Interventions for treating pain associated with hip fracture included regional blocks and analgesics (primarily opioids).

### **Original Research**

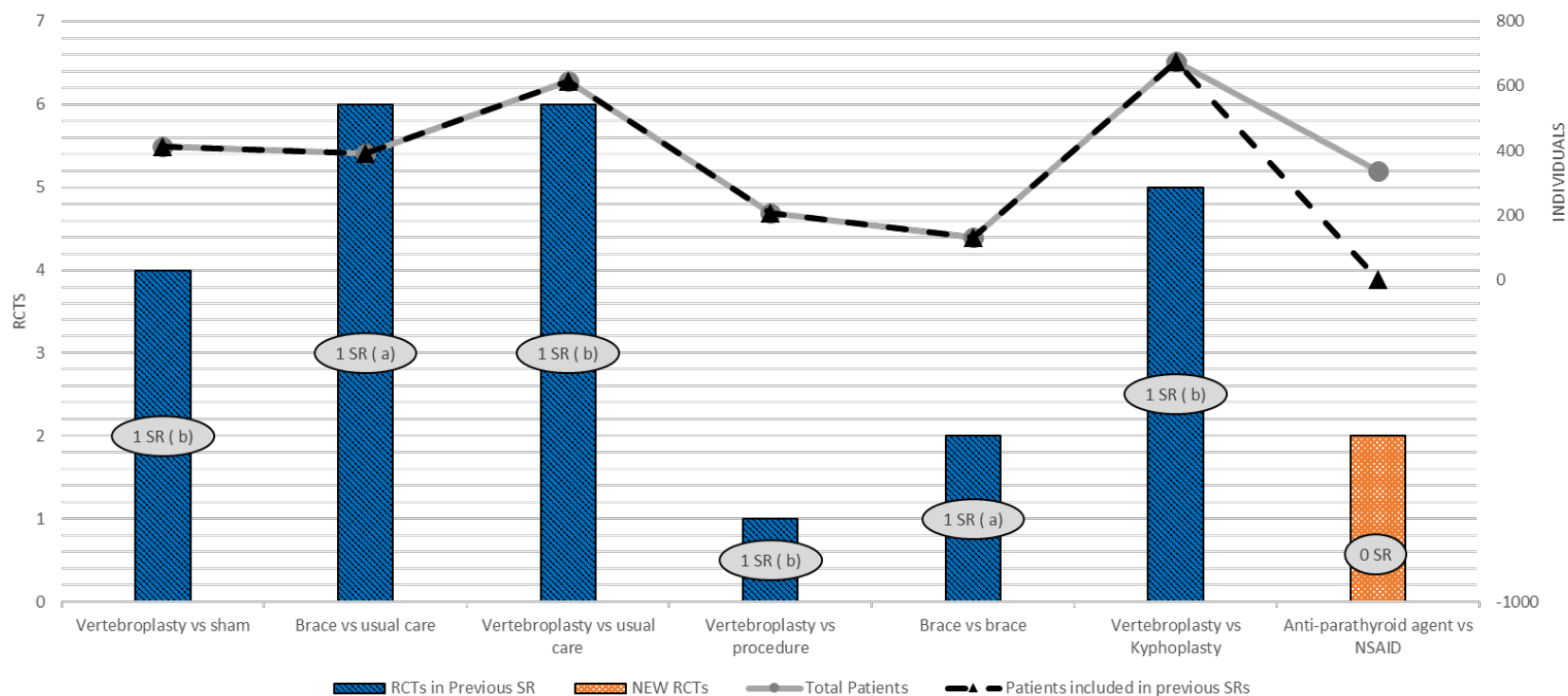
We searched for new RCTs published since the search dates of eligible systematic reviews and identified 108 references. Title and abstract screening of these identified 30 potentially relevant RCTs analyzing pain treatment for fracture. Few new RCTs studied pain treatments for pain attributable to hip fracture and osteoporotic compression fractures, but instead addressed other types of fracture in adults and children. The new RCTs analyzed a variety of drug and nondrug (including opioids) therapies for rib and limb fractures.

### **Research Gaps**

We identified several research gaps. No eligible systematic review addressed pain treatment for fractures in children and adolescents, despite this being a common reason for introduction to opioids in this population. Likewise, no eligible systematic review addressed pain treatment for fractures in individuals with substance use disorder.

Evidence addressing pain treatment for osteoporotic compression fractures and hip fracture could be updated with a rigorous comprehensive systematic review. Systematic reviews did not fully address harms, especially with opioid interventions. Fall risk is an important harm in older adults.

**Figure 6. Comparisons addressed in systematic reviews and new trials: fractures**



a = Goodwin 2016; b = Zhou 2018

## **Visceral Pain**

### **Renal Colic**

Renal colic, the pain attributable to kidney stones, is a common reason for pain and analgesic use. We searched for U.S.-based clinical practice guidelines and systematic reviews addressing treatments for renal colic.

### **Guidelines**

We found no eligible U.S.-based guideline addressing treatment for renal colic. The European Association of Urology published in 2018 a clinical practice guideline strongly recommending treating renal colic with NSAIDs over opioids.<sup>121</sup>

### **Systematic Reviews**

We identified four eligible systematic reviews including 88 trials examining renal colic treatments (Appendix Table K1).<sup>122-125</sup> Two reviews specifically addressed emergency departments, and the other two likely did, as well, but did not specify. The included studies in the reviews only partially overlapped; no one review was subsumed by another. One review included an unpublished study conducted by the review author; although risk of bias was assessed, inclusion criteria was not provided for this review.<sup>124</sup>

Several comparisons studied were addressed in previous systematic reviews (Figure 7). Most medications were delivered intramuscularly or intravenously. The majority of trials and systematic reviews analyzed the comparative effectiveness of NSAIDs versus other NSAIDs (21 trials and two SRs) or versus opioids, antispasmodics, antidiuretics, acetaminophen, or combination therapy. The most common NSAIDs studied were diclofenac, indomethacin, and ketorolac. The majority of NSAID trials have already been included in a systematic review.

All systematic reviews evaluated very short-term pain, and none assessed function, persistent opioid use, or productivity.

### **Original Research**

We searched for new RCTs examining treatments for renal colic and identified 119 references. Screening titles and abstracts of these references identified 40 potentially relevant RCTs examining renal colic treatment. Eleven new RCTs assessed monotherapy versus combination therapy. Most compared an NSAID (mostly diclofenac or ketorolac) versus various combinations of acetaminophen, anticholinergics, antidiuretics, antispasmodics, NSAIDs, and opioids.

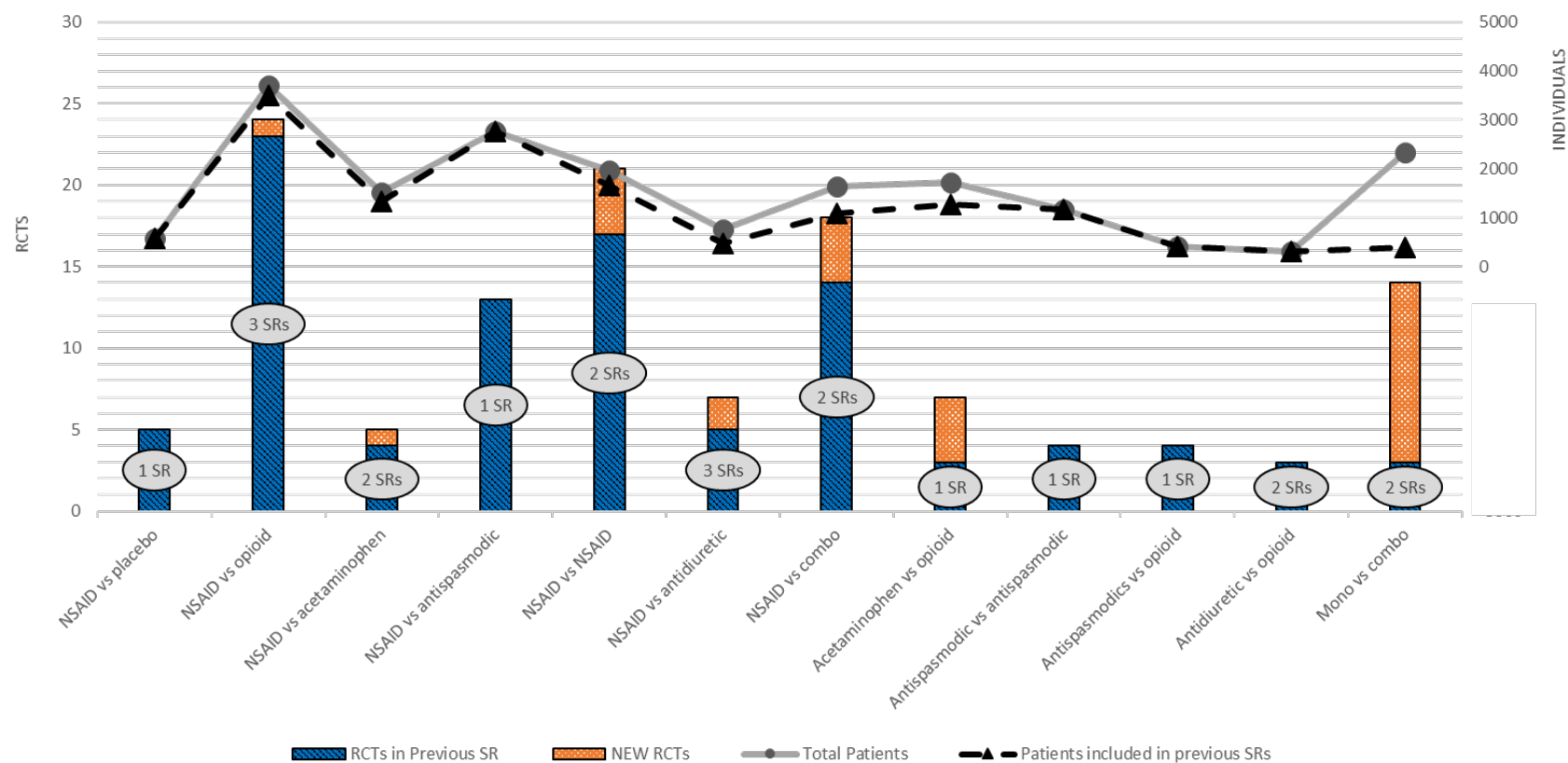
### **Research Gaps**

As with other acute pain conditions, important information could be provided by a rigorous comprehensive systematic review, perhaps with a network meta-analysis, summarizing the full body of literature on drug treatment for renal colic. Available reviews, while not necessarily out of date, present a fragmented view of pain management and pay little attention to nondrug approaches.

The identified reviews did not address subpopulations of interest. Pediatric populations may be less relevant since children differ from adults in terms of the signs and symptoms of nephrolithiasis, because acute flank pain is less common in children.<sup>126</sup> In cases where kidney

stones are not removed surgically, reviews and guidelines are silent on pain management prior to procedures to eliminate the stones. Therefore, attention to several other subpopulations may still be high priority. In the short term, inclusion of observational studies may be necessary to make use of the best evidence available.

**Figure 7. Comparisons addressed in systematic reviews and new trials: renal colic**



a = Afshar 2015; b = Pathan 2018; c = Sin 2017; d = Jalili 2016



## **Orofacial Pain**

### **Dental Pain**

Nonsurgical dental pain primarily involves pulpitis or acute apical abscesses. These conditions often lead to dental procedures (extractions or root canal). Individuals experiencing this type of pain often seek treatment to avoid procedures or to alleviate the pain until procedures can be performed. Relatively low rates of dental insurance coverage further compound this problem of substituting nondefinitive drug therapies for dental procedures which can incur heavy out-of-pocket costs for uninsured patients. Individuals might seek attention from medical providers in emergency departments where treatment is usually restricted to temporary symptom relief by providing prescriptions for pain medication, often opioids.

### **Guidelines**

We identified no eligible guidelines relevant to nonsurgical dental pain.

### **Systematic Reviews**

We identified three eligible systematic reviews which included treatments for some types of dental pain (Appendix Table L1).<sup>73-75</sup>. Included in the three systematic reviews were five RCTs studying interventions for pain management for a variety of conditions, primarily toothache (pulpitis, infection) and postoperative dental pain. None of the trials assessed opioids and only short-term pain (<48 hours) outcomes were reported.

### **Original Research**

We searched for dental pain RCTs not included in previous systematic reviews and identified 10 additional RCTs evaluating treatments for acute nonsurgical dental pain. Interventions addressed include anesthetics, NSAIDs, antibiotics, gabapentinoids, and drug combinations.

### **Research Gaps**

Research was very limited for management of nonsurgical dental pain. No systematic reviews focused solely on nonsurgical dental pain. We found no reviews focusing on children, adolescents, or any subpopulations. Reported pain outcomes were short-term.

Given the limited evidence on the treatment of nonsurgical dental pain, more insight might be gained through a systematic review using observational studies to summarize the incidence and prevalence of this pain as well as the individual behaviors in seeking treatment.

