



Comparative Effectiveness Review  
Number 239

# Acute Treatments for Episodic Migraine



# *Comparative Effectiveness Review*

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Number 239

## **Acute Treatments for Episodic Migraine**

**Prepared for:**

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**Prepared by:**

Mayo Clinic Evidence-based Practice Center  
Rochester, MN

**Investigators:**

Rashmi B. Halker Singh, M.D.  
Juliana H. VanderPluym, M.D.  
Allison S. Morrow, B.A.  
Meritxell Urtecho, M.D.  
Tarek Nayfeh, M.D.  
Victor D. Torres Roldan, M.D.  
Magdoleen H. Farah, M.B.B.S.  
Bashar Hasan, M.D.  
Samer Saadi, M.D.  
Sahrish Shah, M.B.B.S.  
Rami Abd-Rabu, M.B.B.S.  
Lubna Daraz, Ph.D.  
Larry J. Prokop, M.L.S.  
Mohammad Hassan Murad, M.D., M.P.H.  
Zhen Wang, Ph.D.

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**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 healthcare in the United States.

The Centers for Disease Control and Prevention (CDC) requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Mayo Clinic Evidence-based Practice Center (Contract No. 290-2015-00013-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. 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.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

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

If you have comments on this evidence report, 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).

Gopal Khanna, M.B.A.  
Director  
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.  
Director  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

Christine Chang, M.D., M.P.H.  
Acting Director  
Evidence-based Practice Center Program  
Center for Evidence and Practice Improvement  
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D  
Task Order Officer  
Center for Evidence and Practice  
Improvement  
Agency for Healthcare Research and Quality

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## Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows:

Sarah Benish, M.D., FAAN  
Section Head of General Neurology  
Department of Neurology  
University of Minnesota  
Minneapolis, MN

Rebecca Burch, M.D.\*  
Assistant Professor  
Department of Neurology  
Harvard Medical School  
Boston, MA

Beth Darnall, Ph.D.\*  
Associate Professor  
Department of Anesthesiology,  
Perioperative and Pain Medicine  
Stanford University School of Medicine  
Palo Alto, CA

Benjamin W. Friedman, M.D., FAAEM\*  
Vice-Chair for Clinical Investigation  
Department of Emergency Medicine  
Albert Einstein College of Medicine  
New York, NY

Ian Koebner, Ph.D., M.Sc.  
Assistant Professor  
Department of Anesthesiology and Pain  
Medicine  
University of California, Davis  
Sacramento, CA

Margaret Slavin, Ph.D., R.D.N.\*  
Associate Professor  
Department of Nutrition and Food Studies  
College of Health and Human Services  
George Mason University  
Fairfax, VA

\*Provided input on Draft Report.

## 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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The list of Peer Reviewers follows:

A. Laine Green, M.D., M.Sc., FRCPC,  
FAHS  
Assistant Professor of Neurology  
Department of Neurology  
Geisel School of Medicine at Dartmouth  
Dartmouth-Hitchcock Medical Center  
Lebanon, NH

Mia Minen, M.D., M.P.H.  
Associate Professor  
Department of Neurology  
Department of Population Health  
New York University Grossman School of  
Medicine  
New York, NY

# Acute Treatments for Episodic Migraine

## Structured Abstract

**Objectives.** To evaluate the effectiveness and comparative effectiveness of pharmacologic and nonpharmacologic therapies for the acute treatment of episodic migraine in adults.

**Data sources.** MEDLINE<sup>®</sup>, Embase<sup>®</sup>, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, PsycINFO<sup>®</sup>, Scopus, and various grey literature sources from database inception to July 24, 2020. Comparative effectiveness evidence about triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) was extracted from existing systematic reviews.

**Review methods.** We included randomized controlled trials (RCTs) and comparative observational studies that enrolled adults who received an intervention to acutely treat episodic migraine. Pairs of independent reviewers selected and appraised studies.

**Results.** Data on triptans were derived from 186 RCTs summarized in nine systematic reviews (101,276 patients; most studied was sumatriptan, followed by zolmitriptan, eletriptan, naratriptan, almotriptan, rizatriptan, and frovatriptan). Compared with placebo, triptans resolved pain at 2 hours and 1 day, and increased the risk of mild and transient adverse events (high strength of the body of evidence [SOE]). Data on NSAIDs were derived from five systematic reviews (13,214 patients; most studied was ibuprofen, followed by diclofenac and ketorolac). Compared with placebo, NSAIDs probably resolved pain at 2 hours and 1 day, and increased the risk of mild and transient adverse events (moderate SOE). For other interventions, we included 135 RCTs and 6 comparative observational studies (37,653 patients). Compared with placebo, antiemetics (low SOE), dihydroergotamine (moderate to high SOE), ergotamine plus caffeine (moderate SOE), and acetaminophen (moderate SOE) reduced acute pain. Opioids were evaluated in 15 studies (2,208 patients). Butorphanol, meperidine, morphine, hydromorphone, and tramadol in combination with acetaminophen may reduce pain at 2 hours and 1 day, compared with placebo (low SOE). Some opioids may be less effective than some antiemetics or dexamethasone (low SOE). No studies evaluated instruments for predicting risk of opioid misuse, opioid use disorder, or overdose, or evaluated risk mitigation strategies to be used when prescribing opioids for the acute treatment of episodic migraine. Calcitonin gene-related peptide (CGRP) receptor antagonists improved headache relief at 2 hours and increased the likelihood of being headache-free at 2 hours, at 1 day, and at 1 week (low to high SOE). Lasmiditan (the first approved 5-HT<sub>1F</sub> receptor agonist) restored function at 2 hours and resolved pain at 2 hours, 1 day, and 1 week (moderate to high SOE). Sparse and low SOE suggested possible effectiveness of dexamethasone, dipyrrone, magnesium sulfate, and octreotide. Compared with placebo, several nonpharmacologic treatments may improve various measures of pain, including remote electrical neuromodulation (moderate SOE), magnetic stimulation (low SOE), acupuncture (low SOE), chamomile oil (low SOE), external trigeminal nerve stimulation (low SOE), and eye movement desensitization re-processing (low SOE). However, these interventions, including the noninvasive neuromodulation devices, have been evaluated only by single or very few trials.

**Conclusions.** A number of acute treatments for episodic migraine exist with varying degrees of evidence for effectiveness and harms. Use of triptans, NSAIDs, antiemetics, dihydroergotamine, CGRP antagonists, and lasmiditan is associated with improved pain and function. The evidence base for many other interventions for acute treatment, including opioids, remains limited.



# Contents

<b>Evidence Summary .....</b>	<b>ES-1</b>
<b>Introduction.....</b>	<b>1</b>
Background.....	1
Purpose and Scope of the Systematic Review .....	2
<b>Methods.....</b>	<b>3</b>
Review Approach.....	3
Key Questions.....	3
Literature Search Strategy.....	5
Search Strategy .....	5
Inclusion and Exclusion Criteria.....	6
Study Selection .....	8
Data Abstraction and Data Management .....	8
Assessment of the Risk of Bias of Individual Studies .....	9
Assessment of the Credibility of Systematic Reviews .....	9
Data Synthesis.....	9
Grading the Strength of Evidence for Major Comparisons and Outcomes .....	11
Assessing Applicability .....	12
Peer Review and Public Commentary .....	12
<b>Results .....</b>	<b>13</b>
Literature Searches and Evidence Base .....	13
KQ1: Opioid Therapy .....	13
KQ1 Key Points .....	14
KQ1 Results .....	15
KQ 2: Nonopioid Pharmacologic Therapy .....	18
KQ2 Key Points .....	19
KQ2 Results .....	19
KQ3: Nonpharmacologic Therapy.....	36
KQ3 Key Points .....	36
KQ3 Results .....	36
<b>Discussion.....</b>	<b>41</b>
Overview.....	41
Findings in Relation to What Is Known .....	41
Clinical Implications and Applicability of Findings.....	43
Limitations and Suggestions for Future Research .....	44
Conclusion .....	47
<b>References .....</b>	<b>48</b>
<b>Abbreviations and Acronyms .....</b>	<b>60</b>

## Tables

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting).....	6
Table 2. Definition of pain and function outcomes .....	9
Table 3. Categories of adverse events.....	10
Table 4. Comparisons of opioid therapy.....	16
Table 5. Existing systematic reviews about triptans compared with placebo.....	21

Table 6. Existing systematic reviews about nonsteroidal anti-inflammatory drugs compared with placebo .....	21
Table 7. Comparisons of ergot alkaloids .....	22
Table 8. Comparisons of antiemetics.....	25
Table 9. Comparisons of gepants.....	28
Table 10. Comparisons of 5-HT1F .....	30
Table 11. Comparisons of other nonopioid pharmacological interventions .....	33
Table 12. Comparisons of nonpharmacologic interventions .....	38

**Figure**

Figure 1. Analytic framework for Key Questions .....	5
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**Appendixes**

Appendix A. Search Strategy
Appendix B. Flow Chart
Appendix C. Excluded Studies
Appendix D. Characteristics of Included Studies
Appendix E. Risk of Bias
Appendix F. Results From Included Studies
Appendix G. Summary of Systematic Reviews Evaluating Triptans and NSAIDs
Appendix H. Adverse Events
Appendix I. Subgroup Analysis by Dosage
Appendix J. Adverse Events: Subgroup Analysis by Dosage
Appendix K. Subgroup Analysis by Study Settings and Routes of Administration
Appendix L. Sensitivity Analysis
Appendix M. Appendix References

# Evidence Summary

## Main Points

- Compared with placebo, treatments such as triptans, NSAIDs (nonsteroidal anti-inflammatory drugs), dihydroergotamine, antiemetics, and acetaminophen, reduce pain but increase the risk of mild and transient adverse events.
- Only a small number of studies have evaluated opioids. Some opioids may reduce pain of episodic migraine. Some opioids may be less effective than other drugs.
- No studies evaluate instruments for predicting risk of opioid misuse, opioid use disorder or overdose, or evaluate risk mitigation strategies to be used when prescribing opioids for episodic migraine.
- Newer therapies such as calcitonin gene-related peptide receptor antagonists and lasmiditan (5-HT<sub>1F</sub> receptor agonist) probably improve pain relief at 2 hours and increase the likelihood of being pain-free at 2 hours, 1 day, and at 1 week, and restore function. Serious adverse events are more common in patients who received lasmiditan than placebo.
- Although only studied in one or a few small trials, several other therapies available in the United States may improve migraine pain compared with placebo, including dexamethasone, dipyrone, lidocaine, magnesium sulfate octreotide, and secobarbital. Evidence is insufficient to draw conclusions about serious adverse events.
- Although only studied in one or a few small trials, several nonpharmacological treatments for migraine may improve various measures of pain migraine compared with placebo, including noninvasive neuromodulation devices such as remote electrical neuromodulation, magnetic stimulation, and external trigeminal nerve stimulation, as well as other therapies such as acupuncture, chamomile oil, and eye movement desensitization reprocessing. Evidence is insufficient to draw conclusions about serious adverse events.

## Background and Objectives

In patients with migraine, several acute treatment options are available, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy.<sup>1</sup> Current guidelines recommend the use of triptans and NSAIDs as first line acute treatments, as well as acetaminophen for non-incapacitating attacks.<sup>2</sup> However, the evidence supporting the effectiveness of opioids, other nonopioid pharmacologic therapy, and nonpharmacologic therapies remains unclear. Evidence about harms is also unclear. Opioid and butalbital-containing medications have a two-fold higher risk of medication overuse headache compared with simple analgesics and triptans.<sup>3</sup> Additionally, the use of opioids for the acute treatment of migraine has been identified as a risk factor for disease chronification.<sup>4,5</sup> Thus, the American Headache Society recommends that opioids and butalbital-containing drugs should not be used as first-line treatment for migraine and other recurrent headache disorders, and guidelines recommend that triptans and simple analgesics should be tried first.<sup>6</sup> If triptans and NSAIDs are ineffective, contraindicated or not tolerated, patients and clinicians struggle when deciding how to use these other therapies. They need information about the comparative effectiveness and harms of alternative therapies to the first line treatments of triptans and NSAIDs.

This systematic review assesses the comparative effectiveness and harms for acute migraine treatments, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy.

## Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>7</sup> The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.<sup>8</sup> The study protocol was published on AHRQ website (<https://effectivehealthcare.ahrq.gov/products/migraine-treatments/protocol>) and was registered to the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42020163262).

## Results

Evidence on triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) was summarized from 16 existing systematic reviews. For other interventions, we identified 15,247 citations from which we included 141 original studies with a total of 37,653 patients (Appendix Figure A.1.).

### Key Question (KQ) 1: Opioid Therapy

- Fifteen studies (13 randomized controlled trials [RCTs] and 2 comparative observational studies) with 2,208 patients were included for KQ1.
- No studies evaluated instruments for predicting risk of opioid misuse, opioid use disorder or overdose; or evaluated risk mitigation strategies in episodic migraine.

Effectiveness and harms:

- Tramadol in combination with acetaminophen may reduce pain at 2 hours and 1 day, compared with placebo (low strength of evidence [SOE]). However, the evidence for tramadol alone was insufficient. Tramadol plus acetaminophen was associated with significantly increased number of adverse events (AEs).
- Butorphanol may reduce pain at 2 hours, 1 day, and 1 week, compared with placebo (low SOE). It was associated with increased number of gastrointestinal AEs, neurological AEs, and total number of AEs.
- Evidence was insufficient to draw conclusions about serious adverse events.

Comparative effectiveness and harms:

- Meperidine plus hydroxyzine may be worse than dihydroergotamine plus metoclopramide in terms of pain relief at 2 hours and function (low SOE).
- Morphine may be worse than intravenous dexamethasone in terms of pain relief at 2 hours and 1 day (low SOE).
- Hydromorphone may be worse than metoclopramide (low SOE) and worse than diphenhydramine plus prochlorperazine in terms of pain relief at 2 hours (low SOE). Evidence was insufficient to draw conclusions about serious adverse events.

### KQ2: Nonopioid Pharmacologic Therapy

- Evidence on triptans and NSAIDs was summarized from 16 existing systematic reviews. Data on triptans were derived from 186 RCTs summarized in 9 systematic reviews

(101,276 patients), data on NSAIDs were derived from 5 systematic reviews (46 RCTs, 13,214 patients) and two systematic reviews evaluated the combination of triptans and NSAIDs. One hundred ten articles of 108 studies (105 RCTs and 3 comparative observational studies) and 33,687 patients were included for other interventions.

Effectiveness and harms of established treatments:

- Compared with placebo, triptans resolve pain at 2 hours and 1 day (high SOE), and increase the risk of mild and transient adverse events (high SOE).
- Compared with placebo, NSAIDs probably resolve pain at 2 hours and 1 day (moderate SOE), and increase the risk of mild and transient adverse events (moderate SOE).
- Compared with placebo, dihydroergotamine reduces pain (high SOE) and probably increases the likelihood of being pain free at 2 hours, 1 day and 1 week (moderate SOE). Dihydroergotamine probably improves function (moderate SOE) and improves sustained pain relief (high SOE) at 2 hours and 1 day.
- Compared with placebo, ergotamine plus caffeine probably improves pain relief at 2 hours (moderate SOE).
- Antiemetics, including prochlorperazine, chlorpromazine, metoclopramide, droperidol and haloperidol, may resolve pain at 2 hours and 1 day (low SOE) compared with placebo.
- Evidence was insufficient across all pharmacological treatments to draw conclusions about serious adverse events.

Effectiveness and harms of newer treatments:

- Compared with placebo, calcitonin gene-related peptide receptor (CGRP) antagonists (known as gepants), including rimegepant, and ubrogepant, demonstrated improved pain relief at 2 hours (moderate to high SOE) and increased the likelihood of being pain free at 2 hours (moderate to high SOE) and sustained pain free at 1 day and at 1 week (moderate to high SOE). Evidence was insufficient to draw conclusions about serious adverse events.
- Compared with placebo, the 5-HT<sub>1F</sub> receptor agonist lasmiditan restored function at 2 hours (high SOE), and also resolved pain at 2 hours (high SOE), 1 day (high SOE) and 1 week (moderate SOE). Serious adverse events were more common in patients who received lasmiditan than placebo (high SOE).

Other comparisons:

- Although only studied in one or a few small trials, several other therapies may improve migraine pain compared with placebo, including dexamethasone, dipyrone, lidocaine, magnesium sulfate, octreotide, and secobarbital (low SOE). Evidence was insufficient to draw conclusions about serious adverse events.

### **KQ3: Nonpharmacologic Therapy**

- Seventeen RCTs and one comparative observational study with 1,758 patients were included for KQ3.
- Although only studied in one or a few small trials, several nonpharmacological acute treatments of migraine may improve various measures of pain compared with placebo, including acupuncture (low SOE), chamomile oil (low SOE), external trigeminal nerve stimulation (low SOE), eye movement desensitization reprocessing (low SOE), and remote electrical neuromodulation (moderate SOE).

- Evidence was insufficient to draw conclusions about serious adverse events.

## Limitations

For many interventions, very few or a single trial were available and most were small, which limits inferences from the quantitative analysis. The studies were conducted in different settings, from the emergency room to outpatient to inpatient environments. This review does not capture harms that may arise with frequent or long-term intermittent use of the treatments. The inability to capture such harms is due to study design as the majority of trials evaluate the efficacy and harms of the treatments during one or a few attacks. In terms of applicability, several of the established drugs, such as the ergot alkaloids, may not be reliably stocked by pharmacies and some of newer drugs may not be accessible or afforded by all patients. Finally, patients are often advised to use combinations of therapies to treat migraine attacks. This combination can include an antiemetic as well as migraine specific therapy such as a triptan and a nonspecific analgesic such as an NSAID. The trials we analyzed did not sufficiently evaluate these potential combination therapies and their interactions.

## Implications and Conclusions

High and moderate strength of evidence support the effectiveness of triptans and NSAIDs, respectively. These established treatments, along with dihydroergotamine, antiemetics and acetaminophen, are considered established acute treatments for migraine. In general, adverse events of these drugs are mild and transient.

A common challenge in practice is when certain patients do not have pain relief with, or do not tolerate, these established treatments. Newer therapies for acute treatment of migraine such as the calcitonin gene-related peptide antagonists (known as gepants) and the 5-HT<sub>1F</sub> receptor agonist, lasmiditan, were more effective than placebo in improving pain relief at 2 hours and 1 day and at 1 week. However, adverse events of newer medications require further study. For example, lasmiditan increased the risk of serious adverse events compared with placebo. Additionally, several nonpharmacologic acute treatments for migraine are available; however, they have been studied in one or a few small trials.

This systematic review has shown that very few studies evaluated the use of opioids for acute migraine. The strength of evidence supporting the use of the various opioids for acute treatment of migraine was low or insufficient. No included studies evaluated instruments to help in predicting risk of opioid misuse, developing opioid use disorders or overdose in patients with migraine. No included studies evaluated risk mitigation strategies to be used when prescribing opioids for episodic migraine. The lack of risk assessment tools and mitigation strategies has major implications for practical implementation of treatment algorithms that include opioids. When this is viewed in the context of how widely opioids are prescribed for migraine management, it is particularly concerning.<sup>9-15</sup>

The findings of this systematic review can inform shared decision making and choice of therapy. With this information, the place for newer therapies (ex. gepants, ditans and neuromodulatory devices) can be identified among established therapies. Furthermore, the discrepancy between evidence and historical prescribing practices, such as with opioids, has been highlighted.

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# Introduction

## Background

Migraine is a chronic neurological disorder defined by recurrent attacks of headache and other symptoms such as photophobia, phonophobia, nausea and vomiting. It is one of the most common neurologic disorders affecting 12 percent of the general population<sup>1</sup> and is ranked as the 7th highest cause worldwide of years lost due to disability and the leading cause of disability in women under the age of 50.<sup>2</sup> Despite the high prevalence and significant impact of migraine, there are a number of barriers to patients obtaining appropriate migraine management, including seeking a consult, obtaining the diagnosis of migraine, and finally being prescribed migraine-specific treatments. Only 26.3 percent of individuals with episodic migraine traverse these 3 barriers and obtain appropriate acute treatment.<sup>3,4</sup> The fact that migraine can have a varied presentation, and occur in the setting of other concomitant headache disorders, are reasons why it may not be well recognized despite being so prevalent, and contributes to the difficulty experienced by patients when attempting to receive an accurate diagnosis and start on appropriate treatment.

The goals of acute treatment are to provide reliable and effective symptom relief as quickly as possible with minimal adverse effects so that individuals can resume their daily activities without symptom recurrence.<sup>5</sup> In patients with migraine, several acute treatment options are available, including pharmacologic and nonpharmacologic therapy.<sup>6</sup> Because attacks can vary based on intensity and accompanying symptoms, acute treatment of migraine may include outpatient care as well as interventions administered in settings such as the clinician's office, emergency department (ED), urgent care, or inpatient hospitalization. The acute treatment of migraine presents unique challenges that differentiate it from other pain conditions given the paroxysmal nature of the disease. Patients with migraine do not require acute treatment for a limited time as might be the case when someone is recovering from postoperative pain but rather require acute treatments as often as they have attacks, which may vary from 0 to 14 headache days per month in patients with episodic migraine to 15 or more headache days in patients with chronic migraine. Frequent use of acute pharmacologic treatments carries the risk of medication overuse headache, which is considered a secondary headache and a complication of frequent migraine attacks.

Guidelines for outpatient acute treatment recommend the use of triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) as first line interventions, as well as acetaminophen for non-incapacitating attacks. Guidelines for acute treatment of migraine in the ED recommend the use of prochlorperazine based on a high level of evidence, lysine acetylsalicylic acid, metoclopramide and sumatriptan.<sup>7</sup>

Although not a treatment recommended by guidelines, opioids are commonly prescribed for acute treatment of migraine across all clinical settings and age groups.<sup>8-14</sup> Data from the National Ambulatory Medical Care Survey that evaluated outpatient, office-based care has shown that there are nearly as many patients with migraine receiving prescriptions for opioids as there are patients receiving prescriptions for the first line abortive medications recommended by guidelines.<sup>15</sup> Among patients presenting to a tertiary headache care center, approximately 20 percent of patients reported current use of opioids and/or barbiturates; with ED physicians and general neurologists being the most frequent first prescribers of opioids.<sup>16</sup> Based on a review of government health surveillance studies, it was noted that in 2010, opioids were administered in 35 percent of ED visits for headache, while triptans were administered in only 1.5 percent of



visits.<sup>17</sup> The use of opioids for the acute treatment of migraine has been identified as a risk factor for disease chronification.<sup>18-19</sup> The American Headache Society has explicitly stated that opioids and butalbital-containing drugs should not be used as first-line treatment for migraine and other recurrent headache disorders, and guidelines recommend that triptans and simple analgesics should be tried first.<sup>20</sup> Other societies have echoed these sentiments including the Choosing Wisely Program by the American Board of Internal Medicine.<sup>21</sup>

More recently, a number of newer acute treatment options, such as calcitonin gene-related peptide (CGRP) receptor antagonists (known as “gepants”) and 5-HT<sub>1F</sub> agonists (known as “ditans”), have been approved by the Food and Drug Administration and are awaiting guideline updates to determine their place among the established therapies such as triptans and NSAIDs.

In addition to effectiveness, decision makers need information on potential adverse risks, and special considerations in patients who may have certain comorbidities (e.g. kidney disease, sleep disordered breathing, mental illness) or other characteristics (e.g. older population, pregnant/breastfeeding women, or individuals with history of drug abuse/misuse/overdose), as we lack data in these populations.

## **Purpose and Scope of the Systematic Review**

Recognizing the current opioid epidemic, in this systematic review we examine the evidence on the effectiveness and comparative effectiveness of opioids alongside the evidence of effectiveness and comparative effectiveness of nonopioid pharmacologic and nonpharmacologic treatments to provide the full range of evidence to inform clinical decision making in the acute treatment of migraine. Notably, although migraine is more than a headache disorder, the focus of this report is on headache-related outcomes such as pain, function, and quality of life. The intended audience includes the Centers for Disease Control and Prevention, policy and decision makers, and clinicians who treat acute pain. Concurrent systematic reviews addresses treatments for other acute pain conditions.

# Methods

## Review Approach

We developed an analytic framework to guide the process of the systematic review (Figure 1). We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.<sup>22</sup> The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.<sup>23</sup> The study protocol was published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/products/migraine-treatments/protocol>) and registered in the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42020163262).

## Key Questions

The following Key Questions (KQs) were determined based on input from multiple key informants. The related population, interventions, comparisons, outcomes, timing, and setting (PICOTS) are listed in Table 1.

### For Acute Treatment of Patients With Episodic Migraine:

#### KQ1. Opioid therapy

KQ1a. What is the comparative effectiveness of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and cannabis) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture, biofeedback, noninvasive neuromodulation devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life and after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ1b. How does effectiveness of opioid therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status [SES]); (2) patient medical comorbidities (previous opioid use, body mass index [BMI]); (3) dose of opioids; (4) duration of opioid therapy, including number of opioid prescription refills and quantity of pills used?

KQ1c. What are the harms of opioid therapy versus nonopioid pharmacologic therapy or nonpharmacologic therapy with respect to: (1) misuse, opioid use disorder, and related outcomes; (2) overdose; (3) medication overuse headache (MOH); (4) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinologic harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

KQ1d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the dose of opioid used; (4) the duration of opioid therapy?

KQ1e. What are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute treatment of episodic migraine pain on (1) short-term (<3

months) continued need for prescription pain relief, such as need for opioid refills, and (2) long-term opioid use (3 months or greater)?

KQ1f. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the accuracy of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1g. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1h. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the effect of the following risk mitigation strategies on the decision to prescribe opioids: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup?

## KQ2. Nonopioid pharmacologic therapy

KQ2a. What is the comparative effectiveness of nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and cannabis) versus: (1) other nonopioid pharmacologic treatments, such as those in a different medication class; or (2) nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ2b. How does effectiveness of nonopioid pharmacologic therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) duration of treatment?

KQ2c. What are the harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy or nonpharmacologic therapy with respect to: (1) misuse; (2) overdose; (3) MOH; (4) other harms, including gastrointestinal-related harms, cardiovascular-related harms, kidney-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cognitive harms, and psychological harms (e.g., depression)?

KQ2d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) the duration of therapy?

## KQ3. Nonpharmacologic therapy

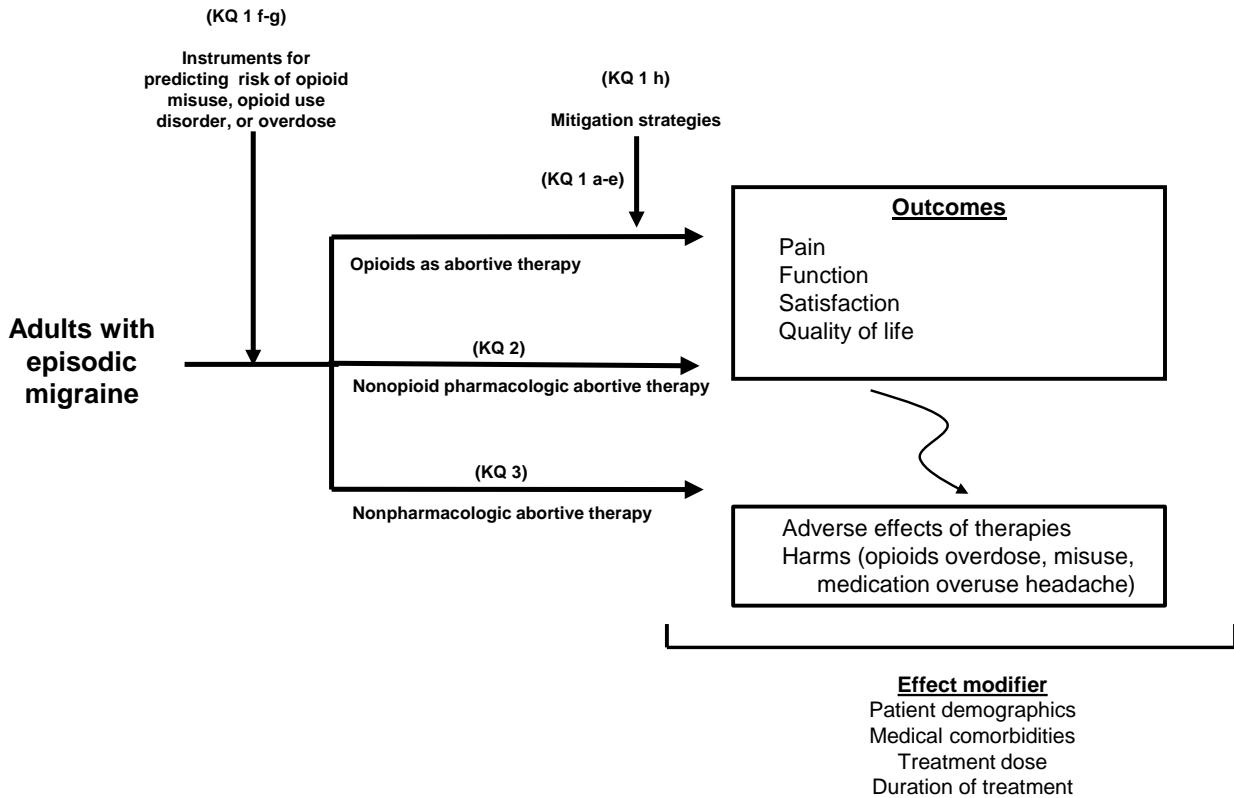
KQ3a. What is the comparative effectiveness of nonpharmacologic therapy versus sham treatment, waitlist, usual care, attention control, and no treatment after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ3b. What is the comparative effectiveness of nonpharmacologic treatments (e.g., exercise, cognitive behavioral therapy, acupuncture, biofeedback, noninvasive neuromodulation devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life?

KQ3c. How does effectiveness of nonpharmacologic therapy vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities?

KQ3d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the type of treatment used; (4) the frequency of therapy; (5) the duration of therapy?

**Figure 1. Analytic framework for Key Questions**



KQ = Key Question

## Literature Search Strategy

### Search Strategy

For interventions other than triptans and NSAIDs, we searched eight bibliographic databases, including Embase<sup>®</sup>, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE<sup>®</sup> Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, PsycINFO<sup>®</sup>, and Scopus from database inception to July 24, 2020. We also searched Food and Drug Administration (FDA), ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Reference mining of existing systematic reviews/meta-analyses, completed trials identified from clinical trial registries, and relevant primary (i.e., randomized controlled trials [RCTs]) and observational studies) was conducted to identify additional literature. In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal was posted to collect additional study-specific information from industry stakeholders, professional societies, and

researchers. The literature search strategy was developed by an experienced medical librarian and peer-reviewed by an independent information specialist. The same medical librarian conducted the literature search. The detailed search strategy is listed in Appendix A. A Federal Register Notice was posted for this review.

Considering the availability of numerous systematic reviews that summarized evidence supporting the use of triptans and NSAIDs for acute treatment of migraine, an overview of systematic reviews approach (also called umbrella systematic review) was used to synthesize the evidence for these two classes of drugs.<sup>22</sup> Another rationale for this approach was that triptans and NSAIDs are recommended as a standard of care in clinical practice guidelines and have longstanding proven record of effectiveness.<sup>24</sup> To identify relevant systematic reviews, we used the same literature search strategy listed above (Appendix A). The systematic reviews have reported on several updates that demonstrated stability of the literature and evidence base, and suggested that future trials about the same comparisons were less likely to be conducted.

## Inclusion and Exclusion Criteria

The eligible studies had to meet all of the following criteria: (1) adult patients (18 years and older) with episodic migraine; (2) received systemic opioid abortive therapy, nonopioid abortive drug, or non-invasive nonpharmacologic abortive therapy; (3) compared with placebo, usual care, another opioid therapy, nonopioid pharmacologic therapy, nonpharmacologic therapy, waitlist, no treatment, or attention control; (4) reported short-term outcomes of interest ( $\leq 4$  weeks after the end of treatments); (5) RCTs and comparative observational studies (all interventions except triptans and NSAIDs) and systematic reviews (triptans and NSAIDs); and (6) published in English. We excluded invasive treatments (defined as surgically implanted) and preventive (prophylactic) treatments, in vitro studies, studies without original data (e.g. narrative review, editorial, secondary analyses of published trials, single-arm studies), and studies published in foreign languages. We included studies of individuals with episodic migraine and used the definition of migraine that was in operation at the time of the study. This definition has been modified over the years, but when looking at older studies we would use the criteria that the authors used as long as it still fit current International Classification of Headache Disorders ICHD-3 criteria for episodic migraine. The detailed inclusion and exclusion criteria are listed in Table 1.

**Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)**

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Population	Patients with episodic migraine seeking abortive treatment Adults 18 years and older *Special populations: General adult Older populations >65 years Patients with history of substance use disorder Patients currently under treatment for opioid use disorder with opioid agonist therapy or naltrexone Patients with a history of mental illness Patients with history of overdose Pregnant/breastfeeding women Patients with comorbidities (e.g. kidney disease, sleep disordered breathing)	Animals Children (age < 18 years)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Interventions	<p>KQ1 a-e: Any systemic opioid abortive therapy, include:  Codeine  Fentanyl (Actiq, Duragesic, Fentora, Abstral, Onsolis)  Hydrocodone (Hysingla, Zohydro ER)  Hydrocodone/acetaminophen (Lorcet, Lortab, Norco, Vicodin)  Hydromorphone (Dilaudid, Exalgo)  Meperidine (Demerol)  Methadone (Dolophine, Methadose)  Morphine (Kadian, MS Contin, Morphabond)  Oxycodone (OxyContin, Oxaydo)  Oxycodone and acetaminophen (Percocet, Roxicet)  Oxycodone and naloxone  And other agonists, partial agonists and mixed mechanism opioids</p> <p>KQ1 f-g: Instruments and genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose</p> <p>KQ1 h: Risk mitigation strategies, including  Existing opioid management plans  Patient education  Clinician and patient values and preferences related to opioids  Urine drug screening  Use of prescription drug monitoring program data  Availability of close followup  And others</p> <p>KQ2: Any oral, injection, infusion, topical nonopioid abortive drug, including:  Acetaminophen  NSAIDs (if compared against active treatment)  Triptans (if compared against active treatment)  Ergot alkaloids  Combination analgesics  Muscle relaxants  Anti-nausea medications  Cannabis  And others</p> <p>KQ3: Any non-invasive nonpharmacologic abortive therapy, including:  Exercise  Cognitive behavioral therapy  Acupuncture  And others</p>	<p>For all KQs, exclude Invasive treatments (surgical interventions, etc), and preventive (prophylactic) treatment</p> <p>For KQ2, exclude NSAIDs vs placebo and triptans vs placebo</p>
Comparators	<p>KQ1: a-e. Usual care, another opioid therapy, nonopioid pharmacologic therapy, nonpharmacologic therapy  KQ1 f. Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks  KQ1 g-h. Usual care  KQ2: Another nonopioid pharmacologic therapy, nonpharmacologic therapy  KQ3: Sham treatment, waitlist, usual care, attention control, and no treatment, another non-invasive nonpharmacologic therapy</p>	None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Outcomes	KQ1. Opioid Therapy: KQ1 a-e. Pain, function, pain relief satisfaction and quality of life, harms/adverse events (including withdrawal, risk of misuse, opioid use disorder [OUD], overdose, MOH). KQ1 f. Measures of diagnostic accuracy KQ1 g-h. Misuse, opioid use disorder, overdose and other harms KQ2. Non-Opioid Therapy: Pain, function, pain relief satisfaction, quality of life, and quality of life, harms/adverse events KQ3: Noninvasive nonpharm Therapy: Pain, function, pain relief satisfaction, quality of life and quality of life, harms, adverse events	None
Timing	At the following intervals: < 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks	None
Settings	ED, physician's office, hospital	None
Study design	Original studies (evaluating interventions other than triptans and NSAIDs) RCTs Comparative observational studies Systematic reviews or meta-analyses (evaluating triptans and NSAIDs) Any sample size Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	In vitro studies, nonoriginal data (e.g. narrative reviews, editorials, letters, or erratum), single-arm observational studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., nonlongitudinal) studies, before-after studies, survey
Publications	Studies published in English only.	Foreign language studies

ED = emergency department; KQ = Key Question; MOH = medication overuse headache; NSAID = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial

## Study Selection

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using prespecified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. When consensus couldn't be reached, a third reviewer resolved the difference. For systematic reviews of triptans and NSAIDs, when more than one systematic review was available per drug, we chose the most recent one with the largest number of included studies.

## Data Abstraction and Data Management

We developed a standardized data extraction form to extract study characteristics (author, year, study design, inclusion and exclusion criteria, patient characteristics, intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form was tested by all study team members using randomly selected studies. Reviewers worked independently to extract study details. A second reviewer reviewed data

extraction and resolved conflicts. When the included studies did not report all necessary information (e.g. methods and results), we contacted authors directly. For systematic reviews of triptans and NSAIDs, we did verify extracted data or risk of bias indicators from original studies.

## Assessment of the Risk of Bias of Individual Studies

We evaluated the risk of bias of the included RCTs using the Cochrane Collaboration’s Risk of Bias 2 tool<sup>25</sup> to assess bias from the randomization process, deviation from intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For observational studies, we selected appropriate items from the Newcastle-Ottawa Scale.<sup>26</sup> We planned to use the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool for studies evaluating instruments for risk of opioid misuse, opioid use disorder, or overdose (KQ1f).<sup>27</sup> However, we did not include any relevant studies.

## Assessment of the Credibility of Systematic Reviews

For systematic reviews evaluating triptans or NSAIDs, we used the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) tool, a measurement tool to assess systematic reviews, to assess the credibility of these systematic reviews. The tool evaluates 11 items: a priori protocol, duplication of reviewers, grey literature search, excluded studies list, description of included studies, risk of bias evaluation, appropriate synthesis methods, publication bias evaluation, and conflict of interest reporting.<sup>28</sup>

## Data Synthesis

We qualitatively summarized key features/characteristics (e.g. study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for each KQ.

Evidence from existing systematic reviews on triptans and NSAIDs was summarized narratively as reported in the original syntheses.

For interventions that are not approved by the FDA or not available in the United States, we did not perform meta-analysis or strength of evidence (SOE) rating. Rather, we summarized key features of such studies in the appendix.

Table 2 lists the definition of pain and function outcomes used in the report. Table 3 lists the categories of adverse events and examples. We used the definition of serious adverse events listed by the original studies.

**Table 2. Definition of pain and function outcomes**

Outcome	Definition
Pain free	No pain at defined assessment time (e.g. 2 hours)
Pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g. 2 hours)
Sustained pain free	No pain at initial assessment (e.g. 2 hours) and remains at followup assessment (e.g. 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Sustained pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g. 2 hours) and remains improved at followup assessment (e.g. 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Function relief	Improvement of function from moderate to severe at baseline to mild or none at defined assessment time (e.g. 2 hours)



Outcome	Definition
Restored function	No restriction to perform work or usual activities at a defined assessment time (e.g. 2 hours)

**Table 3. Categories of adverse events**

Type of adverse events	Example
Cardiovascular adverse event	Bradycardia, chest discomfort, palpitation, presyncope, vasodilation
Dermatological adverse event	Skin rash, application site pain/discomfort, burning sensation, local irritation
Ear, nose and throat adverse event	Ear and labyrinth disorders, hyperacusia, lump in throat or burning throat, nasal congestion, nasal irritation, oropharyngeal pain, pharyngitis
Endocrine adverse event	Recurrent thyroid cancer
Gastrointestinal adverse event	Abdominal discomfort/pain, altered taste, anorexia, abnormal taste constipation, diarrhea, dry mouth, dyspepsia, nausea, vomiting
Genitourinary adverse event	Urinary tract infection, diuresis, nephrolithiasis
Hematologic adverse event	Blood and lymphatic system disorders, bleeding
Immunologic adverse event	Allergy Hypersensitivity, infections and infestations, influenza, shingles, anaphylaxis, viral meningitis
Musculoskeletal adverse event	Muscle cramp/spasms/tightness, myalgia
Neurological adverse event	Akathisia, chills, confusion, disorientation, dizziness, dystonic reaction, fatigue, headache, sedation, seizure, vertigo, tremor
Ophthalmological adverse event	Blurred vision, eyelid swelling, visual disturbances, optic neuritis, lacrimation
Psychological adverse event	Anxiety, restlessness, euphoria, mood change, nervousness
Respiratory adverse event	Cough, respiratory tract infection, shortness of breath
Sleep-related adverse event	Sleepiness
Other adverse event	Edema, heat sensation, warmth, flushing, cold hands

Analyses were based on intention-to-treat principle for RCTs or number of patients initially receiving the interventions at the start of observational studies. We conducted meta-analysis, whenever appropriate (i.e. more than 2 studies address the same PICOTS and provide point estimates and dispersion measures), to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. For crossover RCTs, we chose to meta-analyze outcomes before crossover, as the included crossover RCTs suffered reporting and methodological issues, such as missing data, failure to control within-individual difference, and inhibited pooling with other studies.<sup>29</sup> For those without separately reporting results before crossover, we qualitatively synthesized outcomes (i.e. not included in meta-analyses). Studies that randomized migraine attacks, instead of patients, were also qualitatively synthesized as we were unable to control correlations between attacks. Relative risk and corresponding 95 percent confidence intervals were extracted or calculated for binary outcomes. For continuous outcomes (pain scale and function scale), we calculated standardized mean difference and converted the direction of all measures (e.g. higher score represents better outcome). For adverse events, we calculated rate ratio (i.e. ratio of the incidence rate of events within a given time between the intervention and the comparison). Meta-analyses were conducted based on length of followup (< 1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks). We used the DerSimonian-Laird random effect model with Hartung-Knapp-Sidik-Jonkman variance correction to combine direct comparisons between treatments if the number of studies included in the analysis is larger than 3.<sup>30</sup> The fixed effect method based on the Mantel and Haenszel method was adopted when the number of studies is 3 or less. We evaluated heterogeneity between studies using  $I^2$  indicator. To further explore heterogeneity, we conducted prespecified subgroup analyses based on route of administration, study setting, dose, age (<65 years old vs.  $\geq 65$  years), sex, race (Caucasian vs. non-Caucasian), and BMI (<30 kg/m<sup>2</sup> vs.  $\geq 30$  kg/m<sup>2</sup>). We were unable to conduct other pre-

specified subgroup analyses (e.g. patient medical comorbidities). We conducted sensitivity analyses to evaluate robustness of our findings by excluding studies with high risk of bias.

To classify the magnitude of effects for pain and function, we used the following rule:<sup>31, 32</sup>

Small/slight effect – A mean difference of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), a standardized mean difference (SMD) of 0.2 to 0.5.

Moderate effect – A mean difference of 10 to 20 points on a 0- to 100-point VAS, a SMD of 0.5 to 0.8.

Large/substantial effect – Any value greater than moderate.

Similar thresholds will be used for other outcomes measures.

We were unable to evaluate potential publication bias due to small number of studies included in a direct comparison (n<10).

## **Grading the Strength of Evidence for Major Comparisons and Outcomes**

We graded the SOE following the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews on assessing SOE.<sup>22</sup> We graded SOE for the critical health outcomes, pain, function, quality of life, and serious adverse events. These outcomes were chosen because they are either clinically important from a patient’s perspective or highly relevant for stakeholders’ decision making.

RCTs started as high SOE.<sup>22</sup> The domains used for all KQs were: the methodological limitations of the studies (i.e. risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

We lowered SOE grading for the risk of bias when all the studies in a particular comparison had high or unclear risk of bias. If estimates from high and low risk of bias studies were available and are similar, we combined them and did not rate down SOE. If estimates were different, we only used the low risk of bias estimate and did not rate down SOE (although this could lead to imprecise estimates). We rated down for imprecision when the number of events was small (<300) or the confidence intervals included substantial benefits and harms (defined as 0.25 relative risk reduction or increase). We rated down for inconsistency when the I squared exceeded an arbitrary cutoff >60 percent and visual inspection of forest plots suggested substantial variability in point estimates.

Based on this assessment and the initial study design, we assigned SOE rating as high, moderate, low, or ‘insufficient evidence to estimate an effect’.

High - We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).

Moderate - We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).

Low - We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient - We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

In the narrative description of the treatment effects, we used the terms “may” and “probably for low and moderate SOE; respectively. We produced summary of evidence tables that provided

for each comparison and for each outcome: data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating.

## **Assessing Applicability**

We followed the procedures outlined in the AHRQ Methods Guide to assess the applicability of the findings within and across studies.<sup>22</sup> Applicability for each outcome was summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. The following factors that may affect applicability have been identified, including patient factors (e.g. demographic characteristics (age, race, ethnicity, gender, SES), patient medical comorbidities (e.g. previous opioid use, BMI), intervention factors (e.g. dose/frequency of treatment, type of treatment, and treatment duration), comparisons (e.g. type of comparators), outcomes (e.g. use of unvalidated or nonstandardized outcomes), settings, and study design features (e.g. observational studies, RCTs). We used this information to evaluate applicability of the evidence to real-world clinical practice in typical U.S. settings. We reported any limitations in applicability of individual studies in evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

## **Peer Review and Public Commentary**

A draft report was posted for peer review and public comments. We revised and finalized the draft report in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

# Results

## Literature Searches and Evidence Base

The literature search identified 15,247 citations. An additional 185 references were identified through reference mining, grey literature search, and from Technical Experts. Evidence on triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) was summarized from 16 existing systematic reviews.<sup>33-48</sup> For other interventions, there were 141 original studies reported in 143 articles with a total of 37,653 patients that met inclusion criteria and were included for the analyses (Appendix B.). Of the 141 studies there were 135 randomized controlled trials (RCTs)<sup>49-182</sup> and 6 comparative observational studies.<sup>183-188</sup> Fifty-five studies were conducted in the emergency department (ED),<sup>49, 50, 53, 55, 57, 59, 63-68, 70, 71, 82-84, 87, 89-96, 99, 117-119, 122, 124, 126, 136-139, 141, 147-149, 151, 154, 159, 161-164, 166, 168, 180, 182, 183, 185, 188</sup> 83 were conducted in an outpatient setting<sup>51, 52, 54, 56, 58, 60-62, 69, 72-81, 85, 86, 88, 97, 98, 100-114, 116, 120, 121, 123, 125, 127-133, 135, 140, 142-146, 150, 152, 153, 155-158, 160, 165, 167, 169-179, 181, 184, 187</sup> one study in urgent care<sup>134</sup> and two studies were in an inpatient setting.<sup>115, 186</sup> 64 studies were done in the United States,<sup>51, 52, 59, 63, 65, 67, 68, 70-72, 75, 77, 78, 83, 84, 87, 90-97, 99-101, 103, 105, 112-114, 117-119, 123, 125, 129-131, 133-136, 139, 141, 144, 146, 148, 150, 152, 153, 156, 157, 164, 166, 168, 171, 177-179, 181, 185, 186</sup> 24 in Asia,<sup>50, 60, 66, 74, 82, 85, 89, 122, 124, 128, 137, 142, 145, 154, 155, 159, 163, 172, 173, 175, 176, 183, 187, 188</sup> 22 were in Europe,<sup>54, 61, 76, 80, 81, 86, 88, 98, 106, 115, 116, 120, 127, 132, 140, 143, 151, 160, 161, 165, 169, 170, 180</sup> 5 in South America,<sup>56-58, 167, 184</sup> 6 in Canada,<sup>55, 64, 126, 138, 149, 162</sup> 2 in Australia,<sup>147, 182</sup> and 17 were done in multiple countries.<sup>49, 53, 62, 69, 73, 79, 102, 104, 107-111, 121, 158, 174</sup> Average followup was 11.76 days. There were 22 crossover RCTs.<sup>60, 61, 67, 74, 75, 78, 98, 103, 104, 106, 111, 113, 116, 120, 127, 142, 150, 169, 170, 175, 176, 178</sup> Fifteen studies were included in Key Question (KQs) 1,<sup>49, 61, 65, 90, 96, 114, 123, 126, 148, 153, 157, 162, 163, 185, 188</sup> 108 in KQ2<sup>50-59, 62-64, 66, 67, 69-84, 86-89, 91-95, 97, 99-113, 115-122, 125, 127, 129, 130, 132-135, 137-141, 143-147, 149-152, 154-156, 158-161, 164, 166, 167, 169-171, 177-179, 181-184, 186</sup> and 18 in KQ3.<sup>60, 68, 85, 98, 124, 128, 131, 136, 142, 165, 168, 172-176, 180, 187</sup> Characteristics of included studies are included in Appendix table D.1.

A list of the studies excluded at the full-text review stage is in Appendix C. A search of clinical trial registries identified 28 ongoing clinical trials.

## KQ1: Opioid Therapy

KQ1a. What is the comparative effectiveness of opioid therapy versus: (1) nonopioid pharmacologic therapy (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and cannabis) or (2) nonpharmacologic therapy (e.g., exercise, cognitive behavioral therapy, acupuncture, biofeedback, noninvasive neuromodulation devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life and after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ1b. How does effectiveness of opioid therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status [SES]); (2) patient medical comorbidities (previous opioid use, body mass index [BMI]); (3) dose of opioids; (4) duration of opioid therapy, including number of opioid prescription refills and quantity of pills used?

KQ1c. What are the harms of opioid therapy versus nonopioid pharmacologic therapy or nonpharmacologic therapy with respect to: (1) misuse, opioid use disorder, and related outcomes; (2) overdose; (3) medication overuse headache (MOH); (4) other

harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinologic harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

KQ1d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the dose of opioid used; (4) the duration of opioid therapy?

KQ1e. What are the effects of prescribing opioid therapy versus not prescribing opioid therapy for acute treatment of episodic migraine pain on (1) short-term (<3 months) continued need for prescription pain relief, such as need for opioid refills, and (2) long-term opioid use (3 months or greater)?

KQ1f. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the accuracy of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1g. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the effectiveness of instruments for predicting risk of opioid misuse, opioid use disorder, or overdose?

KQ1h. For patients with episodic migraine being considered for opioid therapy for acute treatment, what is the effect of the following risk mitigation strategies on the decision to prescribe opioids: (1) existing opioid management plans; (2) patient education; (3) clinician and patient values and preferences related to opioids; (4) urine drug screening; (5) use of prescription drug monitoring program data; (6) availability of close followup?

## **KQ1 Key Points**

Effectiveness and harms:

- Tramadol in combination with acetaminophen may reduce pain at 2 hours and 1 day, compared with placebo (low strength of evidence [SOE]). However, the evidence for tramadol alone was insufficient. Tramadol plus acetaminophen was associated with significantly increased number of adverse events (AEs).
- Butorphanol may reduce pain at 2 hours, 1 day, and 1 week, compared with placebo (low SOE). It was associated with increased number of gastrointestinal AEs, neurological AEs, and total number of AEs.
- Evidence was insufficient to draw conclusions about serious adverse events.

Comparative effectiveness and harms:

- Meperidine plus hydroxyzine may be worse than dihydroergotamine plus metoclopramide in terms of pain relief at 2 hours and function (low SOE).
- Morphine may be worse than intravenous dexamethasone in terms of pain relief at 2 hours and 1 day (low SOE).
- Hydromorphone may be worse than metoclopramide (low SOE) and worse than diphenhydramine plus prochlorperazine in terms of pain relief at 2 hours (low SOE).
- Evidence was insufficient to draw conclusions about serious adverse events.

Instruments for predicting risk of opioid therapy and risk mitigation strategy:

- No studies evaluated instruments for predicting risk of opioid misuse, opioid use disorder or overdose; or evaluated risk mitigation strategies in acute treatment of episodic migraine.

## KQ1 Results

Fifteen studies with 2,208 patients were included for KQ1.<sup>49, 61, 65, 90, 96, 114, 123, 126, 148, 153, 157, 162, 163, 185, 188</sup> Thirteen were RCTs.<sup>49, 61, 65, 90, 96, 114, 123, 126, 148, 153, 157, 162, 163</sup> and 2 were comparative observational.<sup>185, 188</sup> Thirteen studies were published before 2010. There was one crossover RCT.<sup>61</sup> Average followup was 7.64 days. Ten studies were conducted in the ED<sup>49, 65, 90, 96, 126, 148, 162, 163, 185, 188</sup> and 5 were in outpatient setting.<sup>61, 114, 123, 153, 157</sup> Two studies were done in Asia,<sup>163, 188</sup> 2 in Canada<sup>126, 162</sup> 1 in Europe,<sup>61</sup> 9 in the United States,<sup>65, 90, 96, 114, 123, 148, 153, 157, 185</sup> and 1 in multiple countries.<sup>49</sup> Details of the interventions used in each study can be found in Appendix Table F.1.

These studies evaluated tramadol (1 RCT in combination with acetaminophen,<sup>157</sup> 1 RCT tramadol alone<sup>49</sup>), butorphanol (1 RCT),<sup>114</sup> meperidine (2 RCTs in combination with dimenhydrinate,<sup>126, 162</sup> 2 RCTs in combination with hydroxyzine<sup>65, 123</sup>, and 1 RCT meperidine alone),<sup>148</sup> hydromorphone (1 RCT,<sup>74</sup> 1 observational<sup>185</sup>), morphine (1 RCT)<sup>163</sup> for the acute treatment of migraine. They evaluated opioids as stand-alone therapy or in combination with other acute treatments of migraine and in certain studies the opioid acted as the comparator. Table 4 lists the pain and function outcomes and Appendix Table H.1 lists adverse events (AE) reported by the included studies. No studies reported opioid misuse, opioid use disorder, opioid overdose, or MOH.

The overall risk of bias is high due to high risk of bias from randomization process and missing outcome data for RCTs and high risk from comparability between groups and blind assessment of outcome for observational studies (Appendix Tables E.1 and E.2). Sensitivity analyses by excluding high risk studies were not conducted due to small number of studies in each comparison.

Tramadol in combination with acetaminophen demonstrated superiority over placebo at every endpoint, including pain free and relief at 2 hours, pain free and relief at 1 day and sustained pain free and relief at 1 day.<sup>157</sup> However, tramadol plus acetaminophen was associated with significantly increased number of adverse events. Tramadol alone versus placebo failed to show a significant difference in pain free and relief at 2 hours or change in pain scale at 2 hours.<sup>49</sup>

Butorphanol demonstrated superiority over placebo at every endpoint, including pain free and relief at 2 hours, pain free and relief at 1 day and pain free and relief at 1 week.<sup>114</sup> Butorphanol was associated with increased number of gastrointestinal AEs, neurological AEs, and total number of AEs.

Meperidine was studied in 5 RCTs (2 RCTs in combination with dimenhydrinate<sup>126, 162</sup> and 2 RCTs in combination with hydroxyzine,<sup>65, 123</sup> and 1 RCT with meperidine alone,<sup>148</sup> each RCT using different comparators). All studies failed to show superiority of the meperidine combinations over the various comparators. Studies reported various increased adverse events of meperidine, including neurological AEs, cardiovascular AEs, and total number of AEs.

Hydromorphone was studied against diphenhydramine and prochlorperazine in 1 RCT<sup>96</sup>; and against metoclopramide in 1 observational study.<sup>185</sup>; in the RCT, hydromorphone did not show superiority over diphenhydramine and prochlorperazine at any of the endpoints, including 2 hour pain free and function free, and 1 week sustained pain free, relief or function. In the observational study where hydromorphone acted as the comparator, metoclopramide was significantly more effective than hydromorphone at the 2 hours' time point but not different at the 1day timepoint based on pain scale. No significance difference was found on adverse events.

Morphine compared with intravenous dexamethasone was significantly less effective at 2 hours and 1 day based on pain scale assessment.<sup>163</sup>

Due to the small number of studies in each comparison, we were unable to conduct subgroup analysis.

No study evaluated effect of prescribing opioid for acute treatment of episodic migraine on short-term (<3 months) and long-term (≥ 3 months) opioid use.

No study evaluated instruments for predicting risk of opioid misuse, opioid use disorder or overdose.

No study evaluated risk mitigation strategies on the decision to prescribe opioids for the acute treatment of migraine.

**Table 4. Comparisons of opioid therapy**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Any opioid vs. any nonopioid	Pain free	2 hours	RR: 0.88; 95% CI: 0.65 to 1.20; I <sup>2</sup> = N/A	1 comparative observational study, <sup>188</sup> 161 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 1.34; 95% CI: 0.82 to 2.18; I <sup>2</sup> = N/A	1 comparative observational study, <sup>188</sup> 161 patients	High risk of bias and severe imprecision	Insufficient
Butorphanol vs. Placebo	Pain free	2 hours	RR: 2.90; 95% CI: 1.20 to 7.01; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
	Pain free	1 day	RR: 1.83; 95% CI: 1.10 to 3.05; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
	Pain free	1 week	RR: 2.08; 95% CI: 1.27 to 3.43; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 3.37; 95% CI: 1.83 to 6.22; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
	Pain relief	1 day	RR: 2.07; 95% CI: 1.43 to 2.98; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
	Pain relief	1 week	RR: 2.09; 95% CI: 1.45 to 3.02; I <sup>2</sup> = N/A	1 RCT, <sup>114</sup> 157 patients	High risk of bias and imprecision	Low
Hydromorphone vs. Diphenhydramine plus prochlorperazine	Pain free	2 hours	RR: 0.54; 95% CI: 0.33 to 0.90; I <sup>2</sup> = N/A	1 RCT, <sup>96</sup> 127 patients	High risk of bias and imprecision	Low
	Restored function	2 hours	RR: 0.45; 95% CI: 0.27 to 0.74; I <sup>2</sup> = N/A	1 RCT, <sup>96</sup> 127 patients	High risk of bias and imprecision	Low
	Restored function	1 week	RR: 0.80; 95% CI: 0.61 to 1.06; I <sup>2</sup> = N/A	1 RCT, <sup>96</sup> 127 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 week	RR: 0.53; 95% CI: 0.35 to 0.81; I <sup>2</sup> = N/A	1 RCT, <sup>96</sup> 127 patients	High risk of bias and imprecision	Low

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Hydromorphone vs. Diphenhydramine plus prochlorperazine (continued)	Sustained pain relief	1 week	RR: 0.53; 95% CI: 0.35 to 0.81; I <sup>2</sup> = N/A	1 RCT, <sup>96</sup> 127 patients	High risk of bias and imprecision	Low
Hydromorphone vs. Metoclopramide	Pain scale	2 hours	SMD: -0.56; 95% CI: -0.90 to -0.21; I <sup>2</sup> = N/A	1 comparative observational study, <sup>185</sup> 200 patients	High risk of bias and Imprecision	Low
	Pain scale	1 day	SMD: -0.32; 95% CI: -0.66 to 0.03; I <sup>2</sup> = N/A	1 comparative observational study, <sup>185</sup> 200 patients	High risk of bias and imprecision	Insufficient
Meperidine plus dimenhydrinate vs. Chlorpromazine	Pain relief	2 hours	RR: 0.65; 95% CI: 0.36 to 1.18; I <sup>2</sup> = N/A	1 RCT, <sup>126</sup> 46 patients	High risk of bias and severe imprecision	Insufficient
	Pain scale	2 hours	SMD: -1.09; 95% CI: -1.71 to -0.47; I <sup>2</sup> = N/A	1 RCT, <sup>126</sup> 46 patients	High risk of bias and imprecision	Low
Meperidine plus hydroxyzine vs. Dihydroergotamine plus metoclopramide	Pain relief	2 hours	RR: 0.23; 95% CI: 0.08 to 0.64; I <sup>2</sup> = N/A	1 RCT, <sup>123</sup> 28 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 0.06; 95% CI: -0.24 to 0.36; I <sup>2</sup> = N/A	1 RCT, <sup>65</sup> 170 patients	High risk of bias and severe imprecision	Insufficient
	Restored function	1 day	RR: 0.44; 95% CI: 0.24 to 0.82; I <sup>2</sup> = N/A	1 RCT, <sup>65</sup> 170 patients	High risk of bias and imprecision	Low
	Serious AE	N/A	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I <sup>2</sup> =N/A	1 RCT, <sup>123</sup> 28 patients	High risk of bias and severe imprecision	Insufficient
Meperidine vs. Droperidol	Pain scale	2 hours	P=0.33	1 RCT, <sup>148</sup> 29 patients	High risk of bias and severe imprecision	Insufficient
Methotrimeprazine vs. Dimenhydrinate plus meperidine	Pain scale	2 hours	SMD: 0.26; 95% CI: -0.20 to 0.72; I <sup>2</sup> = N/A	1 RCT, <sup>162</sup> 74 patients	High risk of bias and severe imprecision	Insufficient
Morphine vs. Intravenous dexamethasone	Pain scale	2 hours	SMD: -0.35; 95% CI: -0.64 to -0.06; I <sup>2</sup> = N/A	1 RCT, <sup>163</sup> 190 patients	High risk of bias and imprecision	Low
	Pain scale	1 day	SMD: -0.38; 95% CI: -0.66 to -0.09; I <sup>2</sup> = N/A	1 RCT, <sup>163</sup> 190 patients	High risk of bias and imprecision	Low
Tramadol vs. Placebo	Pain free	2 hours	RR: 2.50; 95% CI: 0.56 to 11.16; I <sup>2</sup> = N/A	1 RCT, <sup>49</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 2.00; 95% CI: 0.98 to 4.08; I <sup>2</sup> = N/A	1 RCT, <sup>49</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient



Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Tramadol vs. Placebo (continued)	Pain scale	2 hours	SMD: 0.25; 95% CI: -0.43 to 0.92; I <sup>2</sup> = N/A	1 RCT, <sup>49</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
Tramadol plus acetaminophen vs. Placebo	Pain free	2 hours	RR: 2.42; 95% CI: 1.34 to 4.35; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low
	Pain free	1 day	RR: 1.43; 95% CI: 1.09 to 1.88; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 1.68; 95% CI: 1.27 to 2.22; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low
	Pain relief	1 day	RR: 1.75; 95% CI: 1.35 to 2.25; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low
	Serious AE	N/A	Rate Ratio: 0.99; 95% CI: 0.02 to 50.13; I <sup>2</sup> =N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 day	RR: 2.26; 95% CI: 1.15 to 4.46; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low
	Sustained pain relief	1 day	RR: 1.56; 95% CI: 1.08 to 2.27; I <sup>2</sup> = N/A	1 RCT, <sup>157</sup> 375 patients	High risk of bias and imprecision	Low

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD >0 implies the intervention (mentioned first in the comparison) is better.