## **Episodic Pain Conditions**

### **Acute Migraine**

Acute migraine is a painful condition with many available treatment options. Individuals with episodic and chronic migraine are often prescribed medications from their primary or specialty care clinics to have on hand in case of acute migraine, because starting treatment as soon as possible improves effectiveness. Several drug classes in various treatment modes are available for this purpose (pills, sublingual tablets, nasal sprays, intramuscular injections). Acute migraine is also often treated in emergency settings, where the drugs used, except those delivered intravenously, are similar to those prescribed by primary and specialty clinics.

## Guidelines

We identified one eligible guideline on the management of acute migraine (Table 5).<sup>127</sup> It was developed by the 2016 American Headache Society Guideline Committee, and addressed injectable medications for treating adults with acute migraines in emergency settings. The guideline recommends certain medications as first line including metoclopramide, prochlorperazine, and sumatriptan. Opioids are not recommended for treatment of acute migraine.

Other U.S.-based guidelines relevant to acute migraine treatment were out of date. The United States Headache Consortium published a 2000 guideline on the pharmacologic management of acute attacks in primary care settings.<sup>128</sup> It is unclear if this guideline will be updated. We also identified a 2004 guideline on migraine treatment for children and adolescents published by the American Academy of Neurology Quality Standards Committee and the Practice Committee of the Child Neurology Society.<sup>129</sup> An update of this guideline is currently in progress.<sup>130</sup>

**Table 5. Current guidelines: treatments for acute migraine**

Clinical Practice Guideline	Population	Setting	Interventions Addressed	Recommendations	Not Recommended
American Headache Society Guideline Committee (Orr 2016 <sup>127</sup> )	Adults	Emergency	Injectable medications	Metoclopramide Prochlorperazine Sumatriptan	Diphenhydramine Hydromorphone Lidocaine Morphine Octreotide

## Systematic Reviews

We identified 22 systematic reviews including 372 unique trials analyzing treatments for acute migraine (Appendix Table M1). We expanded publication dates because several interventions were obviously missing from the recent set of systematic reviews and we found no comprehensive review that included drug therapies typically provided in primary care and specialty clinic settings. The new search dates allowed for inclusion of a previous AHRQ review and several Cochrane reviews addressing specific drugs for acute migraine published between 2012 and 2014.<sup>131-144</sup> Most reviews evaluated treatments for adults and focused on emergency departments or primary care clinics. The AHRQ review addressed acute migraine treatments in adults treated in emergency settings with injectable medications.<sup>145</sup> A similar review was conducted to inform the American Headache Society Guideline Committee guideline.<sup>127</sup>

Several interventions have been studied in previous systematic reviews (Appendix Table M1), all of which addressed drug treatments via many different comparisons. Many systematic reviews included both placebo-controlled and active-controlled RCTs enrolling adults (Figure 8, Figure 9). Triptans were by far the most studied acute migraine drug with 13 systematic reviews and nearly 80 RCTs reporting placebo comparisons. Many comparisons are analyzed in previous systematic reviews, but again, most frequently these comparisons included triptans.

Treatment of acute migraine in children and adolescents was less frequently studied (Figure 10). The vast majority of the research is on triptans.

Most reviews assessed treatment effectiveness at different time points after treatment initiation. Headache relief, pain reduction, and relapse appeared to be the most commonly reported outcomes. Function was rarely analyzed in the migraine reviews. Several systematic reviews assessed whether patients were free of headache at 24 hours. Longer-term outcomes were rarely reported.

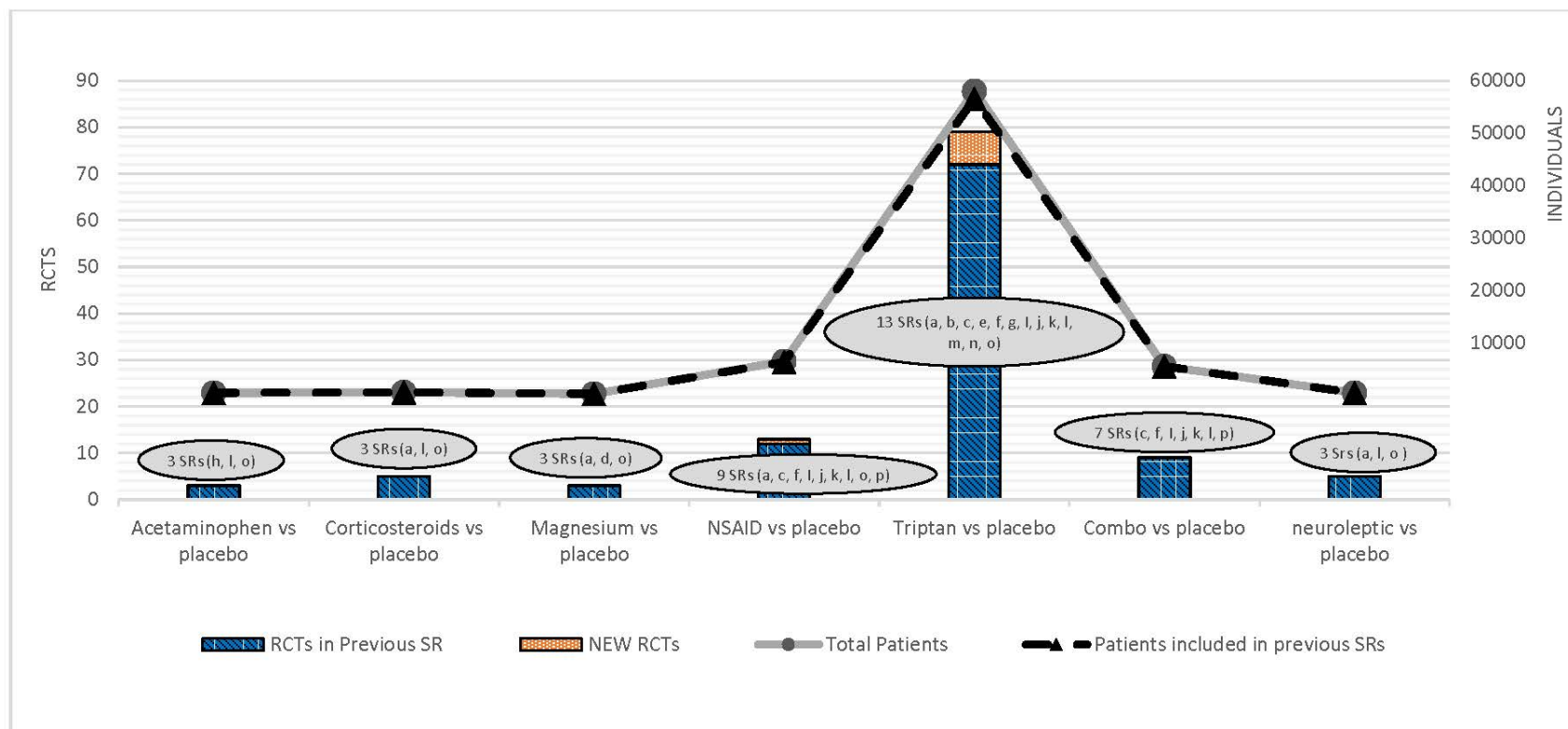
## **Original Research**

We searched for new RCTs published since relevant systematic reviews and identified 578 references. We reviewed the titles and abstracts of those references and identified 65 potentially relevant RCTs analyzing treatment for acute migraine. The majority of these new RCTs analyzed interventions previously analyzed in systematic reviews and could strengthen the evidence base for those interventions.

## **Research Gaps**

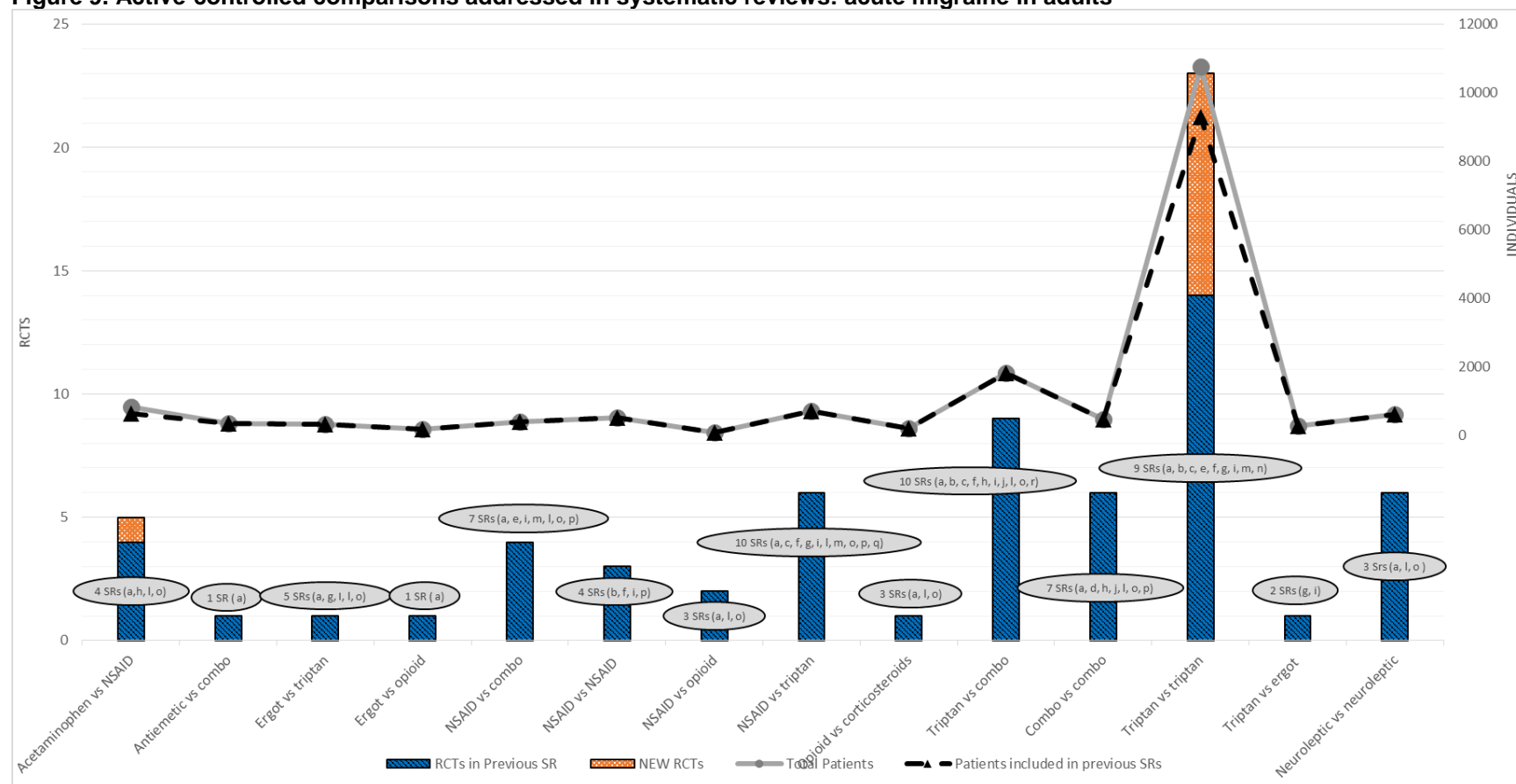
Few guidelines and systematic reviews addressed specific populations other than adults, and children and adolescents. We found no comprehensive review of medications prescribed in primary care or specialty clinics for acute migraine treatment in patients with episodic or chronic migraine. The AHRQ EPC review on injectable medications for acute migraine in emergency departments covers literature published through January 2012. An update of this review would provide timely evidence.