## KQ 2: Nonopioid Pharmacologic Therapy

KQ2a. What is the comparative effectiveness of nonopioid pharmacologic therapy (e.g., acetaminophen, NSAIDs, triptans, ergot alkaloids, combination analgesics, muscle relaxants, anti-nausea medications, and cannabis) versus: (1) other nonopioid pharmacologic treatments, such as those in a different medication class; or (2) nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ2b. How does effectiveness of nonopioid pharmacologic therapy vary depending on: (1) patient demographics (e.g., age, race, ethnicity, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) duration of treatment?

KQ2c. What are the harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic therapy or nonpharmacologic therapy with respect to: (1) misuse; (2) overdose; (3) MOH; (4) other harms, including gastrointestinal-related harms, cardiovascular-related harms, kidney-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cognitive harms, and psychological harms (e.g., depression)?

KQ2d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the type of nonopioid medication; (4) dose of medication; (5) the duration of therapy?

## KQ2 Key Points

Effectiveness and harms of established treatments:

- Compared with placebo, triptans resolve pain at 2 hours and 1 day (high SOE), and increase the risk of mild and transient adverse events (high SOE).
- Compared with placebo, NSAIDs probably resolve pain at 2 hours and 1 day (moderate SOE), and increase the risk of mild and transient adverse events (moderate SOE).
- Compared with placebo, dihydroergotamine reduces pain (high SOE) and probably increases the likelihood of being pain free at 2 hours, 1 day and 1 week (moderate SOE). Dihydroergotamine probably improves function (moderate SOE) and improves sustained pain relief (high SOE) at 2 hours and 1 day.
- Compared with placebo, ergotamine plus caffeine probably improves pain relief at 2 hours (moderate SOE).
- Antiemetics, including prochlorperazine, chlorpromazine, metoclopramide, droperidol and haloperidol, may resolve pain at 2 hours and 1 day (low SOE) compared with placebo.
- Evidence was insufficient across all pharmacological treatments to draw conclusions about serious adverse events.

Effectiveness and harms of newer treatments:

- Compared with placebo, calcitonin gene-related peptide receptor (CGRP) antagonists (known as gepants), including rimegepant, and ubrogepant, demonstrated improved pain relief at 2 hours (moderate to high SOE) and increased the likelihood of being pain free at 2 hours (moderate to high SOE) and sustained pain free at 1 day and at 1 week (moderate to high SOE). Evidence was insufficient to draw conclusions about serious adverse events.
- Compared with placebo, the 5-HT<sub>1F</sub> receptor agonist lasmiditan restored function at 2 hours (high SOE), and also resolved pain at 2 hours (high SOE), 1 day (high SOE) and 1 week (moderate SOE). Serious adverse events were more common in patients who received lasmiditan than placebo (high SOE).

Other comparisons:

- Although only studied in one or a few small trials, several other therapies may improve migraine pain compared with placebo, including dexamethasone, dipyrone, lidocaine, magnesium sulfate, octreotide, and secobarbital (low SOE). Evidence was insufficient to draw conclusions about serious adverse events.

## KQ2 Results

Nine systematic reviews (101,276 patients) compared triptans with placebo;<sup>43, 44, 47, 189-192</sup> five systematic reviews compared NSAIDs with placebo (13,214 patients);<sup>43-46, 193</sup> and two systematic reviews evaluated the combination of triptans and NSAIDs.<sup>47, 48</sup> One hundred ten articles with 108 studies and 33,687 patients were included for other nonopioid pharmacologic therapies.<sup>50-59, 62-64, 66, 67, 69-84, 86-89, 91-95, 97, 99-113, 115-122, 125, 127, 129, 130, 132-135, 137-141, 143-147, 149-152, 154-156, 158-161, 164, 166, 167, 169-171, 177-179, 181-184, 186</sup> One hundred five were RCTs<sup>50-59, 62-64, 66, 67, 69-84, 86-89,</sup>

91-95, 97, 99-113, 115-122, 125, 127, 129, 130, 132-135, 137-141, 143-147, 149-152, 154-156, 158-161, 164, 166, 167, 169-171, 177-179, 181, 182 and 3 were comparative observational studies.<sup>183, 184, 186</sup> There were 16 crossover RCTs.<sup>67, 74, 75, 78, 103, 104, 106, 111, 113, 116, 120, 127, 150, 169, 170, 178</sup> Average followup was 12.55 days. Forty studies were conducted in the ED.<sup>50, 53, 55, 57, 59, 63, 64, 66, 67, 70, 71, 82-84, 87, 89, 91-95, 99, 117-119, 122, 134, 137-139, 141, 147, 149, 151, 154, 159, 161, 164, 166, 182, 183</sup> 65 in outpatients,<sup>51, 52, 54, 56, 58, 62, 69, 72-81, 86, 88, 97, 100-113, 115, 116, 120, 121, 125, 127, 129, 130, 132, 133, 135, 140, 143-146, 150, 152, 155, 156, 158, 161, 167, 169-171, 177-179, 181, 184</sup> 1 in urgent care,<sup>134</sup> and 2 in an inpatient setting.<sup>115, 186</sup> Twelve studies were done in Asia,<sup>50, 66, 74, 82, 89, 122, 137, 145, 154, 155, 159, 183</sup> 2 in Australia,<sup>147, 182</sup> 4 in Canada<sup>55, 64, 138, 149</sup> 19 in Europe,<sup>54, 76, 80, 81, 86, 88, 106, 115, 116, 120, 127, 132, 140, 143, 151, 160, 161, 169, 170</sup> 5 in South America,<sup>56-58, 167, 184</sup> 51 in the United States,<sup>51, 52, 59, 63, 67, 70-72, 75, 77, 78, 83, 84, 87, 91-95, 97, 99-101, 103, 105, 112, 113, 117-119, 125, 129, 130, 133-135, 139, 141, 144, 146, 150, 152, 156, 164, 166, 171, 177-179, 181, 186</sup> and 15 in multiple countries.<sup>53, 62, 69, 73, 79, 102, 104, 107-111, 121, 158</sup> Evidence on triptans and NSAIDs was summarized from existing systematic reviews.

Details of the interventions used in each study can be found in Appendix Tables F.2. to F.6. Risk of Bias for these studies is in Appendix Tables E.1. and E.2.

## **Narrative Summary of Evidence on Triptans and NSAIDs**

Numerous systematic reviews have been published on evaluating the efficacy and adverse events of triptans, NSAIDs, aspirin and acetaminophen. Most of the systematic reviews were judged to have high credibility using the AMSTAR (A MeaSurement Tool to Assess systematic Reviews) tool. Most systematic reviews were published between 2010 and 2013 and summarized trials that were mostly published before 2010. Many systematic reviews had updates or recent evaluations that suggested stability of the evidence base and that future trials on the existing triptans and NSAIDs were less likely to be conducted (Table 5 and Table 6). A summary of these systematic reviews is included in Appendix Tables G.1. to G.3.

Evidence supporting the efficacy of triptans and NSAIDs over placebo was documented in numerous systematic reviews of randomized controlled trials. The most studied medication was oral sumatriptan; but randomized trials were available for oral, subcutaneous and intranasal sumatriptan, zolmitriptan, frovatriptan, eletriptan, naratriptan, rizatriptan, almotriptan, ibuprofen, oral diclofenac, Ketorolac, aspirin, acetaminophen and the oral combination of acetaminophen/aspirin/caffeine.

Triptans and NSAIDs efficacy was documented for the outcomes of 1-2 hours pain free. Triptans and NSAIDs were administered with or without antiemetics. Triptans and NSAIDs had more adverse events than placebo but these adverse events were reported to be minor and transient. Several individual patient data pooled analyses were also identified and their results were consistent with study level meta-analyses. Several network meta-analyses demonstrated that triptans were more efficacious than placebo but were unable to show clear statistically significant differences between the various triptans. Therefore, triptans likely have similar efficacy, provided that dosages were optimized. Network meta-analyses did not show significant differences among triptans in adverse events. Two systematic reviews evaluated the combination of sumatriptan and naproxen and found that the combination of triptans and NSAIDs was also effective, well tolerated and can be used for patients with partial response to either agent.<sup>47, 48</sup>

**Table 5. Existing systematic reviews about triptans compared with placebo**

Outcome	Conclusion	Strength of Evidence (Rationale) <sup>a</sup>
Pain	Improvement in pain resolution at 2 hours and 1 day	High <sup>a</sup>
Adverse events <sup>b</sup>	Increased risk of mild and transient adverse events	High <sup>a</sup>

Evidence base: 186 randomized controlled trials summarized in 9 systematic reviews (101,276 patients).<sup>43, 44, 47, 189-192, 194, 195</sup> The most studied triptan is sumatriptan, followed by zolmitriptan, eletriptan, naratriptan, almotriptan, rizatriptan, and frovatriptan

<sup>a</sup> Some older trials do not report the methods of allocation concealment. However, this concern was not sufficient to rate down strength of evidence particularly in the presence of a large relative effect (relative risk >2)

<sup>b</sup> The number of events is small, particularly for adverse events analyses.

**Table 6. Existing systematic reviews about nonsteroidal anti-inflammatory drugs compared with placebo**

Outcome	Conclusion	Strength of Evidence (Rationale) <sup>a</sup>
Pain	Improvement in pain resolution at 2 hours and 1 day	Moderate <sup>a</sup>
Adverse events	Increased risk of mild and transient adverse events	Moderate <sup>a, b</sup>

Evidence base: 5 systematic reviews (13,214 patients).<sup>43-46, 193</sup> The most studied NSAID is ibuprofen (9 randomized controlled trials, 4,373 patients), followed by diclofenac and ketorolac.

<sup>a</sup> Some older trials do not report the methods of allocation concealment. However, this concern was not sufficient to rate down strength of evidence particularly in the presence of a large relative effect (relative risk >2)

<sup>b</sup> The number of events is small, particularly for adverse events analyses.

## Ergot Alkaloids

There have been 16 RCTs<sup>51, 52, 55, 63, 81, 97, 100, 106, 120, 146, 150, 155, 167, 170, 177, 186</sup> with 2,615 patients, published on evaluating the efficacy of ergot alkaloids for the acute treatment of migraine. These RCTs studied the efficacy of ergotamine, with or without caffeine, as well as dihydroergotamine, either against placebo or lidocaine. Endpoints included pain free or pain relief at 2 hours, pain scale at 2 hours, restored function at 1 day, pain free at 1 day, pain relief at 1 day, sustained pain free at 1 week, and sustained pain relief at 1 week (Table 7). Appendix Tables H.2 and J.1 list the adverse events.

Appendix Tables E.1 and E.2 list the risk of bias of the included studies. The overall risk is high due to moderate risk from randomization process, high risk from missing outcome data, and moderate risk from measurement of outcomes for RCTs and high risk from comparability between groups for observational studies. We did not find significant difference on findings after excluding studies with high risk of bias (Appendix Table L.1).

Five RCTs<sup>51, 52, 63, 100, 177</sup> compared dihydroergotamine with placebo and found dihydroergotamine was more likely to lead to pain free and pain relief at 2 hours, 1 day and 1 week, sustained pain free and pain relief at 1 day and 1 week, and restored function at 2 hours and at 1 day.

Dihydroergotamine was found to be no better than chlorpromazine at the endpoint of pain free at 2 hours per an RCT with 50 subjects.<sup>55</sup>

Dihydroergotamine was no better than lidocaine at the endpoints of pain free at 2 hours according to an RCT with 50 subjects.<sup>55</sup>

A single RCT with 309 subjects evaluated ergotamine plus caffeine, and found it to be no better than placebo at providing function relief at 2 hours or pain free at 2 hours.<sup>81</sup> It was shown to be superior at providing pain relief at 2 hours.

One RCT evaluated the pain scale at 2 hours and found ergotamine to be no different than placebo.<sup>155</sup>

One RCT evaluated the pain scale at 2 hours and found ergotamine to be no different than prochlorperazine.<sup>155</sup>

Appendix Table H.2. lists adverse events. Compared with placebo, ergotamine plus caffeine, and the combination of meperidine, promethazine, dihydroergotamine and metoclopramide were associated with significantly more total number of adverse events. Significantly more adverse events were found in dihydroergotamine (gastrointestinal, and total number), compared with placebo.

### Subgroup Analysis

Appendix Table I.1. lists dosage comparisons. Dihydroergotamine 2 mg and 3 mg was more likely to lead to pain free and restore function at 2 hours and 1 day, compared with placebo.

**Table 7. Comparisons of ergot alkaloids**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Dihydroergotamine vs. Chloropramazine	Pain free	2 hours	RR: 0.69; 95% CI: 0.28 to 1.70; I <sup>2</sup> =N/A	1 RCT, <sup>55</sup> 50 patients	High risk of bias and severe imprecision	Insufficient
Dihydroergotamine vs. Lidocaine	Pain free	2 hours	RR: 3.03; 95% CI: 0.67 to 14.29; I <sup>2</sup> =N/A	1 RCT, <sup>55</sup> 50 patients	High risk of bias and severe imprecision	Insufficient
Dihydroergotamine vs. Placebo	Pain free	2 hours	RR: 2.89; 95% CI: 2.07 to 4.03; I <sup>2</sup> =0.00%	2 RCTs, <sup>51, 52</sup> 989 patients	High risk of bias	Moderate
	Pain free	1 day	RR: 1.74; 95% CI: 1.43 to 2.12; I <sup>2</sup> =N/A	1 RCT, <sup>51</sup> 903 patients	Possible imprecision, single trial	Moderate
	Pain free	1 week	RR: 1.54; 95% CI: 1.25 to 1.89; I <sup>2</sup> =N/A	1 RCT, <sup>51</sup> 903 patients	Possible imprecision, single trial	Moderate
	Pain relief	2 hours	RR: 1.83; 95% CI: 1.58 to 2.13; I <sup>2</sup> =0.00%	3 RCTs, <sup>51, 52, 100</sup> 1,299 patients	N/A	High
	Pain relief	1 day	RR: 1.79; 95% CI: 1.54 to 2.08; I <sup>2</sup> =0.00%	2 RCTs, <sup>51, 100</sup> 1213 patients	N/A	High
	Pain relief	1 week	RR: 1.48; 95% CI: 1.22 to 1.80; I <sup>2</sup> =0.00%	1 RCT, <sup>51</sup> 903 patients	Possible imprecision, single trial	Moderate
	Pain scale	2 hours	SMD: -0.14; 95% CI: -0.82 to 0.53; I <sup>2</sup> =N/A	1 RCT, <sup>63</sup> 34 patients	High risk of bias and severe imprecision	Insufficient
	Restored function	2 hours	RR: 2.38; 95% CI: 1.44 to 3.94; I <sup>2</sup> =N/A	1 RCT, <sup>100</sup> 348 patients	Imprecision	Moderate

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Dihydroergotamine vs. Placebo (continued)	Restored function	1 day	RR: 2.80; 95% CI: 1.82 to 4.40; I <sup>2</sup> =N/A	1 RCT, <sup>100</sup> 348 patients	Imprecision	Moderate
	Serious AE	N/A	Rate Ratio: 0.69; 95% CI: -0.03 to 16.62; I <sup>2</sup> = 0.00%	4 RCTs, <sup>51, 52, 63, 177</sup>	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 day	RR: 3.51; 95% CI: 2.33 to 5.28; I <sup>2</sup> =0.00%	2 RCT, <sup>51, 52</sup> 989 patients	N/A	High
	Sustained pain free	1 week	RR: 2.96; 95% CI: 1.90 to 4.62; I <sup>2</sup> =0.00%	2 RCT, <sup>51, 52</sup> 989 patients	N/A	High
	Sustained pain relief	1 day	RR: 2.23; 95% CI: 1.76 to 2.81; I <sup>2</sup> =N/A	2 RCT, <sup>51, 52</sup> 989 patients	N/A	High
	Sustained pain relief	1 week	RR: 2.11; 95% CI: 1.62 to 2.76; I <sup>2</sup> =N/A	2 RCT <sup>51, 52</sup> 989 patients	N/A	High
Ergotamine plus caffeine vs. Placebo	Improved function	2 hours	RR: 1.38; 95% CI: 0.91 to 2.10; I <sup>2</sup> =N/A	1 RCT, <sup>81</sup> 309 patients	Severe imprecision	Low
	Pain free	2 hours	RR: 2.08; 95% CI: 0.81 to 5.40; I <sup>2</sup> =N/A	1 RCT, <sup>81</sup> 309 patients	Severe imprecision	Low
	Pain relief	2 hours	RR: 1.61; 95% CI: 1.05 to 2.49; I <sup>2</sup> =N/A	1 RCT, <sup>81</sup> 309 patients	Imprecision	Moderate
	Pain scale	2 hours	SMD: 0.01; 95% CI: -1.01 to 1.02; I <sup>2</sup> =N/A	1 RCT, <sup>155</sup> 15 patients	High risk of bias and severe imprecision	Insufficient
Ergotamine plus caffeine vs. Prochlorperazine	Pain scale	2 hours	SMD: -0.58; 95% CI: -1.46 to 0.28; I <sup>2</sup> =N/A	1 RCT, <sup>155</sup> 28 patients	High risk of bias and severe imprecision	Insufficient

AE = adverse events; CI = confidence interval; RCT = randomized controlled trial; RR= relative risk; N/A = not applicable; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

## Antiemetics

Twenty six RCTs<sup>50, 57, 64, 66, 67, 70, 71, 76, 82, 87, 93-95, 99, 115, 117, 118, 132, 138, 139, 149, 151, 154, 156, 164, 166</sup> with 2,442 patients evaluated the efficacy of antiemetic medications for the acute treatment of migraine. These were published between 1987 and 2019. These RCTs studied prochlorperazine, chlorpromazine, metoclopramide, granisetron, droperidol and haloperidol. Endpoints included pain free or pain relief, pain scale, function relief at 2 hours, pain free or pain relief, pain scale, sustained pain free or relief at 1 day, and sustained pain free or relief at 1 week (Table 8). Adverse events are listed in Appendix Tables H.3 and J.2.

The overall risk of bias is moderate due to moderate risk of bias from randomization process and missing outcome data for RCTs (Appendix Tables E.1. and E.2.). Sensitivity analyses by excluding high risk studies were not conducted to due to small number of studies in each comparison (Appendix Table L.2.).

Prochlorperazine was better than placebo at leading to pain free and relief at 2 hours.<sup>57</sup> Additionally, compared with placebo, it showed a moderate to large effect on pain scale at 2 hours. Prochlorperazine also increased number of neurological AEs and total number of AEs. Prochlorperazine, when studied against metoclopramide, failed to show a significant difference for endpoints of pain free or relief at 2 hours, sustained pain free or relief at 1 day, and a difference in number of adverse events.<sup>93</sup> Prochlorperazine was significantly more likely to lead to pain free at 2 hours compared with metoclopramide. Prochlorperazine was better than octreotide at pain relief at 2 hours but had more total AEs.<sup>139</sup> Prochlorperazine showed a greater reduction on the pain scale at 2 hours compared with valproate.<sup>164</sup> Prochlorperazine versus ergotamine showed no significant difference on pain scale at 2 hours.<sup>155</sup> No significant difference on AEs and withdrawals were found.

Chlorpromazine was better than placebo at leading to pain free and pain relief at 2 hours, pain free and pain relief at 1 day, but was no different from placebo in terms of function relief at 2 hours.<sup>57</sup> When chlorpromazine was used as a comparator against metoclopramide, lidocaine or dimenhydrinate plus meperidine, those interventions were not shown to be superior to chlorpromazine for pain free or relief at 2 hours.<sup>64</sup> There was no significant difference on AEs.

Metoclopramide was better than placebo at leading to pain relief at 2 hours but not pain free at 2 hours.<sup>70, 82, 166</sup> Metoclopramide alone was superior to magnesium sulfate plus metoclopramide for pain relief at 2 hours and restored function at 2 hours.<sup>71</sup> Metoclopramide alone was not significantly different from diphenhydramine plus metoclopramide for endpoints of sustained pain relief and free at 1 week.<sup>95</sup>

Granisetron compared with placebo did not show significant differences in the endpoint of pain free at 2 hours or pain scale at 2 hours.<sup>149</sup> There was no significant difference on AEs. Metoclopramide was not superior compared with granisetron when assessing pain scale at 2 hours or 1 day.<sup>50</sup>

Droperidol was better than placebo at pain free and relief at 2 hours.<sup>156</sup> Droperidol was also associated with significantly increased number of neurological AEs, psychological AEs, and total number of AEs.

Haloperidol was better than placebo for 2 hour pain relief and significantly increased total number of AEs.<sup>115</sup> Diphenhydramine plus metoclopramide versus diphenhydramine plus haloperidol showed no significant difference on 2 hour pain scale in support of the metoclopramide combination.<sup>99</sup>

## **Subgroup Analysis**

Appendix Table I.2 lists the dosage comparisons. Compared with placebo and droperidol 0.1 mg, droperidol at doses of 2.75 mg, 5.5 mg, and 8.25 mg were associated with significantly more pain relief at 2 hours. Compared with placebo, droperidol at doses of 2.75 mg and 8.25 mg significantly increased pain free at 2 hours. No significant difference was found among 2.75 mg, 5.5 mg, and 8.25 mg doses of droperidol. There was no significant difference between granisetron 40 µg/ kg and 80 µg/ kg on being pain free at 2 hours and between dosages of metoclopramide 10 mg, 20 mg, and 40 mg on pain relief, being pain free, and restored function at 2 hours and sustained pain free and pain relief at 1 week.

**Table 8. Comparisons of antiemetics**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Chlorpromazine vs. Placebo	Improved function	2 hours	RR: 2.01; 95%CI: 0.76 to 5.36; I <sup>2</sup> =N/A	1 RCT, <sup>138</sup> 36 patients	High risk of bias and imprecision	Low
	Pain free	2 hours	RR: 7.25; 95% CI: 3.20 to 16.42; I <sup>2</sup> =0.00%	2 RCTs, <sup>57</sup> 123 patients	High risk of bias and imprecision	Low
	Pain free	1 day	RR: 1.37; 95% CI: 1.09 to 1.74; I <sup>2</sup> =17.32%	2 RCTs, <sup>57</sup> 123 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 5.46; 95% CI: 2.97 to 10.05; I <sup>2</sup> =0.00%	2 RCTs, <sup>57</sup> 123 patients	High risk of bias and imprecision	Low
	Pain relief	1 day	RR: 1.22; 95% CI: 1.02 to 1.47; I <sup>2</sup> =0.00%	2 RCTs, <sup>57</sup> 123 patients	High risk of bias and imprecision	Low
Diphenhydramine plus metoclopramide vs. Diphenhydramine plus haloperidol	Pain scale	2 hours	SMD: -0.41; 95% CI: -0.90 to 0.08; I <sup>2</sup> =N/A	1 RCT, <sup>99</sup> 64 patients	High risk of bias and severe imprecision	Insufficient
Droperidol vs. Placebo	Pain free	2 hours	RR: 1.60; 95% CI: 1.06 to 2.41; I <sup>2</sup> =N/A	1 RCT, <sup>156</sup> 305 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 1.39; 95% CI: 1.11 to 1.74; I <sup>2</sup> =N/A	1 RCT, <sup>156</sup> 305 patients	High risk of bias and imprecision	Low
Granisetron vs. Placebo	Pain free	2 hours	RR: 1.29; 95% CI: 0.06 to 28.65; I <sup>2</sup> =N/A	1 RCT, <sup>149</sup> 28 patients	High risk of bias and severe imprecision	Insufficient
	Pain scale	2 hours	SMD: 1.10; 95% CI: 0.23 to 1.97; I <sup>2</sup> =N/A	1 RCT, <sup>149</sup> 28 patients	High risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 0.40; 95% CI: 0.01 to 20.16; I <sup>2</sup> =N/A	1 RCT, <sup>149</sup> 28 patients	High risk of bias and severe imprecision	Insufficient
Haloperidol vs. Placebo	Pain relief	2 hours	RR: 5.33; 95% CI: 1.84 to 15.49; I <sup>2</sup> =N/A	1 RCT, <sup>115</sup> 40 patients	High risk of bias and imprecision	Low
Magnesium sulfate vs. Dexamethasone plus metoclopramide	Pain scale	2 hours	SMD: 0.82; 95% CI: 0.33 to 1.31; I <sup>2</sup> =N/A	1 RCT, <sup>154</sup> 70 patients	High risk of bias and imprecision	Low
Metoclopramide vs. Chlorpromazine	Pain free	2 hours	RR: 0.98; 95% CI: 0.48 to 1.99; I <sup>2</sup> =N/A	1 RCT, <sup>64</sup> 91 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 0.84; 95% CI: 0.65 to 1.09; I <sup>2</sup> =N/A	1 RCT, <sup>64</sup> 91 patients	High risk of bias and severe imprecision	Insufficient



Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Metoclopramide vs. Chlorpromazine (continued)	Pain scale	2 hours	SMD: -0.20; 95% CI: -0.61 to 0.21; I <sup>2</sup> =N/A	1 RCT, <sup>64</sup> 91 patients	High risk of bias and severe imprecision	Insufficient
Metoclopramide vs. Diphenhydramine plus metoclopramide	Pain scale	2 hours	SMD: -0.26; 95% CI: -0.54 to 0.01; I <sup>2</sup> =N/A	1 RCT, <sup>95</sup> 208 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 week	RR: 0.82; 95% CI: 0.42 to 1.58; I <sup>2</sup> =N/A	1 RCT, <sup>95</sup> 208 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain relief	1 week	RR: 0.95; 95% CI: 0.67 to 1.35; I <sup>2</sup> =N/A	1 RCT, <sup>95</sup> 208 patients	Severe imprecision	Low
Metoclopramide vs. Granisetron	Pain scale	2 hours	SMD: -1.10; 95% CI: -1.44 to -0.75; I <sup>2</sup> =N/A	1 RCT, <sup>50</sup> 148 patients	High risk of bias and imprecision	Low
	Pain scale	1 day	SMD: -0.41; 95% CI: -0.74 to -0.09; I <sup>2</sup> =N/A	1 RCT, <sup>50</sup> 148 patients	High risk of bias and imprecision	Low
Metoclopramide vs. Magnesium sulfate plus metoclopramide	Pain relief	2 hours	RR: 1.34; 95% CI: 1.01 to 1.78; I <sup>2</sup> =N/A	1 RCT, <sup>71</sup> 44 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 0.54; 95% CI: -0.06 to 1.15; I <sup>2</sup> =N/A	1 RCT, <sup>71</sup> 44 patients	High risk of bias and severe imprecision	Insufficient
	Restored function	2 hours	RR: 1.94; 95% CI: 1.07 to 3.52; I <sup>2</sup> =N/A	1 RCT, <sup>71</sup> 44 patients	High risk of bias and imprecision	Low
Metoclopramide vs. Placebo	Pain free	2 hours	RR: 2.00; 95% CI: 0.40 to 10.08; I <sup>2</sup> =N/A	1 RCT, <sup>118</sup> 86 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 1.91; 95% CI: 1.47 to 2.48; I <sup>2</sup> =67.30%	3 RCTs, <sup>70, 82, 166</sup> 268 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: -0.12; 95% CI: -0.40 to 0.17; I <sup>2</sup> =90.46%	2 RCTs, <sup>82, 166</sup> 198 patients	High risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 1.08; 95% CI: 0.02 to 54.60; I <sup>2</sup> =N/A	1 RCT, <sup>166</sup> 50 patients	High risk of bias and severe imprecision	Insufficient
Prochlorperazine vs. Ergotamine plus caffeine	Pain scale	2 hours	SMD: 0.58; 95% CI: -0.28 to 1.46; I <sup>2</sup> =N/A	1 RCT, <sup>155</sup> 28 patients	High risk of bias and severe imprecision	Insufficient
Prochlorperazine vs. Metoclopramide	Pain free	2 hours	RR: 1.56; 95% CI: 1.00 to 2.45; I <sup>2</sup> =0.00%	2 RCTs, <sup>93, 118</sup> 163 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 0.89; 95% CI: 0.72 to 1.10; I <sup>2</sup> =0.80%	2 RCTs, <sup>70, 93</sup> 147 patients	High risk of bias and imprecision	Low

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Prochlorperazine vs. Metoclopramide (continued)	Pain scale	2 hours	SMD: 0.18; 95% CI: -0.27 to 0.63; I <sup>2</sup> =N/A	1 RCT, <sup>93</sup> 77 patients	High risk of bias and severe imprecision	Insufficient
	Pain scale	1 day	SMD: 0.29; 95% CI: -0.16 to 0.74; I <sup>2</sup> =N/A	1 RCT, <sup>93</sup> 77 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 day	RR: 1.46; 95% CI: 0.45 to 4.77; I <sup>2</sup> =N/A	1 RCT, <sup>93</sup> 77 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain relief	1 day	RR: 1.26; 95% CI: 0.81 to 1.97; I <sup>2</sup> =N/A	1 RCT, <sup>93</sup> 77 patients	High risk of bias and severe imprecision	Insufficient
Prochlorperazine vs. Octreotide	Pain relief	2 hours	RR: 1.66; 95% CI: 1.12 to 2.47; I <sup>2</sup> =N/A	1 RCT, <sup>139</sup> 44 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 0.84; 95% CI: 0.22 to 1.46; I <sup>2</sup> =N/A	1 RCT, <sup>139</sup> 44 patients	High risk of bias and severe imprecision	Insufficient
Prochlorperazine vs. Placebo	Pain free	2 hours	RR: 4.66; 95% CI: 1.10 to 19.70; I <sup>2</sup> =N/A	1 RCT, <sup>118</sup> 86 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 1.80; 95% CI: 1.10 to 2.94; I <sup>2</sup> =0.00%	2 RCTs, <sup>70, 117</sup> 90 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 1.29; 95% CI: 0.58 to 2.01; I <sup>2</sup> = 90.7%	2 RCTs, <sup>117, 155</sup> 49 patients	High risk of bias and inconsistency	Low
Valproate vs. Prochlorperazine	Pain scale	2 hours	SMD: -1.38; 95% CI: -2.07 to -0.69; I <sup>2</sup> =N/A	1 RCT, <sup>164</sup> 40 patients	High risk of bias and imprecision	Low

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

## Calcitonin Gene-Related Peptide Receptor Antagonists (Gepants)

There have been 15 articles reported on 14 studies on CGRP receptor antagonists, collectively known as gepants, for the acute treatment of migraine. These 14 RCTs<sup>69, 72, 80, 107-112, 130, 135, 171, 179, 181</sup> included a total of 14,874 patients. Table 9 shows the pain and functional outcomes of ubrogepant and rimegepant and Appendix Tables H.4 and J.3 list adverse events. The data for BI 44370 and telcagepant are presented in Appendix Tables D.1., E.1., and F.4..

The overall risk of bias is low to moderate (Appendix Tables E.1 and E.2). We did not find significant difference on findings after excluding studies with high risk of bias (Appendix Table L.3.).

Rimegepant has been studied in 3 RCTs from 2014 and 2019 with a combined total of 3336 subjects.<sup>72, 130, 135</sup> It demonstrated superiority over placebo at every endpoint, including restored function at 2 hours, pain free at 1 day, pain free at 2 hours, pain relief at 2 hours, sustained restored function at 1 day, sustained restored function at 1 week, sustained pain free at 1 day,

sustained pain free at 1 week, sustained pain relief at 1 day, sustained pain relief at 1 week. No significant difference on adverse events was found.

Three RCTs with 4,192 subjects compared ubrogepant to placebo and showed superiority of the study drug at 2 hours and 1 day, including pain free, pain relief, sustained pain free, sustained pain relief, and satisfaction.<sup>171, 179, 181</sup> No significant difference was found on gastrointestinal, neurological and total number of AEs, and number of withdrawals.

## Subgroup Analysis

Appendix Table I.3 lists dosage comparisons. The studies evaluated a wide range of rimegepant doses (from 10 mg, to 600 mg), and ubrogepant (from 1 mg to 100 mg). Compared with placebo and low doses, high doses were generally associated with significant better outcomes, including pain free, pain relief at 2 hours and sustained pain free and sustained pain relief at 1 day and 1 week. No significant difference was found between routes of administration (Appendix Table K.2).

**Table 9. Comparisons of gepants**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Rimegepant vs. Placebo	Pain free	2 hours	RR: 1.80; 95% CI: 1.52 to 2.13; I <sup>2</sup> =0.00%	3 RCTs, <sup>72, 130, 135</sup> 3,336 patients	High risk of bias	Moderate
	Pain free	1 day	RR: 1.52; 95% CI: 1.33 to 1.74; I <sup>2</sup> =N/A	1 RCT, <sup>130</sup> 1,186 patients	High risk of bias	Moderate
	Pain relief	2 hours	RR: 1.36; 95% CI: 1.26 to 1.46; I <sup>2</sup> =0.00%	3 RCTs, <sup>72, 130, 135</sup> 3,336 patients	High risk of bias	Moderate
	Restored function	2 hours	RR: 1.43; 95% CI: 1.26 to 1.62; I <sup>2</sup> =0.00%	2 RCTs, <sup>72, 130</sup> 2,652 patients	High risk of bias	Moderate
	Serious AE	N/A	Rate Ratio: 0.54; 95% CI: 0.13 to 2.28; I <sup>2</sup> =0.00%	3 RCTs, <sup>72, 130, 135</sup> 3,336 patients	High risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 day	RR: 2.24; 95% CI: 1.65 to 3.05; I <sup>2</sup> =70.86%	2 RCTs, <sup>130, 135</sup> 1,870 patients	High risk of bias	Moderate
	Sustained pain free	1 week	RR: 2.23; 95% CI: 1.60 to 3.09; I <sup>2</sup> =71.31%	2 RCTs, <sup>130, 135</sup> 1,870 patients	High risk of bias	Moderate
	Sustained pain relief	1 day	RR: 1.65; 95% CI: 1.47 to 1.85; I <sup>2</sup> = 0.00%	2 RCTs, <sup>72, 135</sup> 2,150 patients	High risk of bias	Moderate
	Sustained pain relief	1 week	RR: 1.64; 95% CI: 1.40 to 1.93; I <sup>2</sup> =N/A	1 RCT, <sup>72</sup> 1,466 patients	High risk of bias	Moderate

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Rimegepant vs. Placebo (continued)	Sustained restored function	1 day	RR: 1.73; 95% CI: 1.41 to 2.12; I <sup>2</sup> =N/A	1 RCT, <sup>72</sup> 1,466 patients	High risk of bias	Moderate
	Sustained restored function	1 week	RR: 1.66; 95% CI: 1.33 to 2.07; I <sup>2</sup> =N/A	1 RCT, <sup>72</sup> 1,466 patients	High risk of bias	Moderate
Ubrogepant vs. Placebo	Improved function	2 hours	RR: 1.26; 95% CI: 1.12 to 1.42; I <sup>2</sup> =0.00%	2 RCTs, <sup>179, 181</sup> 3,358 patients	N/A	High
	Improved function	1 day	RR: 1.16; 95% CI: 1.09 to 1.24; I <sup>2</sup> =0.00%	2 RCTs, <sup>179, 181</sup> 3,358 patients	N/A	High
	Pain free	2 hours	RR: 1.58; 95% CI: 1.31 to 1.90; I <sup>2</sup> =0.00%	3 RCTs, <sup>171, 179, 181</sup> 4,192 patients	N/A	High
	Pain relief	2 hours	RR: 1.21; 95% CI: 1.12 to 1.31; I <sup>2</sup> =0.00%	3 RCTs, <sup>171, 179, 181</sup> 4,192 patients	N/A	High
	Pain relief	1 day	RR: 1.63; 95% CI: 1.33 to 2.01; I <sup>2</sup> =N/A	1 RCT, <sup>181</sup> 1,686 patients	N/A	High
	Sustained pain free	1 day	RR: 1.63; 95% CI: 1.29 to 2.07; I <sup>2</sup> = 0.00%	3 RCTs, <sup>171, 179, 181</sup> 4,192 patients	N/A	High
	Sustained pain free	1 week	RR: 1.89; 95% CI: 0.88 to 4.02; I <sup>2</sup> =N/A	1 RCT, <sup>171</sup> 834patients	Severe imprecision	Low
	Sustained pain relief	1 day	RR: 1.55; 95% CI: 1.30 to 1.85; I <sup>2</sup> = 66.05%	2 RCTs, <sup>171, 179</sup> 2,506 patients	Consistency	Moderate
	Sustained pain relief	1 week	RR: 1.29; 95% CI: 0.91 to 1.84; I <sup>2</sup> =N/A	1 RCT, <sup>171</sup> 833 patients	Severe imprecision	Low
	Restored function	2 hours	RR: 1.27; 95% CI: 1.13 to 1.42; I <sup>2</sup> = 0.00%	2 RCTs, <sup>179, 181</sup> 3,358 patients	N/A	High
	Restored function	1 day	RR: 1.17; 95% CI: 1.09 to 1.25; I <sup>2</sup> = 0.00%	2 RCTs, <sup>179, 181</sup> 3,358 patients	N/A	High
	Satisfied with pain relief	2 hours	RR: 1.43; 95% CI: 1.24 to 1.64; I <sup>2</sup> =0.00%	2 RCTs, <sup>179, 181, 196</sup> 3,358 patients	N/A	High

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Ubrogepant vs. Placebo (continued)	Satisfied with pain relief	1 day	RR: 1.55; 95% CI: 1.39 to 1.72; I <sup>2</sup> =30.60%	2 RCTs, <sup>179, 181</sup> 3,358 patients	N/A	High
	Serious AE	N/A	Rate Ratio: 2.54; 95% CI: 0.28 to 23.11; I <sup>2</sup> =N/A	2 RCTs, <sup>179, 181</sup> 3,358 patients	Severe imprecision	Low

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

## 5-HT1F Receptor Agonists (Ditans)

Another new class of drugs for the acute treatment of migraine are 5-HT1F agonists, referred to as ditans. We reviewed 7 articles on the 5-HT1F agonist lasmiditan which were reported on 5 studies. Of the 5 studies, all were RCTs with 7,858 patients evaluating the efficacy lasmiditan for the acute treatment of migraine.<sup>62, 86, 88, 102, 125</sup>

These RCTs showed significant improvements of lasmiditan over placebo for the outcomes of pain free, pain relief, pain scale, restored function and function scale at 2 hours; pain free, sustained pain free and pain relief at 1 day; and sustained pain free at 1 week (Table 10).<sup>62, 86, 88, 102, 125</sup> Lasmiditan was associated with significantly increased risk of gastrointestinal AEs, neurologic AEs, serious AEs, total number of AEs, and number of withdrawals due to AE (Appendix Table H.5 and J.4).

The overall risk of bias is low to moderate (Appendix Tables E.1 and E.2). Sensitivity analyses by excluding high risk studies were not conducted to due to lack of variation in each comparison.

### Subgroup Analysis

Appendix Table I.4. lists dosage comparisons. Studies evaluated a wide range of lasmiditan doses (2.5 mg, 5 mg, 10 mg, 20 mg, 30 mg, 45 mg, 50 mg, 100 mg, 200 mg, 400 mg). Compared with placebo, higher doses were generally associated with improved outcomes, including pain free and pain relief at 2 hours. In addition, lasmiditan 200 mg was more likely to lead to pain free at 2 hours, compared with 50 mg and 100 mg. Lasmiditan 20 mg, 30 mg, and 45 mg was associated with significantly more pain relief at 2 hours, compared with 5 mg. No significant difference was found between routes of administration (Appendix Table K.3), and age, sex, race and BMI (Appendix Tables K.6-9). A subgroup analysis<sup>197</sup> by prior response to triptans based on two RCTs<sup>102, 125</sup> found that, regardless of triptan response, lasmiditan was associated with significantly more pain freedom and pain relief at 2 hours over placebo (Appendix Table K.5).

**Table 10. Comparisons of 5-HT1F**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Lasmiditan vs. Placebo	Function scale	2 hours	SMD: 3.34; 95% CI: 3.04 to 3.64; I <sup>2</sup> =N/A	1 RCT, <sup>86</sup> 512 patients	N/A	High

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Lasmiditan vs. Placebo (continued)	Pain free	2 hours	RR: 1.67; 95% CI: 1.25 to 2.24; I <sup>2</sup> =21.30%	4 RCTs, <sup>86, 88, 102, 125</sup> 5,742 patients	N/A	High
	Pain relief	2 hours	RR: 1.38; 95% CI: 1.14 to 1.68; I <sup>2</sup> =34.00%	4 RCTs, <sup>86, 88, 102, 125</sup> 5,742 patients	N/A	High
	Pain scale	2 hours	SMD: 2.68; 95% CI: 2.41 to 2.95; I <sup>2</sup> =N/A	1 RCT, <sup>86</sup> 512 patients	Possible imprecision, single trial	Moderate
	Restored function	2 hours	RR: 1.42; 95% CI: 1.26 to 1.61; I <sup>2</sup> =0.00%	2 RCTs, <sup>102, 125</sup> 5,100 patients	N/A	High
	Serious AE	N/A	Rate Ratio: 4.05; 95% CI: 1.75 to 9.41; I <sup>2</sup> =33.2%	2 RCTs, <sup>86, 125</sup> 2,743 patients	N/A	High
	Sustained pain free	1 day	RR: 1.38; 95% CI: 1.10 to 1.72; I <sup>2</sup> =33.40%	2 RCTs, <sup>88, 102</sup> 2,999 patients	N/A	High
	Sustained pain free	1 week	RR: 1.38; 95% CI: 1.07 to 1.78; I <sup>2</sup> =N/A	1 RCT, <sup>102</sup> 2,869 patients	Possible imprecision, single trial	Moderate
	Sustained pain relief	1 day	RR: 1.76; 95% CI: 1.08 to 2.87; I <sup>2</sup> =N/A	1 RCT, <sup>88</sup> 130 patients	Imprecision	Moderate

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

## Other Interventions

There have been 47 RCTs and 2 comparative observational studies published with 6,014 patients on evaluating a variety of other nonopioid pharmacological interventions for the acute treatment of migraine.<sup>53-56, 58, 59, 73-75, 77-79, 83, 84, 89, 91, 92, 101, 103-105, 113, 116, 119, 121, 122, 127, 129, 133, 134, 137, 140, 141, 143-145, 147, 152, 158-161, 164, 169, 178, 182-184</sup> Outcomes included pain scale at 2 hours, pain free or pain relief at 1 day, sustained pain free at 1 day, and sustained pain free at 1 week (Table 11). Appendix Table H.6 list comparisons of adverse events. The data for dapitant, lanepitant, selurampanel, tezampanel, tonabersat, and flunarizine are presented in Appendix Tables D.1., E.1., and F.6.

Appendix Table E.1 and E.2 list the risk of bias of the included studies. The overall risk is high due to moderate risk from randomization process and high risk from missing outcome data for RCTs and high risk from comparability between groups for observational studies.

Acetaminophen has been studied in 2 clinical trials from 2000 and 2010 with a combined total of 729 subjects.<sup>129, 144</sup> Acetaminophen was superior to placebo at all endpoints, including restored function at 2 hours, restored function at 1 day, function scale at 2 hours, pain free at 2 hours, pain free at 1 day, pain relief at 2 hours, pain relief at 1 day, pain scale at 2 hours, and pain scale at 1 day. There was no significant difference on AEs.

Dexamethasone was compared with placebo in 2 studies from 2007 and 2008 with a total of 320 subjects.<sup>83, 92</sup> It was found to be superior to placebo at the endpoints of restored function at 1 week, but not at the endpoints of restored function at 1 day, restored function at 2 hours, pain free at 2 hours, or sustained pain free at 1 day. Dexamethasone was associated with increased immunological AE.

Dipyrone was studied in two RCTs that included 206 subjects and was found to be superior at the outcomes of pain free at 1 day, pain free at 2 hours, and pain relief at 2 hours, but not at the outcome of pain relief at 1 day.<sup>56</sup> No significance on AEs was found.

A single RCT from 2018 evaluated greater occipital nerve blocks, and found the procedure was not superior to placebo at any endpoint including pain free at 2 hours, pain relief at 2 hours, and pain scale at 2 hours.<sup>91</sup> No significant difference on AEs was found.

A 2018 RCT with 34 subjects studied ketamine versus placebo and determined that it was no different from placebo at the outcome of function scale at 2 hours, pain scale at 2 hours, and pain relief at 2 hours.<sup>84</sup> No adverse events were reported.

Lidocaine was studied using 3 RCTs from 1996, 2001, and 2017 and a combined total of 292 subjects.<sup>53, 59, 134</sup> This combined data revealed that it is better than placebo at the endpoints of pain relief at 2 hours, but no different from placebo with the endpoint of pain scale at 2 hours, pain free at 1 week, and function scale at 2 hours. A sensitivity analysis by excluding studies with high risk of bias found significant improvement of pain scale in the lidocaine group at 2 hours (Appendix Table L.4.). Lidocaine was associated with increased number of dermatological AEs and total number of AEs.

Lidocaine was compared with chlorpromazine in a single RCT with 50 subjects and found to be inferior at achieving pain free at 2 hours.<sup>55</sup> There was no significant difference on AEs.

Two RCTs from 2001 and 2002 and 150 total subjects were involved in evaluating the efficacy of magnesium sulfate.<sup>58, 74</sup> and demonstrated it as effective in leading to pain free at 2 hours and pain relief at 2 hours, but not effective in providing pain free at 1 day and pain relief at 1 day. There was no significant difference on AEs

A single 2017 observational study with 70 patients compared magnesium sulfate with caffeine citrate and found it to be superior at the endpoint of pain scale at 2 hours.<sup>183</sup>

A single RCT from 1997 with 29 subjects evaluated octreotide and found it to be superior to placebo at pain relief at 1 day but not at pain scale at 2 hours or pain scale at 1 day.<sup>121</sup>

A RCT compared propofol to standard therapy and found that no significant difference in reduction of pain scale at 2 hours and 1 day.<sup>182</sup>

Propofol versus dexamethasone was studied in a single 2012 RCT with 90 subjects and found to be no better at the outcome of pain scale at 2 hours.<sup>159</sup> There were no adverse events in either group.

A single RCT with 30 subjects from 2011 evaluated secobarbital and found it was superior to placebo at the endpoint of pain relief at 1 day.<sup>101</sup> No adverse events were reported.

Three RCTs from 2013 and 2017 with a combined total of 206 subjects compared valproate with dexamethasone and found the two drugs to be no different at the endpoints of pain free at 1 day, pain relief at 1 day, pain relief at 2 hours, pain scale at 1 day, and pain scale at 2 hours.<sup>89, 122</sup> There were no significant differences on AEs.

Valproate was compared with prochlorperazine in one RCT from 2003 with 40 subjects and found to be significant worse at the endpoint of pain scale at 2 hours.<sup>164</sup>

Timolol ophthalmic solution was compared with placebo in a crossover RCT.<sup>178</sup> There was no statistically significant difference between the two groups on pain reduction, pain relief, and satisfaction at 2 hours.

## Subgroup Analysis

Appendix Table I.5. lists the dosage comparisons. No significant difference was found on civamide (20 µg and 150 µg) on 2-hour and 1-day pain relief.

Appendix Table K.4. compared different routes of administration of acute medications. Intravenous prochlorperazine was associated with significantly better pain scale outcomes at 2 hours than buccal absorbed prochlorperazine. When lidocaine was compared with placebo, studies conducted in urgent care reported significantly better pain scale outcomes than studies conducted in the ED (Appendix Table K.1.).

**Table 11. Comparisons of other nonopioid pharmacological interventions**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Acetaminophen vs. Placebo	Function scale	2 hours	SMD: 0.38; 95% CI: 0.18 to 0.59; I <sup>2</sup> = N/A	1 RCT, <sup>144</sup> 378 patients	Imprecision	Moderate
	Pain free	2 hours	RR: 1.89; 95% CI: 1.24 to 2.86; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Pain free	1 day	RR: 1.78; 95% CI: 1.38 to 2.30; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Pain relief	2 hours	RR: 1.61; 95% CI: 1.33 to 1.95; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Pain relief	1 day	RR: 1.71; 95% CI: 1.43 to 2.04; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> ; 729 patients	Moderate risk of bias	Moderate
	Pain scale	2 hours	SMD: 0.39; 95% CI: 0.25 to 0.54; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Pain scale	1 day	SMD: 0.31; 95% CI: 0.10 to 0.52; I <sup>2</sup> = N/A	1 RCT, <sup>129</sup> 351 patients	Moderate risk of bias	Moderate
	Restored function	2 hours	RR: 1.80; 95% CI: 1.27 to 2.54 I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Restored function	1 day	RR: 1.75; 95% CI: 1.41 to 2.17; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias	Moderate
	Serious AE	N/A	Rate Ratio: 0.99; 95% CI: 0.06 to 15.86; I <sup>2</sup> =0.00%	2 RCTs, <sup>129, 144</sup> 729 patients	Moderate risk of bias and severe imprecision	Insufficient
Dexamethasone vs. Placebo	Pain free	2 hours	RR: 1.09; 95% CI: 0.83 to 1.44; I <sup>2</sup> =N/A	1 RCT, <sup>92</sup> 205 patients	Severe imprecision	Low
	Restored function	2 hours	RR: 0.87; 95% CI: 0.73 to 1.04; I <sup>2</sup> =N/A	1 RCT, <sup>92</sup> 205 patients	Severe imprecision	Low
	Restored function	1 day	RR: 1.12; 95% CI: 0.89 to 1.40; I <sup>2</sup> =N/A	1 RCT, <sup>92</sup> 205 patients	Severe imprecision	Low
	Restored function	1 week	RR: 1.49; 95% CI: 1.04 to 2.13; I <sup>2</sup> =N/A	1 RCT, <sup>83</sup> 115 patients	Moderate risk of bias and imprecision	Low
Dexamethasone vs. Placebo (continued)	Sustained pain free	1 day	RR: 1.23; 95% CI: 0.72 to 2.09; I <sup>2</sup> = N/A	1 RCT, <sup>92</sup> 205 patients	Severe imprecision	Low



Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Dipyrrone vs. Placebo	Pain free	2 hours	RR: 7.14; 95% CI: 3.02 to 16.86; I <sup>2</sup> = N/A	1 RCT, <sup>56</sup> 134 patients	High risk of bias and imprecision	Low
	Pain free	1 day	RR: 1.28; 95% CI: 1.01 to 1.63; I <sup>2</sup> = N/A	1 RCT, <sup>56</sup> 134 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 4.32; 95% CI: 2.31 to 8.08; I <sup>2</sup> =N/A	1 RCT, <sup>56</sup> 134 patients	High risk of bias and imprecision	Low
	Pain relief	1 day	RR: 1.09; 95% CI: 0.90 to 1.33; I <sup>2</sup> = N/A	1 RCT, <sup>56</sup> 134 patients	High risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 0.47; 95% CI: 0.01 to 23.66; I <sup>2</sup> =N/A	1 RCT, <sup>169</sup> 72 patients	High risk of bias and severe imprecision	Insufficient
Greater occipital nerve block vs. Sham injection	Pain free	2 hours	RR: 10.29; 95% CI: 0.61 to 174.70; I <sup>2</sup> =N/A	1 RCT, <sup>91</sup> 28 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 2.08; 95% CI: 0.93 to 4.63; I <sup>2</sup> =N/A	1 RCT, <sup>91</sup> 28 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain scale	2 hours	SMD: 0.74; 95% CI: -0.03 to 1.51; I <sup>2</sup> =N/A	1 RCT, <sup>91</sup> 28 patients	Moderate risk of bias and severe imprecision	Insufficient
Ketamine vs. Placebo	Function scale	2 hours	SMD: 0.23; 95% CI: -0.44 to 0.91; I <sup>2</sup> =N/A	1 RCT, <sup>84</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 0.75; 95% CI: 0.14 to 3.94; I <sup>2</sup> =N/A	1 RCT, <sup>84</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain scale	2 hours	SMD: -0.43; 95% CI: -1.11 to 0.25; I <sup>2</sup> =N/A	1 RCT, <sup>84</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 1.13; 95% CI: 0.02 to 56.70; I <sup>2</sup> =N/A	1 RCT, <sup>84</sup> 34 patients	Moderate risk of bias and severe imprecision	Insufficient
Lidocaine vs. Chlorpromazine	Pain free	2 hours	RR: 0.23; 95% CI: 0.05 to 0.98; I <sup>2</sup> =N/A	1 RCT, <sup>55</sup> 50 patients	High risk of bias and imprecision	Low
Lidocaine vs. Placebo	Function scale	2 hours	SMD: 0.39; 95% CI: -0.07 to 0.86; I <sup>2</sup> =N/A	1 RCT, <sup>134</sup> 81 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain free	1 week	RR: 1.45; 95% CI: 0.93 to 2.27; I <sup>2</sup> =N/A	1 RCT, <sup>53</sup> 162 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 2.14; 95% CI: 1.16 to 3.96; I <sup>2</sup> =65.09%	2 RCTs, <sup>59, 134</sup> 130 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD:0.02; 95% CI: -0.21 to 0.26; I <sup>2</sup> =85.02%	3 RCTs, <sup>53, 59, 134</sup> 292 patients	Moderate risk of bias, inconsistency, and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I <sup>2</sup> =N/A	1 RCT, <sup>53</sup> 162 patients	High risk of bias and severe imprecision	Insufficient
Magnesium sulfate vs. Caffeine citrate	Pain scale	2 hours	SMD: 1.62; 95% CI: 1.08 to 2.17; I <sup>2</sup> =N/A	1 comparative observational study, <sup>183</sup> 70 patients	High risk of bias and imprecision	Low

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Magnesium sulfate vs. Placebo	Pain free	2 hours	RR: 5.73; 95% CI: 2.43 to 13.50; I <sup>2</sup> =54.62%	1 RCT <sup>58</sup> and 1 Crossover RCT, <sup>74</sup> 150 patients	High risk of bias and imprecision	Low
	Pain free	1 day	RR: 1.25; 95% CI: 0.97 to 1.61; I <sup>2</sup> =N/A	1 RCT, <sup>58</sup> 120 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 3.86; 95% CI: 2.11 to 7.07; I <sup>2</sup> =60.27%	1 RCT <sup>58</sup> and 1 Crossover RCT, <sup>74</sup> 150 patients	High risk of bias and imprecision	Low
	Pain relief	1 day	RR: 1.14; 95% CI: 0.93 to 1.39; I <sup>2</sup> =N/A	1 RCT, <sup>58</sup> 120 patients	High risk of bias and severe imprecision	Insufficient
Octreotide vs. Placebo	Pain relief	1 day	RR: 3.06; 95% CI: 1.11 to 8.44; I <sup>2</sup> =N/A	1 RCT, <sup>121</sup> 29 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 1.09; 95% CI: 0.30 to 1.88; I <sup>2</sup> =N/A	1 RCT, <sup>121</sup> 29 patients	High risk of bias and imprecision	Low
	Pain scale	1 day	SMD: 1.51; 95% CI: 0.67 to 2.35; I <sup>2</sup> =N/A	1 RCT, <sup>121</sup> 29 patients	High risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 1.15; 95% CI: 0.02 to 57.96; I <sup>2</sup> =N/A	1 RCT, <sup>127</sup> 43 patients	High risk of bias and severe imprecision	Insufficient
Propofol vs. standard therapy ((chlorpromazine, metoclopramide, ondansetron, lignocaine, magnesium sulphate, or morphine))	Pain scale	2 hours	SMD: 0.00; 95% CI: -0.72 to 0.72; I <sup>2</sup> =N/A	1 RCT, <sup>182</sup> 30 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain scale	1 day	SMD: 0.53; 95% CI: -0.18 to 1.28; I <sup>2</sup> =N/A	1 RCT, <sup>182</sup> 30 patients	Moderate risk of bias and severe imprecision	Insufficient
Propofol vs. Dexamethasone	Pain scale	2 hours	SMD: 1.01; 95% CI: 0.58 to 1.45; I <sup>2</sup> =N/A	1 RCT, <sup>159</sup> 90 patients	Moderate risk of bias and imprecision	Low
Secobarbital vs. Placebo	Pain relief	1 day	RR: 1.88; 95% CI: 1.09 to 3.21; I <sup>2</sup> =N/A	1 RCT, <sup>101</sup> 30 patients	High risk of bias and imprecision	Low
	Pain scale	1 day	SMD: 0.79; 95% CI: 0.04 to 1.53; I <sup>2</sup> =N/A	1 RCT, <sup>101</sup> 30 patients	High risk of bias and severe imprecision	Insufficient
Valproate vs. Dexamethasone	Pain free	1 day	RR: 1.25; 95% CI: 0.39 to 3.99; I <sup>2</sup> =N/A	1 RCT, <sup>89</sup> 40 patients	High risk of bias and severe imprecision	Insufficient
	Pain relief	2 hours	RR: 0.83; 95% CI: 0.68 to 1.02; I <sup>2</sup> =N/A	1 RCT, <sup>122</sup> 80 patients	Severe imprecision	Low
		1 day	RR: 0.92; 95% CI: 0.82 to 1.04; I <sup>2</sup> =N/A	1 RCT, <sup>122</sup> 80 patients	Severe imprecision	Low
	Pain scale	2 hours	SMD: -0.16; 95% CI: -0.46 to 0.15; I <sup>2</sup> =0.00%	2 RCTs, <sup>122,137</sup> 166 patients	High risk risk of bias and severe imprecision	Insufficient
	Pain scale	1 day	SMD: -0.15; 95% CI: -0.51 to 0.22; I <sup>2</sup> =73.59%	2 RCTs, <sup>89,122</sup> 120 patients	High risk of bias and severe imprecision	Insufficient
Valproate vs. Dexamethasone (continued)	Serious AE	N/A	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I <sup>2</sup> =N/A	1 RCT, <sup>137</sup> 86 patients	High risk risk of bias and severe imprecision	Insufficient

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Valproate vs. Prochlorperazine	Pain scale	2 hours	SMD: -1.38; 95% CI: -2.07 to -0.69; I <sup>2</sup> =N/A	1 RCT, <sup>164</sup> 40 patients	Imprecision	Moderate

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

## KQ3: Nonpharmacologic Therapy

KQ3a. What is the comparative effectiveness of nonpharmacologic therapy versus sham treatment, waitlist, usual care, attention control, and no treatment after followup at the following intervals: <1 day; 1 day to <1 week; 1 week to <2 weeks; 2 weeks to 4 weeks?

KQ3b. What is the comparative effectiveness of nonpharmacologic treatments (e.g., exercise, cognitive behavioral therapy, acupuncture, biofeedback, noninvasive neuromodulation devices) for outcomes related to pain, function, pain relief satisfaction, and quality of life?

KQ3c. How does effectiveness of nonpharmacologic therapy vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities?

KQ3d. How do harms vary depending on: (1) patient demographics (e.g., age, gender); (2) patient medical comorbidities; (3) the type of treatment used; (4) the frequency of therapy; (5) the duration of therapy?

## KQ3 Key Points

- Several nonpharmacological acute treatments of migraine may improve various measures of pain compared with placebo, although only studied in one or a few small trials, including acupuncture (low SOE), chamomile oil (low SOE), external trigeminal nerve stimulation (low SOE), eye movement desensitization reprocessing (low SOE), and remote electrical neuromodulation (moderate SOE).
- Evidence was insufficient to draw conclusions about serious adverse events.

## KQ3 Results

Seventeen RCTs and one comparative observational study with 1,758 patients were included for KQ3.<sup>60, 68, 85, 98, 124, 128, 131, 136, 142, 165, 168, 172-176, 180, 187</sup> Five were crossover studies.<sup>60, 98, 142, 175, 176</sup> Five were conducted in the emergency department<sup>68, 124, 136, 168, 180</sup> and 13 were in outpatients.<sup>60, 85, 98, 128, 131, 142, 165, 172-176, 187</sup> Ten were done in Asia,<sup>60, 85, 124, 128, 142, 172, 173, 175, 176, 187</sup> 3 in Europe<sup>98, 165, 180</sup> 4 in the United States<sup>68, 131, 136, 168</sup> and 1 was done in multiple countries.<sup>174</sup> Average followup was 10.21 days. Details of the interventions used in each study can be found in Appendix Table F.7. Risk of bias for these studies is in Appendix Tables E.1 and E.2. Adverse events are reported in Appendix Table H.7.

The overall risk of bias is moderate due to moderate risk of bias from randomization process and deviation from intended interventions for RCTs and high risk from comparability between groups and outcome data sources for observational studies (Appendix Tables E.1 and E.2). A sensitivity analysis by excluding studies with high risk of bias found lower pain reduction at 2

hours for studies with low risk of bias when external trigeminal nerve stimulation compared with placebo (Appendix Table L.5).

Three RCTs<sup>128, 172, 63</sup> evaluated acupuncture versus placebo, published in 2009, 2012, and 2018, with outcomes including pain scale at 2 hours, pain free or pain relief at 1 day, sustained pain free at 1 day, and sustained pain free at 1 week (Table 12). Acupuncture was found to be superior to placebo at the endpoint of pain free and pain scale at 1 day, but the other endpoints were not met. There was no significant difference on AEs. No serious AEs were reported in either group.

There has been one study comparing chamomile oil to placebo from 2018 with 98 subjects with the end points of pain scale at 2 hours and pain scale at 1 day.<sup>176</sup> Chamomile oil significantly improved pain scale at 2 hours and 1 day.

There was a single RCT from 2008 with 52 subjects that evaluated eye movement desensitization reprocessing versus placebo.<sup>136</sup> This study's endpoints included pain free at 2 hours, pain scale at 2 hours, pain scale at 1 day, and pain scale at 1 week. The technique appeared to be superior to placebo at pain free at 2 hours and pain scale at 2 hours, but not at the other endpoints.

Noninvasive neuromodulation is a particular area of interest in migraine therapy development, and we included the relevant studies on these devices in this nonpharmacological portion of our analysis.

There have been two RCTs published in 2019 and 2020, with 189 subjects looking at external trigeminal nerve stimulation versus placebo with endpoints of pain free at 2 hours, pain relief at 2 hours, pain scale at 2 hours, pain free at 1 day, pain relief at 1 day, pain scale at 1 day, sustained pain free at 1 day, and sustained pain relief at 1 day.<sup>68, 180</sup> External trigeminal nerve stimulation significantly improved pain scale at 2 hours and 1 day. There was no significant difference on AEs or other outcomes. No serious AEs were reported in either group.

A 2010 RCT evaluated magnetic stimulation versus placebo in 201 subjects.<sup>131</sup> The outcomes studied included pain free and pain relief at 2 hours, sustained pain free at 1 week, and function scale at 1 week. Pain free at 2 hours was the only outcome to reach significance. No significant difference on AEs was reported. No serious AEs were reported in either group.

A 2018 RCT with 248 subjects looked at noninvasive vagus nerve stimulation versus placebo for the acute treatment of migraine.<sup>165</sup> This study met its endpoint of pain relief at 2 hours but did not meet its endpoint of pain free at 2 hours. There was no significant difference on AEs. No serious AEs were reported in either group.

Finally, a 2019 RCT with 252 subjects evaluated remote electrical neuromodulation versus placebo. This study met all of its outcomes, including pain free at 2 hours, pain relief at 2 hours, sustained pain free a 1 week, and sustained pain relief at 1 week.<sup>174</sup> There was no significant difference on AEs. No serious AEs were reported in either group.

## **Subgroup Analysis**

We were unable to conduct preplanned subgroup analysis due to a small number of studies included within each comparison.

**Table 12. Comparisons of nonpharmacologic interventions**

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Acupuncture vs. Sham acupuncture	Pain free	1 day	RR: 2.53; 95% CI: 1.27 to 5.02; I <sup>2</sup> = N/A	1 RCT, <sup>128</sup> 175 patients	Moderate risk of bias and imprecision	Low
	Pain relief	1 day	RR: 0.74; 95% CI: 0.56 to 0.97; I <sup>2</sup> = N/A	1 RCT, <sup>128</sup> 175 patients	Moderate risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 0.19; 95% CI: -0.10 to 0.49; I <sup>2</sup> = 77.86%	2 RCTs, <sup>85, 128</sup> 235 patients	Moderate risk of bias and severe imprecision	Insufficient
	Pain scale	1 day	SMD: 0.49; 95% CI: 0.25 to 0.73; I <sup>2</sup> = 0.00%	2 RCTs, <sup>128, 172</sup> 325 patients	Moderate risk of bias and imprecision	Low
	Sustained pain free	1 day	RR: 2.14; 95% CI: 0.93 to 4.95; I <sup>2</sup> = N/A	1 RCT, <sup>172</sup> 150 patients	Moderate risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 week	RR: 1.12; 95% CI: 0.96 to 1.32; I <sup>2</sup> = N/A	1 RCT, <sup>172</sup> 150 patients	Moderate risk of bias and severe imprecision	Insufficient
	Serious AEs	N/A	RR: 1.03; 95% CI: 0.02 to 52.13; I <sup>2</sup> = N/A	1 RCT, <sup>128</sup> 175 patients	Moderate risk of bias and severe imprecision	Insufficient
Chamomile oil vs. Placebo	Pain scale	2 hours	SMD: 1.51; 95% CI: 1.07 to 1.96; I <sup>2</sup> = N/A	1 RCT, <sup>176</sup> 98 patients	Moderate risk of bias and imprecision	Low
	Pain scale	1 day	SMD: 1.16; 95% CI: 0.74 to 1.58; I <sup>2</sup> = N/A	1 RCT, <sup>176</sup> 98 patients	Moderate risk of bias and imprecision	Low
Eye movement desensitization reprocessing vs. Standard care	Pain free	2 hours	RR: 17.00; 95% CI: 2.44 to 118.55; I <sup>2</sup> = N/A	1 RCT, <sup>136</sup> 52 patients	High risk of bias and imprecision	Low
	Pain scale	2 hours	SMD: 2.28; 95% CI: 1.58 to 2.99; I <sup>2</sup> = N/A	1 RCT, <sup>136</sup> 52 patients	High risk of bias and imprecision	Low
	Pain scale	1 day	SMD: 0.60; 95% CI: 0.04 to 1.16; I <sup>2</sup> = N/A	1 RCT, <sup>136</sup> 52 patients	High risk of bias and severe imprecision	Insufficient
	Pain scale	1 week	SMD: 0.52; 95% CI: -0.03 to 1.08; I <sup>2</sup> = N/A	1 RCT, <sup>136</sup> 52 patients	High risk of bias and severe imprecision	Insufficient
External trigeminal nerve stimulation vs. Sham	Pain free	2 hours	RR: 2.34; 95% CI: 0.77 to 7.12; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
	Pain free	1 day	RR: 2.23; 95% CI: 0.99 to 5.01; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
	Pain relief	2 hours	RR: 1.32; 95% CI: 0.88 to 1.99; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
	Pain relief	1 day	RR: 1.24; 95% CI: 0.87 to 1.77; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
External trigeminal nerve stimulation vs. Sham (continued)	Pain scale	2 hours	SMD: 1.25; 95% CI: 0.90 to 1.60; I <sup>2</sup> = 98.65%	2 RCTs, <sup>68, 180</sup> 189 patients	Moderate risk of bias and imprecision	Low
	Pain scale	1 day	SMD: 0.53; 95% CI: 0.14 to 0.92; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Imprecision	Moderate
	Serious AE	N/A	Rate Ratio: 1.04; 95% CI: 0.02 to 52.34; I <sup>2</sup> =N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
	Sustained pain free	1 day	RR: 7.26; 95% CI: 0.38 to 137.28; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
	Sustained pain relief	1 day	RR: 1.95; 95% CI: 0.90 to 4.20; I <sup>2</sup> = N/A	1 RCT, <sup>68</sup> 106 patients	Severe imprecision	Low
Magnetic stimulation vs. Sham stimulation	Function scale	1 week	SMD: 0.00; 95% CI: -0.28 to 0.27; I <sup>2</sup> = N/A	1 RCT, <sup>131</sup> 201 patients	High risk of bias and severe imprecision	Insufficient
	Pain free	2 hours	RR: 1.73; 95% CI: 1.04 to 2.86; I <sup>2</sup> = N/A	1 RCT, <sup>131</sup> 201 patients	High risk of bias and imprecision	Low
	Pain relief	2 hours	RR: 1.04; 95% CI: 0.82 to 1.33; I <sup>2</sup> = N/A	1 RCT, <sup>131</sup> 201 patients	High risk of bias and severe imprecision	Insufficient
	Serious AE	N/A	Rate Ratio: 0.97; 95% CI: 0.02 to 48.91; I <sup>2</sup> =N/A	1 RCT, <sup>131</sup> 201 patients	High risk risk of bias and severe imprecision	Insufficient
	Sustained pain free	1 week	RR: 1.94; 95% CI: 0.99 to 3.79; I <sup>2</sup> = N/A	1 RCT, <sup>131</sup> 201 patients	High risk of bias and severe imprecision	Insufficient
Noninvasive vagus nerve stimulation vs. Sham stimulation	Pain free	2 hours	RR: 1.43; 95% CI: 0.92 to 2.22; I <sup>2</sup> = N/A	1 RCT, <sup>165</sup> 248 patients	Imprecision	Moderate
	Pain relief	2 hours	RR: 1.49; 95% CI: 1.04 to 2.13; I <sup>2</sup> = N/A	1 RCT, <sup>165</sup> 248 patients	Imprecision	Moderate
	Serious AE	N/A	Rate Ratio: 1.04; 95% CI: 0.02 to 52.05; I <sup>2</sup> = N/A	1 RCT, <sup>165</sup> 248 patients	Severe imprecision	Low
Remote electrical neuromodulation vs. Sham stimulation	Pain free	2 hours	RR: 1.95; 95% CI: 1.19 to 3.19; I <sup>2</sup> = N/A	1 RCT, <sup>174</sup> 252 patients	Imprecision	Moderate
	Pain relief	2 hours	RR: 1.65; 95% CI: 1.22 to 2.24; I <sup>2</sup> = N/A	1 RCT, <sup>174</sup> 252 patients	Imprecision	Moderate
	Serious AE	N/A	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I <sup>2</sup> =N/A	1 RCT, <sup>174</sup> 252 patients	Severe imprecision	Low

Comparison	Outcome	Time	Findings	Study Design and Sample Size	Rationale for Strength of Evidence	Overall Evidence Strength
Remote electrical neuromodulation vs. Sham stimulation (continued)	Sustained pain free	1 week	RR: 2.57; 95% CI: 1.11 to 5.94; I <sup>2</sup> = N/A	1 RCT, <sup>174</sup> 252 patients	Imprecision	Moderate
	Sustained pain relief	1 week	RR: 2.27; 95% CI: 1.30 to 3.95; I <sup>2</sup> = N/A	1 RCT, <sup>174</sup> 252 patients	Imprecision	Moderate

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk; SMD = standardized mean difference

SMD>0 implies the intervention (mentioned first in the comparison) is better.

# Discussion

## Overview

We conducted a systematic review to assess the effectiveness of pharmacologic and nonpharmacologic therapies for acute treatment of episodic migraine in adults. Recognizing the opioid epidemic in the United States of America, therapies were divided into opioids, nonopioid drugs (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], triptans, ergot alkaloids, gepants, ditans, combination analgesics, muscle relaxants, antiemetic medications), and nonpharmacologic therapy (e.g. acupuncture, eye movement desensitization reprocessing, noninvasive neuromodulation devices). Further, we assessed the adverse events.

High and moderate strengths of evidence (SOE) support the effectiveness of triptans and NSAIDs; respectively. Two systematic reviews evaluated the combination of sumatriptan and naproxen and suggested that the combination of triptans and NSAIDs is also effective, well tolerated and can be used for patients with partial response to either agent.<sup>47, 48</sup> These along with dihydroergotamine, antiemetics, and acetaminophen are considered established acute treatments for migraine. In general, the adverse events of these drugs are mild and transient. Newer therapies for acute treatment of migraine such as the gepants and the 5-HT<sub>1F</sub> receptor agonist, lasmiditan, were more effective than placebo in improving pain relief at 2 hours, 1 day, and at 1 week. Adverse events of newer medications require further study. Noninvasive neuromodulation devices are an area of new innovation for the acute treatment of migraine and there are several devices that have been given Food and Drug Administration (FDA) clearance; however, our search revealed that these therapies lack a strong evidence base with very few randomized controlled trials (RCTs). Other nonpharmacologic therapies had low to insufficient evidence.

Although opioids are commonly prescribed for acute treatment of migraine across all clinical settings and age groups,<sup>13-18,181</sup> this systematic review has shown that very few studies (15 studies with 2,208 patients) evaluated the use of opioids for acute treatment of migraine. The strength of evidence supporting the use of the various opioids for acute treatment of migraine was low or insufficient, and increased adverse events were noted. No included studies in the systematic review evaluated instruments to help in predicting risk of opioid misuse, developing opioid use disorders, or overdose in patients with migraine. Moreover, none of the included studies evaluated risk mitigation strategies to be used when prescribing opioids for acute treatment of episodic migraine.

The findings of this systematic review can inform shared decision making and choice of therapy, recognizing the variety in treatment types, clinical settings and routes of administration. Considering efficacy and harm outcomes as well as individual factors, such as characteristics of the migraine attack (including frequency, duration, severity, accompanying symptoms) and patient characteristics and comorbidities will help when selecting acute treatments.

## Findings in Relation to What Is Known

This review provides a comprehensive overview of interventions in acute treatment of episodic migraine to address an urgent need to provide an updated summary of the current state of evidence. In addition to summarizing the evidence on established therapies, this review includes a summary of the newer agents for acute treatment of migraine, such as the gepants and lasmiditan, and nonpharmacologic interventions. With the discovery of novel therapeutic targets in migraine, the literature on acute interventions has proliferated substantially in recent years.



Additionally, there are numerous published systematic reviews on guideline-recommended acute interventions, such as triptans and NSAIDs. It has become a difficult task for providers, health policymakers and other end users of the evidence to keep up with the constantly increasing body of evidence on the acute treatment of migraine and appraise this information relative to historical practice patterns. Guidelines for outpatient acute treatment recommend the use of triptans and NSAIDs as first line interventions, as well as acetaminophen for non-incapacitating attacks.<sup>24</sup> The findings of our systematic review align with these guidelines. Additionally, we have summarized the evidence showing moderate to high strength of evidence for a number of newer acute treatment options, such as gepants and ditans. These newer treatments have been FDA approved and are awaiting guideline updates to determine their place among the established therapies like triptans and NSAIDs.

Opioids were examined separately, and this report highlights the low or insufficient strength of evidence for their use despite them frequently being prescribed. Studies in several acute care settings have shown the use of opioids for migraine ranging from 16 to 71 percent.<sup>14</sup> Both opioids and non-pharmacologic treatments have low strength of evidence. However, despite poor direct evidence on harms from these studies, there are known risks for opioids. The adverse effects captured in this review are those seen during the immediate exposure. Other adverse effects may only become apparent with frequent or long-term use of some of these treatments. Harms with frequent or long-term use of medications may relate to end-organ damage (e.g. nephrotoxicity and cardiotoxicity with NSAIDs, hepatotoxicity with acetaminophen, ergotism or peritoneal fibrosis with ergot alkaloids) and well as secondary conditions that may develop in the setting of consuming medications (e.g., medication overuse headache, misuse, opioid use disorder, and overdose). Medication overuse and the potential to develop medication overuse headache must be considered with the use of pharmacologic interventions for the acute treatment of migraine. Medication overuse headache (MOH) is operationally defined based on headache frequency (15 or more days per month for greater than 3 months) and days of use per month of specific medications.<sup>198</sup> The use of triptans, ergot alkaloids, combination analgesics, or opioids on 10 or more days per month meets criteria for medication overuse. Conversely, simple analgesics including NSAIDs and acetaminophen can be used on 15 or more days per month before this criteria for medication overuse is met.<sup>198</sup> In addition, use of more than one class of medications, for example a triptan and an NSAID, on 10 or more days per month also meets criteria for MOH.<sup>198</sup> Acute treatment options do not have an equal risk of MOH development.<sup>199</sup> Opioids and butalbital-containing medications have a two-fold higher risk of MOH development compared with simple analgesics and triptans.<sup>200</sup> Analgesics and opioids have been associated with a higher risk of developing MOH compared with other treatments.<sup>191</sup> Past studies from the 1980s and 1990s have raised concerns about opioid addiction secondary to treatment of migraine; noting conversion rates of opioid addiction secondary to treatment of migraines at 13 individuals per one million people and drug abuse in 19 percent of patients with three or more emergency department (ED) visits for migraine in a 42-month period and in 2.5 percent of patients with one or two visits.<sup>201, 202</sup> More recent studies have found that opioid use is common in migraine patients and the risk of gastrointestinal-related adverse events and opioid abuse increased with long-term use of opioids.<sup>12</sup> No included studies in the systematic review evaluated instruments to help in predicting risk of opioid misuse, developing opioid use disorders or overdose in patients with migraine. No included studies evaluated risk mitigation strategies to be used when prescribing opioids for acute treatment of episodic migraine. The lack of risk assessment tools and mitigation strategies has major implications for practical implementation of

treatment algorithms that include opioids. Noninvasive neuromodulation is a cutting-edge area of research for migraine treatment. While there are 4 devices currently FDA-approved for the acute treatment of migraine, our analysis of the literature revealed that there are actually few randomized trials to evaluate the effectiveness of their use.

## **Clinical Implications and Applicability of Findings**

Considering patient characteristics, including comorbidities, when selecting acute treatments for migraine is important. For example, triptans and ergot alkaloids are considered vasoactive medications. Studies have shown that numerous patients with migraine have cardiovascular risk factors that may preclude the use of vasoactive medications.<sup>203, 204</sup> Lasmiditan, as well as the gepants showed high SOE for acute treatment of migraine and, given their mechanisms of action, are believed to be nonvasoconstrictive.<sup>205</sup> Treatment guidelines will need to be updated to reflect the evidence supporting newer therapies for acute treatment of migraine, such as the gepants and ditans, especially when considering certain patient populations like those with vascular risk factors. Our analysis uncovered that current acute treatments lack data in specific subpopulations, including the elderly, individuals with specific forms of migraine such as hemiplegic, as well as others with certain medical comorbidities. It will be important for future research to include these groups so that there can be a more robust evidence base to help guide treatment recommendations.

This review captured the acute treatment of migraine in different settings, including ambulatory as well as ED and urgent care. When considering the results of this systematic review, one should consider that the scenarios that would prompt an individual to seek care at an ED or urgent care versus self-treat at home may be different. The implication with presenting to the ED or urgent care with a migraine is that often the attack is refractory to treatments already tried at home and more likely to be severe or incapacitating, and accompanied with significant nausea, vomiting, and potentially dehydration. Although sub-group analyses were conducted to evaluate how settings might have affected outcomes (Appendix Tables K.1 to K.5), these subgroups were inherently limited by small numbers of studies and typically underpowered to detect true differences.

The evidence for opioids in acute treatment of migraine is low or insufficient based on this review. Although not captured in this review, risk for adverse outcomes pertaining to frequent or long-term intermittent use, such as misuse, opioid use disorder, and overdose, must be considered. These findings should prompt a review of the common prescribing practices of opioids for the acute treatment of migraine, as the evidence supports the current guidelines that opioids not be used as first line therapy for migraine. The lack of tools to select patients for opioids use or stratify their risk for abuse and misuse, can greatly impact the applicability of the evidence. Patients would benefit from improved implementation efforts to ensure clinical practice is consistent with guideline recommendations.

Access to interventions can be a barrier to obtaining acute treatment for migraine. Certain medications used for the acute treatment of migraine may not be reliably stocked by pharmacies due to potentially serious adverse effects that require close monitoring (e.g. ergot alkaloids) or due to insurance restrictions and cost (e.g. gepants and ditans). Some of the newer drugs may not be accessible or afforded by all patients. The noninvasive neuromodulation devices, despite being given FDA clearance for the acute treatment of migraine, are not routinely covered by insurance and can be cost prohibitive. Conversely, even though many of the nonpharmacological treatments have only few trials and lack robust evidence per our analysis, guidelines may

consider their favorable safety profile in recommending these as treatment alternatives and they are becoming more commonplace in clinical practice. As they are used more routinely, additional studies will help clarify their role in the treatment algorithms. Furthermore, with the development of gepants and ditans, guidelines may consider how these new drugs may fit among the established options of first line therapies, as well as among other alternatives such as nonpharmacologic options with low SOE but favorable safety profiles, and opioid options with low or insufficient SOE but known risks. Currently, the lack of comparative effectiveness studies amongst all of these different treatment choices is an important research gap.

Although only studied in one or a few small trials, several other therapies may improve migraine pain compared with placebo, including dexamethasone, dipyrone, lidocaine, magnesium sulfate, octreotide, and secobarbital (low SOE). Evidence was insufficient to draw conclusions about serious adverse events of these interventions. Although the strength of evidence is low, clinically these interventions are considered if patients do not respond, encounter side effects, or have contraindication to the more established treatments.

Patients are often advised to use combinations of acute therapy to treat migraine attacks. This combination can include an antiemetic as well as migraine specific therapy such as a triptan and a nonspecific analgesic such as an NSAID. The trials we analyzed did not sufficiently evaluate these potential combination therapies for the acute treatment of migraine and it remains unclear which combination of treatment may have the best evidence, which combinations may have a synergistic benefit, and which may simply be additive.

## **Limitations and Suggestions for Future Research**

For many interventions, very few RCTs, in some cases only one, were available (Key Questions 1-3) and some were small, which limits inferences from the quantitative analysis. Consequently, failure to detect statistical significance for many of the outcomes could have resulted from type II error and lack of power. Although we used very broad search terms and sought Supplemental Evidence and Data from the public to identify all relevant interventions, it is still difficult to be certain that all the appropriate literature and relevant interventions (e.g., nonpharmacologic therapy) has been included.

Most of the studies compared the interventions with placebo. Future trials should focus on comparative trials between different acute medication choices, particularly those that have the highest levels of evidence, to help clinicians decide amongst all of the available options and trials that look at combinations of therapies. This is important to also help clarify the place for the newer therapeutic options, such as gepants and ditans, and nonpharmacologic options compared with the more established therapies, such as NSAIDs and triptans.

The clinical trials included in our analysis generally excluded many important populations, including those with cardiovascular problems, cerebrovascular problems, hemiplegic migraine, and frequently individuals over the age of 65. Further studies evaluating the efficacy of acute treatments in these specific populations will be important, particularly now that we have options that are believed to be safe in some of these groups.

Pain as a main outcome of migraine research is a challenge to all investigations due to the subjective nature and how it is affected by each individual's psychological states and recall. While randomization, blinding and standardized instruments are used in trials, these approaches do not fully address this challenge.

Due to the quantity of literature captured by this review, studied endpoints were limited to those relating to pain freedom and relief, function, and harms. Migraine is defined by a set

constellation of symptoms, including not only headache, but also photophobia, phonophobia, nausea and vomiting, and others. Unfortunately, we were unable to report on these outcomes. For some patients, the pain component may not be as bothersome as the non-pain symptoms of migraine. Recognizing this, most bothersome symptom (MBS) has been suggested as a preferred endpoint. In migraine studies, there is a shift to use more patient-centric endpoints that reflect the quality of life impacted by migraine and its return to normal by acute treatment rather than only pain freedom or pain improvement. Total migraine freedom, or absence of all migraine-related symptoms including pain and all associated symptoms and return to baseline, is another important patient-centric endpoint. Future studies should emphasize these patient-centric endpoints. Patients have also indicated that speed of onset of acute treatment is highly important.<sup>206-208</sup> The available literature did not use these endpoints consistently, and hence the current analysis cannot address them. Consequently, future studies can compare the time it takes to reach to pain freedom, total migraine freedom, and MBS freedom as clinically meaningful endpoints. As mentioned in the limitations section, comparing outcomes relating to non-pain symptoms of migraine such as photophobia, phonophobia, nausea, and vomiting, is also important to reflect the entirety of the patient experience.

The harms outcomes that were captured in this review are those relating to adverse effects seen during the immediate exposure period. Consequently, this review does not capture harms that may arise with frequent or long-term intermittent use of these treatments. The inability to capture such harms is due to limitations in study design as the majority of trials evaluating acute treatment of migraine evaluate the efficacy and harms of the intervention during one or a few attacks. For example, telcagepant was studied against placebo in 6 RCTs between 2007 and 2012 and included a total of 6,021 subjects.<sup>69, 108-112</sup> These studies showed significant improvement of the drug at all endpoints including restored function at 2 hours, being pain free at 2 hours, pain relief at 2 hours, sustained pain free at 1 day, sustained pain free at 1 week, sustained pain relief at 1 day, and sustained pain relief at 1 week. When studies shifted from intermittent acute use to a more chronic use of telcagepant, hepatotoxicity was noted and this halted further research into this medication.<sup>209</sup> This example also speaks to the importance of being mindful of adverse effects which may not yet be known in the newer treatment options. Postmarketing data will be important to monitor for adverse effects of the newer therapeutic options. Additionally, harms from treatments are less likely to arise when taken under the controlled parameters of a trial verses in real world circumstances where individuals may be using interventions outside the parameters of the recommended dosing. Future studies should also routinely report on MOH as an outcome. The International Classification of Headache Disorders, 3rd edition (ICHD-3) has established that frequent use of acute therapies for migraine can lead to increase in migraine attack frequency over time, and this risk varies depending on the acute treatment. Furthermore, medication overuse has been associated with significant disability, as evidenced by the 2016 Global Burden of Disease study,<sup>210</sup> where it was listed amongst the top 20 causes of years lived with disability worldwide. Future studies on the acute treatment of migraine can compare relative risks of MOH with different classes of acute treatments so that this important problem can be better addressed.

The included studies were also conducted in different settings, from the ED to outpatient to inpatient environments, which all have implications regarding the type of migraine attack being treated. It is generally accepted that some acute treatments work best when taken early in an attack whereas others can still work in more refractory situations such as those that prompt ED visits and inpatient stays. Given that patients may not respond to the initial acute treatments that

they receive, future research should look at treatment efficacy in patients that have failed an initial acute treatment as this is clinically relevant information.

Available evidence for opioids in the acute treatment of migraine is low or insufficient. Despite this, they continue to be frequently prescribed. Research to evaluate why opioids are being prescribed may help provide strategies to address the opioid epidemic. One study found that physicians who were more likely to prescribe an opioid for a migraine headache were also more likely to prescribe an opioid to a patient with back pain.<sup>211</sup> This finding may suggest that physicians are lumping different types of acute pain together and not considering the nuances of the individual conditions and the evidence for treatment efficacy specific to those conditions. Factors that may affect opioid prescribing patterns should be studied.

With the advent of noninvasive neuromodulation, further research, including comparative studies with medications, to truly clarify their role as acute therapies for migraine are needed. These devices are being recommended by headache specialists in clinical practice more frequently given their safety profile despite lack of repeated, large-scale studies confirming that they are effective acute treatments. Cost and lack of insurance coverage is a current barrier with these devices; hopefully with additional studies establishing their role as acute therapies for migraine this hurdle can be made easier for patients.

Additionally, it is important to also note that while it is accepted that behavioral pain therapies such as cognitive behavioral therapy, mindfulness based stress reduction, and others can play an important role in the treatment migraine, there was a striking lack of evidence when a critical appraisal of the available data was done. This lack of rigorously designed, high quality clinical trials involving behavioral pain therapies leads clinicians to rely more on pharmacological options for migraine, accepting their risks and adverse effects. The lack of scientific evidence for behavioral pain management of migraine remains a significant limitation. Risk mitigation, using an integrated approach that combines medications and behavioral pain management, can only be successful if we have an improved evidence base. This lack of scientific evidence for behavioral pain management in migraine can be addressed with future studies that help strengthen this body of scientific literature.

This review focused on abortive, not preventive migraine treatment. However, there is a current paradigm shift regarding migraine and when to start preventive treatment. Rather than simply considering prevention based on number of migraine attacks per week or frequency of acute medication consumption, there is a shift to consider migraine-associated disability as an important determinant as to whether an individual should be placed on a preventive medication, regardless of attack frequency. It would be very helpful for shared decision making regarding abortive treatment to know whether people who are on preventive therapy have an improved response to a particular acute treatment.

Disparities based on race and socio-economic status exists in the acute treatment of migraine. Future research to identify the disparities, identify determinants that contribute to these disparities, and explore strategies to overcome these are needed. Cost of acute treatments affect access and may contribute to disparities in prescribing patterns for patients depending on race and socio-economic status including insurance coverage.

Finally, it is important to note that multiple interventions, including BI44370, telcagepant, dapitant, lanepitant, selurampanel, tezampanel, tonabersat, and flunarizine, are not FDA approved or not available in the United States.

## **Conclusion**

A number of acute treatments for episodic migraine exist with varying degrees of evidence. In addition to already established effective treatments, such as triptans, NSAIDs, antiemetics, and ergot alkaloids, newer treatments such as gepants and ditans are associated with improved outcomes in pain and function in acute treatment of episodic migraine. Opioids have low or insufficient strength of evidence for acute treatment of migraine. Despite increasing literature pertaining to migraine, the evidence base for many interventions in migraine remains limited. Selection of acute treatments for migraine must be individualized based on adverse effect profile and patient characteristics such as relevant comorbidities. Continued research is required to assess the comparative effectiveness and harms of several pharmacological and nonpharmacologic treatments.

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## Abbreviations and Acronyms

AE	Adverse events
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
ED	Emergency department
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
ITT	Intention-to-treat
KQs	Key Questions
KG	Kilograms
MG	Milligrams
MHRA	Medicines and Healthcare Products Regulatory Agency
MOH	Medication overuse headache
NSAIDs	Nonsteroidal anti-inflammatory drugs
N/A	Not available
PICOTS	Population, interventions, comparisons, outcomes, timing, and setting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
RR	Relative risk
SEADS	Supplemental Evidence and Data for Systematic Reviews
SES	Socioeconomic status
SMD	Standardized mean difference
SOE	Strength of evidence
VAS	Visual analog scale

# Appendix Contents

## Tables

Table D-1. Characteristics of included studies .....	D-1
Table E-1. Risk of bias (Cochrane ROB tool) for included randomized controlled trial studies .....	E-1
Table E-2. Risk of bias (Newcastle Ottawa tool) for included comparative observational studies .....	E-6
Table F-1. Results from included studies: KQ 1. opioids .....	F-1
Table F-2. Results from included studies: KQ 2. ergot alkaloids .....	F-5
Table F-3. Results from included studies: KQ 2. antiemetic .....	F-8
Table F-4. Results from included studies: KQ 2. calcitonin gene-related peptide receptor antagonists .....	F-13
Table F-5. Results from included studies: KQ 2. 5-HT1F .....	F-17
Table F-6. Results from included studies: KQ 2. other interventions .....	F-19
Table F-7. Results from included studies. KQ 3. nonpharmacologic therapy .....	F-26
Table G-1. Results of systematic reviews evaluating triptans .....	G-1
Table G-2. Results of systematic reviews evaluating nonsteroidal anti-inflammatory drugs (NSAIDs) .....	G-5
Table G-3. Results of systematic reviews evaluating the combination of triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) .....	G-7
Table H-1. Adverse events: KQ 1. opioids .....	H-1
Table H-2. Adverse events: KQ 2. ergot alkaloids .....	H-3
Table H-3. Adverse events: KQ 2. antiemetic .....	H-4
Table H-4. Adverse events: KQ 2. calcitonin gene-related peptide receptor antagonists .....	H-6
Table H-5. Adverse events: KQ 2. 5-HT1F .....	H-7
Table H-6. Adverse events: KQ 2. other interventions .....	H-8
Table H-7. Adverse events: KQ 3. nonpharmacologic therapy .....	H-10
Table I-1. Subgroup analysis by dosage for ergot alkaloids .....	I-1
Table I-2. Subgroup analysis by dosage for antiemetic .....	I-3
Table I-3. Subgroup analysis by dosage for calcitonin gene-related peptide receptor antagonists .....	I-5
Table I-4. Subgroup analysis by dosage for 5-HT1F .....	I-13
Table I-5. Subgroup analysis by dosage for other interventions .....	I-18
Table J-1. Adverse events: KQ 2. ergot alkaloids subgroup analysis by dosage .....	J-1
Table J-2. Adverse events: KQ 2. antiemetic subgroup analysis by dosage .....	J-2
Table J-3. Adverse events: KQ 2. calcitonin gene-related peptide receptor antagonists subgroup analysis by dosage .....	J-5
Table J-4. Adverse events: KQ 2. 5-HT1F subgroup analysis by dosage .....	J-9
Table K-1. Subgroup analysis by study setting for other interventions .....	K-1
Table K-2. Subgroup analysis by route of administration for calcitonin gene-related peptide receptor antagonists .....	K-2
Table K-3. Subgroup analysis by route of administration for 5-HT1F .....	K-3
Table K-4. Subgroup analysis by route of administration for other interventions .....	K-4
Table K-5. Subgroup analysis by prior response to triptans for 5-HT1F .....	K-5
Table K-6. Subgroup analysis by age for 5-HT1F .....	K-6
Table K-7. Subgroup analysis by gender for 5-HT1F .....	K-7

Table K-8. Subgroup analysis by race for 5-HT1F.....	K-8
Table K-9. Subgroup analysis by BMI for 5-HT1F.....	K-9
Table L-1. Sensitivity analysis by excluding studies with high risk of bias for ergot alkaloids .	L-1
Table L-2. Sensitivity analysis by excluding studies with high risk of bias for antiemetic .....	L-2
Table L-3. Sensitivity analysis by excluding studies with high risk of bias for calcitonin gene-related peptide receptor antagonists.....	L-3
Table L-4. Sensitivity analysis by excluding studies with high risk of bias for other interventions.....	L-4
Table L-5. Sensitivity analysis by excluding studies with high risk of bias for nonpharmacologic therapy.....	L-5

**Figures**

Figure B-1. Flow chart.....	B-1
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# Appendix A. Search Strategy

## Ovid

Database(s): APA PsycInfo 1806 to July Week 3 2020, EBM Reviews - Cochrane Central Register of Controlled Trials June 2020, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to July 24, 2020, Embase 1974 to 2020 July 24, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to July 24, 2020  
Search Strategy:

- | #  | Searches   |
|----|--|
| 1  | exp Migraine Disorders/dt, th [Drug Therapy, Therapy]  |
| 2  | migraine*.ti,ab,hw,kw.   |
| 3  | exp narcotic analgesic agent/  |
| 4  | exp Analgesics, Opioid/<br>(acetorphine or acetylcodeine or acetylmethadol or Alfentanil or Alphaprodine or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "Brompton mixture" or Buprenorphine or Butorphanol or ciramadol or cocodamol or Codeine or codydramol or conorfone or cyclazocine or Dextromoramide or Dextropropoxyphene or dextrorphan or dezocine or diamorphine or diconal or dihydrocodeine or dihydroetorphine or Dihydromorphine or dimethylthiambutene or Diphenoxylate or dipipanone or enadoline or eptazocine or ethylketazocine or Ethylketocyclazocine or Ethylmorphine or etonitazene or Etorphine or etoxeridine or faxeladol or Fentanyl or furethidine or gelonida or Heroin or Hydrocodone or isalmadol or isomethadone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or  |
| 5  | levacetylmethadol or levomethadone or Levorphanol or Meperidine or Meptazinol or metazocine or Methadone or "Methadyl Acetate" or methylsamidorphan or Morphine or "morphinomimetic agent*" or "morphinomimetic drug*" or morphinone or Nalbuphine or narcotic* or nicocodine or nicomorphine or noracymethadol or norbuprenorphine or nordextropropoxyphene or normorphine or norpethidine or norpropoxyphene or "o nortramadol" or oliceridine or opiate or Opiate* or opioid* or Opium or oripavine or Oxycodone or Oxymorphone or pentamorphine or Pentazocine or pethidine or phenadoxone or phenaridine or Phenazocine or phencyclidine or Phenoperidine or picenadol or piminodine or Pirinitramide or piritramide or profadol or Promedol or propiram or sameridine or samidorphan or semorphone or Sufentanil or tapentadol or thebaine or tifluadom or Tilidine or tonazocine or Tramadol or trimeperidine).ti,ab,hw,kw. |
| 6  | exp Anti-Inflammatory Agents, Non-Steroidal/   |
| 7  | exp cyclooxygenase inhibitors/   |
| 8  | exp cyclooxygenase 2 inhibitors/   |
| 9  | Aspirin/   |
| 10 | sulindac/  |

#

## Searches

- (Aceclofenac or Acemetacin or "Acetylsalicylic acid" or Alclofenac or Aminopyrine or Amodiaquine or Amoxiprin or Ampyrone or Antipyrine or Apazone or Aspirin or Azapropazone or Benorilate or Benorylate or Bromelains or Bromfenac or "BW-755C" or Celecoxib or "Choline magnesium salicylate" or "Choline magnesium trisalicylate" or clinoril or Clofazimine or Clofezone or Clonixin or "COX-1 inhibitor\*" or "COX-2 inhibitor\*" or "COX-2 selective inhibitor\*" or Coxib\* or Curcumin or "Cyclooxygenase 1 inhibitor\*" or "Cyclooxygenase 2 inhibitor\*" or "Cyclooxygenase inhibitor\*" or "Cyclooxygenase inhibitor\*" or Dapsone or Dexibuprofen or Dexketoprofen or Diclofenac or Diflunisal or Dipyron or Droxicam or Epirizole or Ethenzamide or Etodolac or Etoricoxib or Faislamine or Fenbufen or Fenoprofen or "Flufenamic acid" or Flunoxaprofen or Flurbiprofen or "Glycyrrhizic Acid" or Ibuprofen or Ibuproxam or Indomethacin or Indoprofen or Kebuzone or Ketoprofen or Ketorolac or Licofelone or Lornoxicam or Loxoprofen or Lumiracoxib or "Magnesium salicylate" or "Meclofenamic Acid" or "Mefenamic Acid" or Meloxicam or Mesalamine or Metamizole or "Methyl salicylate" or Mofebutazone or Nabumetone or Naproxen or "Niflumic Acid" or "Nonsteroidal antiinflammator\*" or "Nonsteroidal anti-inflammator\*" or "Non-steroidal antiinflammator\*" or "Non-steroidal anti-inflammator\*" or "Nordihydroguaiaretic Acid" or NSAID\* or osenal or Oxametacin or Oxaprozin or Oxyphenbutazone or Parecoxib or "Pentosan Sulfuric Polyester" or Phenazone or Phenylbutazone or Piroxicam or Pirprofen or Prenazone or Proglumetacin or Rofecoxib or Salicylamide or Salicylate or Sulfasalazine or Sulfinpyrazone or Sulindac or Suprofen or Tenoxicam or "Tiaprofenic acid" or "Tolfenamic acid" or Tolmetin or Valdecocix).ti,ab,hw,kw.
- 11
- 12 exp Tryptamines/
- 13 exp triptan derivative/
- 14 ("5-ht" or "5-hydroxytryptamine\*" or "5-methoxytryptamine\*" or dimethyltryptamine\* or enteramine\* or hippophaine\* or hydroxytryptamine\* or indolyethylamine\* or meksamine\* or methoxydimethyltryptamine\* or methoxytryptamine\* or methylbufotenin or mexamine\* or Serotonin or triptan\* or tryptamine\*).ti,ab,hw,kw.
- 15 exp Ergot Alkaloids/
- (Bromocriptine\* or Cabergoline\* or "clavine alkaloid\*" or "clavines alkaloid\*" or Dihydroergocornine\* or Dihydroergocristine\* or Dihydroergocryptine\* or Dihydroergotamine\* or Dihydroergotoxine\* or Ergoline\* or "Ergoloid Mesylate\*" or Ergonovine\* or "ergot agent\*" or "ergot alkaloid\*" or "ergot drug\*" or "ergot medication\*" or Ergotamine\* or Ergotamines or "ergotoxine alkaloid\*" or "ergots alkaloid\*" or Lisuride\* or "Lysergic Acid" or "Lysergic Acid Diethylamide\*" or Metergoline\* or Methylergonovine\* or Methysergide\* or Nicergoline\* or Pergolide\*).ti,ab,hw,kw.
- 16
- 17 exp Analgesics/

#

## Searches

- (Acetaminophen or Adenosine or Amantadine or Amitriptyline or analgesic\* or analgetic\* or anbesol or anodyne\* or anpirtoline or antalgic\* or antinociceptive\* or antrafenine or auralgan or axomadol or befiradol or bicifadine or brivaracetam or brivolidide or bromadoline or "Calcitonin Gene-Related Peptide Receptor Antagonist\*" or cannabidivarin or capsaicin or Carbachol or Carbamazepine or cebranopadol or cibinetide or cizolirtine or Clonidine or crobenetine or Cyclazocine or dapansutril or dasolampanel or davasaicin or deacetylappaconitine or "Dentin Desensitizing" or "desensitizing agent\*" or "desensitizing drug\*" or "desensitizing medication\*" or Dexmedetomidine or difelikefalin or Dihydroergotamine or dimiracetam or dizatrifone or doxpicomine or drinidene or Dronabino or Duloxetine or ecopladib or edronocaine or efipladib or elismetrep or "embelate potassium" or enkephalin or epibatidine or equagesic or Ergotamine or ethoheptazine or fadolmidine or fasinumab or "floctafenic acid" or floctafenine or flunixin or "flunixin meglumine" or flupirtine or Flurbiprofen or frakefamide or fulranumab or funapide or Gabapentin or gefapixant or giripladib or "glafenic acid" or Glafenine or "gw 493838" or "gw 842166" or hasamal or ibudilast or Ibuprofen or indantadol or Interleukin or Ketamine or lacosamide or lappaconitine or lenabasum or letimide or lexanopadol or "Magnesium Sulfate" or mavatrep or Medetomidine or Methotrimeprazine or Milnacipran or Mitoxantrone or Nefopam or neurotropin or "Nitrous Oxide" or nuvanil or olodanrigan or olorinab or olvanil or "omega conotoxin" or panidex or "pf 3557156" or "pf 4136309" or "pf 4480682" or "pf 592379" or "pf 738502" or Phenacetin or Pizotyline or pravadoline or Pregabalin or Quinine or ralfinamide or retigabine or ruzadolane or sampirtine or senrebotase or shogaol or strascogesic or tanezumab or tazadolene or tebanicline or tetrodotoxin or tivanisiran or traxoprodil or vedaclidine or vixotrigine or Xylazine).ti,ab,hw,kw.
- 18
- 19 exp Muscle Relaxants, Central/  
20 exp muscle relaxant agent/



#

## Searches

- (afloqualone or alcuronium or "atracurium besilate" or azumolene or baclofen or Baclofent or botulinum or branaplam or Carisoprodol or "chandonium iodide" or Chlormezanone or Chlorphenesin or chlorproethazine or Chlorzoxazone or cisatracurium or curare or curaremimetic\* or curariform or curarizing or Dantrolene or decamethonium or "depolarizing neuromuscular" or deutolperisone or diadonium or Diazepam or "dihydro beta erythroidine" or dimethyltubocurarine or doxacurium or duador or eperisone or fazadinium or febarbamate or flumetramide or gallamine or gantacurium or "hexafluronium bromide" or idrocilamide or inaperisone or lanperisone or "mebezonium iodide" or Medazepam or Mephenesin or Meprobamate or metaxalone or Methocarbamol or mivacurium or "Muscle relaxant\*" or "muscle relaxing" or "musculotropic relaxant\*" or "musculotropic relaxing" or myorelaxant or myotonolytic\* or nefopam or nelezaprine or "neuromuscular agent\*" or "neuromuscular blocker\*" or "neuromuscular blocking" or 21 "neuromuscular depolarizing agent\*" or "neuromuscular depolarizing drug\*" or "neuromuscular depolarizing medication\*" or "neuromuscular drug\*" or "neuromuscular medication\*" or "neuromuscular nondepolarizing agent\*" or "neuromuscular nondepolarizing drug\*" or "neuromuscular nondepolarizing medication\*" or "neuromuscular synapse blocking agent\*" or "neuromuscular synapse blocking drug\*" or "neuromuscular synapse blocking medication\*" or "nondepolarizing neuromuscular blocking agent\*" or "nondepolarizing neuromuscular blocking drug\*" or "nondepolarizing neuromuscular blocking medication\*" or norgesic or Orphenadrine or pancuronium or phenprobamate or pipecuronium or promoxolane or pyrocurine or Quinine or "rapacurium bromide" or rocuronium or silperisone or styramate or suxamethonium or "tiemonium methylsulfate" or tizanidine or Tolperisone or toxiferine or "tubocurarine chloride" or vecuronium or vesamicol or Xylazine or Zoxazolamine).ti,ab,hw,kw.
- 22 exp Antiemetics/  
23 exp Nausea/dt [Drug Therapy]  
24 exp Vomiting/dt [Drug Therapy]  
(((drug\* or agent\* or medication\*) adj3 (nausea or vomit\*)) or alizapride or "anti emetic\*" or antiemetic\* or antimetic\* or "anti-metic\*" or antinausea\* or "anti-nausea\*" or antivomit\* or "anti-vomit\*" or Aprepitant or azasetron or batanopride or belidral or bendectin or benzquinamide or bromopride or buclizine or casopitant or chlorcyclizine or chlorphenethazine or Chlorpromazine or cinnarizine or cisapride or clebopride or Cyclizine or dazopride or debendox or Dexamethasone or Diazepam or difenidol or Dimenhydrinate or Diphenhydramine or dixyrazine or "dolasetron mesilate" or Domperidone or Doxylamine or 25 dronabinol or Droperidol or exepanol or ezlopitant or fabesetron or fosaprepitant or fosnetupitant or Granisetron or Haloperidol or hydrodolasetron or icospiramide or indisetron or lerisetron or lintopride or Lorazepam or lurosetron or maropitant or Meclizine or meclizine or Methylprednisolone or Metoclopramide or metopimazine or nabilone or netupitant or norchlorpromazine or Olanzapine or Ondansetron or Palonosetron or pancopride or Prochlorperazine or Promazine or promethazine or ramosetron or renzapride or ricasetron or rolapitant or Scopolamine or sulpiride or telmapitant or tetrahydrocannabinol or Thiethylperazine or transmer or Trifluoperazine or Triflupromazine or trimethobenzamide or Tropisetron or vestipitant or vofopitant or zacopride).ti,ab,hw,kw.
- 26 exp Cannabis/

- | #  | Searches   |
|----|--|
| 27 | exp cannabinoid/   |
| 28 | exp "cannabis use"/  |
| 29 | exp Marijuana Smoking/   |
| 30 | exp Cannabinoids/  |
| 31 | exp Cannabidiol/<br>("1 butyl 3 1 naphthoyl indole" or "11 hydroxydronabinol" or "2 arachidonoylglycerol" or "2 methyl 3 1 naphthoyl 1 propylindole" or "3 1 naphthoyl 1 pentylindole" or "3 2 iodo 5 nitrobenzoyl 1 1 methyl 2 piperidinylmethyl indole" or "3 hydroxy delta9 tetrahydrocannabinol" or "ajulemic acid" or anandamide or bhang or bhanges or cannabi or cannabichromene or cannabidiol or cannabielsoin or cannabigerol or cannabinoid or    |
| 32 | cannabinol or cannabis or cannador or charas or Cindica or deacetyllevonantradol or dexanabinol or dextronantradol or dronabinol or endocannabinoid or ganja or ganjas or hashish or hashishs or hemp or hempes or levonantradol or marihuana* or marijuana* or methanandamide or "n oleoylethanolamine" or nabilone or nabiximols or nantradol or "noladin ether" or palmidrol or tetrahydrocannabinol or "tetrahydrocannabinolic acid" or virodhamine).mp. |
| 33 | exp Biofeedback, Psychology/<br>("alpha feedback*" or biofeedback* or "bogus physiological feedback*" or "brainwave feedback*" or "eeg feedback*" or "electroencephalography feedback*" or   |
| 34 | "electromyography feedback*" or "false physiological feedback*" or myofeedback* or neurofeedback* or "psychophysiologic feedback*").ti,ab,hw,kw.   |
| 35 | Electric Stimulation Therapy/  |
| 36 | exp neuromodulation/<br>(((Electric* or electro or galvano or Transcutaneous*) adj3 (stimulat* or stimulus)) or  |
| 37 | electrostimulation* or electrostimulus or electrotherap* or "E-stim" or ESTIM or FES or galvanostimulation* or galvanostimulus or Neuromodulation or neuromodulatory).ti,ab,hw,kw.   |
| 38 | exp Cognitive Therapy/   |
| 39 | exp Cognitive Behavior Therapy/  |
| 40 | (CBT or "Cognitive behavioral therap*" or "Cognitive therap*").ti,ab,hw,kw.  |
| 41 | exp Acupuncture/   |
| 42 | exp Acupuncture Therapy/   |
| 43 | (acupressure or acupuncture or "auricular needl*" or auriculotherapy or "ear needl*" or electroacupuncture or moxibustion or Shiatsu or "Tui Na").ti,ab,hw,kw.   |
| 44 | exp exercise/  |
| 45 | exp exercise therapy/<br>(aerobics or anaerobics or bicycling or biking or "endurance training" or exercis* or "fitness  |
| 46 | training" or isometrics or "physical exertion" or "physical activit*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting).ti,ab,hw,kw.   |
| 47 | (drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or therap* or treat*).ti,ab,hw,kw.   |

#	Searches
48	or/3-47
49	2 and 48
50	1 or 49
51	exp evidence based medicine/
52	exp meta analysis/
53	exp Meta-Analysis as Topic/
54	exp "systematic review"/
55	exp Guideline/ or exp Practice Guideline/
56	exp controlled study/
57	exp Randomized Controlled Trial/
58	exp triple blind procedure/
59	exp Double-Blind Method/
60	exp Single-Blind Method/
61	exp latin square design/
62	exp Placebos/
63	exp Placebo Effect/
64	exp comparative study/
65	exp intervention studies/
66	exp Cross-Sectional Studies/
67	exp Cross-Over Studies/
68	exp Cohort Studies/
69	exp longitudinal study/
70	exp retrospective study/
71	exp prospective study/
72	exp clinical trial/
73	clinical study/
74	exp case-control studies/
75	exp confidence interval/
76	exp multivariate analysis/

#

## Searches

- ((evidence adj based) or (meta adj analys\*) or (systematic\* adj3 review\*) or guideline\* or (control\* adj3 study) or (control\* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl\* adj blind\*) or (doubl\* adj mask\*) or (singl\* adj blind\*) or (singl\* adj mask\*) or (tripl\* adj blind\*) or (tripl\* adj mask\*) or (trebl\* adj blind\*) or (trebl\* adj mask\*) or "latin square" or placebo\* or nocebo\* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention\* adj2 study) or (intervention\* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort\* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal\* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv\* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv\* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random\* or control\*) and compar\*)).mp,pt.
- 77
- 78 or/51-77
- 79 50 and 78
- 80 limit 79 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase; records were retained]
- 81 limit 80 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in APA PsycInfo,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
- 82 limit 79 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase; records were retained]
- 83 limit 82 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in APA PsycInfo,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
- 84 83 not 81
- 85 79 not 84
- 86 migraine\*.ti.
- 87 85 and 86

#

## Searches

- limit 87 to (dissertation abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
- 88
- 89 from 88 keep 195-218
- 90 (87 not 88) or 89
- 91 limit 90 to yr="2018 -Current"
- 92 remove duplicates from 91
- 93 limit 90 to yr="2015-2017"
- 94 remove duplicates from 93
- 95 limit 90 to yr="2010-2014"
- 96 remove duplicates from 95
- 97 limit 90 to yr="2002-2009"
- 98 remove duplicates from 97
- 99 90 not (91 or 93 or 95 or 97)
- 100 remove duplicates from 99
- 101 92 or 94 or 96 or 98 or 100

## Scopus

- 1 TITLE(migraine\*)
- 2 TITLE-ABS-KEY(acetorphine or acetylcodeine or acetylmethadol or Alfentanil or Alphaprodine or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "Brompton mixture" or Buprenorphine or Butorphanol or ciramadol or cocodamol or Codeine or codydramol or conorfone or cyclazocine or Dextromoramide or Dextropropoxyphene or dextrorphan or dezocine or diamorphine or diconal or dihydrocodeine or dihydroetorphine or Dihydromorphine or dimethylthiambutene or Diphenoxylate or dipipanone or enadoline or eptazocine or ethylketazocine or Ethylketocyclazocine or Ethylmorphine or etonitazene or Etorphine or etoxeridine or faxeladol or Fentanyl or furethidine or gelonida or Heroin or Hydrocodone or isalmadol or isomethadone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or Levorphanol or Meperidine or Meptazinol or metazocine or Methadone or "Methadyl Acetate" or methylsamidorphan or Morphine or "morphinomimetic agent\*" or "morphinomimetic drug\*" or morphinone or Nalbuphine or narcotic\* or nicocodine or nicomorphine or noracymethadol or norbuprenorphine or nordextropropoxyphene or normorphine or norpethidine or norpropoxyphene or "o nortramadol" or oliceridine or opiate or Opiate\* or opioid\* or Opium or oripavine or Oxycodone or Oxymorphone or pentamorphone or Pentazocine or pethidine or phenadoxone or phenaridine or Phenazocine or phencyclidine or

- Phenoperidine or piconadol or piminodine or Pirinitramide or piritramide or profadol or Promedol or propiram or sameridine or samidorphan or semorphone or Sufentanil or tapentadol or thebaine or tifludom or Tilidine or tonazocine or Tramadol or trimeperidine)
- 3 TITLE-ABS-KEY(Aceclofenac or Acemetacin or "Acetylsalicylic acid" or Alclofenac or Aminopyrine or Amodiaquine or Amoxiprin or Ampyrone or Antipyrine or Apazone or Aspirin or Azapropazone or Benorilate or Benorylate or Bromelains or Bromfenac or "BW-755C" or Celecoxib or "Choline magnesium salicylate" or "Choline magnesium trisalicylate" or clinoril or Clofazimine or Clofezone or Clonixin or "COX-1 inhibitor\*" or "COX-2 inhibitor\*" or "COX-2 selective inhibitor\*" or Coxib\* or Curcumin or "Cyclooxygenase 1 inhibitor\*" or "Cyclooxygenase 2 inhibitor\*" or "Cyclooxygenase inhibitor\*" or "Cyclo-oxygenase inhibitor\*" or Dapsone or Dexibuprofen or Dexketoprofen or Diclofenac or Diflunisal or Dipyrone or Droxicam or Epirizole or Ethenzamide or Etodolac or Etoricoxib or Faislamine or Fenbufen or Fenoprofen or "Flufenamic acid" or Flunoxaprofen or Flurbiprofen or "Glycyrrhizic Acid" or Ibuprofen or Ibuproxam or Indomethacin or Indoprofen or Kebuzone or Ketoprofen or Ketorolac or Licofelone or Lornoxicam or Loxoprofen or Lumiracoxib or "Magnesium salicylate" or "Meclofenamic Acid" or "Mefenamic Acid" or Meloxicam or Mesalamine or Metamizole or "Methyl salicylate" or Mofebutazone or Nabumetone or Naproxen or "Niflumic Acid" or "Nonsteroidal antiinflammator\*" or "Nonsteroidal anti-inflammator\*" or "Non-steroidal antiinflammator\*" or "Non-steroidal anti-inflammator\*" or "Nordihydroguaiaretic Acid" or NSAID\* or osenal or Oxametacin or Oxaprozin or Oxyphenbutazone or Parecoxib or "Pentosan Sulfuric Polyester" or Phenazone or Phenylbutazone or Piroxicam or Pirprofen or Prenazone or Proglumetacin or Rofecoxib or Salicylamide or Salicylate or Sulfasalazine or Sulfinpyrazone or Sulindac or Suprofen or Tenoxicam or "Tiaprofenic acid" or "Tolfenamic acid" or Tolmetin or Valdecoxib)
- 4 TITLE-ABS-KEY("5-ht" or "5-hydroxytryptamine\*" or "5-methoxytryptamine\*" or dimethyltryptamine\* or enteramine\* or hippophaine\* or hydroxytryptamine\* or indolyethylamine\* or meksamine\* or methoxydimethyltryptamine\* or methoxytryptamine\* or methylbufotenin or mexamine\* or Serotonin or triptan\* or tryptamine\*)
- 5 TITLE-ABS-KEY(Bromocriptine\* or Cabergoline\* or "clavine alkaloid\*" or "clavines alkaloid\*" or Dihydroergocornine\* or Dihydroergocristine\* or Dihydroergocryptine\* or Dihydroergotamine\* or Dihydroergotoxine\* or Ergoline\* or "Ergoloid Mesylate\*" or Ergonovine\* or "ergot agent\*" or "ergot alkaloid\*" or "ergot drug\*" or "ergot medication\*" or Ergotamine\* or Ergotamines or "ergotoxine alkaloid\*" or "ergots alkaloid\*" or Lisuride\* or "Lysergic Acid" or "Lysergic Acid Diethylamide\*" or Metergoline\* or Methylergonovine\* or Methysergide\* or Nicergoline\* or Pergolide\*)
- 6 TITLE-ABS-KEY(Acetaminophen or Adenosine or Amantadine or Amitriptyline or analgesic\* or analgetic\* or anbesol or anodyne\* or anpirtoline or antalgic\* or antinociceptive\* or antrafenine or auralgan or axomadol or befiradol or bicifadine or brivaracetam or brivolidide or bromadoline or "Calcitonin Gene-Related Peptide Receptor Antagonist\*" or cannabidivarin or capsaicin or Carbachol or Carbamazepine or cebranopadol or cibinetide or cizolirtine or Clonidine or crobenetine or Cyclazocine or dapansutrile or dasolampanel or davsasaicin or deacetylappaconitine or "Dentin Desensitizing" or "desensitizing agent\*" or "desensitizing drug\*" or "desensitizing

medication\*" or Dexmedetomidine or difelikefalin or Dihydroergotamine or dimiracetam or dizatriphone or doxpicomine or drinidene or Dronabino or Duloxetine or ecopladib or edronocaine or efipladib or elismetrep or "embelate potassium" or enkephalin or epibatidine or equagesic or Ergotamine or ethoheptazine or fadolmidine or fasinumab or "floctafenic acid" or floctafenine or flunixin or "flunixin meglumine" or flupirtine or Flurbiprofen or frakefamide or fulranumab or funapide or Gabapentin or gefapixant or girepladib or "glafenic acid" or Glafenine or "gw 493838" or "gw 842166" or hasamal or ibudilast or Ibuprofen or indantadol or Interleukin or Ketamine or lacosamide or lappaconitine or lenabasum or letimide or lexanopadol or "Magnesium Sulfate" or mavatrep or Medetomidine or Methotrimeprazine or Milnacipran or Mitoxantrone or Nefopam or neurotropin or "Nitrous Oxide" or nuvanil or olodanrigan or olorinab or olvanil or "omega conotoxin" or panidex or "pf 3557156" or "pf 4136309" or "pf 4480682" or "pf 592379" or "pf 738502" or Phenacetin or Pizotyline or pravadoline or Pregabalin or Quinine or ralfinamide or retigabine or ruzadolane or sampirtine or senrebotase or shogaol or strascogesic or tanezumab or tazadolene or tebanicline or tetrodotoxin or tivanisiran or traxoprodil or vedaclidine or vixotrigine or Xylazine)

7 TITLE-ABS-KEY(afloqualone or alcuronium or "atracurium besilate" or azumolene or baclofen or Baclofent or botulinum or branaplam or Carisoprodol or "chandonium iodide" or Chlormezanone or Chlorphenesin or chlorproethazine or Chlorzoxazone or cisatracurium or curare or curaremimetic\* or curariform or curarizing or Dantrolene or decamethonium or "depolarizing neuromuscular" or deutolperisone or diadonium or Diazepam or "dihydro beta erythroidine" or dimethyltubocurarine or doxacurium or duador or eperisone or fazadinium or febarbamate or flumetramide or gallamine or gantacurium or "hexafluronium bromide" or idrocilamide or inaperisone or lanperisone or "mebezonium iodide" or Medazepam or Mephenesin or Meprobamate or metaxalone or Methocarbamol or mivacurium or "Muscle relaxant\*" or "muscle relaxing" or "musculotropic relaxant\*" or "musculotropic relaxing" or myorelaxant or myotonolytic\* or nefopam or nelezaprine or "neuromuscular agent\*" or "neuromuscular blocker\*" or "neuromuscular blocking" or "neuromuscular depolarizing agent\*" or "neuromuscular depolarizing drug\*" or "neuromuscular depolarizing medication\*" or "neuromuscular drug\*" or "neuromuscular medication\*" or "neuromuscular nondepolarizing agent\*" or "neuromuscular nondepolarizing drug\*" or "neuromuscular nondepolarizing medication\*" or "neuromuscular synapse blocking agent\*" or "neuromuscular synapse blocking drug\*" or "neuromuscular synapse blocking medication\*" or "nondepolarizing neuromuscular blocking agent\*" or "nondepolarizing neuromuscular blocking drug\*" or "nondepolarizing neuromuscular blocking medication\*" or norgesic or Orphenadrine or pancuronium or phenprobamate or pipecuronium or promoxolane or pyrocurine or Quinine or "rapacuronium bromide" or rocuronium or silperisone or styramate or suxamethonium or "tiemonium methylsulfate" or tizanidine or Tolperisone or toxiferine or "tubocurarine chloride" or vecuronium or vesamicol or Xylazine or Zoxazolamine)

8 TITLE-ABS-KEY(((drug\* or agent\* or medication\*) W/3 (nausea or vomit\*)) or alizapride or "anti emetic\*" or antiemetic\* or antimetic\* or "anti-metic\*" or antinausea\* or "anti-nausea\*" or antivomit\* or "anti-vomit\*" or Aprepitant or azasetron or batanopride or belidral or bendedtin or benzquinamide or bromopride or buclizine or casopitant or chlorcyclizine or chlorphenethazine or Chlorpromazine or cinnarizine or cisapride or clebopride or Cyclizine or dazopride or debendox or Dexamethasone or