**Figure 8. Placebo-controlled comparisons addressed in systematic reviews: acute migraine in adults**



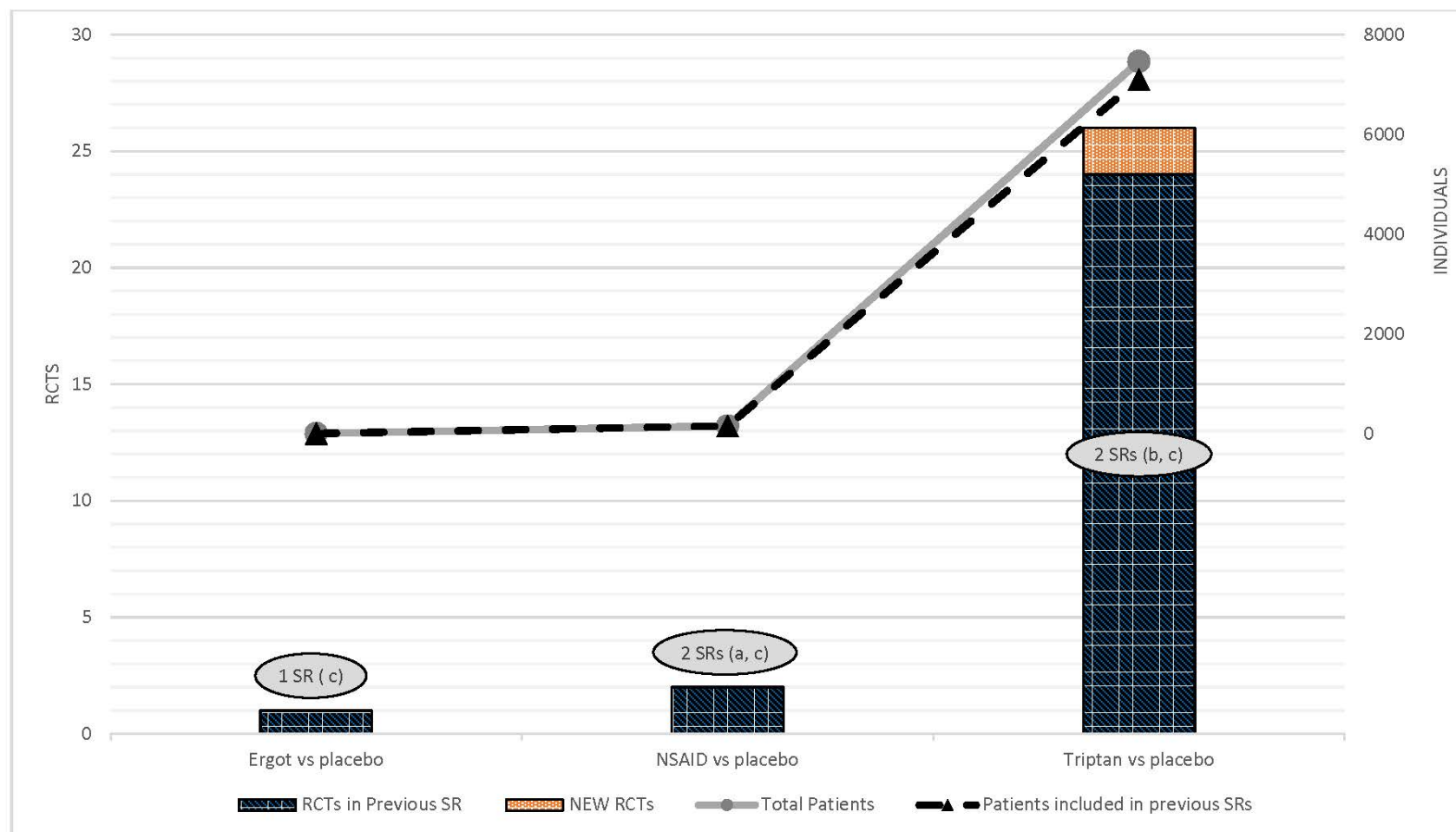
a = AHRQ 2012; b = Bird 2014; c = Cameron 2015; d = Choi 2014; e = Derry 2012 (sum-ins); f = Derry 2012 (sum-oral); g = Derry 2012 (sum-subq); h = Derry 2013 (acetaminophen); i = Derry 2014; j = Kirthi 2013; k = Law 2013; l = Law 2016; m = Menshaw 2018; n = Nirenburg 2015; o = Orr 2016; p = Rabbie 2013; q = Richer 2016; r = Derry 2012 (sum-rectal)

**Figure 9. Active-controlled comparisons addressed in systematic reviews: acute migraine in adults**



a = AHRQ 2012; b = Bird 2014; c = Cameron 2015; d = Choi 2014; e = Derry 2012 (sum-ins); f = Derry 2012 (sum-oral); g = Derry 2012 (sum-subq); h = Derry 2013 (acetaminophen); i = Derry 2014; j = Kirthi 2013; k = Law 2013; l = Law 2016; m = Menshaw 2018; n = Nirenburg 2015; o = Orr 2016; p = Rabbie 2013; q = Richer 2016; r = Derry 2012 (sum-rectal)

**Figure 10. Comparisons addressed in systematic reviews: acute migraine in children and adolescents**



a = Jeric 2018; b = Menshaw 2018; c = Richer 2016

## Sickle Cell Crisis

Individuals with sickle cell disease experience episodic pain related to their disease. These episodes are called sickle cell crisis or vaso-occlusive crisis.

### Guidelines

We identified one eligible guideline addressing acute pain attributable to sickle cell disease (Table 6).<sup>146</sup> The 2014 National Heart, Lung, and Blood Institute (NHLBI) convened a guideline panel, supported by an independent comprehensive systematic review conducted by Mayo Clinic, for management of sickle cell disease. The NHLBI guideline has been endorsed by many professional organizations, including the Academy of Emergency Medicine, American Academy of Pediatrics, and the American Society of Hematology. One section on managing acute complications provided an algorithm and recommended NSAIDs for acute pain in adults and children due to vaso-occlusive crisis.

**Table 6. Current guidelines: treatment for acute pain in sickle cell disease**

Clinical Practice Guideline	Population	Setting	Interventions Addressed	Firstline Treatments	Not Recommended
NHLBI 2014 <sup>146</sup>	Adults and children with sickle cell disease	All settings where patients present; ED or outpatient	Parenteral opioid therapy Meperidine NSAIDs Around the clock vs intermittent analgesics	NSAIDs for mild to moderate pain Parenteral opioid for severe pain	Blood transfusion unless other indications; Meperidine unless only effective opioid for individual patient

**Abbreviations:** ED = emergency department; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trials

### Systematic Reviews

In addition to the comprehensive systematic review conducted for the 2014 NHLBI guideline, we identified two relevant Cochrane systematic reviews (Appendix Table N1).<sup>147,148</sup> The three reviews included nine unique trials (Figure 11). None of the reviews focused on specific settings or subpopulations. Interventions addressed in the reviews for the NHLBI guideline included parenteral opioid therapy, NSAIDs, and meperidine. The review associated with the NHLBI clinical practice guideline also compared continuous versus intermittent analgesic infusion and reported on pain as primary outcome while mentioning few others. One Cochrane review examined fluid replacement for acute pain episodes to improve cellular hydration to slow or stop the sickling process; however, the search found no eligible RCTs.<sup>148</sup> The other Cochrane review examined low-molecular-weight heparins as anticoagulants with only one eligible RCT.<sup>147</sup>

Several comparisons were examined in previous systematic reviews (Figure 8). The NHLBI guideline included eight trials studying opioids, antithrombotics, and NSAIDs for pain control.

### Original Research

We searched for RCTs published since the search dates for these systematic reviews and identified 16 references. Title and abstract review show seven potentially eligible new RCTs evaluating pain treatments for sickle cell crisis. We identified no new RCTs of drugs previously addressed in systematic reviews. One RCT compared sedative and analgesic adjunct (nitric

oxide) versus placebo, and two RCTs assessed nondrug interventions including touch with music (versus attention control) and a weight-based opioid-dosing protocol (versus a patient-specific protocol).

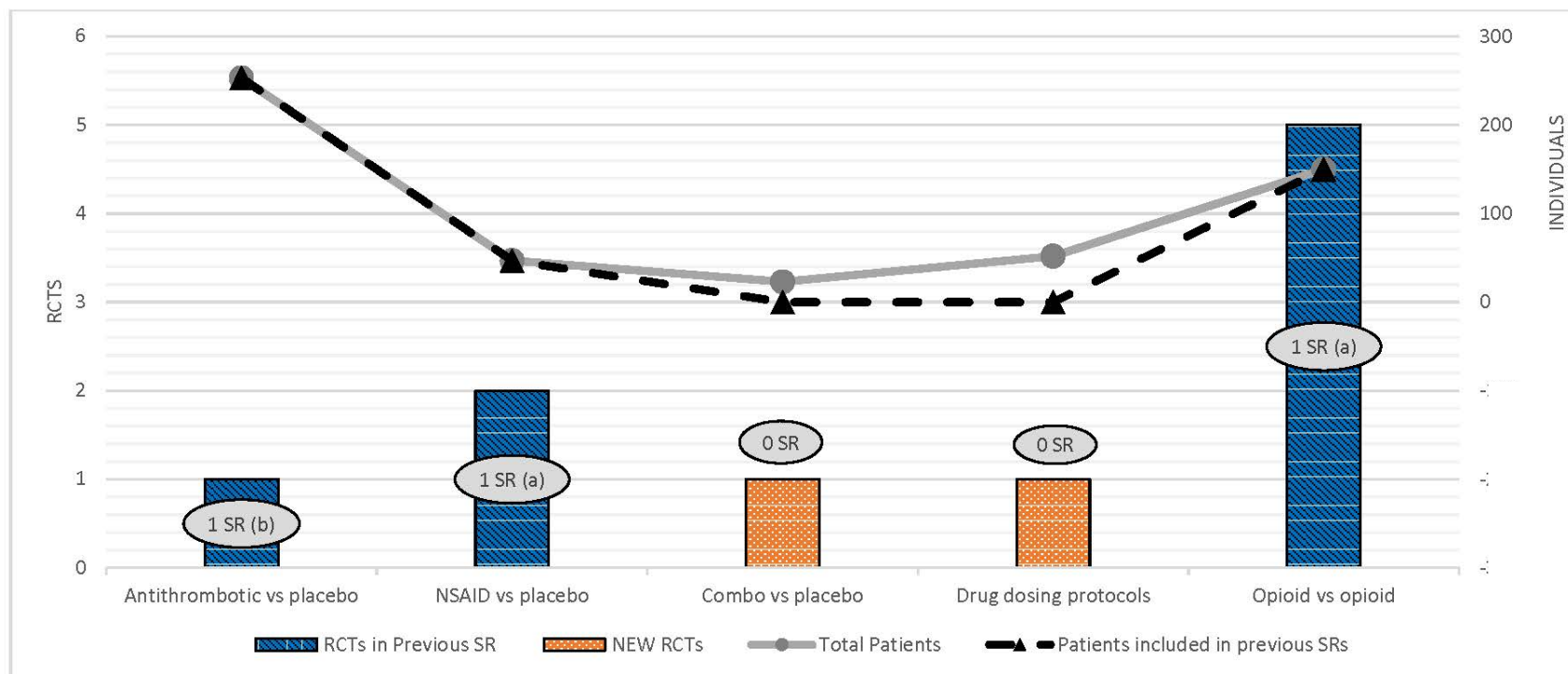
## **Research Gaps**

The NHLBI guideline recommends nondrug treatments for acute pain and parenteral opioids in patients also on long-acting opioids for chronic pain. The latter recommendation was adapted from the American Pain Society's 1999 guideline based on a systematic review of a broader population, since evidence specific to sickle cell populations was lacking. Nondrug treatments named included intravenous hydration, local heat, and distraction. Two trials of nondrug treatments have since been published. However, both were small and assessed very different interventions.

The NHLBI guideline did not address our subpopulations of interest, likely due to a lack of relevant studies



**Figure 11. Comparisons addressed in systematic reviews: sickle cell crisis**



a = NHLB 2014; b = van Zuuren 2015

## Discussion

Our evidence map describes interventions studied to treat acute pain associated with select conditions. Future research should explore effectiveness and comparative effectiveness of these and other interventions used in treating acute pain.

### Current Evidence

We mapped the evidence on the pain treatments for select acute pain conditions, including postoperative, musculoskeletal/fracture, dental pain, migraine, and sickle cell crisis pain. While a large body of research addressed some aspects of pain treatment for these conditions, important gaps remain. Notably, most research evaluated adults and very little addressed adolescents or older adults, despite that these populations both commonly experience these acute pain conditions. We ultimately identified a prominent disconnect between available research and the evidence needed to inform providers, patients, and policymakers about how to best treat the pain associated with these acute pain conditions.

Numerous news stories as well as professional associations and health policy initiatives have acknowledged that opioid prescribing is prevalent and excessive in the U.S. Yet, few systematic reviews or randomized controlled trials focused specifically on opioids. This is likely more common with chronic pain.

The largest evidence gap was for discharge prescribing and early postdischarge pain management in postoperative patients. The dominant focus of postoperative pain management reviews and trials was on inpatient pain management, while few systematic reviews focused on interventions provided at discharge from surgical facilities. The overwhelming majority of systematic reviews of postoperative pain interventions examined how additional perioperative interventions affected standard yet heterogeneous inpatient postoperative opioid use, and most focused on newer drugs (e.g. liposomal bupivacaine) or new approaches and routes for drug delivery (e.g. intra- or peri-articular). Harms, if reported, focused on limited specific adverse effects immediately following surgery; adverse effects after discharge have been insufficiently evaluated.

The evidence for acute low back pain interventions was limited. While there are many systematic reviews on back pain, few focus on acute back pain. Most systematic reviews did not limit eligibility criteria to acute pain, and instead analyzed effectiveness of interventions across acute, subacute, and chronic back pain.