- Diazepam or difenidol or Dimenhydrinate or Diphenhydramine or dixyrazine or "dolasetron mesilate" or Domperidone or Doxylamine or dronabinol or Droperidol or exepanol or ezlopitant or fabesetron or fosaprepitant or fosnetupitant or Granisetron or Haloperidol or hydrodolasetron or icospiramide or indisetron or lerisetron or lintopride or Lorazepam or lurosetron or maropitant or Meclizine or meclizine or Methylprednisolone or Metoclopramide or metopimazine or nabilone or netupitant or norchlorpromazine or Olanzapine or Ondansetron or Palonosetron or pancopride or Prochlorperazine or Promazine or promethazine or ramosetron or renzapride or ricasetron or rolapitant or Scopolamine or sulphuride or telmapitant or tetrahydrocannabinol or Thiethylperazine or transmer or Trifluoperazine or Triflupromazine or trimethobenzamide or Tropisetron or vestipitant or vofopitant or zacopride)
- 9 TITLE-ABS-KEY("1 butyl 3 1 naphthoyl indole" or "11 hydroxydronabinol" or "2 arachidonoylglycerol" or "2 methyl 3 1 naphthoyl 1 propylindole" or "3 1 naphthoyl 1 pentylindole" or "3 2 iodo 5 nitrobenzoyl 1 1 methyl 2 piperidinylmethyl indole" or "3 hydroxy delta9 tetrahydrocannabinol" or "ajulemic acid" or anandamide or bhang or bhangs or cannabi or cannabichromene or cannabidiol or cannabielsoin or cannabigerol or cannabinoid or cannabinol or cannabis or cannador or charas or Cindica or deacetyllevonantradol or dexanabinol or dextronantradol or dronabinol or endocannabinoid or ganja or ganjas or hashish or hashishs or hemp or hemsps or levonantradol or marihuana\* or marijuana\* or methanandamide or "n oleoylethanolamine" or nabilone or nabiximols or nantradol or "noladin ether" or palmidrol or tetrahydrocannabinol or "tetrahydrocannabinolic acid" or virodhamine)
- 10 TITLE-ABS-KEY("alpha feedback\*" or biofeedback\* or "bogus physiological feedback\*" or "brainwave feedback\*" or "eeg feedback\*" or "electroencephalography feedback\*" or "electromyography feedback\*" or "false physiological feedback\*" or myofeedback\* or neurofeedback\* or "psychophysiological feedback\*")
- 11 TITLE-ABS-KEY(((Electric\* or electro or galvano or Transcutaneous\*) W/3 (stimulat\* or stimulus)) or electrostimulation\* or electrostimulus or electrotherap\* or "E-stim" or ESTIM or FES or galvanostimulation\* or galvanostimulus or Neuromodulation or neuromodulatory)
- 12 TITLE-ABS-KEY(CBT or "Cognitive behavioral therap\*" or "Cognitive therap\*")
- 13 TITLE-ABS-KEY(acupressure or acupuncture or "auricular needl\*" or auriculotherapy or "ear needl\*" or electroacupuncture or moxibustion or Shiatsu or "Tui Na")
- 14 TITLE-ABS-KEY(aerobics or anaerobics or bicycling or biking or "endurance training" or exercis\* or "fitness training" or isometrics or "physical exertion" or "physical activit\*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting)
- 15 TITLE-ABS-KEY(drug\* or pharmacotherap\* or medication\* or agent\* or chemotherap\* or intervention\* or manag\* or therap\* or treat\*)
- 16 TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys\*) or (systematic\* W/3 review\*) or guideline\* or (control\* W/3 study) or (control\* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl\* W/1 blind\*) or (doubl\* W/1 mask\*) or (singl\* W/1 blind\*) or (singl\* W/1 mask\*) or (tripl\* W/1 blind\*) or (tripl\* W/1 mask\*) or (trebl\* W/1 blind\*) or (trebl\* W/1 mask\*) or "latin square" or placebo\* or nocebo\* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or



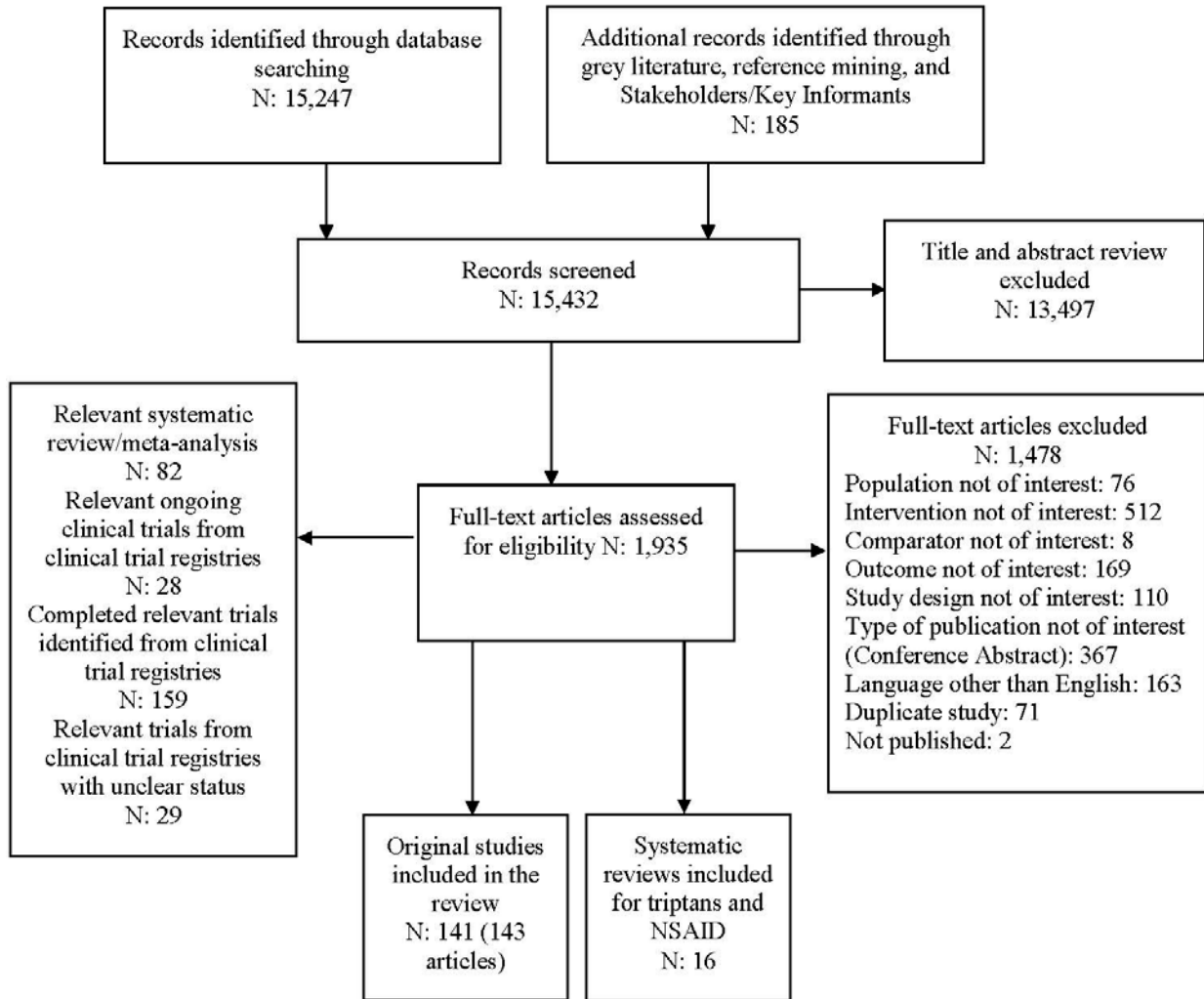
- (intervention\* W/2 study) or (intervention\* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort\* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal\* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv\* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv\* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random\* or control\*) and compar\*)
- 17 1 and (2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15) and 16
- 18 TITLE-ABS-KEY(newborn\* or neonat\* or infant\* or toddler\* or child\* or adolescent\* or paediatric\* or pediatric\* or girl or girls or boy or boys or teen or teens or teenager\* or preschooler\* or "pre-schooler\*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric\* OR "old people" OR "old person\*" OR "older people" OR "older person\*" OR "very old")
- 19 17 and not 18
- 20 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)
- 21 19 and not 20
- 22 INDEX(embase) OR INDEX(medline) OR PMID(0\* OR 1\* OR 2\* OR 3\* OR 4\* OR 5\* OR 6\* OR 7\* OR 8\* OR 9\*)
- 23 21 and not 22

## **Clinicaltrials.gov**

Condition or disease: "migraine"  
 Limited to Adult, Older Adult

# Appendix B. Flow Chart

Figure B-1. Flow chart



## Appendix C. Excluded Studies

1. A clinical trial to study effect Of Yoga As Add On Therapy In Migraine patients.  
[http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2017;03\(008041\)](http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2017;03(008041)). PMID: CN-01879658. [Intervention not of interest]
2. A clinical trial to study the effect of Timolol eyedrops in patients with acute migraine.  
[http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2015;05\(005829\)](http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2015;05(005829)). PMID: CN-01845142. [Population not of interest]
3. A clinical trial to study the effects of two drugs, Palsinuron and Mahavatvidhwans ras in patients suffering from Migraine.  
[http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2012;06\(002739\)](http://www.who.int/trialsearch/Trial2.aspx?TriallID:CTRI.2012;06(002739)). PMID: CN-01848844. [Outcomes not of interest]
4. A Combination Product of Sumatriptan and Naproxen Sodium Versus Single-entity Oral Triptans: An Analysis of Real World Data. 2010 November. PMID: NCT01381523. [Intervention not of interest]
5. A fixed-dose combination of sumatriptan and naproxen for migraine. Medical Letter on Drugs and Therapeutics. 2008 16 Jun;50(1288):45-6. PMID: 355275922. [Type of publication (Conference abstract)]
6. A Randomized Controlled Trial for Comparing Two Diets in the Treatment of migraine.  
<http://www.who.int/trialsearch/Trial2.aspx?TriallID=ChiCTR1900028110>. 2019. PMID: CN-02065507 NEW. [Population not of interest]
7. A randomized controlled trial for modified Wu-Zhu-Yu Decoction integrated with acupuncture at Shaoyang acupoint in the treatment of migraine with cold and stasis obstructing meridian.  
<http://www.who.int/trialsearch/Trial2.aspx?TriallID:ChiCTR1800019502>. 2018. PMID: CN-01950638. [Intervention not of interest]
8. A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group. European Neurology. 1991;31(5):314-22. PMID: 1653139. [Intervention not of interest]
9. A randomized, double-blind, double-dummy, active-placebo controlled, parallel group evaluation of oral naratriptan (2.5mg) compared to oral naproxen sodium (275mg) on migraine-related quality of life. Result summary for S2WA4003. Download.gsk clinicalstudyregister.com/files. 2014. PMID: CN-01383566 NEW. [Intervention not of interest]
10. A randomized, double-blind, double-dummy, active-placebo controlled, parallel group evaluation of oral naratriptan (2.5mg) compared to oral naproxen sodium (275mg) on migraine-related quality of life. Result summary for S2WA4004. Download.gsk clinicalstudyregister.com/files. 2013. PMID: CN-01383567 NEW. [Intervention not of interest]
11. A single dose of rimegepant demonstrates sustained efficacy and low rescue medication use in the acute treatment of migraine: results from 3 phase 3 trials. Headache. 2019;59:180-1. PMID: CN-02003350 NEW. [Duplicate]
12. A Study Investigating the Efficacy and Safety of Sepranolone in Women With Menstrual Migraine.  
<https://clinicaltrials.gov/show/NCT04102995>. 2019. PMID: CN-01992210. [Outcomes not of interest]
13. A Study Investigating the Efficacy and Safety of Sepranolone in Women With Menstrual Migraine.  
<https://clinicaltrials.gov/show/NCT04102995>. 2019. PMID: CN-01992210. [Outcomes not of interest]
14. A Study of Galcanezumab (LY2951742) in Adults With Treatment-Resistant Migraine.  
<https://clinicaltrials.gov/show/nct03559257>. 2018. PMID: CN-01609266 NEW. [Outcomes not of interest]
15. A Study of Rizatriptan for the Treatment of Acute Migraine in Patients on Topiramate for Migraine Prophylaxis.  
<https://clinicaltrials.gov/show/nct00812006>. 2008. PMID: CN-01486067. [Intervention not of interest]
16. A study of the effect of oral LAT8881 on acute migraine headache [Duplicate]
17. A Study to Assess an Auto-injector Being Used to Treat a Migraine Attack. 2007 July. PMID: NCT00510419. [Intervention not of interest]

18. A study to compare oral sumatriptan with oral aspirin plus oral metoclopramide in the acute treatment of migraine. The Oral Sumatriptan and Aspirin plus Metoclopramide Comparative Study Group. *European Neurology*. 1992;32(3):177-84. PMID: 1317294. [Intervention not of interest]
19. A sumatriptan needle-free injection for migraine. *Medical Letter on Drugs and Therapeutics*. 2010 28 Jun;52(1341):50-1. PMID: 359181117. [Type of publication (Conference abstract)]
20. Abbott A. IndoProCaf Effervescent Tablets Effectiveness in Acute Treatment of Migraine and/or Episodic Tension-type Headache and Patients' Satisfaction With the Treatment in Routine Clinical Practice. 2014 June. PMID: NCT02115269. [Population not of interest]
21. Abbott Medical D. Premium Migraine Trial. 2006 January. PMID: NCT00355056. [Outcomes not of interest]
22. Abdolahi M, Jafarieh A, Sarraf P, et al. The Neuromodulatory Effects of omega-3 Fatty Acids and Nano-Curcumin on the COX-2/ iNOS Network in Migraines: A Clinical Trial Study from Gene Expression to Clinical Symptoms. *Endocrine, Metabolic & Immune Disorders Drug Targets*. 2019 Feb 12;12:12. PMID: 30760195. [Outcomes not of interest]
23. Abdolahi M, Sarraf P, Javanbakht MH, et al. A Novel Combination of omega-3 Fatty Acids and Nano-Curcumin Modulates Interleukin-6 Gene Expression and High Sensitivity C-reactive Protein Serum Levels in Patients with Migraine: A Randomized Clinical Trial Study. *CNS & Neurological Disorders Drug Targets*. 2018;17(6):430-8. PMID: 29938621. [Population not of interest]
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29. Afridi SK, Giffin NJ, Kaube H, et al. A randomized controlled trial of intranasal ketamine in migraine with prolonged aura. *Neurology*. 2013 Feb 12;80(7):642-7. PMID: 23365053. [Outcomes not of interest]
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33. Ahmadifard M, Yarahmadi S, Ardalan A, et al. The Efficacy of Topical Basil Essential Oil on Relieving Migraine Headaches: A Randomized Triple-Blind Study. *Complementary Med*. 2020 Mar 10:1-9. PMID: 32155616. [Outcomes not of interest]
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## Appendix D. Characteristics of Included Studies

**Table D-1. Characteristics of included studies**

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Aggarwal, 2020 <sup>1</sup>	Crossover RCT in United States of America, 04/2017 to 02/2018	Outpatient	Timolol	Eye drop, 0.5% solution, once	2 hours	Entire population: 26 Patients aged 41±10.5 years, 96% female
	Crossover RCT in United States of America, 04/2017 to 02/2018	Outpatient	Placebo	Eye drop, once	2 hours	Entire population: 26 Patients aged 41±10.5 years, 96% female
Alemder, 2007 <sup>2</sup>	Crossover RCT in Turkey	ED	Tramadol	IV, 100 mg in 100 ml saline solution, once for 30 minutes	1 day	17 Patients aged 42 ± 11.5 years, 76.5% female, 100% White
	Crossover RCT in Turkey	ED	Placebo	IV, 100 ml saline solution, once for 30 minutes	1 day	17 Patients aged 37.1 ± 9 years, 88.2% female, 100% White
Amiri, 2017 <sup>3</sup>	RCT in Iran	ED	Granisetron	IV, 2 mg, once	4 hours	Entire population: 148 Patients aged 33.5 years, 68.2% female
	RCT in Iran	ED	Metoclopramide	IV, 10 mg, once	4 hours	Entire population: 148 Patients aged 33.5 years, 68.2% female
Aurora, 2011 <sup>4</sup>	RCT in United States of America, 07/2008 to 03/2009	Outpatient	Dihydroergotamine	Inhaled (orally), 0.6 mg emitted dose (1 mg nominal dose, or 0.5 mg systemic) once immediately after attack	2 days	450 Patients aged 40.5 ± 11.3 years, 91.9% female, 8.9% African American, 88.1% White, 1.3% Asian, BMI 28 ± 6.6

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Aurora, 2011 (continued)	RCT in United States of America, 07/2008 to 03/2009	Outpatient	Placebo	Inhaled (orally), once immediately after attack	2 days	453 Patients aged 39.6 ± 11.7 years, 91.2% female, 11.8% African American, 84.4% White, 3.0% Asian, BMI 27.9 ± 6.4
Aurora, 2009 <sup>5</sup>	RCT in United States of America, 07/2006 to 02/2007	Outpatient	Placebo	Inhaled (orally), four times after attack	28 days	18 Patients aged 43.6 ± 9.4 years, 77.8% female, 94.4% White, 5.6% Asian
	RCT in United States of America, 07/2006 to 02/2007	Outpatient	Dihydroergotamine mesylate 0.5 mg	Inhaled (orally), 0.5 mg systemic dose (1 mg nominal dose), twice after attack	28 days	35 Patients aged 41.3 ± 10.9 years, 85.7% female, 5.7% African American, 88.6% White, 5.7% Asian
	RCT in United States of America, 07/2006 to 02/2007	Outpatient	Dihydroergotamine mesylate 1 mg	Inhaled (orally), 1 mg systemic dose (2mg nominal dose), twice after attack	28 days	33 Patients aged 40 ± 10.6 years, 81.8% female, 84.8% White, 6.1% Asian
Avcu, 2017 <sup>6</sup>	RCT in Turkey, 01/2014 to 10/2014	ED	Lidocaine 10%	Intranasal, 10%, once or twice after attack	3 days	81 Patients aged 36 ± 12 years, 69.1% female
	RCT in Turkey, 01/2014 to 10/2014	ED	Placebo	Intranasal, 0.9% saline, once or twice after attack	3 days	81 Patients aged 35 ± 11 years, 85.2% female
Banerjee, 1991 <sup>7</sup>	RCT in United Kingdom	Outpatient	Propranolol	Oral, 40 mg, one to three times after attack	2 days	Entire population: 25 Patients aged 35 ± 11.75 years, 84% female
	RCT in United Kingdom	Outpatient	Placebo	Oral, one to three times after attack	2 days	Entire population: 25 Patients aged 35 ± 11.75 years, 84% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Baratloo, 2017 <sup>8</sup>	Comparative observational study in Iran, 01/2016 to 05/2016	ED	Caffeine citrate	IV, 60 mg in 100ncc 0.9% saline, once for 10 minutes	2 hours	35 Patients aged 30.2 ± 1.5 years, 82.8% female, BMI 23.3 ± 2.7
	Comparative observational study in Iran, 01/2016 to 05/2016	ED	Magnesium sulfate	IV, 2 g in 100 cc 0.9% saline, once for 10 minutes	2 hours	35 Patients aged 36 ± 2.1 years, 54.2% female, BMI 24.1 ± 3.1
Bell, 1990 <sup>9</sup>	RCT in Canada	ED	Chlorpromazine	IV, 12.5 mg, once to three times after attack	1 day	Entire population: 76 Patients, 78.9% female
	RCT in Canada	ED	Dihydroergotamine	IV, 1 mg, once or twice after attack	1 day	Entire population: 76 Patients, 78.9% female
	RCT in Canada	ED	Lidocaine	IV, 50 mg, one to three times after attack	1 day	Entire population: 76 Patients, 78.9% female
Bigal, 2002 <sup>10</sup>	RCT in Brazil, 03/01/1997 to 11/01/1999	Outpatient	Dipyron	IV, 1 g in 10 ml 0.9% saline, once after attack	1 day	74 Patients aged 33.6 years, 69.1% female
	RCT in Brazil, 03/01/1997 to 11/01/1999	Outpatient	Placebo	IV, 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 28.8 years, 68.4% female
Bigal, 2002 <sup>11</sup>	RCT in Brazil, 01/01/1997 to 12/31/1999	ED	Chlorpromazine	IV, 0.1 mg/kg in 10 ml 0.9% saline, once after attack	1 day	68 Patients aged 34.65 years, 74.20% female
	RCT in Brazil, 01/01/1997 to 12/31/1999	ED	Placebo	IV, 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 27.70 years, 68.85% female
Bigal, 2002 <sup>12</sup>	RCT in Brazil, 04/01/1997 to 12/31/1999	Outpatient	Magnesium sulfate	IV, 1 g in 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 29.30 years, 74.80% female
	RCT in Brazil, 04/01/1997 to 12/31/1999	Outpatient	Placebo	IV, 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 27.60 years, 68.40% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Bigal, 2001 <sup>13</sup>	Comparative observational study in Brazil	Outpatient	Dipyrene	IV, 1000 mg (2 ml in 8 ml saline), once after attack	1 hour	149 Patients aged 34.1 years, 70.7% female
	Comparative observational study in Brazil	Outpatient	Placebo	IV, 10 ml saline, once after attack	1 day	60 Patients aged 30.3 ± 8.3 years, 71.7% female
Blanda, 2001 <sup>14</sup>	RCT in United States of America, 07/27/1997 to 11/11/1997	ED	Lidocaine 4%	Intranasal 0.5ml drops, two or four times for unilateral or bilateral pain, respectively	1 day	27 Patients, 85.2% female
	RCT in United States of America, 07/27/1997 to 11/11/1997	ED	Placebo	Intranasal, 0.9% saline, 0.5 ml saline drops, two or four times for unilateral or bilateral pain, respectively	1 day	22 Patients, 86.4% female
Borhani, 2010 <sup>15</sup>	Crossover RCT in Iran, 03/2007 to 03/2008	Outpatient	Menthol-Placebo	Topical on forehead and temporal area, 1 ml of 10% solution of menthol crystals in ethanol, immediately after attack (Initial two attack treated with menthol and the second two attack treated with placebo)	N/A	17 Patients aged 29.8 ± 6.14 years, 76.5% female
	Crossover RCT in Iran, 03/2007 to 03/2008	Outpatient	Placebo-Menthol	Topical on forehead and temporal area, 1 ml of 0.5% ethanol menthol solution, immediately after attack (Initial two attack treated with placebo and the second two attack treated with menthol)	N/A	18 Patients aged 29.5 ± 6.4 years, 83.3% female
Boureau, 1994 <sup>16</sup>	Crossover RCT in France	Outpatient	Acetaminophen 400 mg plus codeine 25 mg	Oral, 400 mg acetaminophen and 25 mg codeine once after attack	2 hours	Entire population: 494 Patients aged 40.1 ± 11.6 years, 76.90% female
	Crossover RCT in France	Outpatient	Placebo	Oral, once after attack	2 hours	Entire population: 494 Patients aged 40.1 ± 11.6 years, 76.90% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Brandes, 2019 <sup>17</sup>	RCT in United States of America, United Kingdom, and Germany, 10/7/2015 to 3/6/2018	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once or twice after attack	365 days	1014 Patients aged 42.7 ± 12.3 years, 85.4% female, 18.8% African American, 77.5% White, 0.7% Asian, BMI 31.2 ± 8.2
	RCT in United States of America, United Kingdom, and Germany, 10/7/2015 to 3/6/2018	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once or twice after attack	365 days	1102 Patients aged 43.8 ± 12.5 years, 85.3% female, 16.6% African American, 79.3% White, 0.6% Asian, BMI 31.0 ± 8.2
Callaham, 1986 <sup>18</sup>	RCT in United States of America, 06/1982 to 06/1984	ED	Dihydroergotamine	IV, 0.75 mg, once after attack	2 days	19 Patients
	RCT in United States of America, 06/1982 to 06/1984	ED	Placebo	IV, once after attack	2 days	15 Patients
Cameron, 1995 <sup>19</sup>	RCT in Canada, 1990 to 1992	ED	Chlorpromazine	IV, 0.1 mg/kg, once (up to three times if needed during the first hour)	2 days	47 Patients aged 32.60 ± 9.5 years, 80.90% female
	RCT in Canada, 1990 to 1992	ED	Metoclopramide	IV, 0.1 mg/kg, once (up to three times if needed during the first hour)	2 days	44 Patients aged 31.60 ± 8.75 years, 79.50% female
Carleton, 1998 <sup>20</sup>	RCT in the United States of America, 11/1991 to 08/1992	ED	Dihydroergotamine mesylate plus Hydroxyzine hydrochloride	IM, dihydroergotamine mesylate, 1 mg, once (second dose after 1 hour if necessary), Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once (second dose of 0.35 mg/kg after 1 hour if necessary)	1 day after discharge	85 Patients aged 32.52 ± 8.82 years, 82.40% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Carleton, 1998 (continued)	RCT in the United States of America, 11/1991 to 08/1992	ED	Meperidine plus Hydroxyzine hydrochloride	IM meperidine, 1.5 mg/kg, once (second dose of 0.75 mg/kg after 1 hour if necessary), Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once (second dose of 0.35 mg/kg after 1 hour if necessary)	1 day after discharge	85 Patients aged 32.36 ± 8.78 years, 82.40% female
Cete, 2005 <sup>21</sup>	RCT in Turkey	ED	Metoclopramide plus normal Saline	IV, 10 mg in 100 ml normal saline, once for 10 minutes	1 day after discharge	37 Patients aged 40 ± 13 years, 89% female
	RCT in Turkey	ED	Magnesium sulfate plus normal saline	IV, 2 g in 100 ml normal saline, once for 10 minutes	1 day after discharge	36 Patients aged 40 ± 12 years, 75% female
	RCT in Turkey	ED	Placebo	IV, 100 mL Normal saline once for 10 minutes	1 day after discharge	40 Patients aged 40 ± 11 years, 88% female
Chappell, 1994 <sup>22</sup>	Crossover RCT in the United States of America	ED	Zatosepron to placebo	IV, 13 mg or 0.19 mg/kg, once for 30 minutes	1.5 hours	9 Patients aged 36.3 ± 2.6 years, 89% female, 78% White, 22% African American
	Crossover RCT in the United States of America	ED	Placebo to zatosepron	IV, 13 mg or 0.19 mg/kg, once for 30 minutes	1.5 hours	10 Patients aged 42.9 ± 6.1 years, 90% female, 100% White
Chou, 2019 <sup>23</sup>	RCT in the United States of America, 02/01/2016 to 03/31/2017	ED	Verum external trigeminal nerve stimulation	Transcutaneously, 1.284 C (total maximum dose), high frequency pulse of 100 Hz with pulse width of 250 µs for 1 hour	1 day	52 Patients aged 39.71 ± 13.62 years, 83% female
	RCT in the United States of America, 02/01/2016 to 03/31/2017	ED	Sham external trigeminal nerve stimulation	Transcutaneously, low frequency pulse of 3 Hz with pulse width of 250 µs for 1 hour	1 day	54 Patients aged 40.09 ± 12.65 years, 91% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Connor, 2009 <sup>24</sup>	RCT in the United States of America, Europe and Latin America, 03/2007 to 11/2007	Outpatient	Telcagepant 50 mg	Oral, 50 mg, once (optional second dose of the initial treatment)	7 days	244 Patients aged 41.4 ± 11.3 years, 88.1% female, 83.6% White
	RCT in the United States of America, Europe and Latin America, 03/2007 to 11/2007	Outpatient	Telcagepant 150 mg	Oral, 150 mg, once (optional second dose of the initial treatment or placebo)	7 days	485 Patients aged 41.6 ± 11 years, 86.4% female, 84% White
	RCT in the United States of America, Europe and Latin America, 03/2007 to 11/2007	Outpatient	Telcagepant 300 mg	Oral, 300 mg, once (optional second dose of the initial treatment or placebo)	7 days	484 Patients aged 41.8 ± 11.6 years, 86.3% female, 81.4% White
	RCT in the United States of America, Europe and Latin America, 03/2007 to 11/2007	Outpatient	Placebo	Oral, once (optional second dose of the initial treatment)	7 days	490 Patients aged 41.9 ± 11.9 years, 87.1% female, 83% White
Coppola, 1995 <sup>25</sup>	RCT in the United States of America, 11/1991 to 06/1993	ED	Metoclopramide hydrochloride	IV, 10 mg in 2 mL, once for 2 minutes	2 days after discharge	24 Patients

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Coppola, 1995 (continued)	RCT in the United States of America, 11/1991 to 06/1993	ED	Prochlorperazine	IV, 10 mg in 2 mL, once for 2 minutes	2 days after discharge	22 Patients
	RCT in the United States of America, 11/1991 to 06/1993	ED	Placebo	IV, 2 mL , normal saline, once for 2 minutes	2 days after discharge	24 Patients
Corbo, 2001 <sup>26</sup>	RCT in the United States of America	ED	Metoclopramide plus magnesium sulfate	IV, Metoclopramide: 20 mg, once for 2 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain, Magnesium sulfate: 2 g in a 10% normal saline solution (a total solution of 50 ml), once for 10 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain	1 day	21 Patients aged 39 ± 12 years, 95% female
	RCT in the United States of America	ED	Metoclopramide plus placebo	IV, Metoclopramide: 20 mg, once for 2 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain, placebo: 50 ml normal saline, once for 10 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain	1 day	23 Patients aged 37 ± 8 years, 96% female
Croop, 2019 <sup>27</sup>	RCT in the United States of America, 02/27/2018 to 08/28/2018	Outpatient	Rimegepant	Sublingual, 75 mg, once	7-9 days	732 Patients aged 40.3 ± 12.1 years, 85% female, 74% White, 21% African American, 1% Asian, 1% American Indian or Alaska Native, 2% Native Hawaiian or other Pacific Islander , 1% Multiple, BMI 31.1 ± 8.2



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Croop, 2019 (continued)		Outpatient	Placebo	Sublingual, once	7-9 days	734 Patients aged 40 ± 11.9 years, 85% female, 76% White, 18% African American, 3% Asian, <1% American Indian or Alaska Native, 1% Native Hawaiian or other Pacific Islander , 1% Multiple, BMI 30.6 ± 8
Dahlöf, 2009 <sup>28</sup>	RCT in Australia, Belgium, Denmark, France, Germany, Holland, Spain, South Africa, Switzerland, Sweden, the United Kingdom and the United States of America, 07/1998 to 12/1998	Outpatient	Placebo	Oral, once	7 days	166 Patients aged 40.4 ± 9.4 years, 79.1% female, 97.8% White, 0.8% African American, 0.8% Asian

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Dahlöf, 2009 (continued)	RCT in Australia, Belgium, Denmark, France, Germany, Holland, Spain, South Africa, Switzerland, Sweden, the United Kingdom and the United States of America, 07/1998 to 12/1998	Outpatient	Tonabersat 20 mg	Oral, 20 mg, once	7 days	168 Patients aged 39.6 ± 10.2 years, 85.8% female, 97% White, 2.2% African American, 0.8% Asian
	RCT in Australia, Belgium, Denmark, France, Germany, Holland, Spain, South Africa, Switzerland, Sweden, the United Kingdom and the United States of America, 07/1998 to 12/1998	Outpatient	Tonabersat 40 mg	Oral, 40 mg, once	7 days	166 Patients aged 38.8 ± 10.9 years, 83.9% female, 99.3% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Demirkaya, 2001 <sup>29</sup>	Crossover RCT in Turkey	Outpatient	Magnesium sulfate	IV, 1 g, once for 15 minutes	1 day	Entire population: 15 Patients (Magnesium sulfate), 15 Patients (Placebo), age 35 ± 8.9 years
	Crossover RCT in Turkey	Outpatient	Placebo	IV, 10 mL, 0.9% saline, once, once. After 30 minutes IV, 1 g of Magnesium sulfate over 15 minutes for those with persistent complaints of pain, nausea, and vomiting	1 day	Entire population: 15 Patients (Magnesium sulfate), 15 Patients (Placebo), age 35 ± 8.9 years
Derosier, 2010 <sup>30</sup>	Crossover RCT in the United States of America, 12/2007 to 08/2009	Outpatient	Butalbital, acetaminophen, caffeine	Oral, butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg, once	2 days	Entire population: 392 Patients (Butalbital, Acetaminophen, Caffeine), 405 Patients (Placebo), age 42.6 ± 7.8 years, 88% female, 83% White, 14% African American, BMI 27.3 ± 7
	Crossover RCT in the United States of America, 12/2007 to 08/2009	Outpatient	Placebo	Oral, once	2 days	Entire population: 392 Patients (Butalbital, Acetaminophen, Caffeine), 405 Patients (Placebo), age 42.6 ± 7.8 years, 88% female, 83% White, 14% African American, BMI 27.3 ± 7
Dexter, 1985 <sup>31</sup>	RCT in the United Kingdom	Outpatient	Paracetamol plus metoclopramide	Oral, 2 tablets, paracetamol 500 mg, metoclopramide 5 mg, once (up to three times)	112 days	22 Patients aged 32 years, 77.27% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Dexter, 1985 (continued)	RCT in the United Kingdom	Outpatient	Placebo	Oral, once (up to three times)	112 days	27 Patients aged 33 years, 59.26% female
Diamond, 2000 <sup>32</sup>	RCT in the United States of America	Outpatient	Civamide 20µg	Intranasal, 20 µg, once	7 days	Entire population: 27 Patients aged 36.5 years, 70.6% female
	RCT in the United States of America	Outpatient	Civamide 150µg	Intranasal, 150 µg, once	7 days	Entire population: 27 Patients aged 36.5 years, 70.6% female
Diamond, 1976 <sup>33</sup>	Crossover RCT in the United States of America	Outpatient	Isometheptene mucate, acetaminophen, and dichloralphenazone	Oral, isometheptene mucate 65 mg, acetaminophen 325 mg, and dichloralphenazone 100 mg, twice (up to five times)	14-60 days	Entire population: 168 Patients aged 49 ± 9.75 years, 71.4% female
	Crossover RCT in the United States of America	Outpatient	Acetaminophen	Oral, 325 mg, twice (up to five times)	14-60 days	Entire population: 168 Patients aged 49 ± 9.75 years, 71.4% female
	Crossover RCT in the United States of America	Outpatient	Placebo	Oral, corn starch and talc, twice (up to five times)	14-60 days	Entire population: 168 Patients aged 49 ± 9.75 years, 71.4% female
Diener, 2011 <sup>34</sup>	RCT, International 08/2008 to 05/2009	Outpatient	BI 44370 TA 50 mg (CGRP antagonist)	Oral, 50 mg, once	3-7 days	79 Patients aged 42.8 ± 11.7 years, 84.4% female, 85.9% White
	RCT, International 08/2008 to 05/2009	Outpatient	BI 44370 TA 200 mg (CGRP antagonist)	Oral, 200 mg, once	3-7 days	85 Patients aged 41.2 ± 9.7 years, 81.5% female, 86.2% White
	RCT, International 08/2008 to 05/2009	Outpatient	BI 44370 TA 400 mg (CGRP antagonist)	Oral, 400 mg, once	3-7 days	84 Patients aged 41.1 ± 10 years, 75.3% female, 86.3% White
	RCT, International 08/2008 to 05/2009	Outpatient	Placebo	Oral, once	3-7 days	84 Patients aged 38.2 ± 10.3 years, 87.1% female, 87.1% White
Diener, 2003 <sup>35</sup>	RCT, international	Outpatient	Placebo	Oral, once	2 days	37 Patients aged 38 years, 83.8% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Diener, 2003 (continued)	RCT, international	Outpatient	Dapitant 1 mg	Oral, 1 mg, once	2 days	38 Patients aged 39 years, 89.5% female
	RCT, international	Outpatient	Dapitant 5 mg	Oral, 5 mg, once	2 days	33 Patients aged 40 years, 93.9% female
	RCT, international	Outpatient	Dapitant 20 mg	Oral, 20 mg, once	2 days	31 Patients aged 41 years, 83.9% female
Diener, 2002 <sup>36</sup>	RCT in Australia, Denmark, Finland, France, Germany, Netherlands, Norway, Spain, Sweden, UK, London, Israel, South africa, Poland	Outpatient	Caffeine plus ergotamine	Oral, 1 mg ergotamine tartrate with 100 mg caffeine, once or twice	7-14 days	203 Patients aged 42 ± 11 years, 86% female
	RCT in Australia, Denmark, Finland, France, Germany, Netherlands, Norway, Spain, Sweden, UK, London, Israel, South africa, Poland	Outpatient	Placebo	Oral, once or twice	7-14 days	106 Patients aged 40 ± 10 years, 86% female
Dodick, 2019 <sup>37</sup>	RCT in United States of America, 07/22/2016 to 12/14/2017	Outpatient	Ubrogepant 100 mg	Oral, 100 mg (2 tablets of Ubrogepant 50 mg), once. An optional second dose of either 2 tablets of placebo, 2 tablet of 50 mg Ubrogepant was allowed.	4 weeks	557 Patients aged 40.6±12 years, 86.2% female, 80.8% White, BMI 30.4±8

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Dodick, 2019 (continued)	RCT in United States of America, 07/22/2016 to 12/14/2017	Outpatient	Ubrogepant 50 mg	Oral, 50 mg (one tablet Ubrogepant 50 mg and one tablet placebo), once. An optional second dose of either 2 tablets of placebo, or one tablet of 50 mg Ubrogepant and one tablet of placebo was allowed.	4 weeks	556 Patients aged 40.1±11.7 years, 89.7% female, 82.2% White, BMI 30.2±8.1
	RCT in United States of America, 07/22/2016 to 12/14/2017	Outpatient	Placebo	Oral, 2 tablets, once. An optional second dose of 2 tablets of placebo was allowed.	4 weeks	559 Patients aged 40.9±11.7 years, 88.7% female, 84.5% White, BMI 30±7.4
Dogan, 2019 <sup>38</sup>	RCT in Turkey, 12/2014 to 01/2017	ED	Metoclopramide	IV, 10 mg in 100 mL normal saline solution, once for 10 minutes	1-3 days	74 Patients aged 35 ± 13.3 years, 67.6% female
	RCT in Turkey, 12/2014 to 01/2017	ED	Placebo	IV, 100 mL normal saline, once for 10 minutes	1-3 days	74 Patients aged 33 ± 13.3 years, 62.2% female
Donaldson, 2008 <sup>39</sup>	RCT in United States of America, 11/2004 to 11/2005	ED	Placebo	IV, 24 mg (5ml) once	30 days	53 Patients aged 35.17 years, 73.6% female
	RCT in United States of America, 11/2004 to 11/2005	ED	Dexamethasone	IV, 24 mg (5ml) once	30 days	62 Patients aged 37.48 years, 87.1% female
Etchison, 2018 <sup>40</sup>	RCT in United States of America, 03/2016 to 03/2017	ED	Ketamine	IV, 0.2 mg/kg in 30 ml aliquots, once for 1 minute	1 hour	16 Patients aged 38.5 ± 13.75 years, 81% female, 19% African American, 62% White, 19% other

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Etchison, 2018 (continued)	RCT in United States of America, 03/2016 to 03/2017	ED	Placebo	IV, 0.2 mg/kg saline in 30 ml aliquots, once for 1 minute	1 hour	18 Patients aged 30.5 ± 8.3 years, 72% female, 11% African American, 72% White, 17% other
Farahmand, 2018 <sup>41</sup>	RCT in Iran, 03/2015 to 05/2016	Outpatient	Verum acupuncture	Skin, sterile metallic needles with a width of 0.25 mm and length of 13 mm, which enter certain points in the ear's skin	1 day	Entire population: 30 Patients (Acupuncture), 30 Patients (Acupuncture placebo) aged 31.4 ± 7.6 years, 83.3% female
	RCT in Iran, 03/2015 to 05/2016	Outpatient	Sham acupuncture	Skin, sterile metallic needles with a width of 0.25 mm and length of 13 mm, inserted into inappropriate acupoints (stomach, and spleen), once	1 day	Entire population: 30 Patients (Acupuncture), 30 Patients (Acupuncture placebo) aged 31.4 ± 7.6 years, 83.3% female
Farkkila, 2012 <sup>42</sup>	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Placebo	Oral, once	14 days	103 Patients aged 40.5 ± 10.3 years, 87% female, 100% White
	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Lasmiditan 50 mg	Oral, 50 mg, once	14 days	106 Patients aged 40.4 ± 12.5 years, 84% female, 99% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Farkkila, 2012 (continued)	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once	14 days	104 Patients aged 42 ± 10.6 years, 83% female, 99% White
	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once	14 days	100 Patients aged 39.5 ± 10.3 years, 92% female, 99% White
	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Lasmiditan 400 mg	Oral, 400 mg, once	14 days	99 Patients aged 38.7 ± 10.3 years, 93% female, 99% White
Fernando, 2019 <sup>43</sup>	RCT in United States of America, 11/2016 to 12/2017	ED	Buccally absorbed prochlorperazine (BAP)	Buccally (under the upper lip), 6 mg of BAP + 2.25 mL IV normal saline solution	1-2 days	40 Patients aged 38.8 ± 12.3 years, 87% female
	RCT in United States of America, 11/2016 to 12/2017	ED	Intravenous prochlorperazine (IVP)	IV, 10 mg of IVP in a volume of 2.25 mL + buccal saccharine pills	1-2 days	40 Patients aged 37.3 ± 12.2 years, 65% female
Ferrari, 2010 <sup>44</sup>	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Placebo	IV, 60 mL infusion, once for 20 minutes	1 day	42 Patients aged 40.3 ± 7.3 years, 90.5% female, 100% White



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ferrari, 2010 (continued)	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 2.5 mg	IV, 2.5 mg in 60 mL infusion, once for 20 minutes	1 day	4 Patients aged 46.8 ± 7.3 years, 75% female, 100% White
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 5 mg	IV, 5 mg in 60 mL infusion, once for 20 minutes	1 day	12 Patients aged 39.2 ± 7.3 years, 83.3% female, 91.7% White, 8.3% Non-Caucasian
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 10 mg	IV, 10 mg in 60 mL infusion, once for 20 minutes	1 day	24 Patients aged 34.2 ± 7.3 years, 87.5% female, 83.3% White, 16.7% Non-Caucasian
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 20 mg	IV, 20 mg in 60 mL infusion, once for 20 minutes	1 day	28 Patients aged 38.9 ± 7.3 years, 85.7% female, 100% White
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 30 mg	IV, 30 mg in 60 mL infusion, once for 20 minutes	1 day	16 Patients aged 40.3 ± 7.3 years, 87.5% female, 100% white
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 45 mg	IV, 45 mg in 60 mL infusion, once for 20 minutes	1 day	4 Patients aged 40.8 ± 7.3 years, 75% female, 100% White
	RCT in The Netherlands, Finland, Germany, 08/2006 to 07/2007	Outpatient	Lasmiditan 45 mg	IV, 45 mg in 60 mL infusion, once for 20 minutes	1 day	4 Patients aged 40.8 ± 7.3 years, 75% female, 100% White

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Foroughipour, 2013 <sup>45</sup>	RCT in Iran, during 2011	ED	Valproate	IV, 900 mg (diluted in 150 cc normal saline) (Patients at a minimum weight of 90 kg received 1200 mg), once for 10 minutes	3 days	20 Patients aged 33.9 ± 13.34 years, 89% female
	RCT in Iran, during 2011	ED	Dexamethasone	IV, 16 mg (diluted in 150 cc normal saline) (Patients at a minimum weight of 90 kg received 20 mg), once for 10 minutes	3 days	20 Patients aged 32.5 ± 11.12 years, 92% female
Freitag, 1993 <sup>46</sup>	RCT in United States of America	ED	Transnasal butorphanol	Transnasal, 1 mg, twice	6 hours	32 Patients aged 39.4 ± 9.25 years, 97% White, 3% African American
	RCT in United States of America	ED	Methadone	IM, 10 mg, once	6 hours	32 Patients aged 38.4 ± 9.5 years, 91% White, 6% African American
	RCT in United States of America	ED	Placebo	Intranasal spray, twice, and IM, once	6 hours	32 Patients aged 37.2 ± 11.75 years, 97% White, 3% African American
Friedman, 2007 <sup>47</sup>	RCT in United States of America, 07/2005 to 07/2006	ED	Dexamethasone sodium phosphate	IV, 10 mg	1 day	106 Patients aged 36 ± 10 years, 82% female, 27% African American, 6% White, 69% Latino
	RCT in United States of America, 07/2005 to 07/2006	ED	Placebo	IV	1 day	99 Patients aged 37 ± 11 years, 88% female, 22% African American, 2% White, 70% Latino
Friedman, 1989 <sup>48</sup>	RCT in United States of America	Outpatient	Cafergot P-B	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	Entire population: 254 Patients aged 34.4 years, 87.4% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Friedman, 1989 (continued)	RCT in United States of America	Outpatient	Cafergot	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	Entire population: 254 Patients aged 34.4 years , 87.4% female
	RCT in United States of America	Outpatient	Placebo	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	Entire population: 254 Patients aged 34.4 years , 87.4% female
Friedman, 2008 <sup>49</sup>	RCT in United States of America, 08/2006 to 03/2007	ED	Prochlorperazine	IV, 10 mg, once for 15 minutes	1 day	39 Patients aged 34 ± 10 years, 85% female, 36% African American, 51% White, 3% Asian, 62% Hispanic/Latino, 10% other
	RCT in United States of America, 08/2006 to 03/2007	ED	Metoclopramide	IV, 20 mg, once for 15 minutes	1 day	38 Patients aged 38 ± 12 years, 95% female, 42% African American, 53% White, 68% Hispanic/Latino, 5% other
Friedman, 2011 <sup>50</sup>	RCT in United States of America, 05/2008 to 02/2010	ED	Metoclopramide 10 mg plus diphenhydramine	IV, 10 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	113 Patients aged 39 ± 11 years, 83% female, 28% African American, 18% White, 70% Hispanic, 0.9% previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Friedman, 2011 (continued)	RCT in United States of America, 05/2008 to 02/2010	ED	Metoclopramide 20 mg plus diphenhydramine	IV, 20 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	118 Patients aged 37 ± 10 years, 87% female, 28% African American, 20% White, 1% Asian, 70% Hispanic, 3.4% previous opioid use
	RCT in United States of America, 05/2008 to 02/2010	ED	Metoclopramide 40 mg plus diphenhydramine	IV, 40 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	118 Patients aged 38 ± 12 years, 82% female, 20% African American, 19% White, 1% Asian, 76% Hispanic, 3.4% previous opioid use
Friedman, 2016 <sup>51</sup>	RCT in United States of America, 04/2013 to 12/2015	ED	Diphenhydramine plus metoclopramide	IV, diphenhydramine 50 mg plus metoclopramide 10 mg, once	2 days	104 Patients aged 41 ± 11 years, 85% female
	RCT in United States of America, 04/2013 to 12/2015	ED	Placebo plus metoclopramide	IV, placebo (saline solution) plus metoclopramide 10 mg, once	2 days	104 Patients aged 36 ± 10 years, 89% female
Friedman, 2018 <sup>52</sup>	RCT in United States of America, 08/2015 to 01/2018	ED	Sham injection	Intradermally, 0.5 mL bupivacaine 0.5% bilaterally (1 mL total), once	2 days	15 Patients aged 40 ± 12 years, 80% female
	RCT in United States of America, 08/2015 to 01/2018	ED	Greater occipital nerve block	Intradermally, 3 mL bupivacaine 0.5% bilaterally (6 mL total), once	2 days	13 Patients aged 35 ± 10 years, 92% female
Friedman, 2017 <sup>53</sup>	RCT in United States of America, 03/2015 to 06/2016	ED	Prochlorperazine plus diphenhydramine	IV, 10 mg prochlorperazine plus 25 mg diphenhydramine, once for 5 minutes (additional optional dose after one hour)	90 days	63 Patients aged 32 ± 9 years, 79% female,

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Friedman, 2017 (continued)	RCT in United States of America, 03/2015 to 06/2016	ED	Hydromorphone plus normal saline placebo	IV, 1 mg hydromorphone, once for 5 minutes (additional optional dose after one hour)	90 days	64 Patients aged 35 ± 11 years,, 88% female,
Fuglsang, 2018 <sup>54</sup>	Crossover RCT in Denmark, 11/2016 to 10/2017	Outpatient	Active partial rebreathing device	Oral, twice for 40 minutes (20 minutes at the onset of the aura followed by 20 minutes after 40 minutes)	1 day	Entire population: 11 Patients aged 35.5 ± 12 years,, 72.7% female, 100% Caucasian
	Crossover RCT in Denmark, 11/2016 to 10/2017	Outpatient	Sham partial rebreathing device	Oral, twice for 40 minutes (20 minutes at the onset of the aura followed by 20 minutes after 40 minutes)	1 day	Entire population: 11 Patients aged 35.5 ± 12 years,, 72.7% female, 100% Caucasian
Gaffigan, 2015 <sup>55</sup>	RCT in United States of America, 06/2013 to 02/2014	ED	Diphenhydramine plus haloperidol	IV, diphenhydramine 25 mg plus haloperidol 5 mg, once for 2 minutes	14 days	31 Patients aged 29 ± 8 years,, 87% female
	RCT in United States of America, 06/2013 to 02/2014	ED	Diphenhydramine plus metoclopramide	IV, diphenhydramine 25 mg plus metoclopramide 10 mg, once for 2 minutes	14 days	33 Patients aged 29 ± 8 years,, 76% female
Gallagher, 1996 <sup>56</sup>	RCT in United States of America, 04/1993 to 06/1994	Outpatient	Dihydroergotamine mesylate 3 mg	Intranasal, 3 mg, 3 times in each nostril	1 day	Entire population: 348 Patients aged 40 ± 7.8 years
	RCT in United States of America, 04/1993 to 06/1994	Outpatient	Dihydroergotamine mesylate 2 mg	Intranasal, 2 mg, 3 times in each nostril	1 day	Entire population: 348 Patients aged 40 ± 7.8 years
	RCT in United States of America, 04/1993 to 06/1994	Outpatient	Placebo	Intranasal, 3 times in each nostril	1 day	Entire population: 348 Patients aged 40 ± 7.8 years

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Gerhardt, 2011 <sup>57</sup>	RCT in United States of America, 01/2002 to 04/2003	Outpatient	Secobarbital	Oral, 100 mg, once or twice	3 days	14 Patients aged 45 ± 1.25 years, 94% female
	RCT in United States of America, 01/2002 to 04/2003	Outpatient	Placebo	Oral, once or twice	3 days	16 Patients aged 44 ± 3.25 years, 100% female
Goadsby, 2019 <sup>58</sup>	RCT in United States of America, UK and Germany, 05/19/2016 to 06/29/2017	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once within 4 hours of onset of migraine attack	7 days	721 Patients aged 41.8 ± 12.4 years, 82.6% female, 80.4% White, BMI 30.1 ± 8.2
	RCT in United States of America, UK and Germany, 05/19/2016 to 06/29/2017	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once within 4 hours of onset of migraine attack	7 days	721 Patients aged 43.4 ± 12.6 years, 84.9% female, 80.2% White, BMI 30.1 ± 8.3
	RCT in United States of America, UK and Germany, 05/19/2016 to 06/29/2017	Outpatient	Lasmiditan 50 mg	Oral, 50 mg, once within 4 hours of onset of migraine attack	7 days	716 Patients aged 42.8 ± 13.2 years, 84.7% female, 80.1% White, BMI 29.7 ± 7.6
	RCT in United States of America, UK and Germany, 05/19/2016 to 06/29/2017	Outpatient	Placebo	Oral, Placebo, once within 4 hours of onset of migraine attack	7 days	711 Patients aged 42.6 ± 12.9 years, 84.5% female, 80% White, BMI 30.4 ± 11.1

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Goldstein, 1997 <sup>59</sup>	Crossover RCT in United States of America	Outpatient	Lanepitant 240 mg	Oral, 240 mg, once	4 days	Entire population: 53 Patients aged 18-65 years, 84.9% female
	Crossover RCT in United States of America	Outpatient	Lanepitant 80 mg	Oral, 80 mg, once	4 days	Entire population: 53 Patients aged 18-65 years, 84.9% female
	Crossover RCT in United States of America	Outpatient	Lanepitant 30 mg	Oral, 30 mg, once	4 days	Entire population: 53 Patients aged 18-65 years, 84.9% female
	Crossover RCT in United States of America	Outpatient	Placebo	Oral, once	4 days	Entire population: 53 Patients aged 18-65 years, 84.9% female
Gomez-Mancilla, 2001 <sup>60</sup>	RCT in United States of America	Outpatient	PNU-142633 (selective 5-HT1D agonist)	Oral, 50 mg, once	0.5 day	34 Patients aged 35.6 ± 8.25 years, 62% female, 78% White
	RCT in United States of America	Outpatient	Placebo	Oral, once	0.5 day	35 Patients aged 40.5 ± 9.5 years, 83% female, 88% White
Gomez-Mancilla, 2014 <sup>61</sup>	Crossover RCT in Germany, Spain and the United States of America, 05/2009 to 08/2010	Outpatient	Selurampanel	Oral, 250 mg, once within 4 hours of onset of migraine attack	1 day	25 Patients aged 37.2 ± 9.25 years, 80% female, 96% White, 4% Hispanic, BMI 24.9 ± 3.6
	Crossover RCT in Germany, Spain and the United States of America, 05/2009 to 08/2010	Outpatient	Placebo	Oral, Placebo, once within 4 hours of onset of migraine attack	1 day	25 Patients aged 41.4 ± 10.99 years, 88% female, 84% White, 8% African American, 4% Pacific islander, 4% Other, BMI 23.7 ± 3.7

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Griffith, 2008 <sup>62</sup>	Comparative observational in United States of America, 10/2002 to 03/2003	ED	Hydromorphone	IV: 48 Patients, IM: 3 Patients, 0.5 mg: 15 Patients, 1.0 mg: 26 Patients, 2.0 mg: 7 Patients, and 4.0 mg: 3 Patients, once	NR	51 Patients aged 36.5 ± 10.3 years, 86.3% female, 80.6% White (Hydromorphone). Entire population: 25.3% African American, 7.8% Hispanic, Asian, and others
	Comparative observational in United States of America, 10/2002 to 03/2003	ED	Metoclopramide	IV, 10 mg: 37 Patients, 20 mg: 58 Patients, once	NR	95 Patients aged 35 ± 9.2 years, 85.3% female, 67.1% White (Metoclopramide). Entire population: 25.3% African American, 7.8% Hispanic, Asian, and others
	Comparative observational in United States of America, 10/2002 to 03/2003	ED	Others (Promethazine, Ondansetron, Sumatriptan, Ibuprofen, Ketorolac, Hydrocodone/acetaminophen, Acetaminophen, Prochlorperazine, Meperidine, Acetaminophen/butalbital/caffeine, Magnesium)	IV, IM, Oral, once	NR	54 Patients aged 36.5 ± 11.7 years, 88.9% female, 54.8% white (All Others). Entire population: 25.3% African American, 7.8% Hispanic, Asian, and others
Hakkarainen, 1982 <sup>63</sup>	Crossover RCT, in Finland	Outpatient	Ergotamine 1 mg	Suppository, once after attack	NR	Entire population: 24 Patients aged 36.3 ± 9 years, 100% female
	Crossover RCT, in Finland	Outpatient	Metoclopramide 20 mg	Suppository, once after attack	NR	Entire population: 24 Patients aged 36.3 ± 9 years, 100% female
	Crossover RCT, in Finland	Outpatient	Ergotamine 1 mg plus metoclopramide 20 mg	Suppository, once after attack	NR	Entire population: 24 Patients aged 36.3 ± 9 years, 100% female



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Hakkarainen, 1982 (continued)	Crossover RCT, in Finland	Outpatient	Ergotamine 2 mg plus metoclopramide 20 mg	Suppository, once after attack	NR	Entire population: 24 Patients aged 36.3 ± 9 years, 100% female
Hewitt, 2011 <sup>64</sup>	RCT in Australia, Czech Republic, Finland, France, Germany, Hungary, India, New Zealand, Norway, Peru, Poland, South Africa, and the United States of America, 12/2008 to 08/2009	Outpatient	Telcagepant plus acetaminophen	Oral, 280 mg telcagepant plus 1000 mg acetaminophen, once, within 4 hours of the attack	2-5 days	171 Patients aged 42.3 ± 12.7 years, 88.7% female, 3.8% previous opioid use
	RCT in Australia, Czech Republic, Finland, France, Germany, Hungary, India, New Zealand, Norway, Peru, Poland, South Africa, and the United States of America, 12/2008 to 08/2009	Outpatient	Telcagepant	Oral, 280 mg, once, within 4 hours of the attack	2-5 days	170 Patients aged 39.3 ± 11.6 years, 86.2% female, 7.3% previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Hewitt, 2011 (continued)	RCT in Australia, Czech Republic, Finland, France, Germany, Hungary, India, New Zealand, Norway, Peru, Poland, South Africa, and the United States of America, 12/2008 to 08/2009	Outpatient	Placebo	Oral, once, within 4 hours of the attack	2-5 days	171 Patients aged 41.9 ± 12 years, 90.5% female, 2.8% previous opioid use
Hewitt, 2011 <sup>65</sup>	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 2.5 mg	Oral, 2.5 mg, once, immediately after attack	14 days	39 Patients aged 43.3 ± 10.5 years, 81.8% female, 97% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 5 mg	Oral, 5 mg, once, immediately after attack	14 days	57 Patients aged 43.4 ± 11.1 years, 85.1% female, 97.9% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 10 mg	Oral, 10 mg, once, immediately after attack	14 days	84 Patients aged 44.1 ± 10.0 years, 92.5% female, 92.5% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Hewitt, 2011 (continued)	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 20 mg	Oral, 20 mg, once, immediately after attack	14 days	86 Patients aged 44.1 ± 11.3 years, 80.6% female, 94.0% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 50 mg	Oral, 50 mg, once, immediately after attack	14 days	84 Patients aged 42.2 ± 10.8 years, 91.2% female, 94.1% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 100 mg	Oral, 100 mg, once, immediately after attack	14 days	83 Patients aged 42.4 ± 10.9 years, 83.9% female, 95.2% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	MK-3207 (CGRP receptor antagonist) 200 mg	Oral, 200 mg, once, immediately after attack	14 days	74 Patients aged 40.5 ± 10.7 years, 85.7% female, 93.7% White
	RCT in United States of America, Canada and Europe, 7/2008 to 01/2009	Outpatient	Placebo	Oral, once, immediately after attack	14 days	169 Patients aged 42.1 ± 11.2 years, 89.3% female, 94.3% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ho, 2007 <sup>66</sup>	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 25 mg	Oral, 25 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	16 Patients aged 43 years, 78.6% female, 71.4% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 50 mg	Oral, 50 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	18 Patients aged 41.5 years, 93.3% female, 73.3% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 100 mg	Oral, 100 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	17 Patients aged 40.9 years, 87.5% female, 68.7% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 200 mg	Oral, 200 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	16 Patients aged 34.3 years, 75% female, 50% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 300 mg	Oral, 300 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	54 Patients aged 40.5 years, 87.2% female, 74.4% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 400 mg	Oral, 400 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	54 Patients aged 40.1 years, 93.3% female, 75.6% White
	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Telcagepant 600 mg	Oral, 600 mg, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	53 Patients aged 44.7 years, 90% female, 95% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ho, 2007 (continued)	RCT in United States of America, 12/2005 to 05/2006	Outpatient	Placebo	Oral, once, immediately after attack (second dose at 2 hours if still experiencing moderate or severe headache)	14 days	147 Patients aged 42.2 years, 90.4% female, 80% White
Ho, 2008 <sup>67</sup>	RCT in Europe and United States of America, 02/2007 to 10/2007	Outpatient	Telcagepant 150 mg	Oral, 150 mg, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	458 Patients aged 42.7 ± 11.2 years, 83% female, 96% White
	RCT in Europe and United States of America, 02/2007 to 10/2007	Outpatient	Telcagepant 300 mg	Oral, 300 mg, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	466 Patients aged 42.6 ± 11.4 years, 85% female, 96% White
	RCT in Europe and United States of America, 02/2007 to 10/2007	Outpatient	Placebo	Oral, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	461 Patients aged 42.3 ± 12 years, 84% female, 93% White
Ho, 2010 <sup>68</sup>	RCT in Europe, United States of America, Canada, Australia and Colombia, 09/2008 to 03/2009	Outpatient	Telcagepant 140 mg	Oral, 140 mg, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	644 Patients aged 43.4 ± 11.7 years, 85.5% female, 94.9% White, 4% previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ho, 2010 (continued)	RCT in Europe, United States of America, Canada, Australia and Colombia, 09/2008 to 03/2009	Outpatient	Telcagepant 280 mg	Oral, 280 mg, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	645 Patients aged 42.4 ± 11.5 years, 85.8% female, 94.7% White, 5.3% previous opioid use
	RCT in Europe, United States of America, Canada, Australia and Colombia, 09/2008 to 03/2009	Outpatient	Placebo	Oral, once immediately after attack (optional second dose at 2 hours if they still had a moderate or severe migraine attack or experienced headache recurrence within 48 hours after initial treatment)	14 days	646 Patients aged 42.5 ± 11.6 years, 83.4% female, 93.9% White, 5% previous opioid use
Ho, 2012 <sup>69</sup>	Crossover RCT in United States of America, Europe, South America, and Asia, 03/2008 to 08/2009	Outpatient	Telcagepant to acetaminophen	Oral, 280 mg tablet/300 mg capsule telcagepant crossing over to 1000 mg acetaminophen, once immediately after attack (optional second dose optional at 2 hours after initial treatment if the patient continued to have a moderate or severe headache or experienced headache recurrence)	98 days	84 Patients aged 56.6 ± 10.1 years, 58.9% female, 85.7% White, 28% previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ho, 2012 (continued)	Crossover RCT in United States of America, Europe, South America, and Asia, 03/2008 to 08/2009	Outpatient	Acetaminophen to telcagepant	Oral, 1000 mg acetaminophen crossing over to 280 mg tablet/300 mg capsule telcagepant, once immediately after attack (optional second dose at 2 hours after initial treatment if the patient continued to have a moderate or severe headache or experienced headache recurrence)	98 days	81 Patients aged 55.7 ± 10 years, 62.1% female, 81% White, 27.6% previous opioid use
Hoffert, 1992 <sup>70</sup>	Crossover RCT in United States of America	Outpatient	Nifedipine	Oral, 20 mg, at onset of the aura. If aura persisted allowed to repeat dose every 20 minutes to the maximum dose	NR	Entire population: 14 Patients (Nifedipine), 13 Patients (Placebo) aged 33 ± 5.75, 66.6% female
	Crossover RCT in United States of America	Outpatient	Placebo	Oral, at onset of the aura. If aura persisted allowed to repeat dose every 20 minutes to the maximum dose	NR	Entire population: 14 Patients (Nifedipine), 13 Patients (Placebo) aged 33 ± 5.75, 66.6% female
Hoffert, 1995 <sup>71</sup>	RCT in United States of America	Outpatient	Butorphanol	Nasal spray, 1 mg per spray, immediately after attack, additional doses were allowed within 30-90 minutes if pain relief had not been achieved then every 2-4 hours as needed, with a maximum of 12 sprays allowed over 1 day	2 days	107 Patients aged 41 ± 7 years, 85% female, 90% White, 7% African American, 1% Asian, 1% Hispanic
	RCT in United States of America	Outpatient	Placebo	Nasal spray, Placebo, immediately after attack, additional doses were allowed within 30-90 minutes if pain relief had not been achieved then every 2-4 hours as needed, with a maximum of 12 sprays allowed over 1 day	2 days	50 Patients aged 40.6 ± 10.25 years, 82% female, 96% White, 4% African American

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Hokenek, 2020 <sup>72</sup>	RCT in Turkey, 06/2019 to 10/2019	ED	Sham stimulation	Transcutaneous electrical nerve stimulation (electrodes over supraorbital nerve), device include 27 kΩ resistance and 47 nF capacitance connected in parallel to the load, a pulse repetition frequency of 50 Hz, a pulse width of 125 μs, an impulse amplitude of 60 voltage, and a pulse energy of 18.4 μJ (±10%) on an oscilloscope, with empty battery and the device was electrically inactive), once for 20 minutes	2 hours	41 Patients aged 33.62±10.2 years
	RCT in Turkey, 06/2019 to 10/2019	ED	Transcutaneous electrical nerve stimulation	Transcutaneous electrical nerve stimulation (electrodes over supraorbital nerve), device include 27 kΩ resistance and 47 nF capacitance connected in parallel to the load, a pulse repetition frequency of 50 Hz, a pulse width of 125 μs, an impulse amplitude of 60 voltage and a pulse energy of 18.4 μJ (±10%) on an oscilloscope, with fully charged battery), once for 20 minutes	2 hours	42 Patients aged 35.62±8.77 years
Honkaniemi, 2006 <sup>73</sup>	RCT in Finland, 01/2002 to 02/2005	Inpatient	Haloperidol	IV, 5 mg in 500 mL normal saline over 20-30 minutes	30 days	Entire population: 20 Patients (in each study group) aged 36 years, 85% female, 17% previous opioid use
	RCT in Finland, 01/2002 to 02/2005	Inpatient	Placebo	IV, 500 mL normal saline over 20-30 minutes (if no relief in pain 1-3 hours after the infusion then received haloperidol as an open trial)	30 days	Entire population: 20 Patients (in each study group) aged 36 years, 85% female, 17% previous opioid use



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Hougaard, 2013 <sup>74</sup>	Crossover RCT in Denmark, 06/2009 to 04/2011	Outpatient	NXN-188	Oral, 600 mg, once	7 days	Entire population: 49 Patients aged 39 ± 11 years, 75.5% female
	Crossover RCT in Denmark, 06/2009 to 04/2011	Outpatient	Placebo	Oral, once	7 days	Entire population: 49 Patients aged 39 ± 11 years, 75.5% female
Jones, 1994 <sup>75</sup>	RCT in United States of America	ED	Prochlorperazine	Rectal, 25 mg, once	2 hours	10 Patients aged 30.5 ± 2.5 years, 100% female
	RCT in United States of America	ED	Placebo	Rectal, once	2 hours	10 Patients aged 28.4 ± 2.3 years, 90% female
Jones, 1996 <sup>76</sup>	RCT in United States of America, 02/1991 to 07/1991	ED	Prochlorperazine-edisylate	IM, 10 mg, once	2 days	28 Patients. Entire population: ), aged 32.1 ± 2.1 years, 73% female
	RCT in United States of America, 02/1991 to 07/1991	ED	Metoclopramide hydrochloride	IM, 10 mg, once	2 days	29 Patients. Entire population: aged 32.1 ± 2.1 years, 73% female
	RCT in United States of America, 02/1991 to 07/1991	ED	Placebo	IM, 2 mL, once	2 days	29 Patients. Entire population: aged 32.1 ± 2.1 years, 73% female
Jones, 2019 <sup>77</sup>	RCT in United States of America, 01/2017 to 09/2017	ED	Fluid group	IV, 1 L of 0.9% saline solution over 1 hour	2 days	25 Patients aged 34 ± 3.75 years, 76% female, 40% White, 40% African American, 40% Hispanic

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Jones, 2019 (continued)	RCT in United States of America, 01/2017 to 09/2017	ED	Control group	IV, 0.9% saline solution at 10 mL/hour over 1 hour	2 days	25 Patients aged 37 ± 5 years, 92% female, 42% White, 33% African American, 29% Hispanic
Kangasniemi, 1992 <sup>78</sup>	Crossover RCT in Finland, 01/1987 to 01/1988	Outpatient	Ergotamine	Suppositories, 2 mg, once	2 days	Entire population: 52 Patients in each group aged 39 ± 10.25 years, 88% female
	Crossover RCT in Finland, 01/1987 to 01/1988	Outpatient	Placebo	Suppositories, once	2 days	Entire population: 52 Patients in each group aged 39 ± 10.25 years, 88% female
Kapicioglu, 1997 <sup>79</sup>	RCT in Turkey	Outpatient	Octreotide	Subcutaneous, 100 mg	1 day	17 Patients aged 39.7 years, 70.5% female
	RCT in Turkey	Outpatient	Placebo	Subcutaneous, isotonic saline	1 day	12 Patients aged 37.11 years, 75% female
Karimi, 2017 <sup>80</sup>	RCT in Iran, 10/2014 to 06/2016	ED	Dexamethasone	IV, 8 mg , once	1 day	40 Patients aged 33.4 ± 9.2 years, 85% female
	RCT in Iran, 10/2014 to 06/2016	ED	Valproate sodium	IV, 400 mg (diluted into 4 mL of normal saline), once	1 day	40 Patients aged 33.9 ± 9.5 years, 77.5% female
Klapper, 1993 <sup>81</sup>	RCT in United States of America	Outpatient	Dihydroergotamine plus metoclopramide plus placebo	IV, 1 mg dihydroergotamine plus 10 mg metoclopramide, IM, placebo	1 hour	14 Patients
	RCT in United States of America	Outpatient	Meperidine plus hydroxyzine plus placebo	IM, 75 mg meperidine plus 75 mg hydroxyzine, IV, placebo	1 hour	14 Patients

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Korucu, 2018 <sup>82</sup>	RCT in Turkey, 01/2016 to 12/2016	ED	Greater occipital nerve blockade	Subcutaneous, 1 mL of 0.5% bupivacaine and 1 mL of normal saline, single injection (if the headache was on one side) or a double injection (if the headache was on both sides (total 4 mL)	45 minutes	20 Patients median age 40 ± 8.9 years, 90% female
	RCT in Turkey, 01/2016 to 12/2016	ED	Dexketoprofen trometamol 50 mg plus metoclopramide 10 mg	IV, 50 mg dexketoprofen plus 10 mg metoclopramide diluted in 100ml normal saline	45 minutes	20 Patients median age 35 ± 8.14, 75% female
	RCT in Turkey, 01/2016 to 12/2016	ED	Placebo	Subcutaneous, 2 mL of normal saline, single injection (if the headache was on one side) or a double injection (if the headache was on both sides (total 4 mL)	45 minutes	20 Patients median age 40 ± 10.4 years, 90% female
Kuca, 2018 <sup>83</sup>	RCT in United States of America, 04/27/2015 to 08/12/2016	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once	7 days	745 Patients aged 41.4 ± 12 years, 84.6 % female, 73.9% White, BMI 31 ± 8.2
	RCT in United States of America, 04/27/2015 to 08/12/2016	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once	7 days	744 Patients aged 42.2 ± 11.7 years, 81.3 % female, 74.8% White, BMI 30 ± 8
	RCT in United States of America, 04/27/2015 to 08/12/2016	Outpatient	Placebo	Oral, once	7 days	742 Patients aged 42.4 ± 12.3 years, 85.1 % female, 77.6% White, BMI 30.3 ± 7.5
Lane, 1989 <sup>84</sup>	RCT in Canada	ED	Chloropramazine	IV, 25 mg diluted to 10 mL plus 10 mL normal saline, every 15 minutes as needed up to a total of three doses	1 hour	24 Patients aged 31 ± 6.5 years, 87.5% female, 75% previously used opioid

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Lane, 1989 (continued)	RCT in Canada	ED	Dimenhydrinate plus meperidine	IV, 50mg dimenhydrinate diluted to 10 mL plus 100 mg meperidine diluted to 10 mL, every 15 minutes as needed up to a total of three doses	1 hour	22 Patients aged 31.09 ± 7.25 years, 81.8 % female, 68.1 % previously used opioid
Levy, 2005 <sup>85</sup>	Crossover RCT in UK	Outpatient	Octreotide	Subcutaneous, 100 µg in 1 mL normal saline, once	2 days	Entire population: 43 Patients aged 48 ± 12 years, female 95%
	Crossover RCT in UK	Outpatient	Placebo	Subcutaneous, 1 mL normal saline, once	2 days	Entire population: 43 Patients aged 48 ± 12 years, female 95%
Li, 2009 <sup>86</sup>	RCT in China	Outpatient	Verum Acupuncture	Skin by filiform Huatao needles, at the following acupoints Waiguan (TE 5), Yanglingquan (GB 34), Qiuxu (GB 40), Jiaosun (TE 20), and Fengchi (GB 20) used bilaterally. once, for 30 minutes	1 day	58 Patients aged 41.84 years ± 14.21, 56.9% female
	RCT in China	Outpatient	Sham Acupuncture 1	Skin by filiform Huatao needles, at nonacupoints located halfway between the triple Energizer and Small Intestine meridians lateral to the acupoints Waiguan (TE 5) horizontally; halfway between the line from Qiuxu (GB 40) to Jiexi (ST 41); halfway between the Gallbladder and Bladder meridians lateral to Yanglingquan (GB 34) horizontally; halfway between the line from Jiaosun (TE 20) to Shuaigu (GB 8); and halfway between the line from Fengchi (GB 20) to Anmian (extra point) bilaterally. Once for 30 minutes	1 day	60 Patients aged 39.65 ± 12.83 years, 55% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Li, 2009 (continued)	RCT in China	Outpatient	Sham Acupuncture 2	Skin by filiform Huatao needles, at nonacupoints located medial arm on the anterior border of the insertion of the deltoid muscle at the junction of the deltoid and biceps muscles; the inside of the mid-thigh region 2 cm lateral to half the distance from the anterior superior iliac spine to the lateral superior corner of the patella on the rectus femoris; 13 the edge of the tibia 1 to 2 cm lateral to the Zusanli (ST 36) point horizontally; halfway between the tip of the elbow and the axillae and halfway between the epicondylus medialis of the humerus and ulnar side of the wrist bilaterally. once for 30 minutes	1 day	57 Patients aged 39.49 ± 11.6 years, 70.2% female
Lipton, 2000 <sup>87</sup>	RCT in United States of America, 03/11/1998 to 08/10/1998	Outpatient	Acetaminophen	Oral, 1000 mg, once	6 hours	176 Patients aged 37.3 ± 10.4 years, 76.9% female, 23.8% African American, 75.5% White, 0.7% others
	RCT in United States of America, 03/11/1998 to 08/10/1998	Outpatient	Placebo	Oral, once	6 hours	175 Patients aged 36 ± 9.3 years, 83.1% female, 28.9% African American, 69.7% white, 1.4% others

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Lipton, 2010 <sup>88</sup>	RCT (non-inferiority) in United States of America, 08/2006 to 02/2008	Outpatient	Single-pulse transcranial magnetic stimulation (sTMS)	Transcranial (below the occipital bone), pulse of nominally 0.9 T peak (measured 1 cm from the device surface) with a rise time of roughly 180 $\mu$ s and a total pulse length of less than 1 ms, two pulses about 30 s apart (treat up to 3 attacks)	90 days	102 Patients aged 38.8 $\pm$ 11.2 years, 82% female
	RCT (non-inferiority) in United States of America, 08/2006 to 02/2008	Outpatient	Sham stimulation	Transcranial (below the occipital bone), two pulses about 30 s apart (treat up to 3 attacks)	90 days	99 Patients aged 40.1 $\pm$ 10.8 years, 77% female
Lipton, 2019 <sup>89</sup>	RCT in United States of America, 07/2017 to 01/2018	Outpatient	Rimegepant	Oral, 75 mg, once	7 days	594 Patients aged 40.2 $\pm$ 11.9 years, 89.2% female, 20.7% African American, 73.4% White, 1.5% Asian, 14.3% Hispanic, 4.47% others, BMI 31.0 $\pm$ 7.9
	RCT in United States of America, 07/2017 to 01/2018	Outpatient	Placebo	Oral, once	7 days	592 Patients aged 40.9 $\pm$ 12.1 years, 88.2% female, 22.1% African American, 74.6% White, 1.5% Asian, 15.5% Hispanic, 1.8% others, BMI 31.8 $\pm$ 8.5

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Lipton, 2019 <sup>90</sup>	RCT in United States of America, 08/26/2016 to 02/26/2018	Outpatient	Ubrogepant 50 mg	Oral, 50 mg, once within 4 hours of a qualifying migraine attack	42 days	562 Patients aged 41.2±12.5 years, 91% female, 16.8% African American, 81.6% White, 0.4% Asian, 21.9% Hispanic, 0.4% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.6% multiple, BMI 30.5±7.5, 3.9% previous opioid use
	RCT in United States of America, 08/26/2016 to 02/26/2018	Outpatient	Ubrogepant 25 mg	Oral, 25 mg, once within 4 hours of a qualifying migraine attack	42 days	561 Patients aged 41.6±12.4 years, 90.2% female, 14% African American, 83.5% White, 1.3% Asian, 23% Hispanic, 0.2% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.8% multiple, BMI 29.6±7, 3.6 % previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Lipton, 2019 (continued)	RCT in United States of America, 08/26/2016 to 02/26/2018	Outpatient	Placebo	Oral, once within 4 hours of a qualifying migraine attack	42 days	563 Patients aged 41.7±12.1 years, 88.6% female, 16.4% African American, 80% White, 1.4% Asian, 19.8% Hispanic, 0.6% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 1.4% multiple, BMI 29.8±7.7, 3.8% previous opioid use
Loisy, 1985 <sup>91</sup>	RCT in France	Outpatient	Placebo	IV, once over 3-5 minutes	2 hours	23 Patients. Entire population: age range 31 – 74 years, 76.6% female
	RCT in France	Outpatient	Bemesetron, 5HT3 receptor antagonist (MDL 72,222)	IV, 20 mL (1mg/mL), once over 3-5 minutes	2 hours	24 Patients. Entire population: age range 31 – 74 years, 76.6% female
Maizels, 1996 <sup>92</sup>	RCT in United States of America, 12/1994 to 10/1995	Urgent Care	Lidocaine	Intranasal, 0.5 mL of 4% lidocaine topical solution dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	1 day	53 Patients median age 43 ± 11.9 years, 87% female
	RCT in United States of America, 12/1994 to 10/1995	Urgent Care	Placebo	Intranasal, 0.5 mL, normal saline dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	1 day	28 Patients median age 40 ± 11.5 years, 75% female



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Maizels, 1999 <sup>93</sup>	RCT in United States of America, 01/1997 to 01/1998	Outpatient	Lidocaine	Intranasal, 0.5 mL of 4% lidocaine topical solution dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	30 days (RCT), 180 days (open label)	66 Patients aged 44.5 ± 9.1 years, 83.1% female
	RCT in United States of America, 01/1997 to 01/1998	Outpatient	Placebo	Intranasal, 0.5 mL, normal saline dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	30 days (RCT), 180 days (open label)	65 Patients aged 47 ± 10.2 years, 87.9% female
Marcus, 2008 <sup>94</sup>	RCT in United States of America	ED	Integrated EMDR (eye movement desensitization reprocessing)	Behavioral intervention, Participant's use of diaphragmatic breathing coupled with head compression by the provider, once for 12-60 minutes	7 days	26 Patients aged 38.33 ± 10.57 years, 95.2% female, 30% White
	RCT in United States of America	ED	Standard Care	Variable interventions (oral / injection; depending on drug type), Variable dosage depends on the drug, once	7 days	26 Patients aged 37.95 ± 9.57 years, 95.5% female, 68.2% White
Marcus, 2014 <sup>95</sup>	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Placebo	Oral, once	7 days	229 Patients aged 37.9 ± 11.36 years, 86% female, 12% African American, 84% White, 3% others
	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 10 mg	Oral, 10 mg, once	7 days	85 Patients aged 41.1 ± 10.36 years, 79% female, 14% African American, 79% White, 7% others

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Marcus, 2014 (continued)	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 25 mg	Oral, 25 mg, once	7 days	68 Patients aged 36.5 ± 11.92 years, 90% female, 10% African American, 87% White, 3% others
	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 75 mg	Oral, 75 mg, once	7 days	91 Patients aged 38.5 ± 11.87 years, 89% female, 7% African American, 90% White, 3% others
	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 150 mg	Oral, 150 mg, once	7 days	90 Patients aged 39.2 ± 11.26 years, 70% female, 20% African American, 72% White, 8% others
	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 300 mg	Oral, 300 mg, once	7 days	121 Patients aged 41.9 ± 11.46 years, 84% female, 13% African American, 84% White, 1% others
	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Rimegepant 600 mg	Oral, 600 mg, once	7 days	92 Patients aged 39.3 ± 13.01 years, 83% female, 11% African American, 87% White, 2% others
Mazaheri, 2015 <sup>96</sup>	RCT in Iran, 04/2012 to 06/2014	ED	Valporate Sodium	IV, 400 mg (plus 50 mL saline normal solution) for 15 minutes, once	2 hours	43 Patients aged 37.29 ± 11.7 years, 82.9% female
	RCT in Iran, 04/2012 to 06/2014	ED	Dexamethasone	IV, 16 mg (plus 50 mL saline normal solution) for 15 minutes, once	2 hours	43 Patients aged 32.05 ± 9.1 years, 81.1% female

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McEwen, 1987 <sup>97</sup>	RCT in Canada, 03/1985 to 11/1985	ED	Chlorpromazine	IM, 50 mg/2mL (1 mg/kg), once	1 day	19 patients aged 30 years, 94.7% female
	RCT in Canada, 03/1985 to 11/1985	ED	Normal saline	IM, 2 mL, normal saline, once	1 day	17 patients aged 36 years, 88.2% female
Miller, 2009 <sup>98</sup>	RCT in United States of America, 02/2006 to 02/2007	ED	Prochlorperazine	IV, 10 mg once for 2 minutes	3 days	20 Patients aged 27.5 ± 5.8 years, 70% female
	RCT in United States of America, 02/2006 to 02/2007	ED	Octreotide	IV, 100 µg, once for 2 minutes	3 days	24 Patients aged 31.1 ± 11.1 years, 78% female
Million, 1984 <sup>99</sup>	RCT in England	Outpatient	Flupirtine	Oral, 100 mg, up to 4 times a day for 5 days	5 days	24 Patients aged 42.6 ± 3.3 years, 80% female
	RCT in England	Outpatient	Paracetamol	Oral, 500 mg, up to 4 times a day for 5 days	5 days	23 Patients aged 49.6 ± 2.8 years, 95% female
Mitra, 2020 <sup>100</sup>	RCT in Australia	ED	Propofol	IV, 1 mg/kg, slowly for 1 min	N/A	15 Patients aged 32.9±10.3 years, 47% female
	RCT in Australia	ED	Standard therapy (chlorpromazine, metoclopramide, ondansetron, lignocaine, magnesium sulphate, or morphine)	N/A	N/A	14 Patients aged 37.9±9.4 years, 89% female.
Molaie, 1987 <sup>101</sup>	RCT in United States of America	ED	Verapamil hydrochloride	IV, 2 cc (10 mg), once	1 hour	6 Patients. Entire population: aged 33.75 ± 8.3 years, 50% female
	RCT in United States of America	ED	Placebo	IV, 2 cc, once	1 hour	6 Patients. Entire population: aged 33.75 ± 8.3 years, 50% female

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Niazi, 2007 <sup>102</sup>	Crossover RCT in Iran	Outpatient	Rose damascene oil	Skin, 2 cc of the rose damascene oil on forehead and temporal zones at onset of migraine attacks	1 day	Entire population: 40 Patients aged 34.89 ± 10.81 years, BMI 25.50 ± 4.77
	Crossover RCT in Iran	Outpatient	Placebo	Skin, 2 cc of the paraffin oil forehead and temporal zones at the onset of migraine attacks	1 day	Entire population: 40 Patients aged 34.89 ± 10.81 years, BMI 25.50 ± 4.77
Pfaffenrath, 1990 <sup>103</sup>	RCT in Germany	Outpatient	Flunarizine 10 mg	IV, 10 mg, once	2 hours	37 Patients aged 39 ± 10.5 years, 70% female
	RCT in Germany	Outpatient	Flunarizine 20 mg	IV, 20 mg, once	2 hours	32 Patients aged 44 ± 13.25 years, 72% female
	RCT in Germany	Outpatient	Placebo	IV, HP-beta-cyclodextrine, once	2 hours	33 Patients aged 43 ± 10.5 years, 61% female
Prior, 2010 <sup>104</sup>	RCT in United States of America, 02/1999 to 06/1999	Outpatient	Acetaminophen	Oral, 1000 mg, once	3 days	190 Patients aged 38.1 ± 11 years, 80.8% female, 87% White
	RCT in United States of America, 02/1999 to 06/1999	Outpatient	Placebo	Oral, placebo, once	3 days	188 Patients aged 39.8 ± 11.8 years, 85.8% female, 85.8% White
Rafieian-Kopaei, 2019 <sup>105</sup>	RCT in Iran	Outpatient	Lidocaine	Intranasal, 4%, once-twice	60 days	41 Patients aged 30.6 ± 6.3 years, 76.3% female
	RCT in Iran	Outpatient	Peppermint essential oil	Intranasal, 1.5%, once-twice	60 days	38 Patients aged 30.42 ± 7.2 years, 76.3.6% female
	RCT in Iran	Outpatient	Placebo	Intranasal, placebo, once-twice	60 days	41 Patients aged 31.8 ± 5.8 years, 68.3% female
Rapoport, 1995 <sup>106</sup>	RCT in the United States of America	Outpatient	Dihydroergotamine	Nasal spray, 2 mg in 0.5 mL, divided into 2 sprays delivered in 15 minutes interval	4 hours	114 Patients. Entire population: age range 18-62, 70% female 0% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Rapoport, 1995 (continued)	RCT in the United States of America	Outpatient	Placebo	Nasal spray, 0.5 mL, divided into 2 sprays delivered in 15 minutes interval	4 hours	115 Patients. Entire population: age range 18-62, 70% female 0% White
Reutens, 1991 <sup>107</sup>	RCT in Australia, 04/1989 to 12/1989	ED	Lidocaine	IV, 66 mg, once for 2 minutes	0.3 hour	13 Patients aged 40 years, 92% female
	RCT in Australia, 04/1989 to 12/1989	ED	Placebo	IV, placebo, once for 2 minutes	0.3 hour	12 Patients aged 30 years, 67% female
Richman, 2002 <sup>108</sup>	RCT in United States of America	ED	Droperidol	IM, 2.5 mg, once	0.5 hour	15 Patients aged 30.7 ± 8.9 years, 73% female
	RCT in United States of America	ED	Meperidine	IM, 1.5 mg/ kg, once	0.5 hour	14 Patients aged 32.7 ± 9.9 years, 71% female
Rowat, 1991 <sup>109</sup>	RCT in Canada	ED	Granisetron 40 µg/kg	IV, 20 mL (1000 µg/ mL diluted in 0.9% saline), once for 3 minutes	3 ±1 days	10 Patients aged 39.5 ± 11.8 years, 50% female, weight 72.4 ± 11.7
	RCT in Canada	ED	Granisetron 80 µg/kg	IV, 20 mL (2000 µg/ mL diluted in 0.9% saline), once for 3 minutes	3 ±1 days	10 Patients aged 38.2 ± 13.8 years, 80% female, weight 59.8 ± 9.2
	RCT in Canada	ED	Placebo	IV, placebo, once for 3 minutes	3 ±1 days	8 Patients aged 41.3 ± 8.6 years, 87.5% female, weight 63.1 ± 11.9
Ryan, 1970 <sup>110</sup>	Crossover RCT in United States of America	Outpatient	Ergostine 1 mg plus caffeine 100 mg	Oral, 1 mg ergostine plus 100 mg caffeine, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	Entire population: 48 Patients aged 46 ± 12.25 years, 68.7% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Ryan, 1970 (continued)	Crossover RCT in United States of America	Outpatient	Ergotamine tartrate 1 mg plus caffeine 100 mg	Oral, 1 mg ergotamine tartrate plus 100 mg caffeine, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	Entire population: 48 Patients aged 46 ± 12.25 years, 68.7% female
	Crossover RCT in United States of America	Outpatient	Placebo	Oral, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	Entire population: 48 Patients aged 46 ± 12.25 years, 68.7% female
Salazar, 2011 <sup>111</sup>	RCT in Spain, 01/2007 to 03/2009	ED	Metoclopramide	IV, 10 mg diluted in 100 cc of saline, once	2 days	43 Patients aged 35 years, 53.48% female
	RCT in Spain, 01/2007 to 03/2009	ED	Paracetamol	IV, 1g diluted in 100 mL of saline, once	2 days	45 Patients aged 42 years, 51.11% female
Sang, 2004 <sup>112</sup>	RCT in United States of America, 08/1999 to 09/2000	Outpatient	Tezampanel	IV, 1.2 mg/ kg, once for 15 minutes	1 day	14 Patients aged 38 ± 8 years, 61% female
	RCT in United States of America, 08/1999 to 09/2000	Outpatient	Placebo	IV, once for 15 minutes	1 day	16 Patients aged 43 ± 12 years, 44% female
Sasannejad, 2012 <sup>113</sup>	Comparative observational in Iran	Outpatient	Lavender essential oil	Topical/ inhale, 2-3 drops of oil, 1-6 times over 15 minutes	2 hours	19 Patients aged 31 ± 8 years, 71.4 female
	Comparative observational in Iran	Outpatient	Placebo	Topical/ inhale, 2-3 drops of placebo, 1-6 times over 15 minutes	2 hours	28 Patients aged 29 ± 7 years, 73.3% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Scherl, 1995 <sup>14</sup>	RCT in United States of America	Outpatient	Dihydroergotamine plus metoclopramide	IV, 0.5 mg dihydroergotamine with 10 mg metoclopramide, once	1 day	14 Patients. Entire population: aged 30.6 ± 7.6 years, 70.4% female
	RCT in United States of America	Outpatient	Meperidine plus promethazine	IM, 75 mg meperidine with 25 mg promethazine, once	1 day	13 patients. Entire population: aged 30.6 ± 7.6 years, 70.4% female
Shahrami, 2015 <sup>15</sup>	RCT in Iran, 2011	ED	Dexamethasone plus metoclopramide	IV, 8 mg dexamethasone and 10 mg metoclopramide in 100 mL normal saline solution, once for 15 minutes	2 hours	35 Patients aged 38 ± 11.2 years, 60% female
	RCT in Iran, 2011	ED	Magnesium sulfate	IV, 1 g in 100 mL normal saline, once for 15 minutes	2 hours	35 Patients aged 36 ± 12.6 years, 45.7% female
Sharma, 2002 <sup>16</sup>	RCT in India	Outpatient	Buccal prochlorperazine	Oral, 3 mg, once	N/A	Entire population: 45 Patients aged 18 to 50 years, 62.2% female
	RCT in India	Outpatient	Buccal placebo	Oral, once	N/A	Entire population: 45 Patients aged 18 to 50 years, 62.2% female
	RCT in India	Outpatient	Ergotamine tartarate plus caffeine	Oral, 1 mg ergotamine tartarate plus 100 mg caffeine, once	N/A	Entire population: 45 Patients aged 18 to 50 years, 62.2% female
Silberstein, 2005 <sup>17</sup>	RCT in United States of America	Outpatient	Acetaminophen plus tramadol	Oral, 75 mg/650 mg, once	1 day	188 Patients aged 39.2 ± 11.29 years, 87% female, 83.8% White, 10.4% Black, 1.3% Asian, 4.5% Other
	RCT in United States of America	Outpatient	Placebo	Oral, once	1 day	187 Patients aged 39.1 ± 10.47 years, 83.4% female, 87.6% White, 6% Black, 2% Asian, 4.6% Other

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Silberstein, 2009a <sup>118</sup>	RCT in Australia, South Africa, Belgium, France, Germany, and UK, 06/1997 to 10/1997	Outpatient	Tonabersat 15 mg	Oral, 15 mg, once	7-10 days	109 Patients aged 39.4 ± 9.9 years, 77.1% female, 94.5% White
	RCT in Australia, South Africa, Belgium, France, Germany, and UK, 06/1997 to 10/1997	Outpatient	Tonabersat 40 mg	Oral, 40 mg, once	7-10 days	115 Patients aged 40.2 ± 11.1 years, 87% female, 93.9% White
	RCT in Australia, South Africa, Belgium, France, Germany, and UK, 06/1997 to 10/1997	Outpatient	Tonabersat 80 mg	Oral, 80 mg, once	7-10 days	109 Patients aged 40.5 ± 11.3 years, 82.6% female, 93.6% White
	RCT in Australia, South Africa, Belgium, France, Germany, and UK, 06/1997 to 10/1997	Outpatient	Placebo	Oral, once	7-10 days	108 Patients aged 39.7 ± 11.2 years, 76.9% female, 91.7% White



Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Silberstein, 2009b <sup>118</sup>	RCT in Canada, United States of America, 06/1997 to 10/1997	Outpatient	Placebo	Oral, once	7-10 days	101 Patients aged 39.6 ± 10.3 years, 82.2% female, 94.1% White
	RCT in Canada, United States of America, 06/1997 to 10/1997	Outpatient	Tonabersat 25 mg	Oral, 25 mg, once	7-10 days	102 Patients aged 40.4 ± 10.6 years, 88.2% female, 95.1% White
	RCT in Canada, United States of America, 06/1997 to 10/1997	Outpatient	Tonabersat 40 mg	Oral, 40 mg, once	7-10 days	106 Patients aged 39.4 ± 9.5 years, 84.9% female, 95.3% White
	RCT in Canada, United States of America, 06/1997 to 10/1997	Outpatient	Tonabersat 80 mg	Oral, 80 mg, once	7-10 days	109 Patients aged 39.5 ± 9.1 years, 83.5% female, 95.4% White
Silberstein, 2003 <sup>119</sup>	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Droperidol 0.1 mg	IM, 0.1 mg, once	7 days	63 Patients aged 42 ± 10.5 years, 81% female
	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Droperidol 2.75 mg	IM, 2.75 mg, once	7 days	61 Patients aged 41 ± 9.1 years, 80% female
	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Droperidol 5.5 mg	IM, 5.5 mg, once	7 days	59 Patients aged 41 ± 10.8 years, 81% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Silberstein, 2003 (continued)	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Droperidol 8.25 mg	IM, 8.25 mg, once	7 days	61 Patients aged 42 ± 10 years, 77% female
	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Placebo	IM, once	7 days	61 Patients aged 41 ± 9.7 years, 85% female
Soleimanpour, 2012 <sup>120</sup>	RCT in Iran	ED	Propofol	IV, 10 mg, every 5-10 minutes (maximum dose of 80 mg) , rate of 1 mL for 10 seconds	N/A	45 Patients aged 35.65 ± 12.55 years, 66.6% female
	RCT in Iran	ED	Dexamethasone	IV, 4 mg/mL with dose of 0.15 mg/kg (maximum dose of 16 mg), rate of 1 mL for 10 seconds	N/A	45 Patients aged 36.27 ± 13.38 years, 62.22% female
Soyka, 1988 <sup>121</sup>	RCT in Germany	Outpatient	Flunarizine	IV, 20 mg, once	0.5 days	33 Patients aged 41±10 years, 80.6% female
	RCT in Germany	Outpatient	Placebo	IV, once	0.5 days	33 Patients aged 38±10 years, 72.4% female
Soyka, 1989 <sup>122</sup>	RCT in Germany	ED	Flunarizine	IV, 20 mg	0.5 days	31 Patients aged 41±10 years, 80.6% female
	RCT in Germany	ED	Placebo	IV, 20 mg	0.5 days	29 Patients aged 38±10 years, 72.4% female
Stiell, 1991 <sup>123</sup>	RCT in Canada, 02/1990 to 09/1990	ED	Methotrimeprazine	IM, 37.5 mg, once	2 days	37 Patients aged 30.9±7.3 years, 67.6% female
	RCT in Canada, 02/1990 to 09/1990	ED	Meperidine plus dimenhydrinate	IM, 75 mg meperidine with 50 mg dimenhydrinate, once	2 days	37 Patients aged 32.5±8.9 years, 83.8% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Swidan, 2005 <sup>124</sup>	Comparative observational in United States of America, 02/1999 to 03/2000	Inpatient	Dihydroergotamine mesylate (DHE-45)	IV, 0.25-1.0 mg, 3 times daily for 3 days	3 days	40 Patients aged 38±14.25 years, 68% female
	Comparative observational in United States of America, 02/1999 to 03/2000	Inpatient	Diphenhydramine	IV, 25-75 mg, 3 times daily for 3 days	3 days	40 Patients aged 46±11.5 years, 70% female
Taheraghdam, 2011 <sup>125</sup>	RCT in Iran, 09/2008 to 05/2009	ED	Dexamethasone	IV, 8 mg, once	1 day	93 Patients aged 45.93±16.1 years, 55.9% female
	RCT in Iran, 09/2008 to 05/2009	ED	Morphine	IV, 0.1 mg/kg, once	1 day	97 Patients aged 42.34±16.2 years, 67% female
Tanen, 2003 <sup>126</sup>	RCT in United States of America, 01/2002 to 08/2002	ED	Sodium valproate	IV, 500 mg, once for 2 minutes	0.5 days	20 Patients aged 31±9.3, 58% female
	RCT in United States of America, 01/2002 to 08/2002	ED	Prochlorperazine	IV, 10 mg, once for 2 minutes	0.5 days	20 Patients aged 38.8±11, 79.2% female
Tassorelli, 2018 <sup>127</sup>	RCT in Italy, 01/11/2016 to 03/31/2017	Outpatient	Noninvasive vagus nerve stimulation	Transdermal, a low-voltage electrical signal comprising a 5-kHz sine wave burst lasting for 1 ms (5 sine waves, each lasting 200 µs), with such bursts repeated once every 40 ms (25 Hz), generating a 24-V peakvoltage and 60-mA peak output current for 2 minutes	5 days	122 Patients aged 38.8±11 years, 79.24% female, 100% White

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Tassorelli, 2018 (continued)	RCT in Italy, 01/11/2016 to 03/31/2017	Outpatient	Sham stimulation	Transdermal, a low-frequency (0.1 Hz) biphasic signal for 2 minutes	5 days	126 Patients aged 39.6±11.8 years, 30% female, 100% White
Tek, 1990 <sup>128</sup>	RCT in United States of America, 08/1987 to 04/1988	ED	Metoclopramide	IV, 10 mg, once	2 days	24 Patients age range 18-60
	RCT in United States of America, 08/1987 to 04/1988	ED	Placebo	IV, 2 mL, once	2 days	26 Patients age range 18-60
Treves, 1998 <sup>129</sup>	RCT in Brazil	Outpatient	Dihydroergotamine 1 mg	Nasal, 1 mg, 2 to 4 times	N/A	19 Patients aged 33.3±12.3 years, 78.9% female
	RCT in Brazil	Outpatient	Dihydroergotamine 0.5 mg	Nasal, 0.5 mg, 2 to 4 times	N/A	17 Patients aged 33.7±10 years, 41.2% female
	RCT in Brazil	Outpatient	Placebo	Nasal, 2 to 4 times	N/A	16 Patients aged 34.8±13.7 years, 62.5% female
Triner, 1999 <sup>130</sup>	RCT in United States of America, 07/10/1995 to 11/30/1995	ED	Nitrous oxide plus oxygen	Inhalation, 50% (NO) 50% Oxygen, once for 20 minutes	0.5 days	10 Patients aged 34.5± 11.8 years, 80% female, 70% White
	RCT in United States of America, 07/10/1995 to 11/30/1995	ED	Oxygen	Inhalation, 100% Oxygen, once for 20 minutes	0.5 days	12 Patients aged 28.1 ± 5.5 years, 91.6% female, 80% White
Tulunay, 2004 <sup>131</sup>	Crossover RCT in Turkey	Outpatient	Dipyrone	Oral, 1g, once	1 day	49 Patients aged 32.7 ± 8.7 years, 81% female
	Crossover RCT in Turkey	Outpatient	Placebo	Oral, once	1 day	23 Patients aged 32.7 ± 8.7 years, 81% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Tulunay, 1987 <sup>132</sup>	Crossover RCT in Turkey	Outpatient	Dipyrene	Intranasal (Puff), 4 mg/mL of DHE in an aqueous solution of 1 % caffeine and 5% glucose, 2 to 3 times	0.5 days	Entire population: 17 Patients aged 26.1 ± 3.34 years, 58.6% female
	Crossover RCT in Turkey	Outpatient	Placebo	Intranasal (Puff), 2 to 3 times	0.5 days	Entire population: 17 Patients aged 26.1 ± 3.34 years, 58.6% female
Voss, 2016 <sup>133</sup>	RCT in United States of America	Outpatient	Ubrogepant 1 mg	Oral, 1 mg, once	14 days	138 Patients aged 39.6 ± 10.7 years, 88.8% female, BMI 29.4±7.3
	RCT in United States of America	Outpatient	Ubrogepant 10 mg	Oral, 10 mg, once	14 days	139 Patients aged 41.1 ± 10.9 years, 85.2% female, 29.6±7.1
	RCT in United States of America	Outpatient	Placebo	Oral, once	14 days	139 Patients aged 40.5 ± 11.7 years, 87.65% female, BMI 28.5±7
	RCT in United States of America	Outpatient	Ubrogepant 25 mg	Oral, 25 mg, once	14 days	139 Patients aged 41.4 ± 11.5 years, 86.8% female, BMI 29.2±8.1
	RCT in United States of America	Outpatient	Ubrogepant 50 mg	Oral, 50 mg, once	14 days	139 Patients aged 40.7 ± 12.3 years, 88.2% female, BMI 27.8±8.1
	RCT in United States of America	Outpatient	Ubrogepant 100 mg	Oral, 100 mg, once	14 days	140 Patients aged 41.9 ± 11 years, 83.3% female, BMI 29.2±7
Wang, 2012 <sup>134</sup>	RCT in China 03/2007 to 02/2009	Outpatient	Verum Acupuncture	Acupoints, once for 30 minutes	3 days	75 Patients aged 37.8 ± 10.6 years, 89.3% female
	RCT in China 03/2007 to 02/2009	Outpatient	Sham Acupuncture	Acupoints, once for 30 minutes	3 days	75 Patients aged 38.6 ± 12.6 years, 84% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Wasay, 2006 <sup>135</sup>	Comparative observational in Pakistan	ED	Any opioid (pethidine, 25; pentazocine, 10; and oral opioidanalgesics, 4)	N/A	N/A	39 Patients aged 30 ± 12 years, 64% female
	Comparative observational in Pakistan	ED	Any non-opioid (diclofenac, 80; ketorolac, 32; tramadol, 10)	N/A	N/A	122 Patients aged 34 ± 15, 64% female
Yang, 2012 <sup>136</sup>	RCT in China, 07/2008 to 09/2009	Outpatient	Traditional acupuncture group	Received specific stimulation of traditional acupoints by electroacupuncture treatment (EAT) for 30 minutes, stimulation frequency was 2/100 Hz, and the stimulation intensity varied from 0.1 to 1.0 mA as long as the patients felt comfortable	1 hour	Entire population: 30 Patients aged 32.87 ± 8.71 years, 60% female
	RCT in China, 07/2008 to 09/2009	Outpatient	Sham acupuncture group	Received nonspecific stimulation by electroacupuncture treatment (EAT) for 30 minutes, stimulation frequency was 2/100 Hz, and the stimulation intensity varied from 0.1 to 1.0 mA as long as the patients felt comfortable	1 hour	Entire population: 30 Patients aged 32.87 ± 8.71 years, 60% female
	RCT in China, 07/2008 to 09/2009	Outpatient	No treatment	Received no treatment	1 hour	Entire population: 30 Patients aged 32.87 ± 8.71 years, 60% female
Yarnitsky, 2017 <sup>137</sup>	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Active remote electrical stimulation (pulse width 50 µs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 50 µs for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 ± 11.7 years, 80% female
	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Active remote electrical stimulation (pulse width 100 µs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 100 µs for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 ± 11.7 years, 80% female

Author, Year	Country, Study Design, Study Period	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup (days)	Patient Characteristics
Yarnitsky, 2017 (continued)	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Active remote electrical stimulation (pulse width 150 $\mu$ s)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 150 $\mu$ s for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 $\pm$ 11.7 years, 80% female
	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Active remote electrical stimulation (pulse width 200 $\mu$ s)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 200 $\mu$ s for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 $\pm$ 11.7 years, 80% female
	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Sham remote electrical stimulation	Transcutaneously, at 0.1 Hz frequency, with pulse width of 45 $\mu$ s for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 $\pm$ 11.7 years, 80% female
Yarnitsky, 2019 <sup>138</sup>	RCT in United States of America, Israel, 12/17/2017 to 10/07/2018	Outpatient	Remote electrical neuromodulation-active group	Applied to lateral arm, once for 30 to 45 minutes	2 days	126 Patients aged 44 $\pm$ 12.25 years, 80.9% female, 86.5% White
	RCT in United States of America, Israel, 12/17/2017 to 10/07/2018	Outpatient	Sham stimulation	Applied to lateral arm, once for 30 to 45 minutes	2 days	126 Patients aged 42 $\pm$ 11.81 years, 80.9% female
Zargarani, 2018 <sup>139</sup>	Crossover RCT in Iran 12/2014 to 05/2015	Outpatient	Chamomile oil	Cutaneous gel, 2mL, twice	1 day	50 Patients aged 37.94 $\pm$ 9.77 years, 86.8% female
	Crossover RCT in Iran 12/2014 to 05/2015	Outpatient	Placebo	Cutaneous gel, 2mL, twice	1 day	50 Patients aged 36.03 $\pm$ 8.79 years, 70.5% female
Ziegler, 1994 <sup>140</sup>	RCT in United States of America	Outpatient	Dihydroergotamine	Nasal spray, 0.5 mg (per nostril repeated after 15 minutes), once to twice for 4 hours	14 days	54 Patients aged 39.3 $\pm$ 10.5 years, 83.3% female

<b>Author, Year</b>	<b>Country, Study Design, Study Period</b>	<b>Study Setting (Outpatient, Inpatient, ED)</b>	<b>Intervention(s) and Comparison</b>	<b>Route of Administration, Dose and Duration</b>	<b>Length of Followup (days)</b>	<b>Patient Characteristics</b>
Ziegler, 1994 (continued)	RCT in United States of America	Outpatient	Placebo	Nasal spray, once to twice for 4 hours	14 days	58 Patients aged 36.7 ±10.75 years, 75% female

BAP = buccally absorbed prochlorperazine; BMI = body mass index; C = centigrade; cm = centimeter; cc = cubic centimeter; ED = emergency department; Hz = hertz; IV = intravenous; IVP = intravenous prochlorperazine; IM = intramuscular; kHz = kilohertz; g = gram; kg = kilogram; mA = milliampere; µg = microgram; µg/ mL = microgram/milliliter; µs = microsecond; mg = milligram; mg/kg = milligram/kilogram; mg/mL = milligram /milliliter; mL = milliliter; mL/hour = milliliter/hour; ms = millisecond; N/A = not available; NO = nitrous oxide; RCT = randomized controlled trial s = second; T = temperature;



## Appendix E. Risk of Bias

**Table E-1. Risk of bias (Cochrane ROB tool) for included randomized controlled trial studies**

Author, Year	Overall ROB	ROB From Randomization Process	ROB due to Deviations From Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Aggarwal, 2020 <sup>1</sup>	High	Moderate	Low	High	Low	Low
Alemdar, 2007 <sup>2</sup>	Moderate	Moderate	Moderate	Moderate	Moderate	Low
Amiri, 2017 <sup>3</sup>	High	Moderate	Low	High	Low	Low
Aurora, 2009 <sup>5</sup>	High	Low	Low	High	Low	Low
Aurora, 2011 <sup>4</sup>	Low	Low	Low	Low	Low	Low
Avcu, 2017 <sup>6</sup>	High	High	Low	Low	Moderate	Low
Banerjee, 1991 <sup>7</sup>	High	Moderate	Low	High	Moderate	Low
Bell, 1990 <sup>9</sup>	High	Moderate	High	High	Moderate	Low
Bigal, 2002 <sup>10</sup>	High	Moderate	Low	High	Low	Low
Bigal, 2002 <sup>11</sup>	High	High	Low	Moderate	Low	Low
Bigal, 2002 <sup>12</sup>	High	Moderate	Low	High	Low	Low
Blanda, 2001 <sup>14</sup>	Moderate	Low	Low	Low	Moderate	Low
Borhani, 2010 <sup>15</sup>	High	Moderate	Low	High	Low	Low
Boureau, 1994 <sup>16</sup>	High	Moderate	Low	Low	Moderate	High
Brandes, 2019 <sup>17</sup>	High	Moderate	Moderate	High	Moderate	Low
Callaham, 1986 <sup>18</sup>	High	Moderate	Low	High	Moderate	High
Cameron, 1995 <sup>19</sup>	Moderate	Low	Low	Low	Moderate	Low
Carleton, 1998 <sup>20</sup>	High	Low	Low	High	Low	Moderate
Cete, 2005 <sup>21</sup>	Moderate	Moderate	Low	Moderate	Low	Low
Chappell, 1994 <sup>22</sup>	High	Moderate	Low	High	Moderate	Moderate
Chou, 2019 <sup>23</sup>	Low	Low	Low	Low	Low	Low
Connor, 2009 <sup>24</sup>	Low	Low	Low	Low	Low	Low
Coppola, 1995 <sup>25</sup>	High	Moderate	Low	High	Moderate	Low
Corbo, 2001 <sup>26</sup>	Low	Low	Low	Low	Low	Low
Croop, 2019 <sup>27</sup>	High	Low	Low	Low	Low	High
Dahlöf, 2009 <sup>28</sup>	High	Low	Low	High	Moderate	Low
Demirkaya, 2001 <sup>29</sup>	High	Moderate	High	High	Moderate	Moderate
Derosier, 2010 <sup>30</sup>	High	Low	Low	High	Moderate	Low
Dexter, 1985 <sup>31</sup>	High	High	Low	High	Moderate	Moderate

<b>Author, Year</b>	<b>Overall ROB</b>	<b>ROB From Randomization Process</b>	<b>ROB due to Deviations From Intended Interventions</b>	<b>ROB due to Missing Outcome Data</b>	<b>ROB in Measurement of Outcomes</b>	<b>ROB in Selection of the Reported Results</b>
Diamond,1976 <sup>33</sup>	High	Moderate	Low	High	Moderate	Moderate
Diamond,2000 <sup>32</sup>	Moderate	Moderate	Low	Low	Moderate	Low
Diener,2002 <sup>36</sup>	Low	Low	Low	Low	Low	Low
Diener,2003 <sup>35</sup>	High	Moderate	Low	High	Moderate	High
Diener,2011 <sup>34</sup>	Moderate	Low	Low	Low	Moderate	Moderate
Dodick, 2019 <sup>37</sup>	Low	Low	Low	Low	Low	Low
Dogan,2019 <sup>38</sup>	Low	Low	Low	Low	Low	Low
Donaldson,2008 <sup>39</sup>	Moderate	Moderate	Low	Moderate	Low	Low
Etchison,2018 <sup>40</sup>	Moderate	Moderate	Low	Low	Low	Low
Farahmand,2018 <sup>41</sup>	Moderate	Moderate	Moderate	Low	Low	Low
Farkkila,2012 <sup>42</sup>	Low	Low	Low	Low	Low	Low
Fernando,2019 <sup>43</sup>	Moderate	Moderate	Low	Moderate	Low	Low
Ferrari,2010 <sup>44</sup>	Low	Low	Low	Low	Low	Low
Foroughipour,2013 <sup>45</sup>	High	Moderate	Low	High	Low	Low
Freitag,1993 <sup>46</sup>	High	Moderate	Low	High	High	Moderate
Friedman,1989 <sup>48</sup>	High	Moderate	Low	High	Moderate	Low
Friedman,2007 <sup>47</sup>	Low	Low	Low	Low	Low	Low
Friedman,2008 <sup>49</sup>	Moderate	Low	Low	Moderate	Low	Low
Friedman,2011 <sup>50</sup>	High	Low	Low	High	Low	Low
Friedman,2016 <sup>51</sup>	Low	Low	Low	Low	Low	Moderate
Friedman,2017 <sup>53</sup>	High	Low	Low	High	Moderate	Low
Friedman,2018 <sup>52</sup>	Moderate	Low	Moderate	Low	Low	Moderate
Fuglsang,2018 <sup>54</sup>	High	Low	Low	High	Moderate	Low
Gaffigan,2015 <sup>55</sup>	High	Low	Low	High	Low	Low
Gallagher,1996 <sup>56</sup>	Moderate	Moderate	Low	Low	Moderate	Low
Gerhardt,2011 <sup>57</sup>	High	Moderate	Low	High	Moderate	Low
Goadsby,2019 <sup>58</sup>	Low	Low	Low	Low	Low	Low
Goldstein,1997 <sup>59</sup>	Moderate	Moderate	Low	Moderate	Moderate	Low
Gomez-Mancilla,2001 <sup>60</sup>	High	High	Low	High	Moderate	High
Gomez-Mancilla,2014 <sup>61</sup>	Moderate	Moderate	Low	Low	Low	Low
Hakkarainen,1982 <sup>63</sup>	High	Moderate	Low	High	Moderate	Low

Author, Year	Overall ROB	ROB From Randomization Process	ROB due to Deviations From Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Hewitt,2011 <sup>64</sup>	High	Moderate	Low	High	Low	Low
Hewitt,2011 <sup>65</sup>	Low	Low	Low	Low	Low	Low
Ho,2007 <sup>66</sup>	Moderate	Moderate	Low	Low	Moderate	Low
Ho,2008 <sup>67</sup>	Low	Low	Low	Low	Low	Low
Ho,2010 <sup>68</sup>	High	Low	Low	Low	Low	High
Ho,2012 <sup>69</sup>	Low	Low	Low	Low	Low	Low
Hoffert,1992 <sup>70</sup>	High	High	Low	Low	Moderate	High
Hoffert,1995 <sup>71</sup>	High	Moderate	Low	High	Moderate	Moderate
Hokenek, 2020 <sup>72</sup>	High	High	Low	Low	Moderate	High
Honkaniemi,2006 <sup>73</sup>	High	Moderate	Low	High	Moderate	Low
Hourgaard,2013 <sup>74</sup>	Moderate	Moderate	Low	Low	Low	Low
Jones,1994 <sup>75</sup>	High	Moderate	Low	High	Moderate	Low
Jones,1996 <sup>76</sup>	High	Moderate	Low	High	Moderate	Low
Jones,2019 <sup>77</sup>	High	Moderate	Moderate	High	Low	Low
Kangasniemi,1992 <sup>78</sup>	High	Moderate	Low	High	Moderate	Low
Kapicioglu,1997 <sup>79</sup>	High	Moderate	Low	High	Moderate	High
Karimi,2017 <sup>80</sup>	Low	Low	Low	Low	Low	Low
Klapper, 1993 <sup>81</sup>	High	Moderate	Low	High	Low	Moderate
Korucu,2018 <sup>82</sup>	High	Moderate	High	High	Moderate	Low
Kuca,2018 <sup>83</sup>	Moderate	Low	Low	Moderate	Low	Low
Lane,1989 <sup>84</sup>	High	Moderate	Low	High	Low	Low
Levy,2005 <sup>85</sup>	High	Moderate	Low	High	Moderate	Moderate
Li,2009 <sup>86</sup>	Moderate	Low	Moderate	Low	Low	Low
Lipton,2000 <sup>87</sup>	Moderate	Moderate	Low	Low	Low	Low
Lipton,2010 <sup>88</sup>	High	Low	Low	High	Low	Low
Lipton,2019 <sup>89</sup>	Moderate	Moderate	Low	Low	Moderate	Low
Lipton 2019 <sup>90</sup>	Low	Low	Low	Low	Low	Low
Loisy,1985 <sup>91</sup>	High	Moderate	Low	High	Moderate	Moderate
Maizels,1996 <sup>92</sup>	Moderate	Moderate	Low	Moderate	Moderate	Low
Maizels,1999 <sup>93</sup>	High	High	Low	Moderate	Low	Low
Marcus,2008 <sup>94</sup>	High	High	Moderate	Moderate	Low	Moderate
Marcus,2014 <sup>95</sup>	High	High	Low	Low	Moderate	Low

Author, Year	Overall ROB	ROB From Randomization Process	ROB due to Deviations From Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Mazaheri,2015 <sup>96</sup>	High	Low	Low	High	Low	Low
McEwen,1987 <sup>97</sup>	High	Moderate	Low	High	Low	Low
Miller,2009 <sup>98</sup>	Moderate	Moderate	Low	Low	Low	Low
Million,1984 <sup>99</sup>	High	High	Low	Low	Moderate	Low
Mitra, 2020 <sup>100</sup>	Moderate	Low	Moderate	Low	Moderate	Low
Molaie,1987 <sup>101</sup>	High	Moderate	Low	High	Moderate	Moderate
Niazi,2017 <sup>102</sup>	High	Moderate	Low	High	Low	Low
Pfaffenrath,1990 <sup>103</sup>	High	High	Low	Low	Moderate	Low
Prior,2010 <sup>104</sup>	Low	Low	Low	Low	Low	Low
Rafieian-Kopaei,2019 <sup>105</sup>	Moderate	Moderate	Low	Low	Moderate	Moderate
Rapoport,1995 <sup>106</sup>	Moderate	Moderate	Low	Low	Moderate	Moderate
Reutens,1991 <sup>107</sup>	High	High	Low	High	Moderate	Low
Richman ,2002 <sup>108</sup>	High	Moderate	Low	High	Moderate	Low
Rowat,1991 <sup>109</sup>	Moderate	Moderate	Low	Moderate	Moderate	Low
Ryan,1970 <sup>110</sup>	High	Moderate	Low	High	High	Moderate
Salazar,2011 <sup>111</sup>	High	Moderate	Low	High	Moderate	Moderate
Sang,2004 <sup>112</sup>	Moderate	Low	Low	Moderate	Low	Moderate
Scherl,1995 <sup>114</sup>	High	Moderate	Low	High	Moderate	Moderate
Shahrami,2015 <sup>115</sup>	High	Moderate	Low	High	Moderate	Low
Sharma,2002 <sup>116</sup>	High	Moderate	Low	High	Moderate	Low
Silberstein,2003 <sup>119</sup>	High	Low	Low	High	Low	High
Silberstein,2005 <sup>117</sup>	High	Moderate	Low	Low	Low	High
Silberstein,2009 <sup>118</sup>	High	Moderate	Low	High	Moderate	Low
Soleimanpour,2012 <sup>120</sup>	Moderate	Moderate	Low	Low	Low	Low
Soyka,1988 <sup>121</sup>	High	Moderate	Low	High	Moderate	Low
Soyka,1989 <sup>122</sup>	High	Moderate	Low	High	Moderate	Low
Stiell,1991 <sup>123</sup>	High	Low	Low	High	Low	Low
Taheraghdam,2011 <sup>125</sup>	High	High	Low	High	Moderate	Low
Tanen,2003 <sup>126</sup>	Low	Low	Low	Low	Low	Low
Tassorelli,2018 <sup>127</sup>	Low	Low	Low	Low	Low	Low
Tek,1990 <sup>128</sup>	High	Low	High	Low	Low	Low
Treves,1998 <sup>129</sup>	High	Low	Low	High	Moderate	Low

<b>Author, Year</b>	<b>Overall ROB</b>	<b>ROB From Randomization Process</b>	<b>ROB due to Deviations From Intended Interventions</b>	<b>ROB due to Missing Outcome Data</b>	<b>ROB in Measurement of Outcomes</b>	<b>ROB in Selection of the Reported Results</b>
Triner,1999 <sup>130</sup>	Moderate	Moderate	Low	Moderate	Low	Low
Tulunay,1987 <sup>132</sup>	High	High	Low	High	Moderate	High
Tulunay,2004 <sup>131</sup>	High	Moderate	Low	High	Low	Low
Voss,2016 <sup>133</sup>	Low	Low	Low	Low	Low	Low
Wang,2012 <sup>134</sup>	Moderate	Moderate	Moderate	Low	Low	Low
Yang,2012 <sup>136</sup>	High	Moderate	High	High	Moderate	Moderate
Yarnitsky,2017 <sup>137</sup>	Moderate	Moderate	Low	Low	Low	Low
Yarnitsky,2019 <sup>138</sup>	Low	Low	Low	Low	Low	Low
Zargaran,2018 <sup>139</sup>	Moderate	Moderate	Low	Moderate	Low	Low
Ziegler,1994 <sup>140</sup>	High	Moderate	Low	High	Moderate	Low

ROB = risk of bias

**Table E-2. Risk of bias (Newcastle Ottawa tool) for included comparative observational studies**

Author, Year	Representativeness of Study Cohort	Ascertainment of Exposure	Outcome not Present Before the Exposure	Comparability Between Groups	Outcome Data Source	Independent Blind Assessment of Outcome	Loss during Followup	Overall ROB
Baratloo,2017 <sup>8</sup>	High	Low	Low	High	Low	High	Moderate	High
Bigal,2001 <sup>13</sup>	Low	Low	Low	High	Low	High	Moderate	High
Griffith,2008 <sup>62</sup>	Low	Low	Low	High	High	High	Moderate	High
Sasanejad,2012 <sup>113</sup>	Moderate	Low	Low	High	High	Low	Moderate	High
Swidan,2005 <sup>124</sup>	Low	Low	Low	High	Low	Low	Moderate	High
Wasay,2006 <sup>135</sup>	Low	Low	Low	High	Low	High	Moderate	High

ROB = risk of bias

## Appendix F. Results From Included Studies

**Table F-1. Results from included studies: KQ 1. opioids**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Alemder, 2007, <sup>2</sup> RCT	ED	Tramadol vs. Placebo	IV, 100 mg, once for 30 minutes vs. IV 100 mg, once for 30 minutes	1 day	Single-dose intravenous tramadol was associated with significantly more pain reduction at 1 hour than placebo. There was no significant difference in pain free and pain reduction at 30 minutes. 1 patient in the tramadol group reported transient blurred vision and dizziness after 1 day.
Boureau, 1994, <sup>16</sup> Crossover RCT	Outpatient	Acetaminophen codeine vs. Placebo	Oral, 400 mg acetaminophen and 25 mg codeine, once vs. Oral, once	2 hours	The combination of acetaminophen 400 mg and codeine 25 mg combination was not significantly different from aspirin 100 mg in complete or almost complete pain relief, and VAS pain scale at 2 hours. Aspirin was more effective than the combination of acetaminophen and codeine in pain intensity scale at 2 hours. Either of the treatments achieved significantly better outcomes than placebo. No serious adverse events were reported. Significantly more nausea and vomiting were reported in the active treatment groups than the placebo group.
Carleton, 1998, <sup>20</sup> RCT	ED	Dihydroergotamine mesylate plus Hydroxyzine hydrochloride vs. Meperidine plus Hydroxyzine hydrochloride	Dihydroergotamine mesylate: Intramuscular, 1 mg, once Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once vs. Meperidine: Intramuscular, 1.5 mg/kg, once, Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once	1 day after discharge	There was no statistically significant difference between the two groups on reduction of headache pain at 1 hour and functional ability at 1 day.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Freitag, 1993, <sup>46</sup> RCT	ED	TNB (Transnasal Butorphanol) vs. Methadone vs. Placebo	Transnasal, 1 mg, twice vs. Intramuscular, 10 mg, once vs. Transnasal, twice and Intramuscular, once	6 hours	Compare with transnasal butorphanol, methadone was associated with significantly less pain reduction at 2 hours. There was no statistical difference at 6-hour post-treatment evaluation or number of adverse events between these two groups. Compare with placebo, methadone was associated with significantly more pain reduction at 2-hour post-treatment evaluation.
Friedman, 2017 <sup>53</sup> RCT	ED	Prochlorperazine plus diphenhydramine vs. Hydromorphone plus normal saline placebo	IV, 10 mg (Prochlorperazine) + 25 mg (Diphenhydramine) vs. IV, 1 mg (hydromorphone)	90 days	IV prochlorperazine plus diphenhydramine was found to have significantly better outcomes on headache relief at 1 hour and 48 hours, and functional impairment at 1 hour than IV hydromorphone. There was no significant difference on functional impairment at 48 hours and incidence of adverse events.
Griffith, 2008, <sup>62</sup> Comparative observational	ED	Hydromorphone vs. Metoclopramide vs. Others	IV: 48 Patients, Intramuscular 3 Patients, 0.5 mg: 15 Patients, 1.0 mg: 26 Patients, 2.0 mg: 7 Patients, and 4.0 mg: 3 Patients, once vs. IV, 10 mg: 37 Patients, 20 mg: 58 Patients, once vs. IV, Intramuscular, Oral, once	NR	Comparing to hydromorphone, metoclopramide was associated with significant more pain reduction at 2 hours. There was no statistical difference in adverse events.
Hoffert, 1995, <sup>71</sup> RCT	Outpatient	Butorphanol vs. Placebo	Nasal spray, 1 mg per spray, maximum of 12 additional sprays vs. Nasal spray, placebo, maximum of 12 additional	NR	Patients in the butorphanol group were found to have statistically significant more pain free, pain reduction, and adverse events than those in placebo group by 1 hour, 6 hours, and 40 hours.



Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Klapper, 1993, <sup>81</sup> RCT	Outpatient	Dihydroergotamine plus metoclopramide plus placebo vs. Meperidine plus hydroxyzine plus placebo	IV, 1 mg Dihydroergotamine +10 mg Metoclopramide vs. IM, 75 mg meperidine+75 mg hydroxyzine	1 hour	Patients in the dihydroergotamine and metoclopramide group had significantly better pain reduction than those in the meperidine and hydroxyzine group. No patients required prolonged observation or additional treatment due to adverse events.
Lane, 1989 <sup>84</sup> RCT	ED	Chlorpromazine vs. Dimenhydrinate plus meperidine	IV, 25 mg, every 15 up to three doses vs. IV, 50mg Dimenhydrinate + 100 mg Meperidine, every 15 minutes up to a total of three doses	1 hour	Patients in the IV chlorpromazine group reported significantly better outcomes on pain reduction at ED discharge.
Richman, 2002, <sup>108</sup> RCT	ED	Droperidol vs. Meperidine	IM, 2.5 mg, once vs. IM, 1.5 mg/ kg, once	0.5 hour	There was no statistical difference between droperidol and meperidine in pain reduction at 30 minutes.
Scherl, 1995, <sup>114</sup> RCT	Outpatient	Dihydroergotamine plus metoclopramide vs. Meperidine plus promethazine	IV, 0.5 mg Dihydroergotamine with 10 mg Metoclopramide, once vs. Intramuscular, 75 mg Meperidine with 25 mg Promethazine, once	1 day	There was no statistical difference between two groups on pain relief at 1 hour. However, patients in the meperidine plus promethazine group reported significantly more severe adverse events.
Silberstein, 2005, <sup>117</sup> RCT	Outpatient	Acetaminophen plus tramadol vs. Placebo	Oral, 75 mg/650 mg, once vs. Oral, placebo, once	1 day	Compare with placebo, tramadol and acetaminophen were associated with significantly more patients of pain free at 2 hours and 1 day, more patients responded to treatment at 2 hours and 6 hours, and more improved functions. Significant more adverse events were reported in the tramadol/acetaminophen than those in the placebo group. There was no serious adverse event in either group.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Stiell, 1991, <sup>123</sup> RCT	ED	Methotrimeprazine vs. Meperidine plus dimenhydrinate	Intramuscular, 37.5 mg, once for 2 days vs. Intramuscular, 75 mg meperidine with 50 mg dimenhydrinate, once for 2 days	2 days	There was no statistical difference on patient reduction at 1 hour and adverse events.
Taheraghdam, 2011, <sup>125</sup> RCT	ED	Dexamethasone vs. Morphine	IV, 8mg, once for 1 day vs. IV, 0.1 mg/kg, once for 1 day	1 day	Dexamethasone was found to have significantly large pain reduction than morphine at 1 hour and 1 day.
Wasay, 2006, <sup>135</sup> Comparative observational	ED	Any opioid (Pethidine, 25; Pentazocine, 10; and oral opioid analgesics, 4) vs. Any non-opioid (Diclofenac, 80; Ketorolac, 32; Tramadol, 10)	NR	NR	There was no statistical difference on pain reduction between opioid analgesics and non-opioid analgesics.

ED = emergency department; IM = intramuscular; IV = intravenous; mg = milligram; mg/kg = milligram/kilogram; NR = not reported; RCT = randomized controlled trial; TNB = transnasal butorphanol

**Table F-2. Results from included studies: KQ 2. ergot alkaloids**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Aurora, 2009, <sup>5</sup> RCT	Outpatient	Placebo vs. Dihydroergotamine mesylate 0.5 mg vs. Dihydroergotamine mesylate 1 mg	Inhaled (orally), four times vs. Inhaled (orally), 0.5 mg, twice vs. Inhaled (orally), 1 mg, twice	28 days	Compare with placebo, significantly more patients in the dihydroergotamine 1.0 mg reached pain freedom, pain relief at 2 hours and sustained pain free at 1 day. There was no significant difference between dihydroergotamine 2.0 mg and placebo. No significant difference on adverse events was reported. There was no serious adverse event.
Aurora, 2011, <sup>4</sup> RCT	Outpatient	Dihydroergotamine vs. Placebo	Inhaled (orally), 1 mg, once vs. Inhaled (orally), once	2 days	Compared to placebo, significantly more patients in the dihydroergotamine reached pain freedom, pain relief, sustained pain free, and sustained free relief at 2 hours, 1 day, and 2 days. No significant difference on adverse events was reported. There was no serious adverse event.
Bell, 1990, <sup>9</sup> RTC	ED	Chlorpromazine vs. Dihydroergotamine vs. Lidocaine	IV, 12.5 mg, once after attack vs. IV, 1 mg, once after attack vs. IV, 50 mg, one to three times	1 day	No significant difference was observed on complete pain relief at 1 hour. Dihydroergotamine reported significantly more adverse events than lidocaine or chlorpromazine.
Callahan, 1986, <sup>18</sup> RCT	ED	Dihydroergotamine vs. Placebo	IV, 0.75 mg, once after attack vs. IV, once after attack	2 days	There was no significant difference between dihydroergotamine and placebo on pain reduction at 1 hour.
Diener, 2002, <sup>36</sup> RCT	Outpatient	Caffeine plus ergotamine vs. Placebo	Oral, 1 mg ergotamine tartrate with 100 mg caffeine, once or twice vs. Oral, once or twice	7-14 days	Significantly more patients in the ergotamine plus caffeine group reported pain relief at 2 hours. No significant difference on pain free at 2 hours and adverse events was reported. There was no serious adverse event.
Friedman, 1989, <sup>48</sup> RCT	Outpatient	Cafergot P-B vs. Cafergot vs. Placebo	Oral, 6 tablets total if needed vs. Oral, 6 tablets total if needed 2 hours vs. Oral, 6 tablets total if needed	3 hours	The combination of ergotamine tartrate, pentobarbital, and bellafoline were significantly better on pain reduction at 2 hours than ergotamine tartrate only or placebo. No significant difference on adverse events was reported.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Gallagher, 1996, <sup>56</sup> RCT	Outpatient	Dihydroergotamine mesylate 3 mg vs. Dihydroergotamine mesylate 2 mg vs. Placebo	Intranasal, 3 mg, 3 times in each nostril vs. Intranasal, 2 mg, 3 times in each nostril vs. Intranasal, 3 times in each nostril	1 day	Dihydroergotamine mesylate 3 mg and 2mg significantly reduced pain and improved function at 2 hours and 4 hours, compare with placebo. The interventions were also significantly associated with more adverse events.
Hakkarainen, 1981, <sup>63</sup> Crossover RCT	Outpatient	Ergotamine 1 mg vs. Metoclopramide 20 mg vs. Ergotamine 1 mg plus metoclopramide 20 mg vs. Ergotamine 2 mg plus metoclopramide 20 mg	Suppository, once after attack vs. Suppository, once after attack vs. Suppository, once after attack vs. Suppository, once after attack	NR	The number of adverse events was comparable between groups.
Kangasniemi, 1992, <sup>78</sup> Crossover RCT	Outpatient	Ergotamine vs. Placebo	Suppositories, 2 mg, twice vs. Suppositories, Placebo, twice	2 hours	No significant difference was reported on pain reduction and working ability at 2 hours
Rapoport, 1995, <sup>106</sup> RCT	Outpatient	Dihydroergotamine vs. Placebo	Nasal spray, 2 mg in 0.5 mL, divided into 2 sprays delivered in 15 minutes interval vs. Nasal spray, 0.5 mL, divided into 2 sprays delivered in 15 minutes interval	4 hours	Dihydroergotamine nasal spray significantly reduced pain than placebo at 4 hours, though not at 2 hours.
Ryan, 1970, <sup>110</sup> Crossover RCT	Outpatient	Ergostine 1 mg plus caffeine 100 mg vs. Ergostamine tartrate 1 mg plus caffeine 100 mg vs. Placebo	Oral, two to six times vs. Oral, two to six times vs. Oral, two to six times	1 day	Ergostine-caffeine and ergotamine-caffeine was significantly better on pain reduction at 1 hour than placebo. Adverse events were only mild to moderate.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Sharma, 2002, <sup>116</sup> RCT	Outpatient	Buccal prochlorperazine vs. Buccal placebo vs. Oral ergotamine tartarate plus caffeine	Oral, 3 mg, once vs. Oral, placebo, once vs. Oral, 1 mg ergotamine tartarate plus 100 mg caffeine, once	NR	Compare with placebo or ergotamine tartarate plus caffeine mg, prochlorperazine significantly reduced more pain at 2 hours. No significant difference was found between placebo and ergotamine.
Swidan, 2005, <sup>124</sup> Comparative observational	Inpatient	Dihydroergotamine mesylate (DHE-45) vs. Diphenhydramine	IV, 0.25-1.0 mg, 3 times daily for 3 days vs. IV, 25-75 mg, 3 times daily for 3 days	3 days	Compare with diphenhydramine, dihydroergotamine mesylate was significantly less effective immediately after treatment but might be more effective at over a 3-day 9-dose period. No serious adverse events were reported.
Treves, 1998, <sup>129</sup> RCT	Outpatient	Dihydroergotamine 1 mg vs. Dihydroergotamine 0.5 mg vs. Placebo	Nasal, 1mg, 2 to 4 times vs. Nasal, 0.5mg, 2 to 4 times vs. Nasal, 2 to 4 times	NR	No significant difference on adverse events was reported.
Tulunay, 1987, <sup>132</sup> Crossover RCT	Outpatient	Dihydroergotamine vs. Placebo	Intranasal (Puff), 4 mg/ml of DHE in an aqueous solution of 1 % caffeine and 5% glucose, 2 to 3 times vs. Intranasal (Puff), 2 to 3 times	0.5 days	The difference between two groups was not statistically different on pain reduction immediately after treatment and adverse events.
Ziegler, 1994, <sup>140</sup> RCT	Outpatient	Dihydroergotamine vs. placebo	Nasal spray, 0.5 mg (per nostril) 1 to 2 times vs. Nasal spray, 1 to 2 times	14 days	Compare with placebo, dihydroergotamine significantly reduced pain at 2 hours. Significantly more adverse events were reported in the dihydroergotamine group, including 6 serious adverse events (nasal congestion 3, vomiting 1, nausea 1, and edema 1)

DHE = dihydroergotamine; ED = emergency department; IV = intravenous; mg = milligram; mg/mL = milligram/milliliter; NR = not reported; RCT = randomized controlled trial

**Table F-3. Results from included studies: KQ 2. antiemetic**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Amiri, 2017, <sup>3</sup> RCT	ED	Granisetron vs. Metoclopramide	IV, 2 mg, once vs. IV, 10 mg, once	4 hours	No significant difference was found on pain reduction at 2 hours and 4 hours.
Bigal, 2002, <sup>11</sup> RCT	ED	Chlorpromazine vs. Placebo	IV, 0.1 mg/kg, once after attack vs. IV, 0.9% saline, once	1 day	Significantly more patients in the chlorpromazine group achieved pain free and pain relief at 1 hour and 1 day, compare with placebo. Chlorpromazine was also significantly associated with more adverse events.
Cameron, 1995, <sup>19</sup> RCT	ED	Chlorpromazine vs. Metoclopramide	IV, 0.1 mg/kg, up to three times vs. IV, 0.1 mg/kg, up to three times	2 days	There was no statistical difference between groups on pain free at emergency room discharge, pain reduction at 30 minutes, and adverse events. No serious adverse events were reported.
Cete, 2004, <sup>21</sup> RCT	ED	Metoclopramide plus normal saline vs. Magnesium sulfate plus normal saline vs. Placebo	Metoclopramide: IV, 10 mg, once for 10 minutes, Normal saline: 100 mL once for 10 minutes vs. Magnesium sulfate: IV, 2 g, once for 10 minutes, Normal saline: 100 mL once for 10 minutes vs. IV, 100 mL once for 10 minutes	1 day after discharge	There was no significant difference across groups on pain reduction at 30 minutes. 1 patient (3%) treated by metoclopramide developed 1 adverse event, compare with 3 patients (8%) in the magnesium group.
Chappell, 1994 <sup>22</sup> Crossover RCT	ED	Zatsetron to placebo vs. Placebo to zatsetron	IV, 13 mg or 0.19 mg/kg, once for 30 minutes vs. IV, 13 mg or 0.19 mg/kg, once for 30 minutes	1.5 hours	No significant difference was found on pain reduction at 1.5 hours and adverse events.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Coppola, 1995, <sup>25</sup> RCT	ED	Metoclopramide vs. Prochlorperazine vs. Placebo	IV, 10 mg in 2ml, once for 2 minutes vs. IV, 10 mg in 2ml, once for 2 minutes vs. IV, 2 ml, once for 2 minutes	2 days after discharge	Significantly more patients in the prochlorperazine reached clinical success at 30 minutes than placebo or metoclopramide. There was no statistical difference between metoclopramide and placebo.
Corbo, 2001, <sup>26</sup> RCT	ED	Metoclopramide plus magnesium sulfate vs. Metoclopramide plus placebo	Metoclopramide: IV, 20 mg, for 2 minutes up to 3 doses, Magnesium sulfate: IV, 2 g in a 10% normal saline solution, for 10 minutes up to three doses vs. Metoclopramide: IV, 20 mg, for 2 minutes up to three doses placebo: IV, 50 ml, for 10 minutes, up to 3 doses	1 day	Patients receiving metoclopramide plus placebo reported significantly less pain, better functioning at 1 hour and more adverse events than those receiving metoclopramide plus magnesium
Dexter, 1985, <sup>31</sup> RCT	Outpatient	Paracetamol plus metoclopramide vs. Placebo	Oral, Paracetamol 500mg plus metoclopramide 5 mg, up to three times vs. Oral, up to three times	112 days	No adverse events were reported in both groups.
Dogan, 2019, <sup>38</sup> RCT	ED	Metoclopramide vs. Placebo	IV, 10mg in 100 ml normal saline solution, once for 10 mins vs. IV 100 ml normal saline, once for 10 minutes	1-3 days	Significant more patients in the metoclopramide group got more 50% pain reduction at 30 minutes of treatment than those in the placebo group. No significant difference was found on adverse events.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Fernando, 2019, <sup>43</sup> RCT	ED	BAP (Buccally a absorbed prochlorperazine) vs. IVP (Intravenous prochlorperazine)	Buccally 6 mg of BAP + 2.25 ml IV normal saline solution vs. IV, 10 mg of IVP in a volume of 2.25 ml + buccal saccharine pills	1-2 days	There was no significant difference between groups on pain reduction at 1 hour and 2 days and adverse events.
Friedman, 2008, <sup>49</sup> RCT	ED	Prochlorperazine vs. Metoclopramide	IV, 10 mg, once for 15 mins vs. IV, 20 mg, once for 15 mins	1 day	There was no significant difference between groups at pain free and pain relief at 2 hours, sustained pain free and pain relief at 1 day, and number of adverse events.
Friedman, 2011, <sup>50</sup> RCT	ED	Metoclopramide 10 mg plus diphenhydramine vs. Metoclopramide 20 mg plus diphenhydramine vs. Metoclopramide 40 mg plus Diphenhydramine	IV, 10 mg Metoclopramide + 25 mg Diphenhydramine, once for 20 mins vs. IV, 20 mg Metoclopramide + 25 mg Diphenhydramine) once for 20 mins vs. IV, 40 mg Metoclopramide + 25 mg Diphenhydramine, once for 20 mins	2 days	There was no significant difference cross groups on pain free, pain relief, and function at 2 hours, and 48 hours. 17% of the overall patients developed drowsiness, the most common adverse events.
Friedman, 2016, <sup>51</sup> RCT	ED	Diphenhydramine plus metoclopramide vs. Placebo plus metoclopramide	IV, 50 mg Diphenhydramine + 10 mg Metoclopramide, once, for 15 minutes vs. IV, 10 mg Metoclopramide, once, for 15 minutes	2 days	There was no significant difference on reduction of pain score at 1 hour, sustained pain relief at 48 hours, and adverse events.



Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Gaffigan, 2015, <sup>55</sup> RCT	ED	Diphenhydramine plus haloperidol I vs. Diphenhydramine plus metoclopramide	IV, 5 mg, once for 2 minutes vs. IV, 10 mg, once for 2 minutes	14 days	There was no significant difference on pain reduction within 80 minutes of treatment. Significantly more patients in the haloperidol group reported restlessness than those in the metoclopramide group. No other significant difference on adverse events were reported.
Honkanimi, 2006, <sup>73</sup> RCT	Inpatient	Haloperidol vs. Placebo	IV, 5 mg in 500 ml normal saline over 20-30 minutes vs. IV, 500 mL normal saline over 20-30 minutes	30 days	Compare with placebo, haloperidol significantly reduced pain at 1-3 hours post-treatment. Significantly more patients in the haloperidol reached pain relief at 1-3 hours and reported adverse events.
Jones, 1994, <sup>75</sup> RCT	ED	Prochlorperazine vs. Placebo	Rectal, 25 mg, once vs. Rectal, Placebo, once	2 hours	Prochlorperazine was associated with significantly more pain reduction at 2 hours than placebo. No adverse events were reported.
Jones, 1996, <sup>76</sup> RCT	ED	Prochlorperazine-edisylate vs. Metoclopramide hydrochloride vs. Saline	Intramuscular, 10 mg, once vs. Intramuscular, 10 mg, once vs. Intramuscular, 2 mL, once	1 hour	Significantly more patients treated by prochlorperazine achieved pain free at 1 hour than those by placebo. There was no statistical difference between prochlorperazine and metoclopramide on adverse events or pain free at 1 hour. The difference between metoclopramide and placebo was not significant.
Loisy, 1985, <sup>91</sup> RCT	Outpatient	Placebo vs. Bemisetron, 5HT <sub>3</sub> receptor antagonist (MDL 72,222)	IV, once vs. IV, 20 ml, once	2 hours	Significantly more patients achieved pain relief (unknown time point) in the bemisetron group than those in the placebo group. No adverse events were reported.
McEwen, 1987, <sup>97</sup> RCT	ED	Chlorpromazine vs. Normal saline	Intramuscular, 50 mg/2ml (1 mg/kg), once vs. Intramuscular, 2 ml, once	1 day	There was no significant difference on pain free at 30 minutes. Significantly more patients in the chlorpromazine group reported drowsiness and blood pressure drop than those in the placebo group.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Miller, 2009, <sup>98</sup> RCT	ED	Prochlorperazine vs. Octreotide	IV, 10 mg once for 2 minutes vs. IV, 100 µg once for 2 minutes	3 days	Compare with octreotide, prochlorperazine significantly reduced more pain and improved treatment success at 1 hour post-treatment.
Rowat, 1991, <sup>109</sup> RCT	ED	Granisetron 40 µg/kg vs. Granisetron 80 µg/kg vs. Placebo	IV, 20 ml, once for 3 minutes vs. IV, 20 ml, once for 3 minutes vs. IV, placebo, once for 3 minutes	3 ±1 days	No significant difference was found on pain reduction and pain free at 2 hours, and adverse events between groups. No serious adverse events were reported.
Salazar, 2011, <sup>111</sup> RCT	ED	Metoclopramide vs. Paracetamol	IV, 10 mg, once vs. IV, 1g, once	2 days	There was no significant difference on pain reduction at 2 hours Significantly more patients in the metoclopramide group reported adverse events than those in the paracetamol group.
Shahrami, 2015, <sup>115</sup> RCT	ED	Dexamethasone plus metoclopramide vs. Magnesium sulfate	IV, 8 mg dexamethasone and 10 mg metoclopramide in 100 ml normal saline solution, once for 15 minutes vs. IV, 1g in 100 ml normal saline, once for 15 minutes	2 hours	Magnesium sulfate significantly reduced more pain at 2 hours and the combination of dexamethasone and metoclopramide. No significant difference was found on adverse events.
Silberstein, 2003, <sup>119</sup> RCT	Outpatient	Droperidol 0.1 mg vs. Droperidol 2.75 mg vs. Droperidol 5.5 mg vs. Droperidol 8.25 mg vs. Placebo	Intramuscular, 0.1 mg, once vs. Intramuscular, 2.75 mg, once vs. Intramuscular, 5.5 mg, once vs. Intramuscular, 8.25 mg, once vs. Placebo	7 days	Patients received droperidol 2.75 mg, 5.5 mg, and 8.25 mg were more likely to report pain free and pain relief at 2 hours.
Tek, 1990, <sup>128</sup> RCT	ED	Metoclopramide vs. Placebo	IV, 10 mg, once vs. IV, 2 ml, once	2 days	Metoclopramide achieved significantly more pain reduction and pain relief than placebo at 1 hour. No adverse events reported in any group.

BAP = buccally absorbed prochlorperazine; cc = cubic centimeter; ED = emergency department; IV = intravenous; g = gram; IVP = intravenous prochlorperazine; mg = milligram; µg/kg = microgram/kilogram; µg/ mL = microgram/milliliter; ml = milliliter; mg/kg = milligram/kilogram; RCT = randomized controlled trial

**Table F-4. Results from included studies: KQ 2. calcitonin gene-related peptide receptor antagonists**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Connor, 2009, <sup>24</sup> RCT	Outpatient	Telcagepant 50 mg vs. Telcagepant 150 mg vs. Telcagepant 300 mg vs. Placebo	Oral, 50 mg, once vs. Oral, 150 mg, once vs. Oral, 300 mg, once vs. Oral, once	7 days	Compare with placebo, significantly more patients in telcagepant 150 mg and 300 mg were pain free and pain relief at 2 hours, 1 day, and 48 hours. No significant difference on adverse events was reported among groups. No patient died. Two serious adverse events reported: 1 in telcagepant 150 mg (hypertension) and 1 in placebo (closed head injury)
Croop, 2019, <sup>27</sup> RCT	Outpatient	Rimegepant vs. Placebo	Sublingual, 75 mg, once vs. Sublingual, once	7 to 9 days	Significantly more patients in the rimegepant group reported pain free and pain relief at 2-hour, 1-day, and 2-day post-treatment. No serious adverse events were reported.
Diener, 2011, <sup>34</sup> RCT	Outpatient	BI 44370 TA 50 mg vs. BI 44370 TA 200 mg vs. BI 44370 TA 400 mg vs. Placebo	Oral, 50mg, once, vs. Oral, 200mg, once, vs. Oral, 400mg, once, vs. Oral, once	3-7 days	Compare with placebo, BI 44370 TA 400 mg was significantly associated with pain freedom at 2 hours, 1 day and 2 days post-treatment. BI 44370 TA 400 mg or 200 mg were significantly better than placebo on pain relief at 2 hours, 1 day, and 2 days. The outcomes of BI 44370 TA 50 mg were similar to placebo. The incidence of adverse events was low across groups.
Dodick, 2019, <sup>37</sup> RCT	Outpatient	Ubrogepant 25 mg vs. Ubrogepant 50 mg vs. Placebo	Oral, 100mg, once vs. Oral, 50mg, once, vs. Oral, once	30 days	Patients in the ubrogepant 50 mg, 100 mg group were significantly more likely to be pain free, pain relief and restored function at 2 hours and sustained pain free and sustained pain relief at 1 day. No significant difference was found on total number of adverse events.
Hewitt, 2011, <sup>64</sup> RCT	Outpatient	Telcagepant + acetaminophen vs. Telcagepant vs. Placebo	Oral, 280 mg Telcagepant +1000 mg Acetaminophen, once, vs. Oral, 280 mg, once, vs. Oral, Placebo, once,	2-5 days	Compare with placebo, combination treatment of telcagepant and acetaminophen and telcagepant. Monotherapy significantly better on pain freedom and pain relief at 2 hours, 1 day, and 2 days. There was no significant difference between the combination treatment and monotherapy. No significant difference on adverse events was reported among groups. No serious adverse events were reported.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Hewitt, 2011, <sup>65</sup> RCT	Outpatient	MK-3207 2.5 mg vs. MK-3207 5 mg vs. MK-3207 10 mg vs. MK-3207 20 mg vs. MK-3207 50 mg vs. Placebo	Oral, 2.5 mg, once, vs. Oral, 5 mg, once, vs. Oral, 10 mg, once, vs. Oral, 20 mg, once, vs. Oral, 50 mg, once, vs. Oral, Placebo, once,	14 days	Compare with placebo, MK-3207 200 mg, 100 mg, and 10 mg was significantly associated with pain freedom at 2 hours post-treatment. No significant difference on adverse events was reported among groups.
Ho, 2007, <sup>66</sup> RCT	Outpatient	Telcagepant 25 mg vs. Telcagepant 50 mg vs. Telcagepant 100 mg vs. Telcagepant 200 mg vs. Telcagepant 300 mg vs. Telcagepant 400 mg vs. Telcagepant 600 mg vs. Placebo	Oral, 25 mg, once, vs. Oral, 50 mg, once, vs. Oral, 100 mg, once, vs. Oral, 300 mg, once, vs. Oral, 400 mg, once, vs. Oral, 600 mg, once, vs. Oral, Placebo, once	14 days	Telcagepant 300 mg and 600 mg was associated with significantly more patients with pain relief and pain free at 2-hour, and 1 day post-treatment. There was no significant difference on adverse events and serious adverse events.
Ho, 2008, <sup>67</sup> RCT	Outpatient	Telcagepant 150 mg vs. Telcagepant 300 mg vs. Placebo	Oral, 150 mg, once vs. Oral, 300 mg, once vs. Oral, placebo, once	14 days	Telcagepant 150 mg and 300 mg was associated with significantly more patients with pain freedom and pain relief at 2 hours, 1 day and 2 day post-treatment, compare with placebo. No patient died. 1 serious adverse event reported in the placebo group.
Ho, 2010, <sup>68</sup> RCT	Outpatient	Telcagepant 140 mg vs. Telcagepant 280 mg vs. Placebo	Oral, 140 mg, once vs. Oral, 280 mg, once vs. Oral, Placebo, once	14 days	Compare with placebo, significantly more patients in telcagepant 140 mg and 280 mg were pain free at 2 hours, and 1 day and pain relief at 2 hours.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Ho, 2012, <sup>69</sup> Crossover RCT	Outpatient	Telcagepant to acetaminophen vs. Acetaminophen to telcagepant	Oral Telcagepant, 280 mg tablet/300 mg capsule + 1000 mg Acetaminophen, once vs. Oral Acetaminophen, 1000 mg + 280 mg tablet/300 mg capsule Telcagepant, once	98 days	There was no significant difference between telcagepant and placebo on pain freedom at 2 hours and 1 day and pain relief at 2 hours. No significant difference on adverse events was reported among groups.
Lipton, 2019, <sup>89</sup> RCT	Outpatient	Rimegepant vs. Placebo	Oral, 75 mg, once vs. Oral, once	7 days	Significantly more patients in the rimegepant group reported pain free and pain relief at 2-hour, 1-day, and 2-day post-treatment. The rimegepant group also reported significantly more patients with ability to function normally 2 hours after treatment. No significant difference on adverse events was reported. One patient in the rimegepant group reported one serious adverse event (back pain), compare with two patients in the placebo group (chest pain and urinary tract infection).
Lipton, 2019, <sup>90</sup> RCT	Outpatient	Ubrogepant 25 mg vs. Ubrogepant 50 mg vs. Placebo	Oral 25 mg once vs. oral 50 mg once vs. oral	2 days	Patients in the ubrogepant 25 mg, 50 mg group were significantly more likely to be pain free, pain relief and restored function at 2 hours and 1 day and sustained pain free at 1 day. No significant difference was found on adverse events and serious adverse events.
Marcus, 2014, <sup>95</sup> RCT	Outpatient	Placebo vs. Rimegepant 10 mg vs. Rimegepant 25 mg vs. Rimegepant 75 mg vs. Rimegepant 150 mg vs. Rimegepant 300 mg	Oral, once vs. oral, 10 mg, once vs. oral, 25 mg, once vs. oral, 75 mg, once vs. oral, 150 mg, once vs. oral, 300 mg, once	7 days	Significantly more patients in the rimegepant group (75 mg, 150 mg, 300 mg) reported pain freedom and pain relief at 2-hour, and 1 day post-treatment than those in the placebo group. No death or treatment related serious adverse events were reported. No significant difference on adverse events were reported among groups.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Voss, 2016, <sup>133</sup> RCT	Outpatient	Ubrogepant 1 mg vs. Ubrogepant 10 mg vs. Ubrogepant 25 mg vs. Ubrogepant 50 mg vs. Ubrogepant 100 mg vs. Placebo	Oral, 1mg once vs. oral 10 mg once vs. oral 25 mg once vs. oral 50 mg once vs. oral 100 mg once vs. oral, once	14 days	Patients in the ubrogepant 25 mg, 50 mg, and 100 mg group were significantly more likely to be pain free at 2 hours and 1 day. Ubrogepant 50 mg, and 100 mg group were associated with sustained pain relief at 1 day and 2 days. No death or treatment related serious adverse events were reported. No significant difference on adverse events was reported among groups.

ED = emergency department; mg = milligram; RCT = randomized controlled trial

**Table F-5. Results from included studies: KQ 2. 5-HT1F**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Brandes, 2019, <sup>17</sup> RCT	Outpatient	Lasmiditan 100 mg vs. Lasmiditan 200 mg	Oral, 100mg, once or twice after attack vs. Oral, 200mg, once or twice after attack	365 days	Significantly more patients in the lasmiditan 200 mg group reached pain free or pain relief at 2 hours. Patients treated by lasmiditan 100 mg reported significant less adverse events than those treated by lasmiditan 200 mg. There were 37 serious adverse events in the 100 mg group and 43 in the 200 mg group.
Farkkila, 2012, <sup>42</sup> RCT	Outpatient	Placebo vs. Lasmiditan 50 mg vs. Lasmiditan 100 mg vs. Lasmiditan 200 mg vs. Lasmiditan 400 mg	Oral, once vs. Oral, 50 mg, once vs. Oral, 100 mg, once vs. Oral, 200 mg, once vs. Oral, 400 mg, once	14 days	Significantly more patients treated by lasmiditan 50mg, 100mg, 200mg, and 400 mg reported pain free and pain reduction at 2 hours, compare with placebo. Lasmiditan 50mg, 100mg, 200mg, and 400 mg also significantly reduced pain and improved function at 2 hours. Significantly more patients reported adverse events in the lasmiditan group. One serious adverse event reported in the 200 mg lasmiditan group.
Ferrari, 2010, <sup>44</sup> RCT	Outpatient	Placebo vs. Lasmiditan 2.5 mg vs. Lasmiditan 5 mg vs. Lasmiditan 10 mg vs. Lasmiditan 20 mg vs. Lasmiditan 30 mg vs. Lasmiditan 45 mg	IV, 60 ml infusion, once for 20 mins vs. IV, 2.5 mg in 60 ml infusion, once for 20 mins vs. IV, 5 mg in 60 ml infusion, once for 20 mins vs. IV, 10 mg in 60 ml infusion, once for 20 mins vs. IV, 20 mg in 60 ml infusion, once for 20 mins vs. IV, 30 mg in 60 ml infusion, once for 20 mins vs. IV, 45 mg in 60 ml infusion, once for 20 mins	1 day	There was a significant linear association between lasmiditan dose and pain free/pain relief at 2 hours. No serious adverse events were reported.

<b>Author, Year, Study Design*</b>	<b>Study Setting (Outpatient, Inpatient, ED)</b>	<b>Intervention (s) and Comparator</b>	<b>Route of Administration, Dose and Duration</b>	<b>Length of Followup</b>	<b>Conclusion</b>
Goadsby, 2019, <sup>58</sup> RCT	Outpatient	Lasmiditan 200 mg vs. Lasmiditan 100 mg vs. Lasmiditan 50 mg	Oral, 200 mg, once vs. Oral 100 mg, once vs. Oral, 50 mg, once	7 days	Compare with placebo, lasmiditan 200 mg, 100 mg, and 50 mg were associated with significantly more pain freedom and pain relief at 2 hours and 1 day, and more adverse events.
Kuca, 2018, <sup>83</sup> RCT	Outpatient	Lasmiditan 200 mg vs. Lasmiditan 100 mg vs. Placebo	Oral, 200 mg, once vs. Oral, 100 mg, once vs. oral Placebo	7 days	Compare with placebo, lasmiditan 200 mg, and 100 mg was associated with significantly more pain freedom and pain relief at 2 hours and 1 day, and adverse events. No serious adverse events were reported.

ED = emergency department; IV = intravenous; mins = minutes; mg = milligram; RCT = randomized controlled trial



**Table F-6. Results from included studies: KQ 2. other interventions**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Aggarwal, 2020, <sup>1</sup> Crossover RCT	Outpatient	Timolol vs. Placebo	Eye drop, 0.5% once vs. Eye drop, once	2 hours	There was no statistically significant difference between the two groups on pain reduction (measured by visual analog pain scale), pain relief, and satisfaction at 2 hours.
Avcu, 2017, <sup>6</sup> RCT	ED	Lidocaine vs. Placebo	Intranasal, 10%, once or twice after attack vs. Intranasal, 0.9% saline, once or twice after attack	3 days	There was no significantly difference on patient reduction between groups at 30 minutes. No serious adverse events were reported. Significantly more patients in the lidocaine group reported adverse events.
Banerjee, 1991, <sup>7</sup> RCT	Outpatient	Propranolol vs. Placebo	Oral, 40 mg, one to three times vs. Oral, one to three times	2 days	Compare with placebo, propranolol had no significant difference on pain reduction and adverse effects.
Baratloo, 2017, <sup>8</sup> Comparative observational	ED	Caffeine citrate vs. Magnesium sulfate	IV, 60 mg, once for 10 minutes vs. IV, 2 g, once for 10 mins	2 hours	Magnesium sulfates significantly reduced more pain at 2 hours than caffeine citrate group. There was no serious adverse event.
Bigal, 2001, <sup>13</sup> Comparative observational	Outpatient	Dipyron vs. Placebo	IV, 1 g, once after attack vs. IV, saline, once after attack	1 hour	Dipyron significantly reduced pain at 1 hour, compare with placebo. One patient in the dipyron reported dyspepsia. No significant difference on adverse events was found.
Bigal, 2002, <sup>10</sup> RCT	Outpatient	Dipyron vs. Placebo	IV, 1 g, once after attack vs. IV, 0.9% saline, once after attack	1 day	Significantly more patients receiving dipyron achieved pain free and pain relief at 1 hour and 1 day, compare with placebo. There was no significant difference on adverse events.
Bigal, 2002, <sup>12</sup> RCT	Outpatient	Magnesium sulphate vs. Placebo	IV, 1 g, once after attack vs. IV, 0.9% saline, once after attack	1 day	Significant more patient in the magnesium sulphate group achieved pain free and pain relief at 1 hour post-treatment. No such difference was found at 1 day.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Blanda, 2001, <sup>14</sup> RCT	ED	Lidocaine vs. Placebo	Intranasal, 4%, two to four times, Intranasal, 0.9% saline, two to four times	1 day	There was no significant difference between the two groups on pain reduction at 5 minutes and 30 minutes.
Dahlöf, 2009, <sup>28</sup> RCT	Outpatient	Placebo vs. Tonabersat 20 mg vs. Tonabersat 40 mg	Oral, once vs. Oral, 20 mg, once vs. Oral, 40 mg, once	7 days	There was no significant difference between groups on 2-hour and 4-hour pain relief and pain freedom. Significant more patients receiving tonabersat reported adverse events than those in the placebo group. No significant difference on adverse events were reported between tonabersat 20 mg and 40 mg.
Demirkaya, 2001, <sup>29</sup> Crossover RCT	Outpatient	Magnesium sulfate vs. Placebo	IV, 1 g, once for 15 minutes vs. IV, 10 ml, once	1 day	Significantly more patients in the magnesium sulfate group achieved pain free and pain relief at 30 minutes than those in the placebo group.
Derosier, 2010 <sup>30</sup> Crossover RCT	Outpatient	Butalbital, acetaminophen, caffeine vs. Placebo	Oral, Butalbital 50 mg, Acetaminophen 325 mg, and Caffeine 40 mg, once vs. Oral, once	2 days	The combination of butalbital, acetaminophen, and caffeine was associated with significantly more sustained pain free at 1 day and 48 hours, compare with placebo. No significant difference was reported on adverse events.
Diamond, 1976, <sup>33</sup> Crossover RCT	Outpatient	Isometheptene mucate, acetaminophen, and dichloralphenazone vs Acetaminophen vs Placebo	Oral, isometheptene mucate 65 mg, acetaminophen 325 mg, and dichloralphenazone 100 mg, up to five times vs. oral, 325 mg, up to five times vs Oral, up to five times	14 – 60 days	The combination of isometheptene mucate, acetaminophen, and dichloralphenazone significantly reduced more pain than placebo or acetaminophen.
Diamond, 2000, <sup>32</sup> RCT	Outpatient	Civamide 20µg vs. Civamide 150µg	Intranasal, 20µg, once vs. Intranasal, 150µg, once	7 days	There was no significant difference between the two groups on pain free and pain relief at 2 hours and 4 hours. No serious adverse events were reported.

<b>Author, Year, Study Design*</b>	<b>Study Setting (Outpatient, Inpatient, ED)</b>	<b>Intervention (s) and Comparator</b>	<b>Route of Administration, Dose and Duration</b>	<b>Length of Followup</b>	<b>Conclusion</b>
Diener, 2003, <sup>35</sup> RCT	Outpatient	Placebo vs. Dapitant 1 mg vs Dapitant 5 mg vs Dapitant 20 mg	Oral, once vs. Oral, 1 mg, once vs. Oral, 5 mg, once vs. Oral, 20 mg, once	2 days	There was no significant difference across groups on pain relief, change in mean pain Intensity, functional disability, and adverse events after 2 hours and 8 hours
Donaldson, 2008, <sup>39</sup> RCT	ED	Placebo vs. Dexamethas one	IV placebo, once vs. IV, 24 mg, once	30 days	No significant difference between dexamethasone and placebo was found on function at 3 days and 1 month, and adverse events.
Etchison, 2018, <sup>40</sup> RCT	ED	Ketamine vs. Placebo	IV, 0.2 mg/kg, once vs. IV, once	1 hour	There was no significant difference between groups on pain reduction, pain relief, and function at 30 minutes. No adverse events were reported in the study.
Foroughipour, 2013, <sup>45</sup> RCT	ED	Valproate vs. Dexamethas one	IV, 900 mg, once for 10 minutes vs. IV, 16 mg, once for 10 minutes	3 days	There was no significant difference between valproate and dexamethasone on pain reduction at 3 hours. There was no adverse event.
Friedman, 2007, <sup>47</sup> RCT	ED	Dexamethas one sodium phosphate vs. Placebo	IV, 10 mg, for 20 minutes vs. IV placebo, for 20 minutes	1 day	There was no significant difference between dexamethasone and placebo on 24 hour sustained pain free, functional impairment, patient satisfaction, or adverse events.
Friedman, 2018, <sup>52</sup> RCT	ED	Sham injection vs. Greater occipital nerve block	Intradermally, 0.5 ml Bupivacaine 0.5%, once vs. Intradermally, 3 ml Bupivacaine 0.5%, once	2 days	There was no significant difference between groups on pain reduction, pain free, and pain relief at 30 minutes, 1 hour, and 48 hours.
Gerhardt, 2011, <sup>57</sup> RCT	Outpatient	Secobarbital vs. Placebo	Oral, 100 mg, once or twice vs. Oral, once or twice	3 days	Secobarbital significantly reduced pain at 1 day, compare with placebo. No adverse events were reported.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Goldstein, 1997, <sup>59</sup> Crossover RCT	Outpatient	Lanepitant 240 mg vs. Lanepitant 80 mg vs. Lanepitant 30 mg vs. Placebo	Oral, 240 mg, once vs. Oral, 80 mg, once vs. Oral, 30 mg, once vs. Oral Placebo, once	4 days	There was no significant difference on pain relief at 2 hours and adverse events across groups.
Gomez-Mancilla, 2001, <sup>60</sup> RCT	Outpatient	PNU-142633 (selective 5-HT1D agonist) vs. Placebo	Oral, 50 mg, once vs. Oral, Placebo, once	0.5 day	There was no statistical difference between PNU-142633 and placebo on pain free at 1 and 2 hours, pain relief at 1 hour and number of adverse events.
Gomez-Mancilla, 2014, <sup>61</sup> Crossover RCT	Outpatient	Selurampanel vs. Placebo	Oral, 250 mg once vs. Oral, Placebo, once	1 day	Compare with placebo, selurampanel was associated with significantly more patients with pain free at 4 hours. There was no statistical difference on pain relief at 2 hours, 4 hours, sustained pain relief at 1 day, and adverse events. 2 patients receiving selurampanel reported serious adverse events.
Hoffert, 1992, <sup>74</sup> Crossover RCT	Outpatient	Nifedipine vs. Placebo	Oral, 20 mg, vs. Oral, Placebo,	NR	Nifedipine was associated with significantly more pain than placebo. No clinically significant adverse events were reported.
Hougaard, 2013, <sup>74</sup> RCT	Outpatient	NXN-188 vs. Placebo	Oral, 600 mg, once vs. Oral, once	7 days	There was no significant difference between groups on pain at 2 hours and 1 day. NXN-188 reported significantly more adverse events than placebo. One patient in the NXN-188 reported 1 serious adverse event.
Jones, 2019, <sup>77</sup> RCT	ED	Fluid group vs. Control group	IV, 1 L of 0.9% saline solution over 1 hour vs. IV, 0.9% saline solution at 10 mL/hour over 1 hour	2 days	There was no significant difference on pain reduction and number of patients with pain free, functional disability at 2 hours and 2 days post treatment.
Kapicioglu, 1997 <sup>79</sup> RCT	Outpatient	Octreotide vs. Placebo	Subcutaneous 100 mg	1 day	Octreotide was associated with significantly better outcomes than placebo, including pain free, pain relief, and pain reduction at 6 hours. 3 patients receiving octreotide reported minor adverse events.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Karimi, 2017, <sup>80</sup> RCT	ED	Dexamethasone vs. Valproate sodium	IV, 8 mg once vs. IV, 400 mg once	1 day	There was no significant on pain reduction at 1 hour and 6 hours. One patient reported adverse events (anxiety, unrest, and shortness of breath) in the valproate group while none reported in the dexamethasone group.
Levy, 2005, <sup>85</sup> Crossover RCT	ED	Octreotide vs. Placebo	Subcutaneous, 100 mg in 1 ml normal saline, once vs. Subcutaneous, 1 ml normal saline, once	2 day	Compare with placebo, octreotide was associated with significantly worse or no different outcomes on pain free, pain relief, and function at 2 hours. There was no serious adverse event. No significant difference on adverse events was reported.
Lipton, 2000 <sup>87</sup> RCT	Outpatient	Acetaminophen vs. Placebo	Oral, 1000 mg, once vs. oral once	6 hours	Acetaminophen was associated with significant better outcomes on pain relief, pain free, and functional disability at 2 hours and 6 hours, compare with placebo. No serious adverse events were reported. There was no significant difference on adverse events.
Maizels, 1996, <sup>92</sup> RCT	Urgent Care	Lidocaine vs. Placebo	Intranasal, 4% vs. Intranasal, 0.5 ml, 1-2 times	1 day	Lidocaine significantly reduced more pain at 15 minutes, compare with placebo.
Maizels, 1999, <sup>93</sup> RCT	Outpatient	Lidocaine vs. Placebo	Intranasal, 4%, 1-2 times vs. Intranasal, 0.5 ml, 1-2 times	180 days	Lidocaine was associated with significantly less pain at 15 minutes, function disability at 30 minutes, and less adverse events, compare with placebo.
Mazaheri, 2015, <sup>96</sup> RCT	ED	Valproate vs. Dexamethasone	IV, 400 mg for 15 minutes, once vs. IV, 16 mg for 15 minutes, once	2 hours	There was no significant difference on pain reduction at 2 hours. There was no serious adverse event.
Million, 1984, <sup>99</sup> RCT	Outpatient	Flupirtine vs. Paracetamol	Oral, 100 mg, up to 4 times a day vs. Oral, 500 mg, up to 4 times a day	5 days	4 patients in the flupirtine reported adverse events compare with 7 patients in the paracetamol group.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Mitra, 2020, <sup>100</sup> RCT	ED	Propofol vs. Standard therapy (chlorpromazine, metoclopramide, ondansetron, lignocaine, magnesium sulphate, or morphine)	IV, 1 mg/kg, slowly for 1 min	NR	There was no significant reduction of pain scale at 2 hours and 1 day.
Molaie, 1987, <sup>101</sup> RCT	ED	Verapamil hydrochloride vs. Placebo	IV, 2 cc (10 mg), once vs. IV, 2 cc normal saline, once	1 hour	There was no significant difference on pain reduction at 1 hour between verapamil hydrochloride and placebo.
Pfaffenrath, 1990, <sup>103</sup> RCT	Outpatient	Flunarizine 10 mg vs. Flunarizine 20 mg vs. Placebo	IV, 10 mg, once vs. IV, 20 mg, once vs IV, HP-beta-cyclodextrine, once	2 hours	Significantly more patients in the flunarizine 20 mg group reported pain relief at 1 hour than those in the placebo or flunarizine 10 mg group. There was no significant difference on adverse effects across the groups.
Prior, 2010, <sup>104</sup> RCT	Outpatient	Acetaminophen vs. Placebo	Oral, 1000 mg, once vs. oral, placebo, once	3 days	Acetaminophen significantly improved pain and function at 2 hours and 6 hours. Significant less patients receiving acetaminophen reported adverse events. No serious adverse events were reported.
Rafieian-Kopaei, 2019, <sup>105</sup> RCT	Outpatient	Lidocaine vs. Peppermint essential oil vs. Placebo	Intranasal, 4%, 1 to 2 times vs. Intranasal, 1.5%, 1 to 2 times vs. Intranasal, placebo, 1 to 2 times	60 days	Significantly more patients treated by peppermint oil or lidocaine reduced pain, compare with placebo.
Reutens, 1991, <sup>107</sup> RCT	ED	Lidocaine vs. Placebo	IV, 66 mg, once for 2 mins vs. IV, placebo, once for 2 mins	20 minutes	No significant difference on pain reduction at 20 minutes was found between two groups. No adverse events were reported.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Sang, 2004, <sup>112</sup> RCT	Outpatient	Tezampanel vs. Placebo	IV, 1.2 mg/ kg, once for 15 minutes vs. IV, Placebo, once for 15 minutes	1 day	Tezampanel was associated with significantly more patients with pain free and pain relief at 2 hours and sustained pain relief and sustained pain free at 1 day. There was no significant difference on serious adverse events and overall adverse events.
Silberstein, 2009, <sup>118</sup> RCT	Outpatient	Tonabersat 15 mg vs. Tonabersat 25 mg vs. Tonabersat 40 mg vs. Tonabersat 80 mg vs. Placebo	Oral, 15 mg, once vs. Oral, 40 mg, once vs. Tonabersat 80 mg vs. Placebo	7-10 days	In one of the two RCTs reported here, more patients receiving tonabersat were pain free at 2 hours and 4 hours and pain relief at 2 hours than those receiving placebo. In the other RCT, no significant difference was found. No patients died in any of the RCTs. 2 patients reported serious adverse events. Tonabersat was well tolerated.
Soleimanpour, 2012, <sup>120</sup> RCT	ED	Propofol vs. Dexamethasone	IV, 10 mg, every 5-10 minutes), rate of 1 ml for 10 seconds vs. IV, 4 mg/ ml with dose of 0.15 mg/ kg, rate of 1 ml for 10 seconds	NR	Dexamethasone significantly reduced more pain than propofol at 45 minutes. There were no adverse effects in either group.
Soyka, 1988, <sup>121</sup> RCT	Outpatient	Flunarizine vs. Placebo	IV, 20 mg, once for 60 minutes vs. IV, once for 60 minutes	0.5 days	Significantly more patients in the flunarizine group reported pain relief and pain free at 1 hour than those in the placebo. There was no significant difference on adverse effects.
Soyka, 1989, <sup>122</sup> RCT	Outpatient	Flunarizine vs. Placebo	IV, 20 mg, for 60 minutes vs. IV, for 60 minutes	0.5 days	Compare with placebo, patients receiving flunarizine reported significantly less pain and more likely to be pain free and pain relief at 1 hour post-treatment.
Tanen, 2003, <sup>126</sup> RCT	ED	Sodium valproate vs. Prochlorperazine	IV, 500 mg, once for 0.5 day vs. IV, 10 mg, once for 0.5 day	0.5 days	Prochlorperazine significantly reduced more pain at 1 hour than sodium valproate.
Tulunay, 2004, <sup>131</sup> Crossover RCT	ED	Dipyrone vs. Placebo	Oral, 1g, once vs. oral once	1 day	Significantly more patients receiving dipyrone achieved pain free and pain relief at 2 hours and 4 hours, compare with placebo. Adverse events were minimal in both groups and no serious adverse events were reported.

cc = cubic centimeter; ED = emergency department; IV = intravenous; kg = kilogram; µg = microgram; mg = milligram; mg/kg = milligram/kilogram; mg/mL = milligram/milliliter; mL = milliliter; NR = not reported; RCT = randomized controlled trial

**Table F-7. Results from included studies. KQ 3. nonpharmacologic therapy**

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Borhani, 2010, <sup>15</sup> Crossover RCT	Outpatient	Menthol vs. Placebo	10% ethanol menthol applied with sponge to forehead and temporal area vs. 0.5% ethanol menthol applied with sponge to forehead and temporal area	NR	10% menthol was associated with significantly more pain free and pain relief at 2-hour post-treatment and 24-hour and 48-hour sustained pain free, compare with placebo. No statistical difference was reported on adverse events.
Chou, 2019, <sup>23</sup> RCT	ED	Verum external trigeminal nerve stimulation vs. Sham external trigeminal nerve stimulation	Transcutaneously, 1.284 C, pulse frequency of 100 Hz with pulse width of 250 $\mu$ s for 1 hour vs. Transcutaneously, pulse frequency of 3 Hz for 1 hour	1 day	Verum external trigeminal nerve stimulation was associated with significantly more pain reduction at 2 hours and 1 day post treatment than the sham group. There was no serious adverse event reported in either group. Five minor adverse events reported in the verum group.
Farahmand, 2018, <sup>41</sup> RCT	Outpatient	Verum acupuncture vs. Sham acupuncture	Skin, once vs. Skin, once	1 day	There was no statistically significant difference on pain score at 2 hours and 4 hours post treatment.
Fuglsang, 2018, <sup>54</sup> Crossover RCT	Outpatient	Active partial rebreathing device vs. Sham partial rebreathing device	Oral, twice for 40 minutes vs. Oral, twice for 40 minutes	1 day	The partial rebreathing device significantly increased the number of pain relief at 2 hours. No adverse events were reported.



Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Hokenek, 2020, <sup>72</sup> RCT	ED	Transcutaneous electrical nerve stimulation vs. Sham stimulation	Transcutaneous electrical nerve stimulation, a pulse repetition frequency of 50 Hz, a pulse width of 125 $\mu$ s, an impulse amplitude of 60 voltage and a pulse energy of 18.4 $\mu$ J, once for 20 minutes vs. Transcutaneous electrical nerve stimulation a pulse repetition frequency of 50 Hz, with empty battery, once for 20 minutes	2 hours	Compared to sham stimulation, transcutaneous electrical nerve stimulation significantly reduced pain at 2 hours.
Korucu, 2018, <sup>82</sup> RCT	ED	Greater occipital nerve blockade vs. Placebo	Subcutaneous, 1 ml of 0.5% bupivacaine and 1 ml of normal saline, single injection or double injection vs. Subcutaneous, 2 ml of normal saline, single injection or double injection	45 minutes	Compare with placebo, significantly reduced pain at 45 minutes. No adverse events were reported.
Li, 2009, <sup>86</sup> RCT	Outpatient	Verum acupuncture vs. Sham acupuncture	Skin, needling at genuine acupoints Vs. Needling at nonacupoints	1 day	Significantly more patients in the acupuncture group reported pain free at 2 hours than the sham group. Patients in the acupuncture group were also found to have significantly more pain reduction at 2 hour and 4 hour post-treatment. No patient reported serious adverse events.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Lipton, 2010, <sup>88</sup> RCT	Outpatient	Single-pulse transcranial magnetic stimulation sTMS vs. Sham stimulation	Transcranial pulse of nominally 0.9 T peak with a rise time of 180 $\mu$ s and a total pulse length of less than 1 ms, two pulses about 30 s apart vs. Transcranial, two pulses about 30 s apart for 180 $\mu$ s	90 days	Patients in the single-pulse transcranial magnetic stimulation were significantly more likely to have pain free after 2 hour and sustained pain free at 1 day and 2 days post-treatment. There was no statistical difference in adverse events. One serious adverse event (optic neuritis) was reported in the intervention group.
Marcus, 2008, <sup>94</sup> RCT	ED	Integrated EMDR (eye movement desensitization reprocessing) vs. Standard care medication	Diaphragmatic breathing, head compression by the provider, once for 12-60 minutes vs. Standard care	7 day	Compare with standard care, integrated EMDR was found to significantly reduced pain at 1 hour post-treatment. However, there was no significant difference on pain reduction at 1 day and 1 week. No adverse events were reported in the Integrated EMDR group.
Niazi, 2007, <sup>102</sup> Crossover RCT	Outpatient	Rose damascene oil vs. Placebo	Skin, 2 cc of the Rose damascene oil forehead and temporal zones vs. Skin, 2 cc of the placebo forehead and temporal zones	1 day	There was no significant difference between groups on pain reduction at 2 hours, and 1 day. One patient in the Rosa damascena Mill. (R. damascena) oil group reported skin redness.
Sasannejad, 2012, <sup>113</sup> Comparative observational	Outpatient	Lavender essential oil vs. Placebo	Topical/ inhale, 2-3 drops of oil, 1-6 times over 15 mins vs. Topical/ inhale, 2-3 drops of placebo, 1-6 times over 15 mins	2 hours	Lavender significantly reduced pain, compare with placebo.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Tassorelli, 2018, <sup>127</sup> RCT	Outpatient	Noninvasive vagus nerve stimulation vs. Sham stimulation	Transdermal, a low-voltage electrical signal comprising a 5-kHz sine wave burst lasting for 1 ms once every 40 ms (25 Hz) for 2 minutes vs. Transdermal, a low-frequency (0.1 Hz) biphasic signal for 2 minutes	5 days	Significantly more patients in the noninvasive vagus nerve stimulation reported pain relief at 2 hours than those in the sham group, though 2-hour pain free was not statistically different. There was no difference in number of adverse events between the two groups. No serious adverse events were reported.
Triner, 1999, <sup>130</sup> RCT	ED	Nitrous oxide plus oxygen vs. Oxygen	Inhalation, 50% (NO) 50% Oxygen, once for 20 minutes vs. Inhalation, 100% Oxygen, once for 20 minutes	0.5 days	Nitrous oxide and oxygen significantly reduced pain immediately after treatments; while there was no significant pain reduction in the oxygen group. No patients reported adverse events.
Wang, 2012, <sup>134</sup> RCT	Outpatient	Verum acupuncture vs. Sham acupuncture	Acupoints, once for 30 minutes vs. Acupoints, once for 30 minutes	3 days	Acupuncture was associated with significantly more pain reduction at 1 day than the sham procedure. No statistical difference was found on number of patients with pain freedom at 1 day, 2 day or 3 day post treatment. No statistical difference was reported on adverse events.
Yang, 2012, <sup>136</sup> RCT	Outpatient	Traditional acupuncture group vs. Sham acupuncture group vs. No treatment	Specific stimulation of traditional acupoints by electroacupuncture treatment for 30 mins vs. Nonspecific stimulation by electroacupuncture treatment for 30 mins, vs. no treatment	1 hour	Acupuncture significantly reduced pain after intervention; while sham procedure also significantly reduced pain. Pain reduction for patients without any procedures was not significantly different from baseline.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Yarnitsky, 2017, <sup>137</sup> Crossover RCT	Outpatient	Active remote electrical stimulation (pulse width 50 $\mu$ s) vs. Active remote electrical stimulation (pulse width 100 $\mu$ s) vs. Active remote electrical stimulation (pulse width 150 $\mu$ s) vs. Active remote electrical stimulation (pulse width 200 $\mu$ s) vs. Sham remote electrical stimulation	Transcutaneously, at 80-120 Hz frequency, with pulse width of 50, 100, 150, 200, $\mu$ s for 20 minutes vs. Transcutaneously, at 0.1 Hz frequency, with pulse width of 45 $\mu$ s for 20 minutes	60 days	Compare with sham procedure, remote skin stimulation was associated with significantly more pain free and pain reduction at 2 hours. No adverse events were reported.
Yarnitsky, 2019, <sup>138</sup> RCT	Outpatient	Remote Electrical Neuromodulation-active group vs. Sham stimulation	Applied to lateral arm, once for 30 to 45 minutes vs. Applied to lateral arm, once for 30 to 45 minutes	2 days	The electrical neuromodulation-active was significantly more effective on pain relief, and pain-free at 2 hours and 48 hours post treatment. No statistical difference was found in adverse events.