Similarly, few systematic reviews or trials evaluated opioid use for dental procedures or oral surgical pain, despite a recent high-profile observational study showing that one third of opioid prescriptions filled by adolescents and young adults came from dental clinicians.<sup>70</sup> These patients were far more likely than a nonopioid exposed cohort to fill a second opioid prescription and be later treated for opioid abuse.<sup>70</sup> Rates of abuse among adolescent and young adult populations may be higher than among adults after first exposure to opioids.<sup>70</sup>

We identified many systematic reviews. Most focused narrowly on a specific intervention or comparison. Several acute pain conditions lacked rigorous, comprehensive reviews that addressed all potential treatments and analyzed comparative effectiveness of the array of potential treatments. With a shortage of head-to-head trials, rigorous comprehensive reviews that engage network meta-analysis where possible would allow various treatments to be compared in a meaningful and methodologically sound way.

## Guidance

Several recent high-quality U.S.-based clinical practice guidelines address several acute pain conditions (back pain, postsurgical pain, treatment of acute migraine in emergency settings, sickle cell crisis). Some of these guidelines intend to change practice and reduce reliance on opioids, and aim to prevent misuse of opioids by recommending the lowest possible dose and shortest duration when prescribed. Surgery-specific clinical practice guidelines are being developed in Europe and by some U.S.-based medical societies, but experts still need to debate whether these will be more valuable than general clinical practice guidelines on postoperative pain. Other acute pain conditions (renal colic, dental procedures and oral surgery, fracture) did not appear to have recent high-quality clinical practice guidelines. Updated versions of older clinical practice guidelines or brand-new guidelines from related associations could help inform clinicians on how to best avoid problems associated with opioid misuse among patients.

Nonetheless, even if up to date and relevant, clinical practice guidelines may not be as influential as they once were. Many health systems in the U.S. are developing guidance using their own data to provide very specific recommendations and standardized prescribing orders for use by clinicians in their systems. Therefore, an environmental scan of these practices and how the recommendations and/or order sets are developed would be valuable. Such information could further understanding of the evidence and the ability to translate it, while ultimately contributing to practice-based evidence when evidence-based practice is unavailable for specific subpopulations. Future research should also provide an overview of the different state-level guidance, as well as how that guidance was developed. An overview of all policies and regulations guiding acute pain treatment is necessary to fully appreciate influences on current practice.

## Future Research Needs

Three acute pain conditions may be in need of an up-to-date comprehensive assessment of the evidence are renal colic, acute migraine in primary care and specialty clinics in individuals with chronic or episodic migraine, and dental pain associated with dental procedures and oral surgery. New studies exist, but it is unclear whether these would change conclusions. In some cases, new comparisons have been addressed. Several systematic reviews addressed treatments for back and neck pain, but few comprehensively addressed acute pain, which is a critical focus for these conditions, because effectively treating acute and episodic musculoskeletal pain can prevent transition to chronic pain.

Future systematic reviews and trials should expand the set of interventions addressed in research on treatments for acute pain. Nondrug interventions, multicomponent interventions, and drugs prescribed at postoperative discharge were not frequently studied in the literature we identified. Expanding the outcomes addressed in future research would also be informative. Systematic reviews and trials should increase followup time and pain assessment beyond 48 hours, and measure analgesic use in the days following discharge. In regard to expanded outcomes, an important one to consider is pain and its impact on function and recovery as measured by multidomain scales that assessing more than just pain intensity. Several such comprehensive pain scales are available, but it is unclear whether their use is increasing in clinical and research settings or if they can reasonably be implemented in acute pain settings.

Few studies addressed subpopulations. This is especially concerning for individuals with a history of substance use disorder, for whom providers likely find pain treatment decisions

challenging. However, individuals with substance use disorder histories may also be challenging to recruit for clinical trials; thus, observational studies may provide insight.

Additionally, future research should continue to examine how patient baseline characteristics (history of substance abuse disorder, fear-avoidance, pain catastrophizing, mental health issues) and condition characteristics (trauma, abuse) modify response to treatment and lead to chronic pain or persistent opioid use.

## Limitations

The scope and scale of this evidence map allowed for only a high-level examination of systematic reviews and clinical practice guidelines for the selected acute pain conditions. Pain is a common symptom and treatment of acute pain varies widely according to the cause or type of pain. Systematically searching for treatments of a symptom is challenging. Even when focusing on a short list of acute pain conditions, the nuances of each pain condition complicate the search for this topic.

An in-depth investigation by a systematic review specific to acute pain conditions and their underlying cause could dive deeper into the issues specific to these populations. Having a depth of knowledge and a technical expert on pain with expertise specific to certain conditions would better facilitate our understanding of particular evidence and identify research gaps relevant to the acute pain condition. Obviously missing interventions can be identified from our evidence map of available research on the select conditions, subpopulations, and comparisons, but specific research gaps require clinical expertise on each acute pain condition. Therefore, we were unable to determine whether or not certain interventions commonly used in practice were overlooked in the eligible systematic reviews.

Mapping the evidence on a topic of this scope and scale presents many challenges. We could not, based on limited time and resources, provide an inventory of all possible acute pain conditions addressed by systematic reviews. We focused on the acute pain conditions *selected a priori* after discussion with several agencies in the Department of Health and Human Services. Valuable information could be gained through a full inventory of which acute pain conditions have up-to-date high-quality systematic reviews, but this would be difficult to assemble given the lack of standard terminology across conditions. First, many acute pain conditions are not indexed using acute pain terminology (i.e., migraine, renal colic, sickle cell crisis), and therefore many conditions would not be identified with a search strategy designed to capture only acute pain. Further, many reviews did not restrict study eligibility to acute pain, but instead included subacute or chronic pain.

Clinical setting was originally outlined as an important concept for mapping the evidence on acute pain treatments, and setting may indeed affect treatment decisions for some acute pain conditions (e.g., migraine). However, our discussions with KIs and our inventory of systematic reviews across the wider range of acute pain conditions did not support the importance of setting for all acute pain conditions. Setting is often restricted by the presenting acute pain condition, and for most conditions, treatment is likely similar across potential settings. The literature provided further challenges because specific settings were rarely specified as eligibility criteria for systematic reviews and thus were often not reported. Setting is likely more important for some acute pain conditions than others. For instance, acute migraine and renal colic might be treated differently in emergency settings than primary care or specialty clinics.

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## Abbreviations and Acronyms

ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks
AAAPT	ACTTION-APS-AAPM Pain Taxonomy
AAPM	American Academy of Pain Medicine
AHRQ	Agency for Healthcare Research and Quality
APMSIG	Acute Pain Medicine Special Interest Group
APS	American Pain Society
CDC	Centers for Disease Control and Prevention
ED	Emergency department
EPC	Evidence-based Practice Centers
FDA	United States Food and Drug Administration
GABA	Gamma-Aminobutyric Acid
GQ	Guiding Question
KI	Key Informant
LBP	Low back pain
NHLBI	The National Heart, Lung, and Blood Institute
NR	Not reported
NSAID	Nonsteroidal anti-inflammatory drug
PD	Postdischarge
RCT	Randomized Controlled Trial
ROB	Risk of Bias
SMT	Spinal manipulative therapy
SR	Systematic Review
VA-DOD	The Office of Veterans Affairs and Department of Defense Health Affairs

# Appendix A. Key Informant Discussion Questions

## Agenda

Introductions

Project Overview

Discussion

Next Steps

Conclusion

## Background: Treatment for Acute Pain Evidence Map

The Minnesota Evidence-based Practice Center (MN EPC) under contract with the Agency for Healthcare Research and Quality (AHRQ) is preparing an Evidence Map on the Treatment for Acute Pain addressing four Guiding Questions (Box 1). We are conducting interviews with Key Informants (KIs) to help address contextual questions about high priority acute pain conditions most relevant to the Evidence Map (GQ1 & GQ2). Our initial literature review and discussions with KIs will be used to address subsequent Guiding Questions (GQ3 & GQ4).

For purposes of the Evidence Map, we are using definitions of acute pain developed by Acute Pain Medicine Shared Interest Group (APMSIG) with timeframe further characterized by the AAAPT (Box 2).

### Box 1. Evidence map on treatment for acute pain Guiding Questions

1. Which acute pain conditions are most commonly treated in select settings (emergency rooms; inpatient and outpatient surgical facilities; primary and specialty care clinics; and dental clinics and dental surgery centers)?
  - a. What assessment methods are used to evaluate/monitor pain and function before/during treatment?
  - b. Which individual characteristics modify perceptions of pain severity, treatment options, and treatment response?
2. Which acute pain conditions have recent, high quality guidelines that address acute pain treatment?
  - a. What treatments do guidelines recommend?
  - b. To what extent do guidelines include treatment modifications based on initial pain assessment, medical history, and setting?
3. Which acute pain conditions have recent, high quality systematic reviews on treatments for acute pain?
  - a. What conclusions were reported about comparative effectiveness and harms of acute pain treatments?
  - b. Which populations, acute pain conditions, and treatments have been sufficiently systematically reviewed?
  - c. What evidence gaps were identified in systematic reviews?
4. What original comparative effectiveness research is available evaluating acute pain treatments for acute pain conditions without recent high quality systematic reviews?
  - a. Which populations and settings have been studied?
  - b. Which primary outcomes have been studied for effectiveness and harms?
  - c. Which study designs have been used?
  - d. Which populations and treatments have sufficient original research for systematic review?



## Box 2. Definition of acute pain

APMSIG working definition: “Acute pain is the physiologic response and experience to noxious stimuli that can become pathologic, is normally sudden in onset, time limited, and motivates behaviors to avoid actual or potential tissue injuries.”{Tighe, 2015 #2672}

AAAPT time-based definition of acute pain: “Acute pain is considered to last up to seven days, with the following qualifications: 1) It’s duration reflects the mechanism and severity of the underlying inciting event; 2) Prolongations from seven to 30 days are common; 3) Prolongations beyond the duration of acute pain but not extending past 90 days postonset/injury are common. This refers to the ill-defined but important period of ‘subacute’ pain that warrants further specification and consideration in future taxonomic, research, and regulatory efforts.”{Kent, 2017 #11}

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**Table 1. Key informant call topics and potential questions**

Topic	Questions
Acute Pain Conditions/Assessment/ Guidelines	<ul style="list-style-type: none"><li>• Which acute pain conditions are of highest priority in terms of identifying alternatives to opioids?</li><li>• Which settings are of highest priority in terms of identifying alternatives to opioids?</li><li>• Which acute pain conditions are most often treated in each setting:<ul style="list-style-type: none"><li>○ Emergency Departments</li><li>○ Inpatient and outpatient surgical facilities</li><li>○ Primary care clinics</li><li>○ Specialty care clinics</li><li>○ Dental clinics</li><li>○ Oral surgery facilities</li></ul></li><li>• How is acute pain assessed before and during treatment?<ul style="list-style-type: none"><li>○ How does the assessment modify treatment?</li><li>○ Does this differ by setting?</li></ul></li><li>• Which individual characteristics modify:<ul style="list-style-type: none"><li>○ Perception of pain?</li><li>○ Treatment options?</li><li>○ Treatment response?</li></ul></li></ul>
Acute Pain Treatment: Guidelines	<ul style="list-style-type: none"><li>• Are you aware of clinical practice guidelines addressing acute pain in general?</li><li>• Are you aware of clinical practice guidelines addressing reducing the use of opioids?</li><li>• Are you aware of clinical practice guidelines addressing specific common acute pain conditions?</li><li>• Is treatment of acute pain guided by these guidelines in your organization?</li><li>• What other guidance informs treatment for acute pain in your organization?</li><li>• We are compiling a list of clinical practice guidelines for treatment of acute pain; do you believe that clinical practice guidelines developed for use in other countries would be useful? If so, which countries or organizations?</li></ul>
Knowledge Gaps	<ul style="list-style-type: none"><li>• Which areas do you feel need additional research to inform the treatment for acute pain?</li></ul>

## Appendix B. Search Strategy

- 1 \*pain/ or \*abdominal pain/ or \*acute pain/ or \*back pain/ or \*low back pain/ or \*headache/ or musculoskeletal pain/ or \*neck pain/ or \*pain, postoperative/ or \*pain, procedural/ or \*renal colic/ (155980)
- 2 pain.ti.)
- 3 (acute or postoperative or perioperative).ti.
- 4 2 and 3
- 5 1 or 4
- 6 chronic.ti.
- 7 5 not 6
- 8 acute.ti.
- 9 6 and 8
- 10 7 or 9
- 11 (tooth adj2 extract\*).ti.
- 12 exp Molar, Third/
- 13 exp Tooth Extraction/
- 14 11 or 12 or 13
- 15 exp \*PAIN/
- 16 14 and 15
- 17 Toothache/
- 18 16 or 17
- 19 sickle cell crisis.ti.
- 20 renal colic.ti.
- 21 exp \*Migraine Disorders/
- 22 (acute or rescue).ti.
- 23 21 and 22
- 24 10 or 18 or 19 or 20 or 23
- 25 limit 24 to (guideline or meta analysis or practice guideline or systematic reviews)
- 26 limit 25 to yr="2016 -Current"

# **Appendix C. Key Informant Call Summaries**

## **KI Call #1**

Friday, September 21: 10 a.m. ET/9 a.m. CT/7 a.m. PT.