Author, Year, Study Design*	Study Setting (Outpatient, Inpatient, ED)	Intervention (s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Zargarani, 2018, <sup>139</sup> Crossover RCT	Outpatient	Chamomile oil (chamomile extraction in sesame oil vs. Placebo	Cutaneous gel, 2ml twice vs. Cutaneous gel, 2ml twice	1 day	Chamomile oil significantly improved pain scale at 2 hours and 1 day than placebo.

cc = cubic centimeter; EMDR = eye movement desensitization reprocessing; ED = emergency department; Hz = hertz; kHz = kilohertz; L = liter;  $\mu$ s = microsecond; ml = milliliter; mins = minutes; NO = nitrous oxide; NR = not reported; RCT = randomized controlled trial; Stmss = single-pulse transcranial magnetic stimulation

## Appendix G. Summary of Systematic Reviews Evaluating Triptans and NSAIDs

**Table G-1. Results of systematic reviews evaluating triptans**

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Ashcroft, 2004 <sup>141</sup>	Naratriptan (Compared with various interventions)	10 RCT (4,499)	Search in 2002  No clear description of study selection methods, risk of bias or excluded studies	Compared with placebo for pain-free response at 2 and 4 hours, naratriptan 2.5 mg were RRs of 2.52 (1.78–3.57) and 2.58 (1.99–3.35)  -Naratriptan 2.5 mg was more effective than naratriptan 1 mg and less effective in pain-free response than either rizatriptan 10 mg at 4 hours, RR0.68 (0.55–0.85) or sumatriptan100 mg at 4 hours, RR 0.79 (0.67–0.93)  - Significantly fewer patients experienced adverse effects with naratriptan 2.5 mg than with rizatriptan 10 mg, RR 0.73 (0.56–0.97) or sumatriptan 100 mg, RR 0.68 (0.55–0.86)
Bird, 2019 <sup>142</sup>	Zolmitriptan	25 RCTs (20,162)	Search in 2014 - Fulfills all AMSTAR criteria	-For all efficacy outcomes, zolmitriptan surpassed placebo. For oral zolmitriptan 2.5 mg, NNTs were 5.0, 3.2, 7.7, and 4.1 for pain free at two hours, headache relief at two hours, sustained pain-free during the 1 day post dose, and sustained headache relief during the 1 day post dose, respectively  -Adverse events were transient and mild and were more common with zolmitriptan than placebo

<b>Systematic Review</b>	<b>Interventions</b>	<b>Studies (Patients)</b>	<b>Methodology*</b>	<b>Main Findings</b>
Chen, 2007 <sup>143</sup> (study level meta-analysis) Two pooled analyses (Caddy 2002 <sup>144</sup> and Dahlof 2006 <sup>145</sup> )	Almotriptan (compared with various interventions)	8 RCTs (4,995)	Search in 2007 -Review authors with industry ties. Duplication of review procedures is not clearly described, no list or clear description of excluded studies	-Almotriptan 12.5 mg was significantly more effective than placebo for all efficacy outcomes (absolute rate differences ranged from 0.01 to 0.28)  - No significant differences in efficacy outcomes comparing almotriptan 12.5 mg against sumatriptan 100 mg and zolmitriptan 2.5 mg, but almotriptan 12.5 mg was associated with significantly fewer adverse events than sumatriptan 100 mg  -Almotriptan 12.5 mg was significantly less effective than almotriptan 25 mg for 1-hour pain-free response but with fewer patients experiencing adverse events  -Conclusions from pooled analyses were similar to study level analyses
Derry, 2012 <sup>146</sup>	Oral sumatriptan (alone or in combination with an antiemetic compared with various interventions)	61 RCTs (37,250)	Search in 2011 but re-evaluation suggested stability of findings. - Fulfills all AMSTAR criteria	-NNTs 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively -25 and 50 mg are likely similar. 100 mg more effective. -Relief of associated symptoms (nausea, photophobia, phonophobia) and use of rescue medication were better with sumatriptan than with placebo -Adverse events were transient and mild and were more common with the sumatriptan than with placebo

<b>Systematic Review</b>	<b>Interventions</b>	<b>Studies (Patients)</b>	<b>Methodology*</b>	<b>Main Findings</b>
Derry, 2012 <sup>147</sup>	Subcutaneous sumatriptan (alone or in combination with an antiemetic compared with various interventions)	35 RCTs (9,365)	Search in 2011 but re-evaluation suggested stability of findings - Fulfills all AMSTAR criteria	-Sumatriptan 6 mg vs placebo: NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively, and 6.1 for sustained pain-free at 1 day. Similar results for other doses -Relief of headache-associated symptoms and use of rescue medications were greater with sumatriptan than with placebo
Ferrari, 2001 <sup>148</sup>	Rizatriptan	7 RCTs (4,814)	Search in 2001 - Fulfills most AMSTAR criteria, does not include clear risk of bias evaluation or a list of excluded studies	-Rizatriptan 10 mg was significantly more effective than placebo or rizatriptan 5 mg on pain relief and pain free at 2 hours and 1 day.
Mandema, 2005 <sup>149</sup>	Eletriptan (Compared with sumatriptan)	19 RCTs (11,400)	Search in 2002 Only searched Medline with no clear description of study selection methods, risk of bias or excluded studies	- Eletriptan 40 mg was associated with statistically significant efficacy compare with sumatriptan 100 mg at any point in time up to 4 h after treatment with an absolute difference at 2 h of 9.1% (7.4–11.5%) more patients achieving pain relief and 7.3% (5.8–8.6%) more patient achieving pain free
Menshawy, 2018 <sup>150</sup>	Intranasal sumatriptan	16 RCTs (5,925)	Search in 2016 - Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Intranasal sumatriptan was superior to placebo in pain relief at 2 h (RR = 1.70, 1.31,2.21) and headache relief at 30 min (RR = 1.31, 1.08, 1.59) and 2 h (RR = 1.58, 1.35, 1.84) -Intranasal sumatriptan was associated with six-fold increase taste disturbances vs placebo
Poolsup, 2005 <sup>151</sup>	Frovatriptan	5 RCTs (2,866)	Search in 2005 - Fulfills most AMSTAR criteria, does not include clear risk of bias evaluation or a list of excluded studies	-Frovatriptan 2.5 mg was more effective than placebo in rendering patient pain-free at 4 h and reducing headache severity and symptoms associated with migraine at 2 hour.



h = hour; mg = milligram; NNT = number needed to treat; RCT = randomized controlled trial; RR = relative risk

**Table G-2. Results of systematic reviews evaluating nonsteroidal anti-inflammatory drugs (NSAIDs)**

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Derry, 2012 <sup>152</sup>	Oral diclofenac (alone or in combination with an antiemetic compared with various interventions)	5 RCTs (1,356)	Search in 2011 -Fulfills all AMSTAR criteria	<p>- A single dose of diclofenac potassium 50 mg, the NNTs were 6.2, 8.9, and 9.5 for pain-free at two hours, headache relief at two hours, and pain-free responses at 1 day, respectively.</p> <p>-Associated symptoms of nausea, photophobia and phonophobia, and functional disability were reduced within two hours.</p> <p>-Adverse events were mild and transient</p>
Derry 2013 <sup>153</sup>	Paracetamol 1000 mg (alone or in combination with an antiemetic compared with various interventions)	11 RCTs (2,942)	Search in 2013 -Fulfills all AMSTAR criteria	<p>-For all efficacy outcomes paracetamol was superior to placebo, with NNTs of 12 (19% response vs 10%), 5.0 (56% response vs 36%) and 5.2 (39% response vs 20%) for 2-hour pain-free and 2- and 1-hour headache relief, respectively.</p> <p>-Nausea, photophobia and phonophobia were reduced more with paracetamol than with placebo at 2 hours.</p> <p>-Adding metoclopramide 10 mg was not significantly different from 100 mg sumatriptan for 2-hour headache relief</p>

<b>Systematic Review</b>	<b>Interventions</b>	<b>Studies (Patients)</b>	<b>Methodology*</b>	<b>Main Findings</b>
Kirthi, 2013 <sup>154</sup>	Aspirin (alone or in combination with an antiemetic compared with various interventions)	13 RCTs (4,222)	Search in 2013 -Fulfills all AMSTAR criteria	-Aspirin 900 mg or 1000 mg vs placebo was effective with NNTs of 8.1, 4.9 and 6.6 for 2-hour pain-free, 2-hour headache relief, and 24-hour headache relief.  -Sumatriptan 50 mg did not differ from aspirin alone for 2-hour pain-free and headache relief, while sumatriptan 100 mg was better than the combination of aspirin plus metoclopramide for 2-hour pain-free, but not headache relief.
Rabbie, 2013 <sup>155</sup>	Ibuprofen (alone or in combination with an antiemetic compared with various interventions)	9 RCTs (4,373)	Search in 2013 but re-evaluation suggested stability of findings -Fulfills all AMSTAR criteria	-Ibuprofen 400 mg vs placebo: NNTs for 2-hour pain-free (26% versus 12% with placebo), 2-hour headache relief (57% versus 25%) and 24-hour sustained headache relief (45% versus 19%) were 7.2, 3.2 and 4.0, respectively.  -Ibuprofen 400 mg did not differ from rofecoxib 25 mg and was better than ibuprofen 200 mg.
Taggart, 2013 <sup>156</sup>	Ketorolac	8 RCTs (321)	Search in 2010 -Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Ketorolac and meperidine resulted in similar pain scores at 60 minutes.  -Ketorolac was more effective than intranasal sumatriptan.  - Ketorolac was not significantly more effective in pain relief at 60 minutes compare with phenothiazine agents.  -Side effect profiles were similar between Ketorolac and comparison groups

mg = milligram; NNT = number needed to treat; RCT = randomized controlled trial

**Table G-3. Results of systematic reviews evaluating the combination of triptans and nonsteroidal anti-inflammatory drugs (NSAIDs)**

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Law, 2013 <sup>157</sup>	Sumatriptan plus naproxen	12 RCTs (7,345)	Search in 2013 -Fulfills all AMSTAR criteria	-At two hours and compare with placebo, NNT for pain-free response was 3.1 for mild pain (50% response vs 18%), and 4.9 for moderate or severe pain (28% response vs 8%).  -Treating early, when pain was still mild, was significantly better than treating once pain was moderate or severe.  -Adverse events were mostly mild or moderate and rarely led to withdrawal.  -Combination treatment was superior to either monotherapy.
Xu, 2016 <sup>158</sup> (Network meta-analyses)	Triptans, NSAIDs and combination of triptans and NSAIDs	88 RCTs (44,222)	Searches in 1993-2016 Well- connected network geometry Bayesian framework-Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Sumatriptan and naproxen was effective, well tolerated and can be used for patients with partial response to either agent.

mg = milligram; MOH = medication overdose headache; NMA = network meta-analysis; RCT = randomized controlled trial

\* Credibility was assessed using the AMSTAR tool (A measurement tool to assess systematic reviews)

## Appendix H. Adverse Events

**Table H-1. Adverse events: KQ 1. opioids**

Comparison	Adverse Events	Findings	Study Design
Butorphanol vs. Placebo	ENT AE	Rate Ratio: 4.21; 95% CI: 0.53 to 33.2; I <sup>2</sup> =N/A	1 RCT <sup>71</sup>
	Gastrointestinal AE	Rate Ratio: 3.05; 95% CI: 1.61 to 5.80; I <sup>2</sup> =0.00%	2 RCTs <sup>46, 71</sup>
	Neurological AE	Rate Ratio: 8.31; 95% CI: 4.47 to 15.47; I <sup>2</sup> =11.50%	2 RCTs <sup>46, 71</sup>
	Ophthalmological AE	Rate Ratio: 4.00; 95% CI: 0.45 to 35.97; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Psychological AE	Rate Ratio: 1.64; 95% CI: 0.54 to 4.97; I <sup>2</sup> =N/A	1 RCT <sup>71</sup>
	Total AE	Rate Ratio: 6.08; 95% CI: 4.19 to 8.82; I <sup>2</sup> =94.00%	2 RCTs <sup>46, 71</sup>
Hydromorphone vs. Diphenhydramine plus prochlorperazine	Total AE	Rate Ratio: 2.95; 95% CI: 0.80 to 10.91; I <sup>2</sup> =N/A	1 RCT <sup>53</sup>
	Withdrawal	RR: 0.33; 95% CI: 0.01 to 7.91; I <sup>2</sup> =N/A	1 RCT <sup>53</sup>
Hydroxyzine plus meperidine vs. Dihydroergotamine plus hydroxyzine	Total AE	Rate Ratio: 1.31; 95% CI: 0.92 to 1.86; I <sup>2</sup> =N/A	1 RCT <sup>20</sup>
Meperidine vs. Droperidol	Neurological AE	Rate Ratio: 0.71; 95% CI: 0.12 to 4.27; I <sup>2</sup> =N/A	1 RCT <sup>108</sup>
	Total AE	Rate Ratio: 0.71; 95% CI: 0.12 to 4.27; I <sup>2</sup> =N/A	1 RCT <sup>108</sup>
Meperidine plus dimenhydrinate vs. Chloropramazine	Gastrointestinal AE	Rate Ratio: 0.73; 95% CI: 0.12 to 4.35; I <sup>2</sup> =N/A	1 RCT <sup>84</sup>
	Neurological AE	Rate Ratio: 0.78; 95% CI: 0.25 to 2.46; I <sup>2</sup> =N/A	1 RCT <sup>84</sup>
	Total AE	Rate Ratio: 0.51; 95% CI: 0.21 to 1.25; I <sup>2</sup> =N/A	1 RCT <sup>84</sup>
Meperidine plus hydroxyzine vs. Dihydroergotamine plus hydroxyzine	Gastrointestinal AE	Rate Ratio: 0.40; 95% CI: 0.13 to 1.28; I <sup>2</sup> =N/A	1 RCT <sup>20</sup>
	Neurological AE	Rate Ratio: 1.74; 95% CI: 1.18 to 2.58; I <sup>2</sup> =N/A	1 RCT <sup>20</sup>
	Total AE	Rate Ratio: 1.31; 95% CI: 0.92 to 1.86; I <sup>2</sup> =N/A	1 RCT <sup>20</sup>
	Withdrawal due to AE	RR: 1.00; 95% CI: 0.37 to 2.73; I <sup>2</sup> =0.00%	1 RCT <sup>20</sup>
Meperidine plus promethazine vs. Dihydroergotamine plus metoclopramide	Cardiovascular AE	Rate Ratio: 8.62; 95% CI: 1.08 to 68.88; I <sup>2</sup> =N/A	1 RCT <sup>114</sup>
	Gastrointestinal AE	Rate Ratio: 1.79; 95% CI: 0.43 to 7.51; I <sup>2</sup> =N/A	1 RCT <sup>114</sup>
	Neurological AE	Rate Ratio: 4.85; 95% CI: 1.64 to 14.32; I <sup>2</sup> =N/A	1 RCT <sup>114</sup>
	Total AE	Rate Ratio: 4.17; 95% CI: 1.92 to 9.08; I <sup>2</sup> =N/A	1 RCT <sup>114</sup>
Methadone vs. Butorphanol	Gastrointestinal AE	Rate Ratio: 0.17; 95% CI: 0.02 to 1.38; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Neurological AE	Rate Ratio: 0.81; 95% CI: 0.49 to 1.31; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Ophthalmological AE	Rate Ratio: 0.50; 95% CI: 0.09 to 2.73; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Psychological AE	Rate Ratio: 0.20; 95% CI: 0.02 to 1.71; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Total AE	Rate Ratio: 0.86; 95% CI: 0.50 to 1.47; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>

<b>Comparison</b>	<b>Adverse Events</b>	<b>Findings</b>	<b>Study Design</b>
Methadone vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.50; 95% CI: 0.05 to 5.51; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Neurological AE	Rate Ratio: 4.83; 95% CI: 2.01 to 11.64; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Ophthalmological AE	Rate Ratio: 2.00; 95% CI: 0.18 to 22.06; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
	Total AE	Rate Ratio: 1.79; 95% CI: 0.93 to 3.44; I <sup>2</sup> =N/A	1 RCT <sup>46</sup>
Methotrimeprazine vs. Dimenhydrinate plus meperidine	Cardiovascular AE	Rate Ratio: 10.00; 95% CI: 1.28 to 78.12; I <sup>2</sup> =N/A	1 RCT <sup>123</sup>
	Gastrointestinal AE	Rate Ratio: 0.80; 95% CI: 0.32 to 2.03; I <sup>2</sup> =N/A	1 RCT <sup>123</sup>
	Neurological AE	Rate Ratio: 1.31; 95% CI: 0.85 to 2.04; I <sup>2</sup> =N/A	1 RCT <sup>123</sup>
	Total AE	Rate Ratio: 1.39; 95% CI: 0.95 to 2.03; I <sup>2</sup> =N/A	1 RCT <sup>123</sup>
Tramadol plus acetaminophen vs. Placebo	Total AE	Rate Ratio: 2.49; 95% CI: 1.48 to 4.18; I <sup>2</sup> =N/A	1 RCT <sup>117</sup>
	Withdrawal	RR: 0.94; 95% CI: 0.62 to 1.43; I <sup>2</sup> =N/A	1 RCT <sup>117</sup>
	Withdrawal due to AE	RR: 0.99; 95% CI: 0.06 to 15.79; I <sup>2</sup> =N/A	1 RCT <sup>117</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

**Table H-2. Adverse events: KQ 2. ergot alkaloids**

Comparison	Adverse Events	Findings	Study Design
Dihydroergotamine vs. Chlorpromazine	Gastrointestinal AE	Rate Ratio: 2.54; 95% CI: 0.81 to 7.97; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
	Total AE	Rate Ratio: 2.54; 95% CI: 0.81 to 7.97; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
Dihydroergotamine vs. Lidocaine	Gastrointestinal AE	Rate Ratio: 0.45; 95% CI: 0.16 to 1.31; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
	Total AE	Rate Ratio: 0.45; 95% CI: 0.16 to 1.31; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
Dihydroergotamine vs. Placebo	Cardiovascular AE	Rate Ratio: 0.46; 95% CI: 0.12 to 1.78; I <sup>2</sup> =N/A	1 RCT <sup>140</sup>
	ENT AE	Rate Ratio: 0.58; 95% CI: 0.24 to 1.37; I <sup>2</sup> =N/A	1 RCT <sup>4</sup>
	Gastrointestinal AE	Rate Ratio: 2.78; 95% CI: 1.70 to 4.55; I <sup>2</sup> =0.3%	3 RCTs <sup>4, 5, 18</sup>
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.17 to 4.71; I <sup>2</sup> =0.0%	3 RCTs <sup>4, 5, 18</sup>
	Respiratory AE	Rate Ratio: 1.30; 95% CI: 0.69 to 2.45; I <sup>2</sup> =N/A	1 RCT <sup>4</sup>
	Total AE	Rate Ratio: 2.17; 95% CI: 0.65 to 7.31; I <sup>2</sup> =66%	4 RCTs <sup>4, 5, 18, 140</sup>
	Withdrawal AE	RR: 2.81; 95% CI: 0.61 to 12.93; I <sup>2</sup> =N/A	4 RCTs <sup>4, 5, 129, 140</sup>
Ergotamine vs. Placebo	Neurological AE	Rate Ratio: 1.21; 95% CI: 0.11 to 13.39; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Total AE	Rate Ratio: 1.21; 95% CI: 0.11 to 13.39; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Withdrawal	Rate Ratio: 1.67; 95% CI: 0.56 to 4.98; I <sup>2</sup> =N/A	2 RCTs <sup>78, 116</sup>
Ergotamine vs. Prochlorperazine	Neurological AE	Rate Ratio: 0.20; 95% CI: 0.03 to 1.52; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Total AE	Rate Ratio: 0.19; 95% CI: 0.02 to 1.41; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Withdrawal	Rate Ratio: 1.28; 95% CI: 0.45 to 3.70; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
Ergotamine plus caffeine vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.00; 95% CI: 0.50 to 2.01; I <sup>2</sup> =N/A	1 RCT <sup>36</sup>
	Neurological AE	Rate Ratio: 1.24; 95% CI: 0.54 to 2.83; I <sup>2</sup> =N/A	1 RCT <sup>36</sup>
	Other AE	Rate Ratio: 2.61; 95% CI: 0.31 to 22.35; I <sup>2</sup> =N/A	1 RCT <sup>36</sup>
	Total AE	Rate Ratio: 2.34; 95% CI: 0.00 to 91814.93; I <sup>2</sup> =77%	2 RCTs <sup>36, 48</sup>
	Withdrawal	Rate Ratio: 0.78; 95% CI: 0.23 to 2.72; I <sup>2</sup> =N/A	1 RCT <sup>36</sup>
	Withdrawal due to AE	RR: 2.01; 95% CI: 0.54 to 7.35; I <sup>2</sup> =67%	2 RCTs <sup>36, 48</sup>
Ergotamine plus caffeine plus pentobarbital plus bellafoline vs. Ergotamine plus caffeine	Gastrointestinal AE	Rate Ratio: 0.52; 95% CI: 0.12 to 2.17 I <sup>2</sup> =N/A	1 RCT <sup>48</sup>
	Total AE	Rate Ratio: 0.94; 95% CI: 0.42 to 2.14; I <sup>2</sup> =N/A	1 RCT <sup>48</sup>
	Withdrawal due to AE	RR: 0.43; 95% CI: 0.08 to 2.25; I <sup>2</sup> =N/A	1 RCT <sup>48</sup>
Ergotamine plus caffeine plus pentobarbital plus bellafoline vs. Placebo	Total AE	Rate Ratio: 6.00; 95% CI: 1.34 to 26.81; I <sup>2</sup> =N/A	1 RCT <sup>48</sup>
	Withdrawal due to AE	RR: 5.00; 95% CI: 0.25 to 101.68; I <sup>2</sup> =N/A	1 RCT <sup>48</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, throat; N/A = not applicable; RCT = randomized controlled trial

**Table H-3. Adverse events: KQ 2. antiemetic**

Comparison	Adverse Events	Findings	Study Design
Chlorpromazine vs. Placebo	Cardiovascular AE	Rate Ratio: 2.98; 95% CI: 0.82 to 10.84; I <sup>2</sup> =N/A	1 RCT <sup>97</sup>
	Neurological AE	Rate Ratio: 2.09; 95% CI: 0.96 to 4.56; I <sup>2</sup> =N/A	1 RCT <sup>97</sup>
	Total AE	Rate Ratio: 1.61; 95% CI: 0.54 to 4.81; I <sup>2</sup> =N/A	1 RCT <sup>97</sup>
	Withdrawal	RR: 1.06; 95% CI: 0.62 to 1.79; I <sup>2</sup> =42.00% <sup>6</sup>	2 RCTs <sup>11, 97</sup>
Diphenhydramine plus metoclopramide vs. Diphenhydramine plus haloperidol	Neurological AE	Rate Ratio: 0.38; 95% CI: 0.12 to 1.20; I <sup>2</sup> =N/A	1 RCT <sup>55</sup>
	Sleep-related AE	Rate Ratio: 1.69; 95% CI: 0.57 to 5.05; I <sup>2</sup> =N/A	1 RCT <sup>55</sup>
	Total AE	Rate Ratio: 0.77; 95% CI: 0.38 to 1.57; I <sup>2</sup> =N/A	1 RCT <sup>55</sup>
Droperidol vs. Placebo	Dermatological AE	Rate Ratio: 0.43; 95% CI: 0.19 to 0.93; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 1.25; 95% CI: 0.43 to 3.66; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 1.52; 95% CI: 1.03 to 2.23; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 7.25; 95% CI: 1.77 to 29.68; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.61; 95% CI: 1.18 to 2.20; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Granisetron vs. Placebo	Cardiovascular AE	Rate Ratio: 0.80; 95% CI: 0.15 to 4.37 ; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Dermatological AE	Rate Ratio: 0.27; 95% CI: 0.03 to 2.56; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Gastrointestinal AE	Rate Ratio: 1.87; 95% CI: 0.54 to 6.50; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Neurological AE	Rate Ratio: 1.20; 95% CI: 0.22 to 6.55; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Other AE	Rate Ratio: 0.80; 95% CI: 0.05 to 12.79; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Total AE	Rate Ratio: 1.10; 95% CI: 0.34 to 3.56; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
Haloperidol vs. Placebo	Total AE	Rate Ratio: 6; 95% CI: 2.12 to 120.65; I <sup>2</sup> =N/A	1 RCT <sup>73</sup>
Magnesium sulfate vs. Dexamethasone plus metoclopramide	Gastrointestinal AE	Rate Ratio: 0.80; 95% CI: 0.21 to 2.98; I <sup>2</sup> =N/A	1 RCT <sup>115</sup>
	Total AE	Rate Ratio: 0.57; 95% CI: 0.17 to 1.95; I <sup>2</sup> =N/A	1 RCT <sup>115</sup>
Metoclopramide vs. Chlorpromazine	Gastrointestinal AE	Rate Ratio: 1.60; 95% CI: 0.27 to 9.59; I <sup>2</sup> =N/A	1 RCT <sup>19</sup>
	Neurological AE	Rate Ratio: 0.98; 95% CI: 0.43 to 2.22; I <sup>2</sup> =N/A	1 RCT <sup>19</sup>
	Psychological AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.08; I <sup>2</sup> =N/A	1 RCT <sup>19</sup>
	Total AE	Rate Ratio: 0.84; 95% CI: 0.43 to 1.66; I <sup>2</sup> =N/A	1 RCT <sup>19</sup>
Metoclopramide vs. Diphenhydramine plus metoclopramide	Neurological AE	Rate Ratio: 0.97; 95% CI: 0.58 to 1.61; I <sup>2</sup> =N/A	1 RCT <sup>51</sup>
	Total AE	Rate Ratio: 0.97; 95% CI: 0.58 to 1.61; I <sup>2</sup> =N/A	1 RCT <sup>51</sup>
	Withdrawal	Rate Ratio: 0.20; 95% CI: 0.02 to 1.68; I <sup>2</sup> =N/A	1 RCT <sup>51</sup>
	Neurological AE	Rate Ratio: 0.30; 95% CI: 0.03 to 2.93; I <sup>2</sup> =N/A	1 RCT <sup>26</sup>



Comparison	Adverse Events	Findings	Study Design
Metoclopramide vs. Magnesium sulfate plus metoclopramide	Other AE	Rate Ratio: 0.42; 95% CI: 0.14 to 1.19; I <sup>2</sup> =N/A	1 RCT <sup>26</sup>
	Total AE	Rate Ratio: 0.39; 95% CI: 0.15 to 1.02; I <sup>2</sup> =N/A	1 RCT <sup>26</sup>
	Withdrawal	RR: 0.61; 95% CI: 0.11 to 3.29; I <sup>2</sup> =N/A	1 RCT <sup>26</sup>
Metoclopramide vs. Placebo	Neurological AE	Rate Ratio: 0.21; 95% CI: 0.37 to 4.03 ; I <sup>2</sup> =N/A	2 RCTs <sup>38, 128</sup>
	Total AE	Rate Ratio: 1.21; 95% CI: 0.37 to 4.03; I <sup>2</sup> =N/A	2 RCTs <sup>38, 128</sup>
Metoclopramide plus paracetamol vs. Placebo	Withdrawal	RR: 1.64; 95% CI: 0.41 to 6.55; I <sup>2</sup> =N/A	1 RCT <sup>31</sup>
Paracetamol vs. Metoclopramide	Total AE	Rate Ratio: 0.09; 95% CI: 0.01 to 0.67; I <sup>2</sup> =N/A	1 RCT <sup>111</sup>
Prochlorperazine vs. Metoclopramide	Neurological AE	Rate Ratio 0.95; 95% CI: 0.50 to 1.81; I <sup>2</sup> =0.00%	3 RCTs <sup>25, 49, 76</sup>
	Total AE	Rate Ratio: 1.34; 95% CI: 0.89 to 2.03; I <sup>2</sup> =N/A	3 RCTs <sup>25, 49, 76</sup>
	Withdrawal	RR: 2.92; 95% CI: 0.32 to 26.88; I <sup>2</sup> =N/A	1 RCT <sup>49</sup>
	Withdrawal due to AE	RR: 1.09; 95% CI: 0.17 to 7.10; I <sup>2</sup> =N/A	1 RCT <sup>49</sup>
Prochlorperazine vs. Octreotide	Neurological AE	Rate Ratio: 4.2; 95% CI: 0.87 to 20.22; I <sup>2</sup> =N/A	1 RCT <sup>98</sup>
	Total AE	Rate Ratio: 3.36; 95% CI: 1.21 to 9.33; I <sup>2</sup> =N/A	1 RCT <sup>98</sup>
	Withdrawal	RR: 0.40; 95% CI: 0.02 to 9.24; I <sup>2</sup> =N/A	1 RCT <sup>98</sup>
	Withdrawal due to AE	RR:0.40; 95% CI: 0.02 to 9.24; I <sup>2</sup> =N/A	1 RCT <sup>98</sup>
Prochlorperazine vs. Placebo	Neurological AE	Rate Ratio: 6.07; 95% CI: 1.39 to 26.55; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Total AE	Rate Ratio: 6.48; 95% CI: 1.49 to 28.17; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>
	Withdrawal	Rate Ratio: 1.89; 95% CI: 0.57 to 6.22; I <sup>2</sup> =N/A	1 RCT <sup>116</sup>

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

**Table H-4. Adverse events: KQ 2. calcitonin gene-related peptide receptor antagonists**

Comparison	Adverse Events	Findings	Study Design
Rimegepant vs. Placebo	Cardiovascular AE	Rate Ratio: 0.42; 95% CI: 0.01 to 21.10; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Gastrointestinal AE	Rate Ratio: 1.69; 95% CI: 1.00 to 2.87; I <sup>2</sup> =N/A	3 RCTs <sup>27, 89, 95</sup>
	Genitourinary AE	Rate Ratio: 1.77; 95% CI: 0.81 to 3.88; I <sup>2</sup> =N/A	2 RCTs <sup>27, 89</sup>
	Musculoskeletal AE	Rate Ratio: 1.67; 95% CI: 0.08 to 37.13; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.40 to 2.00; I <sup>2</sup> =N/A	2 RCTs <sup>27, 95</sup>
	Other AE	Rate Ratio: 0.42; 95% CI: 0.01 to 21.10; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.23; 95% CI: 1.00 to 1.50; I <sup>2</sup> =N/A	3 RCTs <sup>27, 89, 95</sup>
	Withdrawal due to AE	RR: 3.01; 95% CI: 0.12 to 73.72; I <sup>2</sup> =N/A	1 RCT <sup>27</sup>
Ubrogepant vs. Placebo	Cardiovascular AE	Rate Ratio: 2.00; 95% CI: 0.11 to 36.61; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	ENT AE	Rate Ratio: 8.02; 95% CI: 1.06 to 60.48; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Dermatological AE	Rate Ratio: 0.10; 95% CI: 0.00 to 2.98; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Gastrointestinal AE	Rate Ratio: 1.46 ; 95% CI: 0.99 to 2.16; I <sup>2</sup> =0%	3 RCT <sup>37, 90, 133</sup>
	Neurological AE	Rate Ratio: 1.19; 95% CI: 0.76 to 1.85; I <sup>2</sup> =0%	3 RCT <sup>37, 90, 133</sup>
	Other AE	Rate Ratio: 0.20 ; 95% CI: 0.00 to 10.08; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 1.11; 95% CI: 0.96 to 1.28; I <sup>2</sup> =0%	3 RCT <sup>37, 90, 133</sup>
	Withdrawal due to AE	RR: 0.63; 95% CI: 0.17 to 2.33; I <sup>2</sup> =4.68	2 RCT <sup>37, 90</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, throat; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

**Table H-5. Adverse events: KQ 2. 5-HT1F**

<b>Comparison</b>	<b>Adverse Events</b>	<b>Findings</b>	<b>Study Design</b>
Lasmiditan vs. Placebo	Cardiovascular AE	Rate Ratio=1.83; 95% CI: 0.56 to 6.01; I <sup>2</sup> = 0.00%	3 RCTs <sup>44, 58, 83</sup>
	Gastrointestinal AE	Rate Ratio=2.41; 95% CI: 1.50 to 3.85; I <sup>2</sup> = 0.00%	3 RCTs <sup>42, 58, 83</sup>
	Neurological AE	Rate Ratio=4.61; 95% CI: 2.39 to 8.90; I <sup>2</sup> = 61.90%	4 RCTs <sup>42, 44, 58, 83</sup>
	Other AE	Rate Ratio=4.77; 95% CI: 0.26 to 87.36; I <sup>2</sup> = N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio=2.67; 95% CI: 2.10 to 3.39; I <sup>2</sup> = 0.00%	4 RCTs <sup>42, 44, 58, 83</sup>
	Withdrawal	RR: 1.07; 95% CI: 0.97 to 1.19; I <sup>2</sup> = N/A	3 RCTs <sup>42, 58, 83</sup>
	Withdrawal due to AE	RR: 2.49; 95% CI: 0.12 to 51.87; I <sup>2</sup> =N/A	1 RCT <sup>83</sup>

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

**Table H-6. Adverse events: KQ 2. other interventions**

Comparison	Adverse Events	Findings	Study Design
Acetaminophen vs. Placebo	ENT AE	Rate Ratio: 0.91; 95% CI: 0.57 to 1.45; I <sup>2</sup> =N/A	1 RCT <sup>104</sup>
	Gastrointestinal AE	Rate Ratio: 0.81; 95% CI: 0.62 to 1.07; I <sup>2</sup> =72.8	2 RCTs <sup>87, 104</sup>
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.60 to 1.37; I <sup>2</sup> =0.00%	2 RCTs <sup>87, 104</sup>
	Other AE	Rate Ratio: 0.75; 95% CI: 0.45 to 1.27; I <sup>2</sup> =N/A	1 RCT <sup>87</sup>
	Total AE	Rate Ratio: 0.82; 95% CI: 0.64 to 1.06; I <sup>2</sup> =0.00%	2 RCTs <sup>87, 104</sup>
	Withdrawal	RR: 0.69; 95% CI: 0.54 to 0.88; I <sup>2</sup> =0.00%	2 RCTs <sup>87, 104</sup>
	Withdrawal due to AE	RR: 1.98; 95% CI: 0.18 to 21.64; I <sup>2</sup> =N/A	1 RCT <sup>104</sup>
Chlorpromazine vs. Lidocaine	Gastrointestinal AE	Rate Ratio: 0.87; 95% CI: 0.23 to 3.23; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
	Total AE	Rate Ratio: 0.87; 95% CI: 0.23 to 3.23; I <sup>2</sup> =N/A	1 RCT <sup>9</sup>
Dexamethasone vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.95; 95% CI: 0.39 to 2.34; I <sup>2</sup> =N/A	1 RCT <sup>39</sup>
	Immunological AE	Rate Ratio: 8.41; 95% CI: 1.06 to 66.35; I <sup>2</sup> =N/A	1 RCT <sup>47</sup>
	Musculoskeletal AE	Rate Ratio: 0.28; 95% CI: 0.03 to 2.74; I <sup>2</sup> =N/A	1 RCT <sup>39</sup>
	Neurological AE	Rate Ratio: 1.21; 95% CI: 0.55 to 2.65; I <sup>2</sup> =0.00%	2 RCTs <sup>39, 47</sup>
	Psychological AE	Rate Ratio: 0.85; 95% CI: 0.12 to 6.07; I <sup>2</sup> =N/A	1 RCT <sup>39</sup>
	Total AE	Rate Ratio: 0.80; 95% CI: 0.51 to 1.26; I <sup>2</sup> =0.00%	2 RCTs <sup>39, 47</sup>
	Withdrawal	RR: 0.39; 95% CI: 0.14 to 1.05; I <sup>2</sup> =N/A	1 RCT <sup>39, 47</sup>
Dipyron vs. Placebo	Cardiovascular AE	Rate Ratio: 1.62; 95% CI: 0.15 to 17.88; I <sup>2</sup> =N/A	1 RCT <sup>10</sup>
	Gastrointestinal AE	Rate Ratio: 0.97; 95% CI: 0.54 to 1.72; I <sup>2</sup> =N/A	1 RCT <sup>10</sup>
	Neurological AE	Rate Ratio: 0.81; 95% CI: 0.34 to 1.95; I <sup>2</sup> =N/A	1 RCT <sup>10</sup>
	Total AE	Rate Ratio: 1.08; 95% CI: 0.55 to 2.11; I <sup>2</sup> =N/A	1 RCT <sup>10</sup>
	Withdrawal	RR: 0.78; 95% CI: 0.32 to 1.89; I <sup>2</sup> =N/A	1 RCT <sup>131</sup>
Greater occipital nerve block vs. Placebo	Musculoskeletal AE	Rate Ratio: 1.15; 95% CI: 0.07 to 18.45; I <sup>2</sup> =N/A	1 RCT <sup>52</sup>
	Total AE	Rate Ratio: 2.31; 95% CI: 0.42 to 12.6; I <sup>2</sup> =N/A	1 RCT <sup>52</sup>
Lidocaine vs. Placebo	Dermatological AE	Rate Ratio: 4.44; 95% CI: 2.16 to 9.16; I <sup>2</sup> =N/A	1 RCT <sup>6</sup>
	Neurological AE	Rate Ratio: 1.22; 95% CI: 0.34 to 4.33; I <sup>2</sup> =N/A	1 RCT <sup>14</sup>
	Total AE	Rate Ratio: 3.30; 95% CI: 1.76 to 6.17; I <sup>2</sup> =68.10%	2 RCTs <sup>6, 14</sup>
	Withdrawal	RR: 0.16; 95% CI: 0.01 to 3.25; I <sup>2</sup> =N/A	1 RCT <sup>14</sup>
Octreotide vs. Placebo	Gastrointestinal AE	Rate Ratio: 5.75; 95% CI: 0.67 to 49.22; I <sup>2</sup> =N/A	1 RCT <sup>85</sup>
	Total AE	Rate Ratio: 1.73; 95% CI: 0.49 to 6.11; I <sup>2</sup> =N/A	1 RCT <sup>85</sup>

<b>Comparison</b>	<b>Adverse Events</b>	<b>Findings</b>	<b>Study Design</b>
Octreotide vs. Placebo (continued)	Withdrawal	RR: 1.15; 95% CI: 0.08 to 17.22; I <sup>2</sup> =N/A	1 RCT <sup>85</sup>
Valproate vs. Dexamethasone	Gastrointestinal AE	Rate Ratio: 1.50; 95% CI: 0.25 to 8.98; I <sup>2</sup> =N/A	1 RCT <sup>96</sup>
	Neurological AE	Rate Ratio: 4.00; 95% CI: 0.45 to 35.79; I <sup>2</sup> =0.00%	1 RCT <sup>96</sup>
	Total AE	Rate Ratio: 2.33; 95% CI: 0.60 to 9.02; I <sup>2</sup> =N/A	1 RCT <sup>96</sup>
	Withdrawal	RR: 0.64; 95% CI: 0.29 to 1.40; I <sup>2</sup> =79.11%	3 RCTs <sup>45, 80, 96</sup>
Valproate vs. Prochlorperazine	Withdrawal	RR: 3; 95% CI: 0.13 to 69.52; I <sup>2</sup> =N/A	1 RCT <sup>126</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

**Table H-7. Adverse events: KQ 3. nonpharmacologic therapy**

Comparison	Adverse Events	Findings	Study Design
Acupuncture vs. Sham acupuncture	Hematological AE	Rate Ratio: 1.50; 95% CI: 0.25 to 8.89; I <sup>2</sup> =N/A	1 RCT <sup>134</sup>
	Total AE	Rate Ratio: 1.75; 95% CI: 0.51 to 5.98; I <sup>2</sup> =N/A	1 RCT <sup>134</sup>
	Withdrawal	RR: 0.55; 95% CI: 0.23 to 1.33; I <sup>2</sup> =0.00%	2 RCTs <sup>86, 134</sup>
	Withdrawal due to AE	RR: 0.52; 95% CI: 0.05 to 5.55; I <sup>2</sup> =N/A	1 RCT <sup>86</sup>
Chamomile oil vs. Placebo	Withdrawal	RR: 0.75; 95% CI: 0.40 to 1.42; I <sup>2</sup> =N/A	1 Crossover RCT <sup>139</sup>
	Withdrawal due to AE	RR: 5; 95% CI: 0.25 to 101.58; I <sup>2</sup> =N/A	1 Crossover RCT <sup>139</sup>
External trigeminal nerve stimulation vs. Sham external trigeminal nerve stimulation	Neurological AE	Rate Ratio: 2.22; 95% CI: 0.58 to 8.88; I <sup>2</sup> =0	2 RCTs <sup>23, 72</sup>
	Total AE	Rate Ratio: 2.46; 95% CI: 0.62 to 9.72; I <sup>2</sup> =0	2 RCTs <sup>23, 72</sup>
	Withdrawal due to AE	RR: 1.46; 95% CI: 0.26 to 8.31; I <sup>2</sup> =N/A	1 RCT <sup>72</sup>
Eye movement desensitization reprocessing vs. Standard care	Withdrawal	RR: 1.25; 95% CI: 0.38 to 4.14; I <sup>2</sup> =N/A	1 RCT <sup>94</sup>
Magnetic stimulation vs. Sham stimulation	ENT AE	Rate Ratio: 1.94; 95% CI: 0.18 to 21.41; I <sup>2</sup> =N/A	1 RCT <sup>88</sup>
	Gastrointestinal AE	Rate Ratio: 0.97; 95% CI: 0.06 to 15.52; I <sup>2</sup> =N/A	1 RCT <sup>88</sup>
	Neurological AE	Rate Ratio: 1.94; 95% CI: 0.49 to 7.76; I <sup>2</sup> =N/A	1 RCT <sup>88</sup>
	Total AE	Rate Ratio: 1.51; 95% CI: 0.65 to 3.49; I <sup>2</sup> =N/A	1 RCT <sup>88</sup>
	Withdrawal	RR: 1.14; 95% CI: 0.64 to 2.05; I <sup>2</sup> =N/A	1 RCT <sup>88</sup>
Noninvasive vagus nerve stimulation vs. Sham stimulation	Dermatological AE	Rate Ratio: 0.44; 95% CI: 0.11 to 1.71; I <sup>2</sup> =N/A	1 RCT <sup>127</sup>
	ENT AE	Rate Ratio: 0.69; 95% CI: 0.12 to 4.12; I <sup>2</sup> =N/A	1 RCT <sup>127</sup>
	Total AE	Rate Ratio: 0.99; 95% CI: 0.55 to 1.77; I <sup>2</sup> =N/A	1 RCT <sup>127</sup>
	Withdrawal	RR: 0.69; 95% CI: 0.12 to 4.05; I <sup>2</sup> =N/A	1 RCT <sup>127</sup>
	Withdrawal due to AE	RR: 0.21; 95% CI: 0.01 to 4.26; I <sup>2</sup> =N/A	1 RCT <sup>127</sup>
Remote electrical neuromodulation vs. Sham stimulation	Dermatological AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>
	Musculoskeletal AE	Rate Ratio: 1.00; 95% CI: 0.06 to 15.99; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>
	Neurological AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>
	Other AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>
	Total AE	Rate Ratio: 1.27; 95% CI: 0.64 to 2.49; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>
	Withdrawal	RR: 1.17; 95% CI: 0.71 to 1.93; I <sup>2</sup> =N/A	1 RCT <sup>138</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized controlled trial; RR = relative risk

# Appendix I. Subgroup Analysis by Dosage

**Table I-1. Subgroup analysis by dosage for ergot alkaloids**

Comparison	Outcome	Findings
Dihydroergotamine 1 mg vs. Placebo	Pain free at 2 hours	RR: 5.65; 95% CI: 0.79 to 40.42; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.95; 95% CI: 0.87 to 4.36; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 5.14; 95% CI: 0.71 to 37.07; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 5.14; 95% CI: 0.71 to 37.07; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.82; 95% CI: 0.70 to 11.41; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 2.82; 95% CI: 0.70 to 11.41; I <sup>2</sup> =N/A
Dihydroergotamine 2 mg vs. Placebo	Pain free at 2 hours	RR: 3.81; 95% CI: 0.50 to 28.64; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 2.59; 95% CI: 1.81 to 3.71; I <sup>2</sup> =45.00%
	Pain relief at 1 day	RR: 2.68; 95% CI: 1.89 to 3.79; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 2.73; 95% CI: 1.62 to 4.60; I <sup>2</sup> =N/A
	Restored function at 1 day	RR: 3.12; 95% CI: 1.98 to 4.91; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.72; 95% CI: 0.34 to 21.58; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.63; 95% CI: 0.18 to 14.60; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.45; 95% CI: 0.59 to 10.15; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 2.18; 95% CI: 0.51 to 9.20; I <sup>2</sup> =N/A
Dihydroergotamine 2 mg vs. Dihydroergotamine 1 mg	Pain free at 2 hours	RR: 0.67; 95% CI: 0.29 to 1.53; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.78; 95% CI: 0.47 to 1.28; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.53; 95% CI: 0.20 to 1.38; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.31; 95% CI: 0.09 to 1.05; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.86; 95% CI: 0.41 to 1.82; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 0.77; 95% CI: 0.35 to 1.67; I <sup>2</sup> =N/A
Dihydroergotamine 3 mg vs. Placebo	Pain relief at 2 hours	RR: 1.97; 95% CI: 1.27 to 3.04; I <sup>2</sup> =0.00%
	Pain relief at 1 day	RR: 2.13; 95% CI: 1.47 to 3.07; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 2.01; 95% CI: 1.15 to 3.51; I <sup>2</sup> =N/A
	Restored function at 1 day	RR: 2.52; 95% CI: 1.57 to 4.04; I <sup>2</sup> =N/A
Dihydroergotamine 3 mg vs. Dihydroergotamine 2 mg	Pain relief at 2 hours	RR: 0.67; 95% CI: 0.51 to 0.89; I <sup>2</sup> =N/A
	Pain relief at 1 day	RR: 0.79; 95% CI: 0.64 to 0.97; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Dihydroergotamine 3 mg vs. Dihydroergotamine 2 mg (continued)	Restored function at 2 hours	RR: 0.73; 95% CI: 0.50 to 1.07; I <sup>2</sup> =N/A
	Restored function at 1 day	RR: 0.80; 95% CI: 0.61 to 1.06; I <sup>2</sup> =N/A
Oral ergotamine vs. Placebo	Pain scale at 2 hours	SMD: 0.13; 95% CI: 1.12 to 0.85; I <sup>2</sup> =N/A
Oral ergotamine vs. Buccal PCZ	Pain scale at 2 hours	SMD: 0.58; 95% CI: 1.45 to 0.28; I <sup>2</sup> =N/A

CI = confidence interval; mg = milligram; N/A = not available; PCZ = prochlorperazine; RR = relative risk; SMD = standardized mean deviation



**Table I-2. Subgroup analysis by dosage for antiemetic**

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Droperidol 0.1 mg vs. Placebo	Pain free at 2 hours	RR: 1.18; 95% CI: 0.71 to 1.98; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.13; 95% CI: 0.86 to 1.50; I <sup>2</sup> =N/A
Droperidol 2.75 mg vs. Placebo	Pain free at 2 hours	RR: 2.11; 95% CI: 1.37 to 3.26; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.51; 95% CI: 1.19 to 1.92; I <sup>2</sup> =N/A
Droperidol 2.75 mg vs. Droperidol 0.1 mg	Pain free at 2 hours	RR: 1.78; 95% CI: 1.21 to 2.63; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.34; 95% CI: 1.09 to 1.64; I <sup>2</sup> =N/A
Droperidol 5.5 mg vs. Placebo	Pain free at 2 hours	RR: 1.49; 95% CI: 0.92 to 2.42; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.42; 95% CI: 1.11 to 1.82; I <sup>2</sup> =N/A
Droperidol 5.5 mg vs. Droperidol 0.1 mg	Pain free at 2 hours	RR: 1.26; 95% CI: 0.81 to 1.97; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.25; 95% CI: 1.00 to 1.56; I <sup>2</sup> =N/A
Droperidol 5.5 mg vs. Droperidol 2.75 mg	Pain free at 2 hours	RR: 0.71; 95% CI: 0.50 to 1.00; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.94; 95% CI: 0.80 to 1.09; I <sup>2</sup> =N/A
Droperidol 8.25 mg vs. Placebo	Pain free at 2 hours	RR: 1.61; 95% CI: 1.01 to 2.58; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.49; 95% CI: 1.17 to 1.89; I <sup>2</sup> =N/A
Droperidol 8.25 mg vs. Droperidol 0.1 mg	Pain free at 2 hours	RR: 1.36; 95% CI: 0.89 to 2.09; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.31; 95% CI: 1.06 to 1.61; I <sup>2</sup> =N/A
Droperidol 8.25 mg vs. Droperidol 2.75 mg	Pain free at 2 hours	RR: 0.76; 95% CI: 0.55 to 1.06; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.98; 95% CI: 0.85 to 1.13; I <sup>2</sup> =N/A
Droperidol 8.25 mg vs. Droperidol 5.5 mg	Pain free at 2 hours	RR: 1.08; 95% CI: 0.73 to 1.59; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.05; 95% CI: 0.89 to 1.23; I <sup>2</sup> =N/A
Granisetron 40 µg/ kg vs. Placebo	Pain free at 2 hours	RR: 2.45; 95% CI: 0.11 to 53.25; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 1.22; 95% CI: 0.20 to 2.24; I <sup>2</sup> =N/A
Granisetron 80 µg/ kg vs. Placebo	Pain scale at 2 hours	SMD: 1.79; 95% CI: 0.67 to 2.91; I <sup>2</sup> =N/A
Granisetron 80 µg/ kg vs. Granisetron 40 µg/ kg	Pain free at 2 hours	RR: 0.33; 95% CI: 0.02 to 7.32; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 0.21; 95% CI: -0.67 to 1.09; I <sup>2</sup> =N/A
Metoclopramide 20 mg vs. Metoclopramide 10 mg	Pain free at 2 hours	RR: 1.04; 95% CI: 0.77 to 1.38; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.97; 95% CI: 0.85 to 1.10; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 0.07; 95% CI: -0.18 to 0.33; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 0.93; 95% CI: 0.75 to 1.15; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Metoclopramide 20 mg vs. Metoclopramide 10 mg (continued)	Sustained pain free at 1 week	RR: 1.22; 95% CI: 0.70 to 2.14; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.04; 95% CI: 0.81 to 1.33; I <sup>2</sup> =N/A
Metoclopramide 40 mg vs. Metoclopramide 10 mg	Pain free at 2 hours	RR: 1.00; 95% CI: 0.74 to 1.34; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.03; 95% CI: 0.92 to 1.15; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 0.21; 95% CI: -0.05 to 0.47; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.09; 95% CI: 0.90 to 1.32; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.28; 95% CI: 0.73 to 2.22; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.14; 95% CI: 0.90 to 1.44; I <sup>2</sup> =N/A
Metoclopramide 40 mg vs. Metoclopramide 20 mg	Pain free at 2 hours	RR: 0.96; 95% CI: 0.72 to 1.28; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.06; 95% CI: 0.94 to 1.20; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 0.14; 95% CI: -0.12 to 0.40; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.18; 95% CI: 0.96 to 1.43; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.04; 95% CI: 0.63 to 1.74; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.10; 95% CI: 0.87 to 1.37; I <sup>2</sup> =N/A

CI = confidence interval; kg = kilograms; mg = milligrams; N/A = not applicable; RR = risk ratio; SMD = standardized mean difference; ug = micrograms

**Table I-3. Subgroup analysis by dosage for calcitonin gene-related peptide receptor antagonists**

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Rimegepant 10 mg vs. Placebo	Pain free at 2 hours	RR: 1.30; 95% CI: 0.74 to 2.29; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.09; 95% CI: 0.84 to 1.41; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.62; 95% CI: 0.74 to 3.55; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.44; 95% CI: 0.63 to 3.27; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.19; 95% CI: 0.89 to 1.59; I <sup>2</sup> =N/A
Rimegepant 25 mg vs. Placebo	Pain free at 2 hours	RR: 1.30; 95% CI: 0.71 to 2.40; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.20; 95% CI: 0.92 to 1.55; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.25; 95% CI: 1.06 to 4.77; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.02; 95% CI: 0.93 to 4.41; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.29; 95% CI: 0.96 to 1.74; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Placebo	Pain free at 2 hours	RR: 2.19; 95% CI: 1.39 to 3.46; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.50; 95% CI: 1.23 to 1.83; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 4.03; 95% CI: 2.21 to 7.32; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 4.03; 95% CI: 2.21 to 7.32; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.76; 95% CI: 1.40 to 2.19; I <sup>2</sup> =N/A
Rimegepant 150 mg vs. Placebo	Pain free at 2 hours	RR: 2.30; 95% CI: 1.47 to 3.60; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.27; 95% CI: 1.01 to 1.60; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 4.07; 95% CI: 2.24 to 7.40; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 4.07; 95% CI: 2.24 to 7.40; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.51; 95% CI: 1.18 to 1.93; I <sup>2</sup> =N/A
Rimegepant 300 mg vs. Placebo	Pain free at 2 hours	RR: 2.01; 95% CI: 1.30 to 3.12; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.53; 95% CI: 1.27 to 1.84; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 3.66; 95% CI: 2.04 to 6.56; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 3.66; 95% CI: 2.04 to 6.56; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.83; 95% CI: 1.49 to 2.24; I <sup>2</sup> =N/A
Rimegepant 600 mg vs. Placebo	Pain free at 2 hours	RR: 1.61; 95% CI: 0.97 to 2.67; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.53; 95% CI: 1.26 to 1.86; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.82; 95% CI: 1.47 to 5.41; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Rimegepant 600 mg vs. Placebo (continued)	Sustained pain free at 1 week	RR: 2.82; 95% CI: 1.47 to 5.41; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.68; 95% CI: 1.34 to 2.11; I <sup>2</sup> =N/A
Rimegepant 25 mg vs. Rimegepant 10 mg	Pain free at 2 hours	RR: 1.00; 95% CI: 0.50 to 1.99; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.10; 95% CI: 0.81 to 1.50; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.39; 95% CI: 0.60 to 3.22; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.41; 95% CI: 0.57 to 3.45; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.09; 95% CI: 0.77 to 1.53; I <sup>2</sup> =N/A
Rimegepant 25 mg vs. Rimegepant 150 mg	Pain free at 2 hours	RR: 0.57; 95% CI: 0.31 to 1.03; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.94; 95% CI: 0.71 to 1.25; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.55; 95% CI: 0.28 to 1.07; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.50; 95% CI: 0.25 to 1.00; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.86; 95% CI: 0.63 to 1.16; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Rimegepant 10 mg	Pain free at 2 hours	RR: 1.68; 95% CI: 0.96 to 2.94; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.38; 95% CI: 1.07 to 1.78; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.49; 95% CI: 1.23 to 5.05; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.80; 95% CI: 1.33 to 5.89; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.47; 95% CI: 1.12 to 1.95; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Rimegepant 25 mg	Pain free at 2 hours	RR: 1.68; 95% CI: 0.92 to 3.07; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.25; 95% CI: 0.97 to 1.62; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.79; 95% CI: 0.92 to 3.50; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.99; 95% CI: 0.99 to 4.01; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.36; 95% CI: 1.02 to 1.81; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Rimegepant 150 mg	Pain free at 2 hours	RR: 0.95; 95% CI: 0.61 to 1.48; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.18; 95% CI: 0.94 to 1.48; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.99; 95% CI: 0.61 to 1.61; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.99; 95% CI: 0.61 to 1.61; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.16; 95% CI: 0.92 to 1.47; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Rimegepant 300 mg	Pain free at 2 hours	RR: 1.09; 95% CI: 0.71 to 1.67; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.98; 95% CI: 0.82 to 1.18; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Rimegepant 75 mg vs. Rimegepant 300 mg (continued)	Sustained pain free at 1 day	RR: 1.10; 95% CI: 0.69 to 1.76; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.10; 95% CI: 0.69 to 1.76; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.96; 95% CI: 0.79 to 1.16; I <sup>2</sup> =N/A
Rimegepant 75 mg vs. Rimegepant 600 mg	Pain free at 2 hours	RR: 1.36; 95% CI: 0.83 to 2.25; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.98; 95% CI: 0.81 to 1.19; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.43; 95% CI: 0.82 to 2.47; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.43; 95% CI: 0.82 to 2.47; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.05; 95% CI: 0.84 to 1.30; I <sup>2</sup> =N/A
Rimegepant 150 mg vs. Rimegepant 10 mg	Pain free at 2 hours	RR: 1.76; 95% CI: 1.01 to 3.06; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.17; 95% CI: 0.89 to 1.54; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.52; 95% CI: 1.24 to 5.10; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.83; 95% CI: 1.35 to 5.96; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.27; 95% CI: 0.94 to 1.71; I <sup>2</sup> =N/A
Rimegepant 300 mg vs. Rimegepant 10 mg	Pain free at 2 hours	RR: 1.55; 95% CI: 0.90 to 2.66; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.40; 95% CI: 1.10 to 1.80; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.26; 95% CI: 1.13 to 4.53; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.55; 95% CI: 1.22 to 5.29; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.53; 95% CI: 1.18 to 2.00; I <sup>2</sup> =N/A
Rimegepant 300 mg vs. Rimegepant 25 mg	Pain free at 2 hours	RR: 1.55; 95% CI: 0.86 to 2.79; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.28; 95% CI: 1.00 to 1.63; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.63; 95% CI: 0.85 to 3.14; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.81; 95% CI: 0.91 to 3.60; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.41; 95% CI: 1.08 to 1.86; I <sup>2</sup> =N/A
Rimegepant 300 mg vs. Rimegepant 150 mg	Pain free at 2 hours	RR: 0.88; 95% CI: 0.57 to 1.34; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.20; 95% CI: 0.97 to 1.49; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.90; 95% CI: 0.56 to 1.43; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.90; 95% CI: 0.56 to 1.43; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.21; 95% CI: 0.97 to 1.50; I <sup>2</sup> =N/A
Rimegepant 600 mg vs. Rimegepant 10 mg	Pain free at 2 hours	RR: 1.23; 95% CI: 0.68 to 2.25; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Rimegepant 600 mg vs. Rimegepant 10 mg (continued)	Pain relief at 2 hours	RR: 1.41; 95% CI: 1.09 to 1.82; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.75; 95% CI: 0.82 to 3.70; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.96; 95% CI: 0.89 to 4.31; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.41; 95% CI: 1.06 to 1.87; I <sup>2</sup> =N/A
Rimegepant 600 mg vs. Rimegepant 25 mg	Pain free at 2 hours	RR: 1.23; 95% CI: 0.65 to 2.34; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.28; 95% CI: 0.99 to 1.65; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.26; 95% CI: 0.61 to 2.57; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.40; 95% CI: 0.66 to 2.94; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.30; 95% CI: 0.97 to 1.74; I <sup>2</sup> =N/A
Rimegepant 600 mg vs. Rimegepant 150 mg	Pain free at 2 hours	RR: 0.70; 95% CI: 0.43 to 1.15; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.20; 95% CI: 0.96 to 1.50; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.69; 95% CI: 0.40 to 1.20; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.69; 95% CI: 0.40 to 1.20; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.11; 95% CI: 0.88 to 1.41; I <sup>2</sup> =N/A
Rimegepant 600 mg vs. Rimegepant 300 mg	Pain free at 2 hours	RR: 0.80; 95% CI: 0.49 to 1.29; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.00; 95% CI: 0.84 to 1.20; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.77; 95% CI: 0.45 to 1.31; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.77; 95% CI: 0.45 to 1.31; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.92; 95% CI: 0.75 to 1.12; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.74; 95% CI: 1.51 to 2.00; I <sup>2</sup> =0.00%
	Restored function at 2 hours	RR: 1.69; 95% CI: 1.36 to 2.09; I <sup>2</sup> =53.80%
	Sustained pain free at 1 day	RR: 2.07; 95% CI: 1.18 to 3.65; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.20; 95% CI: 1.49 to 3.23; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.82; 95% CI: 1.48 to 2.25; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.87; 95% CI: 1.49 to 2.33; I <sup>2</sup> =N/A
Ubrogepant 1 mg vs. Placebo	Pain free at 2 hours	RR: 0.60; 95% CI: 0.23 to 1.62; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.81; 95% CI: 0.57 to 1.14; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.72; 95% CI: 0.23 to 2.21; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.72; 95% CI: 0.23 to 2.21; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Ubrogapant 1 mg vs. Placebo (continued)	Sustained pain relief at 1 day	RR: 0.60; 95% CI: 0.36 to 1.00; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 0.65; 95% CI: 0.38 to 1.11; I <sup>2</sup> =N/A
Ubrogapant 10 mg vs. Placebo	Pain free at 2 hours	RR: 1.60; 95% CI: 0.75 to 3.40; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.14; 95% CI: 0.85 to 1.54; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.43; 95% CI: 0.56 to 3.65; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.43; 95% CI: 0.56 to 3.65; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.22; 95% CI: 0.81 to 1.83; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.25; 95% CI: 0.81 to 1.94; I <sup>2</sup> =N/A
Ubrogapant 25 mg vs. Placebo	Pain free at 2 hours	RR: 1.50; 95% CI: 1.14 to 1.97; I <sup>2</sup> =27.20%
	Pain relief at 2 hours	RR: 1.18; 95% CI: 1.04 to 1.34; I <sup>2</sup> =0.00%
	Pain relief at 1 day	RR: 1.49; 95% CI: 1.18 to 1.88; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.19; 95% CI: 1.00 to 1.42; I <sup>2</sup> =N/A
	Restores function at 1 day	RR: 1.13; 95% CI: 1.01 to 1.26; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.60; 95% CI: 1.11 to 2.29; I <sup>2</sup> =0.00%
	Sustained pain free at 1 week	RR: 2.14; 95% CI: 0.90 to 5.09; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.28; 95% CI: 0.86 to 1.91; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.39; 95% CI: 0.91 to 2.13; I <sup>2</sup> =N/A
Ubrogapant 50 mg vs. Placebo	Pain free at 2 hours	RR: 1.59; 95% CI: 1.29 to 1.95; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.23; 95% CI: 1.13 to 1.35; I <sup>2</sup> =10.90%
	Pain relief at 1 day	RR: 1.78; 95% CI: 1.42 to 2.23; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.23; 95% CI: 1.08 to 1.40; I <sup>2</sup> =0.00%
	Restores function at 1 day	RR: 1.18; 95% CI: 1.10 to 1.28; I <sup>2</sup> =0.00%
	Sustained pain free at 1 day	RR: 1.63; 95% CI: 1.26 to 2.12; I <sup>2</sup> =0.00%
	Sustained pain free at 1 week	RR: 2.14; 95% CI: 0.90 to 5.09; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.59; 95% CI: 1.30 to 1.94; I <sup>2</sup> =0.00%
	Sustained pain relief at 1 week	RR: 1.61; 95% CI: 1.07 to 2.42; I <sup>2</sup> =N/A
Ubrogapant 100 mg vs. Placebo	Pain free at 2 hours	RR: 1.89; 95% CI: 1.43 to 2.52; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.22; 95% CI: 1.09 to 1.38; I <sup>2</sup> =0.00%
	Restored function at 2 hours	RR: 1.42; 95% CI: 1.18 to 1.71; I <sup>2</sup> =N/A
	Restored function at 1 day	RR: 1.16; 95% CI: 1.05 to 1.29; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Ubrogепant 100 mg vs. Placebo (continued)	Sustained pain free at 1 day	RR: 1.96; 95% CI: 1.40 to 2.75; I <sup>2</sup> =37.20%
	Sustained pain free at 1 week	RR: 2.98; 95% CI: 1.31 to 6.78; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.70; 95% CI: 1.40 to 2.06; I <sup>2</sup> =0.00%
	Sustained pain relief at 1 week	RR: 1.56; 95% CI: 1.03 to 2.35; I <sup>2</sup> =N/A
Ubrogепant 10 mg vs. Ubrogепant 1 mg	Pain free at 2 hours	RR: 2.65; 95% CI: 1.07 to 6.57; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.41; 95% CI: 1.02 to 1.97; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.99; 95% CI: 0.70 to 5.66; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.99; 95% CI: 0.70 to 5.66; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.04; 95% CI: 1.24 to 3.34; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.93; 95% CI: 1.15 to 3.24; I <sup>2</sup> =N/A
Ubrogепant 25 mg vs. Ubrogепant 1 mg	Pain free at 2 hours	RR: 3.64; 95% CI: 1.52 to 8.70; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.37; 95% CI: 0.98 to 1.90; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.98; 95% CI: 1.11 to 7.97; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.98; 95% CI: 1.11 to 7.97; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.14; 95% CI: 1.31 to 3.50; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 2.15; 95% CI: 1.30 to 3.57; I <sup>2</sup> =N/A
Ubrogепant 25 mg vs. Ubrogепant 10 mg	Pain free at 2 hours	RR: 1.38; 95% CI: 0.75 to 2.50; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.96; 95% CI: 0.72 to 1.28; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.50; 95% CI: 0.70 to 3.22; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.50; 95% CI: 0.70 to 3.22; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.05; 95% CI: 0.73 to 1.52; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.11; 95% CI: 0.75 to 1.65; I <sup>2</sup> =N/A
Ubrogепant 25 mg vs. Ubrogепant 100 mg	Pain free at 2 hours	RR: 0.85; 95% CI: 0.51 to 1.43; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.92; 95% CI: 0.70 to 1.22; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.69; 95% CI: 0.37 to 1.27; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.72; 95% CI: 0.39 to 1.34; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.88; 95% CI: 0.62 to 1.24; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 0.89; 95% CI: 0.62 to 1.28; I <sup>2</sup> =N/A
Ubrogепant 50 mg vs. Ubrogепant 1 mg	Pain free at 2 hours	RR: 3.64; 95% CI: 1.52 to 8.70; I <sup>2</sup> =N/A