## **Participants**

Steven Stanos (KI), Michelle Brasure, Mary Butler, Tim Wilt, Torie Nelson, Jay Saha, Shivani Rao, Shellina Scheiner, Suchi Iyer

## **Acute Pain Conditions**

Acute low back pain is a very common complaint and seen by a wide range of providers. However, the treatment is complex because people experiencing acute low back pain are a heterogeneous group. Treatment is guided by several potential underlying causes of the pain; many of which opioids would not be appropriate for.

Other common pains/injuries include those involving a large joint: shoulder, knee, and hip. These pains are often treated by sports medicine physicians. Opioids are rarely prescribed in this setting.

Headaches and perioperative dental pain are also important issues pertaining to acute pain treatment.

Younger children present with many different types of pain so it could be challenging to address acute pain in this population. Adolescents' presentation is similar to adults.

Another common source of acute pain includes trauma-related fracture pain, and perioperative pain (e.g. elective surgeries such as hernia repair).

Several factors play a role in how individuals experience acute pain and respond to treatments. These include psychosocial factors such as depression, anxiety, fear avoidance, and catastrophizing. These same factors may also make individuals at higher risk for their acute pain to convert to chronic pain.

Nonpharmacologic interventions for acute pain are often used, especially with sprains and strains. These are commonly treated with RICE (rest, ice, compression, and elevation) along with anti-inflammatory medications.

Many nonanalgesic medications are also used. Often, there is no high quality evidence available for their use. Examples include drug classes that are thought to help quiet down symptoms (muscle relaxants and prescription anti-inflammatory medications).

## **Assessment**

Physical exams with assessment of history and risk factors for a negative outcome with opioid prescriptions should be a priority before writing medication prescriptions.

Pain assessment should be multidimensional, and must assess function as well as pain intensity. We assess pain for each individual and use a more global assessment. We typically use PEG which measures pain, enjoyment of life, and general activity.

The PHQ-9 is another instrument that incorporates general anxiety.

## **Guidelines**

KI is aware of several groups that have developed guidelines for perioperative pain including Johns Hopkins, Cleveland Clinic, and UMICH. These guidelines are fairly specific, breaking down recommended dosage and duration for several types of surgeries.

Other guidelines that may address acute pain conditions outside of perioperative include those published by ACP, American College Sports Medicine (guideline on ultrasound guided procedures for musculoskeletal pain), and the American Academy of Physical Medicine and Rehab Musculoskeletal group. Other countries have established guidelines on treatment for acute pain (Australians in musculoskeletal pain, injury, NICE, and other European countries). Many state level guidelines or policies also guide acute pain treatment (Washington).

Acute pain treatment likely varies by provider type as well as among individual providers. The Mayo Clinic, sports and physical medicine group, is very active in this area. Their approach is typically more conservative; they are less likely to prescribe opioids if any medications at all.

Different practice styles are very common.

## **Other Issues**

CDC is putting together a large workgroup for opioids/acute pain. It is unclear which specific conditions are being addressed.

Unclear which acute pain conditions need opioids vs alternatives. Comparative effectiveness research is limited.

We are currently experiencing a response to the previous prescribing crisis. State legislative interventions for limiting prescriptions are now becoming commonplace.

Settings in which acute pain conditions are treated may or may not affect treatment options. For instance, emergency departments and primary care prescribing are likely similar. Emergency departments are more worried about doctor shopping for opioid prescriptions.

## **Future Research Needs**

High priority research needs include the identification of risk factors for converting from acute pain to chronic pain.

This area is challenging to study because it is often difficult to conduct research on conditions where the pain is only severe for a short period of time.

Models that could be useful to study for acute pain include those established for bunionectomy, wisdom teeth removal, and various sports injuries.

Stem cells are being investigated for their potential to treat pain (Mayo).

Acute inpatient pain management is another evolving area (Mike Kent, Patrick Tighe). They are currently working on the taxonomy specific to acute pain conditions.

## **KI Call #2**

Monday, September 24: 3:30 p.m. ET/2:30 p.m. CT

## **Participants**

Roger Chou (KI), Suchi Iyer, Michelle Brasure, Mary Butler, Torie Nelson, Mary Forte, Tim Wilt

## **Acute Pain Conditions**

Postoperative pain is a very common acute pain conditions in both outpatient and inpatient surgeries. The challenge is there are so many different procedures/surgeries. It is difficult to know how specific the guidelines should be and how to lump procedures/surgeries in a meaningful way. Multimodal approaches are standard. Common surgeries include knee and hip replacement.

The American Pain Society perioperative pain guideline addresses 10 common surgical procedures/surgeries. The level of aggregation varies widely in available guidelines. The APS guideline focused on perioperative pain. The PROSPECT group (Europe) develops surgery-specific guidelines. They have developed guidelines for 10 to 15 procedures.

The perioperative pain topic is challenging due to the volume of literature (thousands of trials).

The policy issues are interesting. The state and health system level policies that guide the use of opioids have never been identified and summarized. Many are developed using internal data as opposed to traditional evidence from systematic reviews.

Framing the literature about acute pain treatments within settings makes logical sense. The variability within settings will be a challenge.

Certain acute pain conditions are cross-cutting and treated across multiple settings (Sickle cell crisis, DVT).

There is a growing interest in pediatric population and the consequences of early exposure.

## **Guidelines**

Recent focus of acute pain guidelines targets dose limits. These guidelines/policies aren't the typical society guidelines, but developed by state and local agencies or healthcare systems. They are often based on registry data. Percentiles are used to develop procedure-specific dose and duration guidance. This guidance has likely not been rigorously studied, but it does affect practice. This guidance largely addresses opioids as opposed to alternative treatments. Examples include:

- Michigan – OPEN network
- Washington state – collaborative project
- Oregon – working to develop
- Dartmouth – shown amount of opioids given at discharge predictive of future opioid use

For dental pain, there is evidence that opioids are no more effective than other alternatives for certain procedures.

## **Assessment**

Evidence on acute pain assessment is likely less than that of chronic pain. The short-lived nature of acute pain has traditionally made it less interesting and less feasible for research. There are probably published guidelines or published literature specific to acute pain.

There is also unlikely to be a risk predictor score to help identify individuals at higher risk for opioid misuse.

## **Future Research Needs**

Acute pain treatment in adolescents needs additional study. Differences among data sources and study designs would be an interesting area of research. We need additional randomized controlled trials exploring the comparative efficacy of various multimodal treatments. We need research that explores long term consequences of acute pain treatments.

Policy research could focus on identifying the ideal opioid dose and duration. More research should focus on opioid alternatives.

Identifying what works for different conditions may be a research gap. Much of the research focusses on opioids from a clinical policy level. Further exploration of the relationship between acute prescribing and long-term use.

## **Other Issues**

The field seems to be shifting from focusing on how to manage chronic opioid use to how to prevent opioid use/abuse in the first place. This would include the study of using nonopioid medications for pain. There is increased interest in using cannabis for acute pain. Nonpharmacologic treatments are also on the horizon (music, guided imagery, cold packs, TENS).

## **KI Call #3**

Tuesday, September 25: 12 p.m. ET/11 a.m. CT

## **Participants:**

Christina Mikosz (KI), Michelle Brasure, Torie Nelson, Christine Chang, Suchi Ayer, Mary Forte, Jay Saha, Shivani Rao, Shellina Scheiner, Tim Wilt

## **Acute Pain Conditions**

Acute low back pain is always a frequently encountered condition. Other conditions include sickle cell crisis, kidney stones, dental pain (including wisdom tooth extraction; simple extraction), postoperative pain, neuropathic pain (shingles), musculoskeletal pain (including neck and back pain), and migraines. There appear to be high quality guidelines and policy in treatment of acute migraine.

There are many ways to aggregate acute pain conditions; could try to bundle by pain severity. Focusing on a few specific diagnoses may provide a more useful level of detail.

## **Assessment**

Pain itself may not be a useful reference point. One reason is because it is very subjective. Function goals may be more useful (true of chronic pain, may be applicable for acute as well). Other domains that may be useful to assess include depression and anxiety; patient history with pain; medical comorbidities. Biomarkers may be useful in assessing acute pain, but in some cases where patients do not have appropriate coping mechanisms they can be subjective as well.

## **Guidelines**

The National Institutes of Health did a great job with their guideline on sickle cell crisis. The Dartmouth paper on correlation between meds prescribed at discharge and future opioid use was important in terms of guiding treatment with opioids. There may be guidelines geared specifically to broad areas like emergency medicine. Postoperative pain is a large area with many groups developing relevant guidelines (American College of Obstetrics and Gynecology, American Dental Association, BRIEF collaborative in Washington State, and many other institutional guidelines such as those developed by the Mayo Clinic).

Other guidelines address acute pain in general. The American College of Physicians has broad-based guidelines that address acute pain. Many of the state level guidelines are based on these. The American College of Occupational and Environmental Medicine has guidelines that

address certain conditions. Other guideline groups include the Centers for Disease Control and Prevention, the National Institutes of Health, and Johns Hopkins.

Guidelines from other countries may be useful in filling in some gaps in American guidelines, where applicable. However, pain management practice is much different in the United States (e.g., many more opioids are prescribed in the United States.)

## **Future Research Needs**

We need a better understanding of the efficacy of non-opioid pain management approaches. Research to support a wider variety of intervention types would help inform treatment decisions. We especially need comparative effectiveness research to demonstrate what else works.

ALTOs (alternatives to opioids) programs are currently being used in emergency departments encouraging nonopioid use. This is a well endorsed program that is as evidence-based as it can be. The Colorado state guidelines are broken down to the diagnosis level. This program is a multipronged policy level intervention that shows promise in decreasing the use of opioids in emergency department settings.

## **Other Issues**

In general, we do not have good guidance for opioid prescribing for acute pain. There is a lot of variation in practice.

Settings may be important as a way to break out the evidence. There is likely differences in training and resources available across different settings such as urgent care vs. emergency departments.

## **KI Call #4**

Thursday, September 27: 12 p.m. ET/11 a.m. CT

## **Participants:**

Michelle Brasure, Mary Butler, Shellina Scheiner, Sanket Nagarkar, Suchi Iyer, Tim Wilt, Erin Krebs (KI), Corey Leinum (KI)

## **Acute Pain Conditions**

Frequently encountered types of acute pain include postoperative pain, visceral pain (e.g., appendicitis, pancreatitis), sickle cell crisis, back pain, headache/migraine, sprains/strains, and toothache.

There is substantial variation in care and a wide range of influences in the prescribing of treatments for acute pain. Physicians develop individual styles, which may affect prescriptions more than their clinic.

Patient characteristics that might modify the pain experience and response to treatment include the severity of condition and patient preference. There do not appear to be data that help to make objective treatment decisions. Treatment tends to be rather idiosyncratic.

## **Guidelines**

Medical systems have taken steps to provide guidance primary with respect to opioid prescriptions by developing specific order sets (prescription recommendations). Health systems discharge prescription recommendations are based on type of procedure. These are often developed by setting prescribing goals for all patients by type of surgery based on the internal



healthcare system's medical records (e.g., 25<sup>th</sup> percentile based on past procedures as maximum dosage). System level guidance probably influencing prescriber decisions more than professional guidance. There's so much out there in terms of research and guidance, and acute pain treatment is such a rapidly evolving field, that it is difficult for providers to keep up. Order sets are convenient and practice-based. The order sets are developed to minimize opioid prescribing and may not give sufficient attention to nonopioid alternatives. Order sets are likely very specific to the local healthcare system. Most inpatient prescribing is done via order sets.

System multimodal pain order set developed to encourage multimodal pain treatment, but has limited availability for nonpharm treatment. Use of nonpharm treatments are offered, but decisions typically come down to funding. Health systems are developing 'comfort menus' that include interventions such as heat, ice, aromatherapy, fans, and lip balm. These types of programs are system specific and may get programmed locally based on local preferences and decision factors. Some nonpharm interventions are seen as under the nursing domain, so may not make it into "order sets."

An evidence map on the treatment for acute pain being developed at a highly aggregated level while maintaining usefulness is challenging. Lumping conditions together may be appropriate, but context should be maintained. For instance, emergency department decisions may be made before underlying cause of pain is identified.

## **Assessment**

Pain assessment in some healthcare systems has changed and moved away from scales that primarily measure pain intensity. Inpatient pain assessment may include a CAPA score, which is a conversational approach assessing 5 domains (comfort, how pain has been managed, change in pain, pain control overall, functioning, sleep).

In some healthcare systems, official mandates to use numerical scales have not been removed. So numerical scales in hospital settings may be standard in certain healthcare systems or hospitals.

The PEG scale is a good option to expand assessment beyond only pain intensity. A qualitative approach is preferred. These provide better information to guide treatment than standardized measures applied broadly. Pain intensity scales alone are not useful to determine treatment; they are most useful in assessing pain in the same patient over a time period. KI is not aware of evidence that pain assessment improves treatment.

## **Future Research Needs**

Several areas around acute pain treatment could use additional study. First, whether pain assessment improves treatment may be an important area for future study. Secondly, more information is needed about patient characteristics that put people at higher risk of opioid misuse. While there are tools that have been used for longterm treatment (e.g., DIRE tool), it is unclear which tool is best.

More information on which acute pain conditions are best treated with nonopioids would help inform treatment decisions. There are a few good studies for comparative efficacy of opioids vs nonopioids in emergency medicine, but additional study is needed.

## **Other**

One way to focus the evidence map could be on efficacious treatments. To be feasible, probably best to select a few specific conditions.

One challenge is patient preference. In large part, patients do not think their pain is being treated if they are not prescribed opioids. A cultural change is necessary to shift the focus of pain management away from opioids.

## Appendix D. Intervention Categorization

**Appendix Table D1. Classification of drugs identified in eligible systematic reviews**

<b>Key Drug Classes</b>	<b>Key Drugs (generic)</b>
Analgesic	Acetaminophen
Adrenergic blocker	Esmolol
Anesthetic/anesthetic adjunct	Benzocaine Bupivacaine Ketamine Levobupivacaine Lidocaine Lignocaine Mepivacaine Ropivacaine
Antiarrhythmic	Adenosine
Antibiotics	Amoxicillin Erythromycin Metronidazole Penicillin
Anticholinergic	Butylscopolamine Scopolamine (hyoscine)
Antidepressant	Amitriptyline
Antidiuretic	Desmopressin
Antiseptic	Chlorhexidine
Antithrombotic	Tinzaparin
Antiemetic	Ondansetron
Antispasmodic	drotaverine Phloroglucinol Pitofenone Tiropramide
<b>Blood pressure support and vasoconstrictor</b>	Epinephrine
Calcitonin gene-related peptide (CGRP) antagonist	Telcagepant
Calcium channel blocker	Nifedipine
Laxative	Lactulose
Mucolytic	N-acetylcysteine (NAC)
Gamma Aminobutyric Acid (GABA) analog	Gabapentin Pregabalin
Corticosteroid	Betamethasone Dexamethasone Methylprednisolone Prednisolone
Keratolytic	Salicylic acid
Nicotinic agonist	nicotine
Nitrates	Nitroglycerin

<b>Key Drug Classes</b>	<b>Key Drugs (generic)</b>
NSAIDs	Aspirin Bromfenac Celecoxib Diclofenac Diflunisal Etodolac Etofenamate Etoricoxib Fentiazac Flurbiprofen Glafenine Ibuprofen indomethacin Ketoprofen ketorolac Lornoxicam Mefanamic acid Meloxicam Metamizole naproxen Nimesulide Parecoxib Pirprofen Piroxicam Rofecoxib tenoxicam
Opioid	Alfentanil Buprenorphine Butorphanol Codeine Dihydrocodeine Fentanyl Hydrocodone Hydromorphone Morphine Nalbuphine Oxycodone Pentazocine Pethidine Tapentadol Tramadol
Sedatives and Anesthetic Adjunct	Alprazolam Dexmedetomidine Nitrous oxide propofol midazolam
Triptans	Sumatriptan Zolmitriptan,

**Appendix Table D2. Classification of nondrug interventions for pain treatment**

<b>Key Intervention Classes</b>	<b>Examples</b>
Exercise	Strengthening/stabilization
	Stretching
	Range of motion (ROM)
	Aerobic
	Combined (any)
	Exercise instruction (any)
	Other
Spinal manipulative therapy (SMT)	Manipulation
	Mobilization
Muscle therapy	Massage
	Trigger point therapy (TPT)
	TPT + myofascial band
	Integrated neuromuscular inhibition
	Muscle energy techniques
	TPT with Activator device
	Dry-needling (trigger points)
	Strain-counterstrain
	Taping
	TENs (Transcutaneous nerve stimulation)
Physiotherapy modality	Ultrasound
	Low-level laser therapy (LLLT) <sup>±</sup>
	Superficial Hot or cold
	Traction
Acupuncture	Accupuncture
Brace/support	Brace/support
Multimodal (nondrug)	2 or more nondrug interventions
Multimodal (drug/nondrug)	Drug plus nondrug intervention(s)

## Appendix E. Excluded References

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## Appendix F. Evidence Tables: Postoperative Postdischarge Pain

**Table F1. Systematic reviews: perioperative interventions for managing postdischarge postoperative pain**

Systematic Review Surgery Type(s)	End Search Date	Population	Intervention Addressed	Outcomes	Eligible Studies (total participants)	Setting(s)
Fan 2018a <sup>2</sup> Total knee replacement	December 2017	Adults	Dexamethasone	24-48 hr. (postoperative) pain, 24 hr. morphine consumption, nausea, hospital LOS, 24 hr. CRP	8 studies [(7 RCT (923), 1 CCT] 7 report PD pain	Not specified (inpatient)
Fan 2018b <sup>1</sup> Total hip replacement	June 2017	Adults	Dexamethasone	24-48 hr. pain, 48 hr. morphine consumption, nausea, hospital LOS	3 RCTs (207) 2 report PD pain	Not specified (inpatient)
Li 2018a <sup>4</sup> Total knee replacement	December 2017	Adults	Local vs. epidural analgesia	12-48 hr. pain, 12-48 hr. opioid us, ROM, nausea, hospital LOS	7 RCTs (416) 5 report PD pain	Not specified (inpatient)
Li 2018b <sup>5</sup> Laparoscopic cholecystectomy	November 2017	Adults	Lidocaine, IV	Pain reduction (72h and less); opioid use; length of hospital stay; AEs	6 RCTs (354) 6 report PD pain	Not specified
Li 2018c <sup>3</sup> Total knee replacement	February 2018	Adults	Dexamethasone	12-48 hr. pain, total narcotic use, LOS, AE	4 RCTs (496) 4 report PD pain	Not specified (inpatient)
Liu 2018 <sup>6</sup> Hemorrhoidectomy	August 2015	Adults	Glyceryl trinitrate	Pain at 14 d and less); analgesia consumption; return to work; AEs	12 RCTs (1025) 4 report PD pain	Not specified
Sun 2018 <sup>7</sup> Total knee or hip replacement	September 2017	Adults	Acetaminophen, IV vs. oral	12-48 hr. pain, 12-48 hr. opioid consumption, hospital LOS, AE	2 RCTs (236) 2 report PD pain	NR; assume inpatient
Weibel 2018 <sup>9</sup>	January 2017	Adults	Lidocaine, IV	Pain at 24 h, 48 h; gastrointestinal recovery; use of rescue analgesic; length of hospital stay; AEs	68 RCTs (4525) 2 report PD pain	Surgical facility
Wilson-Smith 2018 <sup>10</sup> Spine surgery	August 2017	Adults	Epidural steroids	24 hr. pain, 30 day pain, postoperative opioid analgesics (drugs or timeframe NR), hospital LOS	17 RCT" (1727) 4 report PD pain	Not specified (inpatient)
Yu 2018 <sup>11</sup> Total knee replacement	May 2017	Adults	Liposome bupivacaine	24-72 hr. pain, morphine consumption (drugs, timeframe NR), hospital LOS, ROM, nausea	7 RCT (825) 1 reports PD pain	Not specified (inpatient)
Zhao 2018a <sup>12</sup> Laparoscopic cholecystectomy	August 2017	Adults	Lidocaine, IV	Pain scores (12, 24, 48 hours); opioid use; length of hospital stay; AEs	5 RCTs (274) 5 report PD pain	Not specified

<b>Systematic Review Surgery Type(s)</b>	<b>End Search Date</b>	<b>Population</b>	<b>Intervention Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies (total participants)</b>	<b>Setting(s)</b>
Zhao 2018b <sup>13</sup> Laparoscopic cholecystectomy	November 2017	Adults	Nefopam	Pain reduction; opioid consumption (24h and less); length of hospital stay; AEs	4 RCTs (215) 4 report PD pain	Not specified
Zhou 2018 <sup>14</sup> Total knee replacement	December 2017	Adults	Dexamethasone, periarticular or IV	12-48 hr. pain, 12-48 hr. opioid consumption, hospital LOS, AE	6 RCT (576) 6 report PD pain	Not specified (inpatient)
Cao 2017 <sup>15</sup> Total shoulder replacement	May 2017	Adults	Liposomal bupivacaine	12-48 hr. pain, 12-48 hr. opioid consumption, hospital LOS, nausea/vomiting	4 RCT (510) 4 report PD pain	Not specified (inpatient)
Chen 2017a <sup>16</sup> Total joint replacement	December 2016	Adults	Glucocorticoids, IV	12-48 hr. pain, hospital LOS, infection, nausea/vomiting, blood glucose	13 RCT (821) 6 report PD pain	Not specified (inpatient)
Jia 2017 <sup>17</sup> Total hip replacement	July 2016	Adults	Intrathecal vs. local morphine	24 hr. pain, 24-48 hr. morphine consumption, AE, hospital LOS	4 RCTs (207) 4 report PD pain	Not specified (inpatient)
Lal 2017 <sup>18</sup> Tonsillectomy	June 2016	Children	Honey	Pain; analgesia use; waking at night; healing; AEs (10 days and less)	8 RCTs (545) 3 report PD pain	Inpatient and outpatient
Liang 2017 <sup>19</sup> Total knee or hip replacement	September 2017	Adults	Adjunctive IV acetaminophen	24-72 hr. pain, 24-72 hr. morphine consumption (IV), nausea, hospital LOS	4 studies [3 RCTs (256)] 3 report PD pain	Not specified (inpatient)
Lyons 2017 <sup>20</sup> Hemorrhoidectomy	January 2017	Adults	Metronidazole	Pain at 2-28 d Analgesia use	8 RCTs (437) 6 report PD pain	Not specified
Ma 2017 <sup>21</sup> Total hip replacement	April 2017	Adults	Adjunctive liposomal vs. standard bupivacaine	24-72 hr. pain, 24 hr. morphine consumption, hospital LOS	6 studies [2 RCTs (141)] 1 reports PD pain	Not specified (inpatient)
Qiu 2017 <sup>22</sup> Mammoplasty	September 2015	Adults	Bupivacaine	Pain; opioid use; length of hospital stay	4 RCTs (264) 1 reports PD pain	Not specified
Wang 2017a(Liposomal...) <sup>23</sup> China	May 2017	Adults undergoing TSR	Adjuvant liposomal bupivacaine vs. interscalene nerve block (2 methods)	12-48 hr. pain, 12- 24 hr. opioid consumption, nausea/vomiting, hospital LOS	4 RCT (510) 4 report PD pain	Not specified (inpatient)
Wanis 2017 <sup>8</sup> Hemorrhoidectomy	July 2016	Adults	Metronidazole	Pain at 14d and less; time to return to normal activities	5 RCTs (337) 4 report PD pain	Not specified
Xing 2017 <sup>25</sup> Total knee replacement	July 2017	Adults	Adductor canal block	48 hr. pain, 48 hr. opioid consumption, AE, hospital LOS	4 RCTs (297) 4 report PD pain	Not specified (inpatient)

<b>Systematic Review Surgery Type(s)</b>	<b>End Search Date</b>	<b>Population</b>	<b>Intervention Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies (total participants)</b>	<b>Setting(s)</b>
Yan 2017 <sup>26</sup> Total shoulder replacement/reverse total shoulder replacement	May 2017	Adults	Liposomal bupivacaine	4-24 and 2 wk. pain, 24 hr. morphine consumption, hospital LOS	5 RCTs (573) 4 report PD pain	Not specified (inpatient)
Yang 2017a <sup>27</sup> Total hip replacement	November 2016	Adults	Preoperative IV glucocorticoids	6-72 hr. pain, total morphine consumption, nausea, hospital LOS	7 RCTs (411) 3 report PD pain	Not specified (inpatient)
Yang 2017b <sup>28</sup> Total knee or hip replacement	July 2017	Adults	Adjunctive IV acetaminophen	24-72 hr. pain, 72 hr. opioid consumption, nausea, hospital LOS	3 RCTs (865) 3 report PD pain	Not specified (inpatient)
Yue 2017 <sup>29</sup> Total knee or hip replacement	February 2017	Adults	Adjunctive perioperative systemic steroids (most IV)	2-48 hr. pain, 30 day pain, AE, function, hospital LOS, inflammatory markers, thrombogenic markers	11 RCTs (774) 9 report PD pain	Not specified (inpatient)
Zhang 2017a <sup>31</sup> Total knee replacement	August 2016	Adults	Adjunctive local anesthetic infusion pump	24-72 hr. pain, 24-48 hr. morphine consumption, ROM, AE, hospital LOS	7 RCTs (587) 6 report PD pain	Not specified (inpatient)
Zhang 2017b <sup>24</sup> Total hip replacement	June 2016	Adults	Liposomal bupivacaine	12-48 hr. pain, 12-48 hr. opioid consumption, hospital LOS, nausea	4 retrospective observational (308) 4 report PD pain	Not specified (inpatient)
Zhang 2017c <sup>30</sup> Total knee or hip replacement	March 2017	Adults	Adjunctive fascia iliaca block	12-24 hr. pain, 12-24 hr. opioid consumption, AE, hospital LOS	5 RCT (270) 3 report PD pain	Not specified (inpatient)
Ma 2016(Liposomal...) <sup>32</sup> Total knee replacement	July 2016	Adults	Liposomal bupivacaine	0-48 hr. pain, 0-48 hr. morphine use, nausea, hospital LOS	6 studies (1,289); 1 was RCT (80) 1 reports PD pain	Not specified (inpatient)
Powell 2016 <sup>33</sup> Multiple surgery types (general anesthesia)	May 2014	Adults	Psychological preparation	Pain; AE; hospital stay	105 RCTs (10,302) 3 report PD pain	Surgical facility
Sproat 2016 <sup>34</sup> Tonsillectomy	August 2014	Adults Children	Hemostatic glues Electrocautery Fibrin sealant Conventional techniques	Pain at 1d, 3d, 10d; bleeding; AEs	7 RCTs (748) 2 report PD pain	Not specified
Wu 2016 <sup>35</sup> Total knee replacement	April 2016	Adults	Liposomal bupivacaine	24-72 hr. pain, nausea, hospital LOS	5 RCTs (574 ) 3 report PD pain	Not specified (inpatient)
Roberts 2012{Roberts, 2012 #5121}	December 2010	Adults	Postoperative analgesics	Pain (time NR), global patient evaluation, rescue analgesia, withdrawals, AEs	23 RCTs (1,944) 22 report PD pain	Not specified

\*AHRQ EPC Review; \*\*Cochrane review

AE = adverse effects; BA = before-after study; EDs = emergency departments; IV = intravenous; IM = intramuscular; NR = not reported; PD = postdischarge; OS = observational

study; SR = systematic review



## **RCTs included in Previous SRs and New RCTs: Postop Postdischarge Pain<sup>1-143</sup>**

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## Appendix G. Evidence Tables: Dental Procedures and Oral Surgery

**Table G1. Systematic reviews: treatments for perioperative pain – dental procedures and oral surgery**

Systematic Review	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
Fernandes 2018 <sup>1</sup>	March 2018	Adults undergoing third molar extraction	Dexamethasone (injectable)	Pain at 24 h, 72 h, 168 h; oedema; trismus	15 RCTs (859)	Not specified
Larsen 2018 <sup>2</sup>	December 2017	Adults undergoing third molar extraction	Corticosteroids	Pain (time NR); swelling; trismus	7 RCTs (430)	Not specified
Nath 2018 <sup>3</sup>	May 2018	Adults undergoing endodontic treatment	Corticosteroids (any mode of administration)	Pain at 4 h, 6 h; AEs	14 RCTs (1,462)	Dental clinics
Noreugia 2018 <sup>4</sup>	NR	Adults with endodontic pain (irreversible pulpitis)	Dexamethasone	Pain (4 h, 6 h, 8 h, 12 h, 24 h, 48 h)	5 RCTs (260)	Not specified
Shamszadeh 2018 <sup>5</sup>	October 2017	Adolescents and adults (age>15) undergoing endodontic treatment	Corticosteroids	Pain at 6 h, 12 h, 24 h	18 RCTs (1,088)	Not specified
Suneelkumar 2018 <sup>6</sup>	January 2018	Adults with symptomatic pulpitis undergoing a root canal	Corticosteroids	Pain at 6 h, 12 h, 24 h, 48 hr; rescue medication; adverse effects	5 RCTs (721)	Not specified
Chen 2017 <sup>7</sup>	April 2016	Adults undergoing third molar extraction	Dexamethasone (injectable)	Pain; oedema; trismus	8 RCTs (612)	Oral surgery clinics
Falci 2017 <sup>8</sup>	April 2015	Adults undergoing third molar extraction	Dexamethasone	Pain (2 days, 4 days, 7 days); swelling; trismus	7 RCTs (232)	Not specified
Shirvani 2017 <sup>9</sup>	NR (latest study 2016)	Adolescents and adults undergoing third molar extraction	NSAIDS (any mode of administration) with or without acetaminophen; tramadol	Pain at 0 h, 6 h, 12 h, 24 h	27 RCTs (2,188)	Dental clinics
Smith 2017 <sup>10</sup>	December 2015	Adults undergoing endodontic treatment	Acetaminophen; aspirin; NSAIDS	Pain at 6 h; AEs	15 RCTs (unclear)	Dental clinics
Aminoshariae 2016 <sup>11</sup>	April 2016	Adults	Preoperative NSAIDS	Pain; AEs	27 RCTs (NR)	Not specified
Aminoshariae 2016 <sup>12</sup>	September 2015	Adults undergoing endodontic treatment	Antibiotics	Pain (time NR)	5 RCTs (271)	Not specified
Ashley 2016 <sup>13</sup>	March 2012	Children and adolescents undergoing extraction/restoration or orthodontic procedures	Preoperative analgesics	Pain; AEs	5 RCTs (190)	Dental clinics/oral surgery clinics

<b>Systematic Review</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Bates 2016 <sup>14</sup>	May 2014	Adults undergoing oral or maxillofacial surgery	Hilotherapy	Pain at 48 h, 72 h; oedema at 48 h, 72 h; trismus	5 RCTs (206)	Oral surgery clinics/other surgical facilities
Moraschini 2016 <sup>15</sup>	June 2015	Adults undergoing third molar extraction	Dexamethasone (submucosal injectable)	Pain, oedema, trismus	8 RCTs (476)	Oral surgery clinics
Costa 2015 <sup>16</sup>	NR	Adults and adolescents undergoing third molar extraction	NSAIDs	Pain (time NR); AEs	6 RCTs (420)	Not specified
Baily 2014 <sup>17</sup>	May 2013	Adults and adolescents undergoing third molar extraction	Acetaminophen NSAIDs	Pain at 2 h, 6 hr; rescue medication at 8 hr	7 RCTs (2,241)	Oral surgery clinics/other surgical facilities

AE = adverse effects; ED = emergency department; h = hour(s); NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs

## RCTs Included in Previous SRs and New RCTs: Dental Procedures and Oral Surgery

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## Appendix H. Evidence Tables: Acute Back Pain

**AppendixTable H1. Systematic reviews: treatments for acute back pain**

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes*</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Song 2018 <sup>1</sup>	March 2017	Adults with LBP	Combination drug therapy versus monotherapy or placebo	Pain; function; AEs	12 RCTs (1,989) 6 addressed acute LBP	Not specified
Strudwick 2018 <sup>2</sup> Australia	April 2015	Adults with nonchronic musculoskeletal LBP seen in ED	Opioids/analgesia (dexamethasone (adjunct to routine); promethazine+ morphine vs. morphine; paracetamol vs. morphine vs. dexketoprofen (non-USA use); early physiotherapy, education, reassurance, cold vs. heat, exercise recommendations	Pain, unclear	14 of 38 articles on treatment: analgesia/opioids [4 RCT, 2 SR, 8 guidelines]; 11 other interventions [listed at left: 1 RCT, 2 SR, 8 guidelines] (unclear)] 4 addressed acute LBP	ED
Abdel 2017 <sup>3</sup> Australia	October 2015	Adults with non-specific low back pain (from scapulae to lower buttocks, with/without radiation in legs)	Muscle relaxant (single or combination, 7 drugs) vs. (placebo or other muscle relaxant)	Pain, function, AE [short-term ≤ 3 mo.]	15 RCTs (3,362) 11 addressed acute LBP	Not specified
Chou 2017(nonpharm) <sup>4</sup> ACP (update) USA	February 2016	Adults with acute (<4 wks.), subacute (4-12 wks.) or chronic (> 12 wks.) nonradicular or radicular LBP	Nonpharmacologic, nonsurgical therapies: spinal manipulation, exercise, multidisciplinary rehabilitation, acupuncture, massage, mind-body (yoga, tai chi, MBSR), & psychological interventions; passive physical therapies (interferential, SWD, traction, ultrasound, lumbar support, taping, EMS, low-level laser, superficial heat)	Pain, function, AE [acute <4 wks.]	114 publications. 6 RCTs on acute &/or subacute LBP: exercise (unclear), acupuncture (unclear), spinal manipulation [2 RCTs of acute (239)]. Also mentions 2 SLRs (6 RCTs (unclear). Superficial heat (NR). Acute radicular pain (unclear) 10 addressed acute LBP	Not specified

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes*</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Chou 2017(pharm) <sup>5</sup> ACP (update) USA	November 2016	Adults with acute (<4 wks.), subacute (4-12 wks.) or chronic nonradicular or radicular LBP	Systemic pharmacologic therapies: acetaminophen, NSAIDs, opioids, tramadol, tapentadol, antidepressants, skeletal muscle relaxants, benzodiazepines, anti-seizure, & corticosteroid medications vs. (placebo, no treatment, or other therapies). Also 2 vs. 1 drug.	Pain, function, AE [acute <4 wks.]	Drug vs. placebo: 15 RCTs for acute LBP (unclear): acetaminophen (1 RCT), NSAIDs (5 RCTs), opioids (0 RCT), SMR (5 RCTs), antiseizure drugs (0 RCT), systemic corticosteroids (2 RCT) 9 addressed acute LBP	Not specified
Machado 2017 <sup>6</sup> Australia	February 2016	Persons with low back or neck pain, with/without radicular pain	NSAIDs (topical, oral or injection) vs. placebo	Pain, function, quality of life, AE	35 RCTs (unclear) 19 addressed acute LBP	Not specified
Paige 2017 <sup>7</sup> USA	February 2017	Adults with acute ( $\leq$ 6 wks.) LBP	Spinal manipulative therapy (SMT)	Pain, function, AE	26 RCTs (unclear): short-term pain (1421); function (1381); 8 RCTs AEs (1041) 25 addressed acute LBP	Ambulatory
Rasmussen-Barr 2017** <sup>8</sup> Sweden, Switzerland, the Netherlands	June 2015	Age 16 yrs. or older, acute, subacute or chronic sciatica	NSAID vs. (placebo, other NSAID, or other medication)	Pain, global improvement, AE	10 RCTs (1651); most for acute sciatica < 3 wks. 9 addressed acute LBP	Not specified
Rothberg 2017 <sup>9</sup> USA	May 2016	Adult with nonchronic, nonradicular LBP (<12 wk.)	Combined (CAM + standard medical care) vs. standard medical care [CAM= SMT, massage, exercise or yoga]	Pain, function	6 RCT: 2 SMT (344), 4 exercise (930) 6 addressed acute LBP	Multiple
Gagnier 2016** <sup>10</sup> USA, Canada, the Netherlands	September 2014	Adults with acute ( $\leq$ 6 wks.), sub-acute or chronic nonspecific LBP	Plants used for medicinal purposes (herbal medicines, 6 substances, ingested or topical) vs. placebo	Pain, function	14 RCTs (2,050) 7 addressed acute LBP	Not specified
Liu 2016 <sup>11</sup> China	June 2015	Adults with lumbosacral radicular pain (from disc herniation &/or spinal stenosis)	Transforaminal vs. caudal ESI route (using triamcinolone, betamethasone, and depo- medrol)	Pain, function	8 studies [6 RCTs (278)] 5 addressed acute LBP	Not specified

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes*</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Macedo 2016** <sup>12</sup> Canada, Australia, Brazil, the Netherlands	April 2015	Adults with acute (< 3 mo.) nonspecific LBP	Motor control exercises vs. (no treatment, other treatment, or adjunct to other intervention/s)	Pain, function, quality of life, recurrence	3 RCTs (197) 2 addressed acute LBP	Not specified
Poquet 2016** <sup>13</sup> Australia	August 2015	Adults with acute/subacute nonspecific LBP (report section)	Back schools (therapeutic program of exercise & education) vs. (another treatment, no treatment or placebo (sham or attention control)	Pain, function, work status, AE	4 RCT/quasi-RCT (643) 2 addressed acute LBP	Not specified
Wei 2016 <sup>14</sup> China	January 2016	Adults with LBP & lumbosacral radicular pain	Transforaminal vs interlaminar ESI	Pain, function, ESI frequency, surgery rate, ventral epidural spread	13 studies (931); 9 were RCTs 6 addressed acute LBP	Not specified

\*AHRQ EPC Review; \*\*Cochrane review

ACP = American College of Physicians AE = adverse effects; ED = emergency department; h = hour(s); ESI = epidural steroid injection; LBP = low back pain; MBSR = mindfulness-based stress reduction; NR = not reported; NSAIDS = nonsteroidal anti-inflammatory drugs; EMG-FB = electromyography feedback; OMT = osteopathic manipulative treatment; RCT = randomized controlled trial; RUSI = real time ultrasound imaging; SI = sacroiliac; SMT = spinal manipulative therapy; SMR = skeletal muscle relaxants; wks. = weeks

## **RCTs Included in Previous SRs and New RCTs: Acute Back Pain**

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## Appendix I. Evidence Tables: Acute Neck Pain

**Appendix Table I1. Systematic reviews: treatments for acute neck pain**

Systematic Review Organization Country	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
Hidalgo 2017 <sup>1</sup>	December 2015	Adults	Manual therapy	Pain; overall health; quality of life	9 RCT (680) 7 acute pain	NR
Bussieres 2016 <sup>2</sup>	December 2015	NR	Neck manipulation, Integrated neuromuscular inhibition tech., home exercises, multimodal care, Supervised graded strengthening exercises, LLLT, work disability prevention interventions, cervical collar, cervical traction structured patient education, supervised qigong exercise, supervised yoga, TENS, massage, Work-based hardening, group exercise,	Pain; function	52 RCT (NR) 4 acute pain	Multiple
Gross 2016 <sup>**3</sup>	May 2014	Adult	Exercise therapy as part of a multidisciplinary treatment, multimodal treatment, or exercise requiring manual therapy techniques by a trained individual	Pain; function; satisfaction; global perceived effect, quality of life; AEs	27 RCT +4 comparisons (NR) 1 acute pain	NR
Sutton 2016 <sup>4</sup>	May 2013	Adults and children	Multimodal care	Pain; recovery; function; disability; quality of life; psychological outcomes; AEs	14 RCTs (2,502) 2 acute pain	Multiple
Wong 2016 <sup>5</sup>	February 2014	Mixed ages	Manual therapies, passive physical modalities, or acupuncture	Pain; recovery; quality of life; psychological outcomes; AEs	38 RCT, cohort and case-control (NR)	Multiple
Gross 2015 <sup>**6</sup>	November 2014	Adults	Neck manipulation and mobilization	Pain; function; disability; quality of life; psychological outcomes; global perceived effect; AEs	51 RCTs (2,920) 2 acute pain	Multiple
Gross 2013 <sup>7</sup>	February 2012	Adults	Low level laser therapy	Pain; function; disability; quality of life; patient satisfaction; global perceived effect	17 RCTs (919) 2 acute pain	NR
Kadhim-Saleh 2013 <sup>8</sup>	January 2012	Adults	Low level laser therapy	Pain; AEs	8 RCTs (443) 1 acute pain	NR

\*AHRQ EPC Review; \*\*Cochrane review

AE = adverse effects; ED = emergency department; h = hour(s); NR = not reported; NSAIDS = nonsteroidal anti-inflammatory drugs

## **RCTs Included in Previous SRs and New RCTs: Acute Neck Pain**

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## Appendix J. Evidence Tables: Fractures

**Appendix Table J1. Systematic reviews: treatments for acute pain attributable to fractures**

Systematic Review	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
Zuo 2018 <sup>1</sup>	October 2017	Older Adults with osteoporotic compression fractures	Percutaneous vertebroplasty; percutaneous kyphoplasty; nerve block; conservative treatment	Pain; function; recovery; quality of life; AEs	18 RCTs (1994)	Not specified
Ameis 2017 <sup>2</sup> Overview of reviews	May 2015	Older Adults with osteoporotic compression fractures	Bracing; pharmacotherapy; exercise; passive physical modalities	recovery; pain, quality of life; depression; AEs	6 SRs (NR)	Not specified
Hartmann 2017 <sup>3</sup>	November 2014	Older adults with hip fracture	IV fentanyl; nerve blocks	Pain	2 RCTs (148)	Not specified
Goodwin 2016 <sup>4</sup>	April 2015	Older adults with hip or femoral neck fractures	Orthotics; taping	Pain; postural stability; back strength; angle of kyphosis and fracture union	6RCT+1OS+2 BA=9 (468)	Not specified
Riddell 2016 <sup>5</sup>	May 2014	Older Adults with hip fracture	femoral nerve blocks	Pain	7 RCTs (224)	EDs
Ritcey 2016 <sup>6</sup>	January 2014	Older Adults with osteoporotic compression fractures	IV opioids	Pain	9 RCTs (547)	EDs

\*AHRQ EPC Review; \*\*Cochrane review

Abbreviations: AE = adverse effects; BA = before-after study; EDs = emergency departments; IV = intravenous; NR = not reported; OS = observational study; SR = systematic review

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## Appendix J References

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## Appendix K. Evidence Tables: Renal Colic

**Table K1. Systematic reviews: medical management of renal colic**

Systematic Review	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
Pathan 2018 <sup>1</sup>	December 2016	Adults (16+ years)	NSAIDs with opioids and paracetamol (acetaminophen); almost all intramuscular or intravenous	Pain reduction at 30 min; rescue treatment; acute and serious adverse events	36 RCT (4887)	ED
Sin 2017 <sup>2</sup>	April 2016	Adults (16+ years)	Intravenous acetaminophen with piroxicam, morphine, diclofenac	Pain reduction after 30 min of treatment;	5 RCT (1745)	ED
Jalili 2016 <sup>3</sup>	June 2015	Adults	Desmopressin with intramuscular or intravenous opioids/NSAID (Diclofenac, Meperidine, Tramadol, Indomethacin)	Pain reduction at 30 min; rescue treatment	10 RCT (1000)	NR (ED likely)
Afshar 2015 <sup>**4</sup>	November 2014	Adults (16+ years)	NSAIDs and non-opioids (antispasmodics, calcium channel blockers and desmopressin); almost all intramuscular or intravenous	Pain reduction at 30 min; rescue treatment; Adverse event (e.g. gastrointestinal bleed, kidney dysfunction)	50 RCT/quasi-RCT (5734)	NR (ED likely)

\*AHRQ EPC Review; \*\*Cochrane review

Abbreviations: AE = adverse effects; BA = before-after study; EDs = emergency departments; IV = intravenous; NR = not reported; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trials; SR = systematic review

## **RCTs Included in Previous SRs and New RCTs: Renal Colic**

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## Appendix L. Evidence Tables: Orofacial Pain

**Appendix Table L1. Systematic reviews: treatments for dental pain, nonsurgical**

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Aminoshariae 2016 <sup>1</sup>	April 2016	Adults	Preoperative NSAIDS	Pain; AEs	27 RCTs (NR)	Not specified
Aminoshariae 2016 <sup>2</sup>	September 2015	Adults undergoing endodontic treatment	Antibiotics	Pain (time NR)	5 RCTs (271)	Not specified
Ashley 2016 <sup>3</sup>	March 2012	Children and adolescents undergoing extraction/restoration or orthodontic procedures	Preoperative analgesics	Pain; AEs	5 RCTs (190)	Dental clinics/oral surgery clinics

\*AHRQ EPC Review; \*\*Cochrane review

Abbreviations: AE = adverse events; NR = not reported; NSAIDS = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trials

## **RCTs included in Previous SRs and New RCTs: Orofacial Pain**

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## Appendix M. Evidence Tables: Acute Migraine

**AppendixTable M1. Systematic reviews: treatments for acute migraine**

Systematic Review Organization Country	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
Menshawy 2018 <sup>1</sup>	August 2016	Primarily adults	Intranasal sumatriptan	Pain relief at 15, 30 minutes, 1 h, 2 h, 2 to 24 h, 2 to 48 h; clinical disability free at 1, 1.5, 2 h; need for rescue meds at 2 h; sustained pain free at 1 to 24 h; meaningful relief; AEs	16 RCTs (5,925)	Not specified
Jeric 2018 <sup>2</sup>	April 2017	Children and adolescents	Ibuprofen and paracetamol	Pain free at 2 h; headache relief at 2 h; AEs	3 RCTs (201) 10 SRs (unclear)	Not specified
Hong 2017 <sup>3</sup>	April 2015	Adults	Calcitonin gene-related peptide (CGRP)	pain free at 2 h; 2–24 h sustained headache relief; phonophobia and nausea free at 2 h;	10 RCTs (6803)	Not specified
Law 2016** <sup>4</sup>	October 2015	Adults	Sumatriptan plus naproxen tablets	Pain free at 2 hrs; headache relief; sustained pain free at 24 h; AEs	12 RCTs (9,300)	Not specified
Orr 2016 <sup>5</sup>	NR, likely during 2015	Adults	Injectable medications (28 different medications)	Pain improvement; pain intensity; headache recurrence; AEs	68 RCTs (unclear)	Not specified
Richer 2016** <sup>6</sup>	February 2016	Children and adolescents	Pharmacologic interventions by drug and route of administration	Pain free at 2 h; headache relief; AEs	27 RCTs (7,630)	Primary care/specialty clinics
Cameron 2015 <sup>7</sup>	October 2013	Adults	Triptans (any mode of administration)	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	133 RCTs (unclear, 20,000+)	Not specified
Cui 2015 <sup>8</sup>	January 2013		Telcagepant, CGRP receptor antagonist	Pain free at 2 h; headache relief at 2 h; AEs	8 RCTs (4,382)	Not specified
Nierenburg 2015 <sup>9</sup>	August 2014	Adolescent and adult women (with acute menstrual migraine)	Triptans, combination therapy, prostaglandin synthesis inhibitor, ergotamine derivative	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	11 RCTs (1,704)	Not specified
Choi 2014 <sup>10</sup>	2012	Adults	IV magnesium sulphate	Pain relief at 30 mins; AE	5 RCTs (295)	Mixed

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Bird 2014**11	March 2014	Adults	Zolmitriptan, any mode of administration	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	25 RCTs (20,162)	Primary care/specialty clinics
Derry 2014**12 Overview of Cochrane reviews	October 2011	Adults	Sumatriptan, all modes of administration	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	111 RCTs (52,236)	Not specified
Rabbie 2013**13	February 2013	Adults	Ibuprofen with and without antiemetic	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	9 RCTs (4,373)	Not specified
Law 2013**14	May 2013	Adults	Naproxen with and without antiemetic	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	4 RCTs (2,149)	Primary care/specialty clinics
Kirthi 2013**15	January 2013	Adults	Aspirin with and without antiemetic	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	13 RCTs (4,222)	Not specified
Derry 2013- diclofenac**16	February 2013	Adults	Diclofenac with and without antiemetic	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	5 RCTs (1,356)	Not specified
Derry 2013- paracetamol**17	February 2013	Adults	Acetaminophen with and without antiemetic	Pain free at 2 h; headache relief; sustained pain-free for 24 h; sustained headache relief for 24 h; AEs	11 RCTs (2,942)	Not specified
Derry 2012- sumatriptan oral**18	October 2011	Adults	Sumatriptan, oral tablets	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	61 RCTs (37,250)	Not specified
Derry 2012- sumatriptan intranasal**19	October 2011	Adults	Sumatriptan, intranasal	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	12 RCTs (4,755)	Not specified
Derry 2012- sumatriptan rectal**20	October 2011	Adults	Sumatriptan, rectal	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	3 RCTs (866)	Not specified

<b>Systematic Review Organization Country</b>	<b>End Search Date</b>	<b>Population</b>	<b>Interventions Addressed</b>	<b>Outcomes</b>	<b>Eligible Studies by Study Design (total participants)</b>	<b>Setting(s)</b>
Derry 2012- sumatriptan subcutaneous** <sup>21</sup>	October 2011	Adults	Sumatriptan, subcutaneous	Pain free at 2 h; headache relief at 2 h; sustained pain free and sustained headache relief at 24 h; AEs	35 RCTs (9,365)	Not specified
Sumamo Schellenberg 2012* <sup>22</sup>	January 2012	Adults	IV, intramuscular, or subcutaneous interventions from nine drug classes (antiemetics, neuroleptics, ergotamines, NSAIDS, opioids, corticosteroids, triptans, magnesium sulfate, antihistamines)	Pain intensity; change in pain; headache relief at 1 h; pain free at 1 h; headache recurrence at 24 h; AEs	69 RCTs 2 NRCTs (unclear)	ED

\*AHRQ EPC Review; \*\*Cochrane review

Abbreviations: AE = adverse effects; EDs = emergency departments; NR = not reported; NSAIDS = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trials; SR = systematic review

## **RCTs Included in Previous SRs and New RCTs: Migraine**

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## Appendix N. Evidence Tables: Sick Cell Crisis

**Appendix Table N1. Systematic reviews: treatments for acute pain in sickle cell disease**

Systematic Review	End Search Date	Population	Interventions Addressed	Outcomes	Eligible Studies by Study Design (total participants)	Setting(s)
NHLBI 2014 <sup>1</sup>	July 2014	Adults and children with sickle cell disease	Parenteral opioid therapy Meperidine NSAIDS Around the clock vs intermittent analgesics	Pain (presumed – no specifics given or evidence tables provided)	4 total, RCT and observational (NR)	All settings where patients present; ED or outpatient
Okomo 2017 <sup>**2</sup>	February 2017	NR	Fluid replacement therapy	Pain	0 (0)	NR
van Zuuren 2015 <sup>**3</sup>	September 2015	Adults and children with sickle cell disease	Low-molecular-weight heparins	Pain Requirement for treatment with opioids Complications Quality of life Hospitalizations Participant satisfaction Adverse events	2 total, 1 RCT 2 CCT (253)	All settings where patients present; ED or outpatient

\*AHRQ EPC Review; \*\*Cochrane review

CCT = controlled clinical trial; ED = emergency department; NR = not reported; NSAIDS = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trials

## **RCTs Included in Previous SRs and New RCTs: Sickle Cell**

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## Appendix N References

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