<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Ubrogепant 50 mg vs. Ubrogепant 1 mg (continued)	Pain relief at 2 hours	RR: 1.49; 95% CI: 1.08 to 2.06; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 3.18; 95% CI: 1.20 to 8.43; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.98; 95% CI: 1.11 to 7.97; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.51; 95% CI: 1.56 to 4.04; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 2.48; 95% CI: 1.52 to 4.06; I <sup>2</sup> =N/A
Ubrogепant 50 mg vs. Ubrogепant 10 mg	Pain free at 2 hours	RR: 1.38; 95% CI: 0.75 to 2.50; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.05; 95% CI: 0.80 to 1.39; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.60; 95% CI: 0.75 to 3.40; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.50; 95% CI: 0.70 to 3.22; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.23; 95% CI: 0.87 to 1.75; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.29; 95% CI: 0.88 to 1.87; I <sup>2</sup> =N/A
Ubrogепant 50 mg vs. Ubrogепant 25 mg	Pain free at 2 hours	RR: 1.10; 95% CI: 0.87 to 1.39; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.10; 95% CI: 0.99 to 1.23; I <sup>2</sup> =0.00%
	Pain relief at 1 day	RR: 1.19; 95% CI: 0.98 to 1.45; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.01; 95% CI: 0.86 to 1.20; I <sup>2</sup> =N/A
	Restores function at 1 day	RR: 1.09; 95% CI: 0.99 to 1.20; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.17; 95% CI: 0.87 to 1.58; I <sup>2</sup> =0.00%
	Sustained pain free at 1 week	RR: 1.00; 95% CI: 0.51 to 1.97; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.17; 95% CI: 0.83 to 1.65; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.15; 95% CI: 0.81 to 1.65; I <sup>2</sup> =N/A
Ubrogепant 50 mg vs. Ubrogепant 100 mg	Pain free at 2 hours	RR: 0.85; 95% CI: 0.67 to 1.09; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 0.95; 95% CI: 0.85 to 1.06; I <sup>2</sup> =0.00%
	Restored function at 2 hours	RR: 0.89; 95% CI: 0.75 to 1.05; I <sup>2</sup> =N/A
	Restores function at 1 day	RR: 0.98; 95% CI: 0.89 to 1.08; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.77; 95% CI: 0.57 to 1.03; I <sup>2</sup> =0.00%
	Sustained pain free at 1 week	RR: 0.72; 95% CI: 0.39 to 1.34; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.94; 95% CI: 0.80 to 1.10; I <sup>2</sup> =0.00%
	Sustained pain relief at 1 week	RR: 1.03; 95% CI: 0.73 to 1.45; I <sup>2</sup> =N/A
Ubrogепant 100 mg vs. Ubrogепant 1 mg	Pain free at 2 hours	RR: 4.27; 95% CI: 1.81 to 10.05; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Ubrogепant 100 mg vs. Ubrogепant 1 mg (continued)	Pain relief at 2 hours	RR: 1.48; 95% CI: 1.07 to 2.04; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 4.34; 95% CI: 1.69 to 11.13; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 4.14; 95% CI: 1.61 to 10.67; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.44; 95% CI: 1.51 to 3.93; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 2.41; 95% CI: 1.47 to 3.95; I <sup>2</sup> =N/A
Ubrogепant 100 mg vs. Ubrogепant 10 mg	Pain free at 2 hours	RR: 1.61; 95% CI: 0.91 to 2.87; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.05; 95% CI: 0.79 to 1.38; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.18; 95% CI: 1.07 to 4.44; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 2.09; 95% CI: 1.02 to 4.26; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.20; 95% CI: 0.84 to 1.70; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.25; 95% CI: 0.86 to 1.82; I <sup>2</sup> =N/A

CI = confidence interval; kg = kilograms; mg = milligrams; N/A = not applicable; RR = risk ratio; ug = micrograms

**Table I-4. Subgroup analysis by dosage for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Lasmiditan 2.5 mg vs. Placebo	Pain free at 2 hours	RR: 0.50; 95% CI: 0.03 to 7.51; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.10; 95% CI: 0.39 to 3.11; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.57; 95% CI: 0.03 to 8.60; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.42; 95% CI: 1.17 to 4.99; I <sup>2</sup> =N/A
Lasmiditan 5 mg vs. Placebo	Pain free at 2 hours	RR: 0.19; 95% CI: 0.01 to 3.14; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 0.37; 95% CI: 0.09 to 1.36; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.22; 95% CI: 0.01 to 3.61; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.07; 95% CI: 0.42 to 2.69; I <sup>2</sup> =N/A
Lasmiditan 10 mg vs. Placebo	Pain free at 2 hours	RR: 1.09; 95% CI: 0.40 to 2.97; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.19; 95% CI: 0.73 to 1.96; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.75; 95% CI: 0.21 to 2.63; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.75; 95% CI: 0.97 to 3.13; I <sup>2</sup> =N/A
Lasmiditan 20 mg vs. Placebo	Pain free at 2 hours	RR: 1.50; 95% CI: 0.64 to 3.53; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.42; 95% CI: 0.92 to 2.19; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.07; 95% CI: 0.37 to 3.04; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.84; 95% CI: 1.06 to 3.21; I <sup>2</sup> =N/A
Lasmiditan 30 mg vs. Placebo	Pain free at 2 hours	RR: 1.97; 95% CI: 0.81 to 4.78; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.52; 95% CI: 0.95 to 2.42; I <sup>2</sup> = N/A
	Sustained pain free at 1 day	RR: 1.12; 95% CI: 0.33 to 3.82; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 2.22; 95% CI: 1.26 to 3.88; I <sup>2</sup> =N/A
Lasmiditan 45 mg vs. Placebo	Pain free at 2 hours	RR: 1.31; 95% CI: 0.21 to 8.01; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.65; 95% CI: 0.86 to 3.19; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.50; 95% CI: 0.24 to 9.32; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.80; 95% CI: 0.13 to 4.67; I <sup>2</sup> =N/A
Lasmiditan 50 mg vs. Placebo	Function scale at 2 hours	SMD: 1.13; 95% CI: 0.84 to 1.43; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 1.39; 95% CI: 1.13 to 1.72; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.30; 95% CI: 1.16 to 1.46; I <sup>2</sup> =0.00%
	Pain scale at 2 hours	SMD: 1.04; 95% CI: 0.75 to 1.34; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Lasmiditan 50 mg vs. Placebo (continued)	Restored function at 2 hours	RR: 1.29; 95% CI: 1.07 to 1.57; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.32; 95% CI: 1.01 to 1.75; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.29; 95% CI: 0.96 to 1.75; I <sup>2</sup> =N/A
Lasmiditan 100 mg vs. Placebo	Function scale at 2 hours	SMD: 1.74; 95% CI: 1.42 to 2.06; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 1.57; 95% CI: 1.34 to 1.85; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.41; 95% CI: 1.29 to 1.54; I <sup>2</sup> =73.00%
	Pain scale at 2 hours	SMD: 0.57; 95% CI: 0.29 to 0.85; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.41; 95% CI: 1.23 to 1.63; I <sup>2</sup> =0.00%
	Sustained pain free at 1 day	RR: 1.31; 95% CI: 0.99 to 1.72; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.24; 95% CI: 0.92 to 1.68; I <sup>2</sup> =N/A
Lasmiditan 200 mg vs. Placebo	Function scale at 2 hours	SMD: 8.46; 95% CI: 7.59 to 9.34; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 1.90; 95% CI: 1.63 to 2.21; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 1.37; 95% CI: 1.26 to 1.49; I <sup>2</sup> =0.00%
	Pain scale at 2 hours	SMD: 7.10; 95% CI: 6.36 to 7.85; I <sup>2</sup> = N/A
	Restored function at 2 hours	RR: 1.47; 95% CI: 1.28 to 1.68; I <sup>2</sup> =0.00%
	Sustained pain free at 1 day	RR: 1.64; 95% CI: 1.26 to 2.13; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.60; 95% CI: 1.21 to 2.14; I <sup>2</sup> =N/A
Lasmiditan 400 mg vs. Placebo	Function scale at 2 hours	SMD: 10.15; 95% CI: 9.12 to 11.18; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 3.29; 95% CI: 1.37 to 7.91; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 2.18; 95% CI: 1.40 to 3.38; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 8.14; 95% CI: 7.30 to 8.98; I <sup>2</sup> =N/A
Lasmiditan 2.5 mg vs. Lasmiditan 10 mg	Pain free at 2 hours	RR: 0.45; 95% CI: 0.03 to 6.97; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 0.92; 95% CI: 0.32 to 2.63; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.71; 95% CI: 0.04 to 11.78; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.38; 95% CI: 0.70 to 2.71; I <sup>2</sup> =N/A
Lasmiditan 5 mg vs. Lasmiditan 2.5 mg	Sustained pain relief at 1 day	RR: 0.44; 95% CI: 0.16 to 1.18; I <sup>2</sup> = N/A
Lasmiditan 5 mg vs. Lasmiditan 10 mg	Pain free at 2 hours	RR: 0.17; 95% CI: 0.01 to 2.92; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 0.31; 95% CI: 0.08 to 1.15; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.27; 95% CI: 0.01 to 4.92; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Lasmiditan 5 mg vs. Lasmiditan 10 mg (continued)	Sustained pain relief at 1 day	RR: 0.61; 95% CI: 0.25 to 1.48; I <sup>2</sup> =N/A
Lasmiditan 5 mg vs. Lasmiditan 20 mg	Pain free at 2 hours	RR: 0.13; 95% CI: 0.01 to 2.10; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.26; 95% CI: 0.07 to 0.94; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.20; 95% CI: 0.01 to 3.40; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.58; 95% CI: 0.24 to 1.38; I <sup>2</sup> =N/A
Lasmiditan 5 mg vs. Lasmiditan 30 mg	Pain free at 2 hours	RR: 0.10; 95% CI: 0.01 to 1.63; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.24; 95% CI: 0.06 to 0.89; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.18; 95% CI: 0.01 to 3.30; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.48; 95% CI: 0.20 to 1.15; I <sup>2</sup> =N/A
Lasmiditan 5 mg vs. Lasmiditan 45 mg	Pain free at 2 hours	RR: 0.13; 95% CI: 0.01 to 2.65; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.22; 95% CI: 0.05 to 0.88; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.12; 95% CI: 0.01 to 2.65; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.33; 95% CI: 0.20 to 8.70; I <sup>2</sup> =N/A
Lasmiditan 20 mg vs. Lasmiditan 2.5 mg	Pain free at 2 hours	RR: 2.93; 95% CI: 0.21 to 43.16; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.89; 95% CI: 0.12 to 29.2; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.76; 95% CI: 0.39 to 1.46; I <sup>2</sup> =N/A
Lasmiditan 20 mg vs. Lasmiditan 10 mg	Pain free at 2 hours	RR: 1.37; 95% CI: 0.52 to 3.63; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.18; 95% CI: 0.75 to 1.88; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.42; 95% CI: 0.38 to 5.36; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.05; 95% CI: 0.64 to 1.71; I <sup>2</sup> =N/A
Lasmiditan 30 mg vs. Lasmiditan 2.5 mg	Pain free at 2 hours	RR: 3.82; 95% CI: 0.26 to 56.78; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.37; 95% CI: 0.48 to 3.86; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.05; 95% CI: 0.12 to 33.5; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.91; 95% CI: 0.47 to 1.76; I <sup>2</sup> =N/A
Lasmiditan 30 mg vs. Lasmiditan 10 mg	Pain free at 2 hours	RR: 1.80; 95% CI: 0.66 to 4.91; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.27; 95% CI: 0.77 to 2.08; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.50; 95% CI: 0.34 to 6.52; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.26; 95% CI: 0.77 to 2.08; I <sup>2</sup> =N/A
Lasmiditan 30 mg vs. Lasmiditan 20 mg	Pain free at 2 hours	RR: 1.31; 95% CI: 0.55 to 3.11; I <sup>2</sup> =N/A

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Lasmiditan 30 mg vs. Lasmiditan 20 mg (continued)	Sustained pain free at 1 day	RR: 1.05; 95% CI: 0.28 to 3.82; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.20; 95% CI: 0.75 to 1.90; I <sup>2</sup> =N/A
Lasmiditan 45 mg vs. Lasmiditan 2.5 mg	Pain free at 2 hours	RR: 3.00; 95% CI: 0.16 to 57.36; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.50; 95% CI: 0.48 to 4.65; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 3.00; 95% CI: 0.15 to 57.36; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.33; 95% CI: 0.05 to 1.99; I <sup>2</sup> =N/A
Lasmiditan 45 mg vs. Lasmiditan 10 mg	Pain free at 2 hours	RR: 1.20; 95% CI: 0.18 to 7.77; I <sup>2</sup> = N/A
	Pain relief at 2 hours	RR: 1.38; 95% CI: 0.70 to 2.72; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 2.00; 95% CI: 0.27 to 14.78; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.46; 95% CI: 0.08 to 2.62; I <sup>2</sup> =N/A
Lasmiditan 45 mg vs. Lasmiditan 20 mg	Pain free at 2 hours	RR: 0.87; 95% CI: 0.14 to 5.27; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.07; 95% CI: 0.69 to 1.64; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.40; 95% CI: 0.21 to 9.12; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.43; 95% CI: 0.07 to 2.46; I <sup>2</sup> =N/A
Lasmiditan 45 mg vs. Lasmiditan 30 mg	Pain free at 2 hours	RR: 0.66; 95% CI: 0.11 to 4.08; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.09; 95% CI: 0.56 to 2.10; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.33; 95% CI: 0.18 to 9.65; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 0.36; 95% CI: 0.06 to 2.04; I <sup>2</sup> =N/A
Lasmiditan 50 mg vs. Lasmiditan 100 mg	Function scale at 2 hours	SMD: 0.68; 95% CI: 0.96 to 0.41; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 0.96; 95% CI: 0.79 to 1.16; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 0.92; 95% CI: 0.83 to 1.02; I <sup>2</sup> =80.20%
	Pain scale at 2 hours	SMD: 0.66; 95% CI: 0.38 to 0.94; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 0.97; 95% CI: 0.82 to 1.16; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.04; 95% CI: 0.78 to 1.37; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 1.01; 95% CI: 0.78 to 1.31; I <sup>2</sup> =N/A
Lasmiditan 50 mg vs. Lasmiditan 200 mg	Function scale at 2 hours	SMD: 8.66; 95% CI: 9.55 to 7.78; I <sup>2</sup> = N/A
	Pain free at 2 hours	RR: 0.78; 95% CI: 0.65 to 0.93; I <sup>2</sup> =0.00%
	Pain relief at 2 hours	RR: 0.96; 95% CI: 0.87 to 1.06; I <sup>2</sup> =0.00%
	Pain scale at 2 hours	SMD: 6.84; 95% CI: 7.56 to 6.13; I <sup>2</sup> =N/A

Comparison	Outcome	Findings
Lasmiditan 50 mg vs. Lasmiditan 200 mg (continued)	Restored function at 2 hours	RR: 0.90; 95% CI: 0.76 to 1.06; I <sup>2</sup> =N/A
	Sustained pain free at 1 day	RR: 0.81; 95% CI: 0.63 to 1.02; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 0.80; 95% CI: 0.62 to 1.04; I <sup>2</sup> =N/A
Lasmiditan 50 mg vs. Lasmiditan 400 mg	Function scale at 2 hours	SMD: 10.66; 95% CI: 11.74 to 9.59; I <sup>2</sup> = N/A
	Pain free at 2 hours	RR: 0.54; 95% CI: 0.27 to 1.07; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.72; 95% CI: 0.51 to 1.03; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 8.11; 95% CI: 8.94 to 7.27; I <sup>2</sup> =N/A
Lasmiditan 200 mg vs. Lasmiditan 100 mg	Function scale at 2 hours	SMD: 8.27; 95% CI: 7.42 to 9.13; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 1.20; 95% CI: 1.06 to 1.37; I <sup>2</sup> =0.00%
	Pain free at 1 day	RR: 0.66; 95% CI: 0.51 to 0.87; I <sup>2</sup> =5.90%
	Pain relief at 2 hours	RR: 0.96; 95% CI: 0.90 to 1.04; I <sup>2</sup> =50.60%
	Pain scale at 2 hours	SMD: 8.56; 95% CI: 7.59 to 9.34; I <sup>2</sup> =N/A
	Restored function at 2 hours	RR: 1.04; 95% CI: 0.92 to 1.17; I <sup>2</sup> =0.00%
	Sustained pain free at 1 day	RR: 1.25; 95% CI: 0.98 to 1.59; I <sup>2</sup> =N/A
	Sustained pain free at 1 week	RR: 1.29; 95% CI: 0.99 to 1.67; I <sup>2</sup> =N/A
	Sustained pain relief at 1 day	RR: 1.23; 95% CI: 0.94 to 1.62; I <sup>2</sup> =N/A
	Sustained pain relief at 1 week	RR: 1.08; 95% CI: 0.81 to 1.42; I <sup>2</sup> =N/A
Lasmiditan 400 mg vs. Lasmiditan 100 mg	Function scale at 2 hours	SMD: 10.34; 95% CI: 9.31 to 11.39; I <sup>2</sup> =N/A
	Pain free at 2 hours	RR: 1.81; 95% CI: 0.91 to 3.61; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 0.88; 95% CI: 0.66 to 1.19; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 10.38; 95% CI: 9.33 to 11.4; I <sup>2</sup> =N/A
Lasmiditan 400 mg vs. Lasmiditan 200 mg	Function scale at 2 hours	SMD: 2.00; 95% CI: 1.66 to 2.34; I <sup>2</sup> = N/A
	Pain free at 2 hours	RR: 1.47; 95% CI: 0.77 to 2.82; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR: 1.26; 95% CI: 0.89 to 1.79; I <sup>2</sup> =N/A
	Pain scale at 2 hours	SMD: 0.73; 95% CI: 0.44 to 1.02; I <sup>2</sup> =N/A

CI = confidence interval; mg = milligram; N/A = not available; RR = relative risk; SMD = standardized mean deviation

**Table I-5. Subgroup analysis by dosage for other interventions**

Comparison	Outcome	Findings
Buccal PCZ vs. Placebo	Pain scale at 2 hours	SMD: 0.45; 95% CI:-0.34 to 1.24; I <sup>2</sup> =N/A
Civamide 20 µg vs. Civamide 150 µg	Pain free at 2 hours	RR:0.63; 95% CI:0.14 to 2.85; I <sup>2</sup> =N/A
	Pain free at 1 day	RR:1.25; 95% CI:0.39 to 3.99; I <sup>2</sup> =N/A
	Pain relief at 2 hours	RR:1.09; 95% CI:0.56 to 2.14; I <sup>2</sup> =N/A
	Pain relief at 1 day	RR:0.97; 95% CI:0.52 to 1.83; I <sup>2</sup> =N/A

CI = confidence interval; µg = microgram; mg = milligram; N/A = not applicable; PCZ = prochlorperazine; RR = relative risk; SMD = standardized mean difference



## Appendix J. Adverse Events: Subgroup Analysis by Dosage

**Table J-1. Adverse events: KQ 2. ergot alkaloids subgroup analysis by dosage**

Comparison	Adverse Events	Findings	Study Design
Dihydroergotamine 1 mg vs. Placebo	Total AE	Rate Ratio: 0.70; 95% CI: 0.13 to 4.62; I <sup>2</sup> =N/A	1 RCT <sup>5</sup>
Dihydroergotamine 2 mg vs. Placebo	Total AE	Rate Ratio: 2.18; 95% CI: 0.46 to 10.27; I <sup>2</sup> =N/A	1 RCT <sup>5</sup>
Dihydroergotamine 1 mg vs. Dihydroergotamine 0.5 mg	Neurologic AE	Rate Ratio: 0.89; 95% CI: 0.06 to 14.30; I <sup>2</sup> =N/A	1 RCT <sup>129</sup>
Dihydroergotamine 2 mg vs. Dihydroergotamine 1 mg	Total AE	Rate Ratio: 2.83; 95% CI: 0.57 to 14.01; I <sup>2</sup> =N/A	1 RCT <sup>5</sup>

AE = adverse event; CI = confidence interval; Rate Ratio = incidence rate ratio; mg= milligrams N/A = not applicable, RCT = randomized controlled trial

**Table J-2. Adverse events: KQ 2. antiemetic subgroup analysis by dosage**

Comparison	Adverse Events	Findings	Study Design
Droperidol 0.1 mg vs. Placebo	Dermatological AE	Rate Ratio: 0.39; 95% CI: 0.12 to 1.23; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 1.45; 95% CI: 0.41 to 5.15; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 0.65; 95% CI: 0.37 to 1.14; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 1.94; 95% CI: 0.35 to 10.57; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 0.74; 95% CI: 0.47 to 1.14; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 2.75 mg vs. Placebo	Dermatological AE	Rate Ratio: 0.40; 95% CI: 0.13 to 1.28; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 1.00; 95% CI: 0.25 to 4; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 1.80; 95% CI: 1.15 to 2.81; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 8.00; 95% CI: 1.84 to 34.79; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.78; 95% CI: 1.24 to 2.56; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 5.5 mg vs. Placebo	Dermatological AE	Rate Ratio: 0.31; 95% CI: 0.09 to 1.13; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 0.52; 95% CI: 0.09 to 2.82; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 1.90; 95% CI: 1.21 to 2.96; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 9.31; 95% CI: 2.16 to 40.1; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.84; 95% CI: 1.28 to 2.64; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 8.25 mg vs. Placebo	Dermatological AE	Rate Ratio: 0.60; 95% CI: 0.22 to 1.65; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 2.00; 95% CI: 0.6 to 6.64; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 1.77; 95% CI: 1.13 to 2.76; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 10.00; 95% CI: 2.34 to 42.78; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 2.13; 95% CI: 1.5 to 3.02; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 2.75 mg vs. Droperidol 0.1 mg	Dermatological AE	Rate Ratio: 1.03; 95% CI: 0.26 to 4.13; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 2.07; 95% CI: 0.13 to 33.02; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 0.69; 95% CI: 0.22 to 2.13; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 2.79; 95% CI: 1.5 to 5.18; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 4.13; 95% CI: 1.03 to 16.52; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 2.42; 95% CI: 1.51 to 3.87; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 5.5 mg vs. Droperidol 0.1 mg	Dermatological AE	Rate Ratio: 0.80; 95% CI: 0.18 to 3.58; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.07; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 0.36; 95% CI: 0.07 to 1.76; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>

Comparison	Adverse Events	Findings	Study Design
Droperidol 5.5 mg vs. Droperidol 0.1 mg (continued)	Neurological AE	Rate Ratio: 2.94; 95% CI: 1.76 to 4.9; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 4.81; 95% CI: 1.63 to 14.2; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 2.50; 95% CI: 1.68 to 3.72; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 5.5 mg vs. Droperidol 2.75 mg	Dermatological AE	Rate Ratio: 0.78; 95% CI: 0.17 to 3.46; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 0.52; 95% CI: 0.05 to 5.7; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 0.52; 95% CI: 0.09 to 2.82; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 1.05; 95% CI: 0.72 to 1.53; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 1.16; 95% CI: 0.59 to 2.28; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.03; 95% CI: 0.76 to 1.4; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 8.25 mg vs. Droperidol 0.1 mg	Dermatological AE	Rate Ratio: 1.55; 95% CI: 0.44 to 5.49; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 6.20; 95% CI: 0.75 to 51.47; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 1.38; 95% CI: 0.48 to 3.97; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 2.74; 95% CI: 1.64 to 4.58; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 5.16; 95% CI: 1.77 to 15.1; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 2.89; 95% CI: 1.97 to 4.25; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 8.25 mg vs. Droperidol 2.75 mg	Dermatological AE	Rate Ratio: 1.50; 95% CI: 0.42 to 5.32; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 3.00; 95% CI: 0.61 to 14.86; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 2.00; 95% CI: 0.6 to 6.64; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 0.98; 95% CI: 0.67 to 1.43; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 1.25; 95% CI: 0.65 to 2.41; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.20; 95% CI: 0.89 to 1.6; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Droperidol 8.25 mg vs. Droperidol 5.5 mg	Dermatological AE	Rate Ratio: 1.93; 95% CI: 0.48 to 7.73; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	ENT AE	Rate Ratio: 5.80; 95% CI: 0.7 to 48.2; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Gastrointestinal AE	Rate Ratio: 3.87; 95% CI: 0.82 to 18.22; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Neurological AE	Rate Ratio: 0.93; 95% CI: 0.64 to 1.36; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Psychological AE	Rate Ratio: 1.07; 95% CI: 0.57 to 2.03; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
	Total AE	Rate Ratio: 1.16; 95% CI: 0.86 to 1.55; I <sup>2</sup> =N/A	1 RCT <sup>119</sup>
Granisetron 40 µg/kg vs. Placebo	Cardiovascular AE	Rate Ratio: 0.80; 95% CI: 0.11 to 5.68; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Gastrointestinal AE	Rate Ratio: 1.40; 95% CI: 0.36 to 5.41; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>

Comparison	Adverse Events	Findings	Study Design
Granisetron 40 µg/kg vs. Placebo (continued)	Neurological AE	Rate Ratio: 0.80; 95% CI: 0.11 to 5.68; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Total AE	Rate Ratio: 0.80; 95% CI: 0.2 to 3.2; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
Granisetron 80 µg/kg vs. Placebo	Cardiovascular AE	Rate Ratio: 0.80; 95% CI: 0.11 to 5.68; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Gastrointestinal AE	Rate Ratio: 1.40; 95% CI: 0.36 to 5.41; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Neurological AE	Rate Ratio: 0.80; 95% CI: 0.11 to 5.68; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Total AE	Rate Ratio: 1.00; 95% CI: 0.27 to 3.72; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
Granisetron 80 µg/kg vs. Granisetron 40 µg/kg	Cardiovascular AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.1; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Gastrointestinal AE	Rate Ratio: 1.00; 95% CI: 0.35 to 2.85; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Neurological AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.1; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
	Total AE	Rate Ratio: 1.25; 95% CI: 0.31 to 5; I <sup>2</sup> =N/A	1 RCT <sup>109</sup>
Metoclopramide 20 mg vs. Metoclopramide 10 mg	Neurological AE	Rate Ratio: 0.69; 95% CI: 0.42 to 1.14; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>
	Total AE	Rate Ratio: 0.86; 95% CI: 0.52 to 1.43; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>
Metoclopramide 40 mg vs. Metoclopramide 10 mg	Neurological AE	Rate Ratio: 0.67; 95% CI: 0.38 to 1.17; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>
	Total AE	Rate Ratio: 0.67; 95% CI: 0.38 to 1.17; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>
Metoclopramide 40 mg vs. Metoclopramide 20 mg	Neurological AE	Rate Ratio: 0.97; 95% CI: 0.55 to 1.72; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>
	Total AE	Rate Ratio: 0.78; 95% CI: 0.44 to 1.38; I <sup>2</sup> =N/A	1 RCT <sup>50</sup>

AE = adverse event; ENT = ear, nose, throat; Rate Ratio = incidence rate ratio; N/A = not applicable; RCT = randomized controlled trial.

**Table J-3. Adverse events: KQ 2. calcitonin gene-related peptide receptor antagonists subgroup analysis by dosage**

Comparison	Adverse Events	Findings	Study Design
Rimegepant 10 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.89; 95% CI: 0.72 to 4.95; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.35; 95% CI: 0.25 to 7.35; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 2.12; 95% CI: 0.96 to 4.66; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 25 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.67; 95% CI: 0.15 to 3.07; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.84; 95% CI: 0.09 to 7.53; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.72; 95% CI: 0.21 to 2.51; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 75 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.26; 95% CI: 0.43 to 3.68; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.63; 95% CI: 0.07 to 5.63; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.08; 95% CI: 0.41 to 2.81; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 150 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.76; 95% CI: 0.21 to 6.95; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.27; 95% CI: 0.23 to 6.95; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.91; 95% CI: 0.33 to 2.52; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 300 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.14; 95% CI: 0.41 to 3.12; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.81; 95% CI: 0.31 to 2.11; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 2.24; 95% CI: 0.91 to 5.51; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.87; 95% CI: 0.42 to 8.34; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 2.13; 95% CI: 0.99 to 4.61; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 25 mg vs. Rimegepant 10 mg	Gastrointestinal AE	Rate Ratio: 0.36; 95% CI: 0.13 to 1.02; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.63; 95% CI: 0.09 to 4.44; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.34; 95% CI: 0.15 to 0.79; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 75 mg vs. Rimegepant 10 mg	Gastrointestinal AE	Rate Ratio: 0.67; 95% CI: 0.21 to 2.1; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.47; 95% CI: 0.04 to 5.15; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.51; 95% CI: 0.19 to 1.38; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 75 mg vs. Rimegepant 25 mg	Gastrointestinal AE	Rate Ratio: 1.87; 95% CI: 0.36 to 9.63; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.75; 95% CI: 0.05 to 11.95; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.49; 95% CI: 0.37 to 5.98; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 150 mg vs. Rimegepant 10 mg	Gastrointestinal AE	Rate Ratio: 0.40; 95% CI: 0.10 to 1.57; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 0.94; 95% CI: 0.13 to 6.7; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>

Comparison	Adverse Events	Findings	Study Design
Rimegepant 150 mg vs. Rimegepant 10 mg (continued)	Total AE	Rate Ratio: 0.43; 95% CI: 0.15 to 1.24; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 150 mg vs. Rimegepant 25 mg	Gastrointestinal AE	Rate Ratio: 1.13; 95% CI: 0.19 to 6.78; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.51; 95% CI: 0.14 to 16.66; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.26; 95% CI: 0.3 to 5.27; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 150 mg vs. Rimegepant 75 mg	Gastrointestinal AE	Rate Ratio: 0.61; 95% CI: 0.14 to 2.54; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 2.02; 95% CI: 0.18 to 22.3; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.84; 95% CI: 0.26 to 2.76; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 300 mg vs. Rimegepant 10 mg	Gastrointestinal AE	Rate Ratio: 0.60; 95% CI: 0.2 to 1.79; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.38; 95% CI: 0.14 to 1.04; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 300 mg vs. Rimegepant 25 mg	Gastrointestinal AE	Rate Ratio: 1.69; 95% CI: 0.34 to 8.35; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.12; 95% CI: 0.28 to 4.49; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 300 mg vs. Rimegepant 75 mg	Gastrointestinal AE	Rate Ratio: 0.9; 95% CI: 0.28 to 2.96; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.75; 95% CI: 0.24 to 2.33; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 300 mg vs. Rimegepant 150 mg	Gastrointestinal AE	Rate Ratio: 1.49; 95% CI: 0.37 to 5.95; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 0.89; 95% CI: 0.27 to 2.92; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Rimegepant 10 mg	Gastrointestinal AE	Rate Ratio: 1.19; 95% CI: 0.44 to 3.19; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.39; 95% CI: 0.23 to 8.29; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.01; 95% CI: 0.44 to 2.28; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Rimegepant 25 mg	Gastrointestinal AE	Rate Ratio: 3.33; 95% CI: 0.72 to 15.39; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 2.22; 95% CI: 0.23 to 21.32; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 2.96; 95% CI: 0.83 to 10.48; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Rimegepant 75 mg	Gastrointestinal AE	Rate Ratio: 1.78; 95% CI: 0.6 to 5.31; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 2.97; 95% CI: 0.31 to 28.53; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 1.98; 95% CI: 0.74 to 5.27; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Rimegepant 150 mg	Gastrointestinal AE	Rate Ratio: 2.93; 95% CI: 0.79 to 10.84; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Neurological AE	Rate Ratio: 1.47; 95% CI: 0.25 to 8.78; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 2.35; 95% CI: 0.83 to 6.66; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
Rimegepant 600 mg vs. Rimegepant 300 mg	Gastrointestinal AE	Rate Ratio: 1.97; 95% CI: 0.7 to 5.54; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>
	Total AE	Rate Ratio: 2.63; 95% CI: 0.99 to 7.01; I <sup>2</sup> =N/A	1 RCT <sup>95</sup>

Comparison	Adverse Events	Findings	Study Design
Ubrogapant 1 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 2.01; 95% CI: 0.86 to 4.71; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 1.59; 95% CI: 0.77 to 3.29; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 1.19; 95% CI: 0.72 to 1.96; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogapant 10 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.00; 95% CI: 0.38 to 2.66; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 1.00; 95% CI: 0.45 to 2.23; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 1.04; 95% CI: 0.62 to 1.74; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogapant 25 mg vs. Placebo	ENT AE	Rate Ratio: 5.02; 95% CI: 0.59 to 42.95; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Gastrointestinal AE	Rate Ratio: 1.34; 95% CI: 0.72 to 2.46; I <sup>2</sup> =0%	2 RCTs <sup>90, 133</sup>
	Neurological AE	Rate Ratio: 1.00; 95% CI: 0.55 to 1.84; I <sup>2</sup> =0.00%	2 RCTs <sup>90, 133</sup>
	Respiratory AE	Rate Ratio: 0.67; 95% CI: 0.32 to 1.39; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Total AE	Rate Ratio: 0.90; 95% CI: 0.71 to 1.15; I <sup>2</sup> =0.00%	2 RCTs <sup>90, 133</sup>
Ubrogapant 50 mg vs. Placebo	ENT AE	Rate Ratio: 11.02; 95% CI: 1.42 to 85.35; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Gastrointestinal AE	Rate Ratio: 1.12; 95% CI: 0.70 to 1.80; I <sup>2</sup> =0.00%	3 RCTs <sup>37, 90, 133</sup>
	Neurological AE	Rate Ratio: 0.85; 95% CI: 0.47 to 1.52; I <sup>2</sup> =0.00%	3 RCTs <sup>37, 90, 133</sup>
	Respiratory AE	Rate Ratio: 1.20; 95% CI: 0.71 to 2.04; I <sup>2</sup> = 39.80%	2 RCTs <sup>37, 90</sup>
	Total AE	Rate Ratio: 1.12; 95% CI: 0.94 to 1.33; I <sup>2</sup> =0.00%	3 RCTs <sup>37, 90, 133</sup>
Ubrogapant 100 mg vs. Placebo	Gastrointestinal AE	Rate Ratio: 2.13; 95% CI: 1.30 to 3.50; I <sup>2</sup> =0.00%	2 RCTs <sup>37, 133</sup>
	Neurological AE	Rate Ratio: 1.50; 95% CI: 0.79 to 2.86; I <sup>2</sup> =53.40%	2 RCTs <sup>37, 133</sup>
	Respiratory AE	Rate Ratio: 1.25; 95% CI: 0.50 to 3.18; I <sup>2</sup> = N/A	1 RCT <sup>37</sup>
	Total AE	Rate Ratio: 1.20; 95% CI: 0.96 to 1.50; I <sup>2</sup> =0.00%	2 RCTs <sup>37, 133</sup>
Ubrogapant 10 mg vs. Ubrogapant 1 mg	Gastrointestinal AE	Rate Ratio: 0.50; 95% CI: 0.25 to 0.99; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.63; 95% CI: 0.33 to 1.18; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 0.87; 95% CI: 0.54 to 1.41; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogapant 25 mg vs. Ubrogapant 1 mg	Gastrointestinal AE	Rate Ratio: 0.62; 95% CI: 0.28 to 1.37; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.52; 95% CI: 0.24 to 1.12; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 0.63; 95% CI: 0.37 to 1.09; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogapant 25 mg vs. Ubrogapant 10 mg	Cardiovascular AE	Rate Ratio: 1.00; 95% CI: 0.06 to 15.99; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Gastrointestinal AE	Rate Ratio: 1.25; 95% CI: 0.49 to 3.17; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.83; 95% CI: 0.36 to 1.93; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>

Comparison	Adverse Events	Findings	Study Design
Ubrogepant 25 mg vs. Ubrogepant 10 mg (continued)	Total AE	Rate Ratio: 0.72; 95% CI: 0.41 to 1.27; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 50 mg vs. Ubrogepant 1 mg	Gastrointestinal AE	Rate Ratio: 0.81; 95% CI: 0.39 to 1.68; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.37; 95% CI: 0.15 to 0.87; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 0.69; 95% CI: 0.41 to 1.18; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 50 mg vs. Ubrogepant 10 mg	Cardiovascular AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Gastrointestinal AE	Rate Ratio: 1.63; 95% CI: 0.67 to 3.92; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.58; 95% CI: 0.23 to 1.48; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 0.79; 95% CI: 0.46 to 1.37 I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 50 mg vs. Ubrogepant 25 mg	Cardiovascular AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	ENT AE	Rate Ratio: 2.20; 95% CI: 0.76 to 6.30; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Gastrointestinal AE	Rate Ratio: 1.04; 95% CI: 0.59 to 1.83; I <sup>2</sup> =0.00%	2 RCTs <sup>90, 133</sup>
	Neurological AE	Rate Ratio: 0.81; 95% CI: 0.43 to 1.54 I <sup>2</sup> =0.00%	2 RCTs <sup>90, 133</sup>
	Respiratory AE	Rate Ratio: 2.16; 95% CI: 1.09 to 4.29; I <sup>2</sup> =N/A	1 RCT <sup>90</sup>
	Total AE	Rate Ratio: 1.24; 95% CI: 0.98 to 1.56; I <sup>2</sup> =0.00%	2 RCTs <sup>90, 133</sup>
Ubrogepant 100 mg vs. Ubrogepant 1 mg	Gastrointestinal AE	Rate Ratio: 0.99; 95% CI: 0.49 to 1.97; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 0.67; 95% CI: 0.33 to 1.37; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 0.90; 95% CI: 0.55 to 1.47; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 100 mg vs. Ubrogepant 10 mg	Gastrointestinal AE	Rate Ratio: 1.99; 95% CI: 0.85 to 4.64; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 1.08; 95% CI: 0.49 to 2.36; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 1.03; 95% CI: 0.62 to 1.71; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 100 mg vs. Ubrogepant 25 mg	Gastrointestinal AE	Rate Ratio: 1.59; 95% CI: 0.72 to 3.50; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Neurological AE	Rate Ratio: 1.29; 95% CI: 0.57 to 2.94; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
	Total AE	Rate Ratio: 1.42; 95% CI: 0.81 to 2.48; I <sup>2</sup> =N/A	1 RCT <sup>133</sup>
Ubrogepant 100 mg vs. Ubrogepant 50 mg	Gastrointestinal AE	Rate Ratio: 1.91; 95% CI: 1.17 to 3.12; I <sup>2</sup> =61.40%	2 RCTs <sup>37, 133</sup>
	Neurological AE	Rate Ratio: 2.24; 95% CI: 1.10 to 4.56; I <sup>2</sup> =0%	2 RCTs <sup>37, 133</sup>
	Respiratory AE	Rate Ratio: 2.00; 95% CI: 0.68 to 5.84; I <sup>2</sup> =N/A	1 RCT <sup>37</sup>
	Serious AE	Rate Ratio: 0.67; 95% CI: 0.11 to 3.98; I <sup>2</sup> = N/A	1 RCT <sup>37</sup>
	Total AE	Rate Ratio: 1.13; 95% CI: 0.91 to 1.41; I <sup>2</sup> =0.00%	2 RCTs <sup>37, 133</sup>

AE = adverse event; CI = confidence interval; ENT = ear, nose, throat; Rate Ratio = incidence rate ratio; mg = milligrams; N/A = not applicable; RCT = randomized controlled trial



**Table J-4. Adverse events: KQ 2. 5-HT1F subgroup analysis by dosage**

Comparison	Adverse Events	Findings	Study Design
Lasmitidan 2.5 mg vs. Placebo	Neurological AE	Rate Ratio: 2.10; 95% CI: 0.46 to 9.58; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 2.10; 95% CI: 0.46 to 9.58; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 5 mg vs. Placebo	Neurological AE	Rate Ratio: 0.70; 95% CI: 0.15 to 3.19; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 0.70; 95% CI: 0.15 to 3.19; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 10 mg vs. Placebo	Neurological AE	Rate Ratio: 2.80; 95% CI: 1.27 to 6.17; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 2.80; 95% CI: 1.27 to 6.17; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 20 mg vs. Placebo	Neurological AE	Rate Ratio: 3.45; 95% CI: 1.64 to 7.25; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 3.75; 95% CI: 1.80 to 7.81; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 30 mg vs. Placebo	Neurological AE	Rate Ratio: 4.46; 95% CI: 2.04 to 9.75; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 5.25; 95% CI: 2.46 to 11.22; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Placebo	Neurological AE	Rate Ratio: 2.10; 95% CI: 0.46 to 9.58; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 2.10; 95% CI: 0.46 to 9.58; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 50 mg vs. Placebo	Cardiovascular AEs	Rate Ratio: 1.99; 95% CI: 0.18 to 21.90; I <sup>2</sup> =N/A	1 RCT <sup>58</sup>
	Gastrointestinal AE	Rate Ratio: 2.36; 95% CI: 1.03 to 5.39; I <sup>2</sup> =N/A	1 RCT <sup>58</sup>
	Neurological AE	Rate Ratio: 3.61; 95% CI: 2.66 to 4.89; I <sup>2</sup> =62.0%	2 RCTs <sup>44, 58</sup>
	Serious AEs	Rate Ratio: 3.11; 95% CI: 1.14 to 8.49; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 2.30; 95% CI: 1.60 to 4.58; I <sup>2</sup> =0.00%	2 RCTs <sup>44, 58</sup>
Lasmitidan 100 mg vs. Placebo	Cardiovascular AEs	Rate Ratio: 1.65; 95% CI: 0.39 to 6.93; I <sup>2</sup> =0.00%	2 RCTs <sup>58, 83</sup>
	Gastrointestinal AE	Rate Ratio: 2.10; 95% CI: 1.23 to 3.59; I <sup>2</sup> =0.0%	2 RCTs <sup>58, 83</sup>
	Neurological AE	Rate Ratio: 4.60; 95% CI: 3.72 to 5.68; I <sup>2</sup> =69.60%	3 RCTs <sup>42, 58, 83</sup>
	Serious AEs	Rate Ratio: 4.56; 95% CI: 1.73 to 11.98; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 1.31; 95% CI: 1.10 to 1.57; I <sup>2</sup> =0.00%	2 RCTs <sup>42, 83</sup>
Lasmitidan 200 mg vs. Placebo	Cardiovascular AEs	Rate Ratio: 2.64; 95% CI: 0.70 to 9.97; I <sup>2</sup> =0.00%	2 RCTs <sup>58, 83</sup>
	Gastrointestinal AE	Rate Ratio: 2.53; 95% CI: 1.51 to 4.24; I <sup>2</sup> =0.00%	2 RCTs <sup>58, 83</sup>
	Neurological AE	Rate Ratio: 5.27; 95% CI: 4.28 to 6.50; I <sup>2</sup> =74.90%	3 RCTs <sup>44, 58, 83</sup>
	Serious AEs	Rate Ratio: 4.99; 95% CI: 2.06 to 12.09; I <sup>2</sup> =0.00%	2 RCTs <sup>42, 83</sup>
	Total AE	Rate Ratio: 2.92; 95% CI: 2.48 to 3.43; I <sup>2</sup> =17.90%	3 RCTs <sup>44, 58, 83</sup>
Lasmitidan 400 mg vs. Placebo	Neurological AE	Rate Ratio: 11.44; 95% CI: 6.17 to 21.22; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Serious AEs	Rate Ratio: 6.45; 95% CI: 2.51 to 16.59; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>

Comparison	Adverse Events	Findings	Study Design
Lasmitidan 400 mg vs. Placebo (continued)	Total AE	Rate Ratio:3.23; 95% CI: 1.93 to 5.42; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
Lasmitidan 5 mg vs. Lasmitidan 2.5 mg	Neurological AE	Rate Ratio: 0.33; 95% CI: 0.05 to 2.37; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 0.33; 95% CI: 0.05 to 2.37; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 10 mg vs. Lasmitidan 2.5 mg	Neurological AE	Rate Ratio: 1.33; 95% CI: 0.31 to 5.80; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.33; 95% CI: 0.31 to 5.80; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 10 mg vs. Lasmitidan 5 mg	Neurological AE	Rate Ratio: 4.00; 95% CI: 0.92 to 17.40; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 4.00; 95% CI: 0.92 to 17.40; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 20 mg vs. Lasmitidan 2.5 mg	Neurological AE	Rate Ratio: 1.64; 95% CI: 0.39 to 6.97; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.79; 95% CI: 0.42 to 7.54; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 20 mg vs. Lasmitidan 5 mg	Neurological AE	Rate Ratio: 4.93; 95% CI: 1.16 to 20.90; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 5.36; 95% CI: 1.27 to 22.62; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 20 mg vs. Lasmitidan 10 mg	Neurological AE	Rate Ratio: 1.23; 95% CI: 0.65 to 2.33; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.34; 95% CI: 0.72 to 2.51; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 30 mg vs. Lasmitidan 2.5 mg	Neurological AE	Rate Ratio: 2.13; 95% CI: 0.49 to 9.20; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 2.50; 95% CI: 0.58 to 10.70; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 30 mg vs. Lasmitidan 5 mg	Neurological AE	Rate Ratio: 6.38; 95% CI: 1.47 to 27.59; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 7.50; 95% CI: 1.75 to 32.09; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 30 mg vs. Lasmitidan 10 mg	Neurological AE	Rate Ratio: 1.59; 95% CI: 0.81 to 3.15; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.88; 95% CI: 0.97 to 3.62; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 30 mg vs. Lasmitidan 20 mg	Neurological AE	Rate Ratio: 1.29; 95% CI: 0.69 to 2.42; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.40; 95% CI: 0.78 to 2.52; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Lasmitidan 2.5 mg	Neurological AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 1.00; 95% CI: 0.14 to 7.10; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Lasmitidan 5 mg	Neurological AE	Rate Ratio: 3.00; 95% CI: 0.42 to 21.30; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 3.00; 95% CI: 0.42 to 21.30; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Lasmitidan 10 mg	Neurological AE	Rate Ratio: 0.75; 95% CI: 0.17 to 3.26; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 0.75; 95% CI: 0.17 to 3.26; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Lasmitidan 20 mg	Neurological AE	Rate Ratio: 0.61; 95% CI: 0.14 to 2.58; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
	Total AE	Rate Ratio: 0.56; 95% CI: 0.13 to 2.36; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 45 mg vs. Lasmitidan 30 mg	Neurological AE	Rate Ratio: 0.47; 95% CI: 0.11 to 2.04; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>

Comparison	Adverse Events	Findings	Study Design
Lasmitidan 45 mg vs. Lasmitidan 30 mg (continued)	Total AE	Rate Ratio: 0.40; 95% CI: 0.09 to 1.71; I <sup>2</sup> =N/A	1 RCT <sup>44</sup>
Lasmitidan 100 mg vs. Lasmitidan 50 mg	Cardiovascular AEs	Rate Ratio: 0.99; 95% CI: 0.14 to 7.05; I <sup>2</sup> =N/A	1 RCT <sup>58</sup>
	Gastrointestinal AE	Rate Ratio: 1.24; 95% CI: 0.73 to 2.1; I <sup>2</sup> =0.00%	2 RCTs <sup>44, 58</sup>
	Neurological AE	Rate Ratio: 1.58; 95% CI: 1.32 to 1.89; I <sup>2</sup> =0.00%	2 RCTs <sup>44, 58</sup>
	Serious AEs	Rate Ratio: 1.47; 95% CI: 0.77 to 2.77; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 1.31; 95% CI: 1.10 to 1.57; I <sup>2</sup> =0.00%	2 RCTs <sup>42, 58</sup>
Lasmitidan 200 mg vs. Lasmitidan 100 mg	Cardiovascular AEs	Rate Ratio: 1.60; 95% CI: 0.52 to 4.89; I <sup>2</sup> =0.00%	2 RCTs <sup>58, 83</sup>
	Serious AEs	Rate Ratio: 1.24; 95% CI: 0.89 to 1.72; I <sup>2</sup> =0.00%	2 RCTs <sup>17, 44</sup>
	Gastrointestinal AE	Rate Ratio: 1.16; 95% CI: 0.52 to 2.58; I <sup>2</sup> =53.10%	4 RCTs <sup>17, 44, 58, 83</sup>
	Neurological AE	Rate Ratio: 1.28; 95% CI: 0.90 to 1.81; I <sup>2</sup> =83.80%	4 RCTs <sup>17, 44, 58, 83</sup>
	Total AE	Rate Ratio: 1.20; 95% CI: 0.98 to 1.48; I <sup>2</sup> =60.40%	4 RCTs <sup>17, 42, 58, 83</sup>
Lasmitidan 400 mg vs. Lasmitidan 50 mg	Gastrointestinal AE	Rate Ratio: 0.89; 95% CI: 0.27 to 2.92; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Neurological AE	Rate Ratio: 1.99; 95% CI: 1.47 to 2.69; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Serious AEs	Rate Ratio: 2.07; 95% CI: 1.13 to 3.79; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 1.19; 95% CI: 0.82 to 1.73; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
Lasmitidan 400 mg vs. Lasmitidan 100 mg	Gastrointestinal AE	Rate Ratio: 0.66; 95% CI: 0.21 to 2.01; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Neurological AE	Rate Ratio: 1.32; 95% CI: 1.01 to 1.73; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Serious AEs	Rate Ratio: 1.42; 95% CI: 0.83 to 2.43; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 1.05; 95% CI: 0.73 to 1.51; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
Lasmitidan 400 mg vs. Lasmitidan 200 mg	Gastrointestinal AE	Rate Ratio: 1.68; 95% CI: 0.40 to 7.04; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Neurological AE	Rate Ratio: 1.07; 95% CI: 0.83 to 1.38; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Serious AEs	Rate Ratio: 1.12; 95% CI: 0.67 to 1.86; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>
	Total AE	Rate Ratio: 0.98; 95% CI: 0.68 to 1.40; I <sup>2</sup> =N/A	1 RCT <sup>42</sup>

AE = adverse event; CI = confidence interval; Rate Ratio = incidence rate ratio; mg = milligrams; N/A = not applicable; RCT = randomized controlled trial

## Appendix K. Subgroup Analysis by Study Settings and Routes of Administration

**Table K-1. Subgroup analysis by study setting for other interventions**

Comparison	Outcome	Subgroup	Findings
Lidocaine vs. Placebo	Pain Relief 2 hours	ED	RR: 0.54; 95% CI: 0.10 to 2.97; I <sup>2</sup> =N/A
	Pain Relief 2 hours	Urgent Care	RR: 2.64; 95% CI: 1.33 to 5.25; I <sup>2</sup> =N/A
	Pain Scale 2 hours	ED	SMD: -0.22; 95% CI: -0.49 to 0.05; I <sup>2</sup> =5.28%
	Pain Scale 2 hours	Urgent Care	SMD: 0.75; 95% CI: 0.28 to 1.23; I <sup>2</sup> =N/A

CI = confidence interval; ED = emergency department; IV = intravenous; N/A = not applicable; RR = relative risk; SMD = standardized mean difference

**Table K-2. Subgroup analysis by route of administration for calcitonin gene-related peptide receptor antagonists**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup</b>	<b>Findings</b>
Rimegepant vs. Placebo	Pain Free 2 hours	Oral	RR:1.71; 95% CI: 1.37 to 2.14; I <sup>2</sup> =0.00%
	Pain Free 2 hours	Sublingual	RR:1.92; 95% CI: 1.48 to 2.50; I <sup>2</sup> =N/A
	Pain Relief 2 hours	Oral	RR:1.36; 95% CI: 1.24 to 1.50; I <sup>2</sup> =0.00%
	Pain Relief 2 hours	Sublingual	RR:1.35; 95% CI: 1.21 to 1.51; I <sup>2</sup> =N/A
	Restored Function 2 hours	Oral	RR: 1.40; 95% CI:1.14 to 1.70; I <sup>2</sup> =N/A
	Restored Function 2 hours	Sublingual	RR:1.45; 95% CI: 1.22 to 1.74; I <sup>2</sup> =N/A
	Restored Function 1 week	Oral	RR: 1.73; 95% CI:1.39 to 2.15; I <sup>2</sup> =N/A
	Restored Function 1 week	Sublingual	RR:1.66; 95% CI: 1.32 to 2.09; I <sup>2</sup> =N/A
	Sustained Pain Free 1 day	Oral	RR:2.24; 95% CI:1.64 to 13.04; I <sup>2</sup> =70.86%
	Sustained Pain Free 1 day	Sublingual	RR:1.70; 95% CI: 1.46 to 1.97; I <sup>2</sup> =N/A

CI = confidence interval; IV = intravenous; N/A = not applicable; RR = relative risk

**Table K-3. Subgroup analysis by route of administration for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup</b>	<b>Findings</b>
Lasmiditan vs. Placebo	Pain Free 2 hours	IV	RR:1.18; 95% CI: 0.57 to 2.48; I <sup>2</sup> =N/A
	Pain Free 2 hours	Oral	RR:1.69; 95% CI: 1.47 to 1.95; I <sup>2</sup> =33.51%
	Pain Relief 2 hours	IV	RR:1.23; 95% CI: 0.84 to 1.80; I <sup>2</sup> =N/A
	Pain Relief 2 hours	Oral	RR:1.38; 95% CI: 1.28 to 1.49; I <sup>2</sup> =53.37%
	Sustained Pain Free 1 day	IV	RR:0.82; 95% CI: 0.35 to 1.93; I <sup>2</sup> =N/A
	Sustained Pain Free 1 day	Oral	RR:1.42; 95% CI: 1.13 to 1.80; I <sup>2</sup> =N/A

CI = confidence interval; IV = intravenous; N/A = not applicable; RR = relative risk

**Table K-4. Subgroup analysis by route of administration for other interventions**

<b>Comparison</b>	<b>Outcome</b>	<b>Findings</b>
Intravenous prochlorperazine vs. Buccally absorbed prochlorperazine	Pain scale at 2 hours	SMD:0.45; 95% CI: 0.00 to 0.89; I <sup>2</sup> =N/A

CI = confidence interval; N/A = not applicable; SMD = standardized mean difference

**Table K-5. Subgroup analysis by prior response to triptans for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup*</b>	<b>Findings</b>
Lasmiditan vs. Placebo	Pain free at 2 hours	Triptan-naive	RR: 2.01; 95% CI: 1.52 to 2.67; I <sup>2</sup> =N/A
	Pain free at 2 hours	Good	RR: 2.28; 95% CI: 1.47 to 3.53; I <sup>2</sup> =N/A
	Pain free at 2 hours	Insufficient	RR: 1.52; 95% CI: 1.29 to 1.80; I <sup>2</sup> =N/A
	Pain relief at 2 hours	Triptan-naive	RR: 1.59; 95% CI: 1.39 to 1.83; I <sup>2</sup> =N/A
	Pain relief at 2 hours	Good	RR: 1.47; 95% CI: 1.20 to 1.79; I <sup>2</sup> =N/A
	Pain relief at 2 hours	Insufficient	RR: 1.24; 95% CI: 1.13 to 1.36; I <sup>2</sup> =N/A

CI = confidence interval; N/A = not applicable; RR = relative risk

\* An overall response of “good” or “poor/none” to the most recent use of triptan at baseline were defined as “good” or “insufficient”.



**Table K-6. Subgroup analysis by age for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup</b>	<b>Findings*</b>
Lasmiditan 50 mg vs. Placebo	Pain free at 2 hours	< 65 years	OR: 1.49; 95% CI: 1.11 to 1.94; I <sup>2</sup> =N/A
	Pain free at 2 hours	≥ 65 years	OR: 1.04; 95% CI: 0.36 to 2.89 ; I <sup>2</sup> =N/A
Lasmiditan 100 mg vs. Placebo	Pain free at 2 hours	< 65 years	OR: 1.94; 95% CI: 1.58 to 2.40; I <sup>2</sup> =N/A
	Pain free at 2 hours	≥ 65 years	OR: 1.00; 95% CI: 0.40 to 2.47; I <sup>2</sup> =N/A
Lasmiditan 200 mg vs. Placebo	Pain free at 2 hours	< 65 years	OR: 2.53; 95% CI: 2.06 to 3.08; I <sup>2</sup> =N/A
	Pain free at 2 hours	≥ 65 years	OR: 1.75; 95% CI: 0.64 to 4.81; I <sup>2</sup> =N/A

CI = confidence interval; mg = milligrams; N/A = not applicable; OR = odds ratio

\* Tepper et al.<sup>159</sup> reported OR instead of RR. No conversion to RR was made.

**Table K-7. Subgroup analysis by gender for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup</b>	<b>Findings*</b>
Lasmiditan 50 mg vs. Placebo	Pain free at 2 hours	Female	OR: 1.62; 95% CI: 1.21 to 2.15; I <sup>2</sup> =N/A
	Pain free at 2 hours	Male	OR: 0.74; 95% CI: 0.36 to 1.53
Lasmiditan 100 mg vs. Placebo	Pain free at 2 hours	Female	OR: 1.87; 95% CI: 1.51 to 2.36; I <sup>2</sup> =N/A
	Pain free at 2 hours	Male	OR: 1.98; 95% CI: 1.19 to 3.26; I <sup>2</sup> =N/A
Lasmiditan 200 mg vs. Placebo	Pain free at 2 hours	Female	OR: 2.66; 95% CI: 2.19 to 3.32; I <sup>2</sup> =N/A
	Pain free at 2 hours	Male	OR: 1.58; 95% CI: 0.94 to 2.64; I <sup>2</sup> =N/A

CI = confidence interval; mg = milligrams; N/A = not applicable; OR = odds ratio

\* Tepper et al.<sup>159</sup> reported OR instead of RR. No conversion to RR was made.

**Table K-8. Subgroup analysis by race for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup*</b>	<b>Findings*</b>
Lasmiditan 50 mg vs. Placebo	Pain free at 2 hours	Caucasian	OR: 1.49; 95% CI: 1.09 to 2.00; I <sup>2</sup> =N/A
	Pain free at 2 hours	non-Caucasian	OR: 1.28; 95% CI: 0.77 to 2.40; I <sup>2</sup> =N/A
Lasmiditan 100 mg vs. Placebo	Pain free at 2 hours	Caucasian	OR: 2.09; 95% CI: 1.58 to 2.60; I <sup>2</sup> =N/A
	Pain free at 2 hours	non-Caucasian	OR: 1.40; 95% CI: 0.91 to 2.09; I <sup>2</sup> =N/A
Lasmiditan 200 mg vs. Placebo	Pain free at 2 hours	Caucasian	OR: 2.70; 95% CI: 2.09 to 3.30; I <sup>2</sup> =N/A
	Pain free at 2 hours	non-Caucasian	OR: 1.89; 95% CI: 1.30 to 2.81; I <sup>2</sup> =N/A

CI = confidence interval; mg = milligrams; N/A = not applicable; OR = odds ratio

\* Tepper et al.<sup>159</sup> reported OR instead of RR. No conversion to RR was made.

**Table K-9. Subgroup analysis by BMI for 5-HT1F**

<b>Comparison</b>	<b>Outcome</b>	<b>Subgroup*</b>	<b>Findings*</b>
Lasmiditan 50 mg vs. Placebo	Pain free at 2 hours	$\geq 30 \text{ kg/m}^2$	OR: 1.42; 95% CI: 0.94 to 2.13; $I^2=N/A$
	Pain free at 2 hours	$< 30 \text{ kg/m}^2$	OR: 1.47; 95% CI: 1.02 to 2.08; $I^2=N/A$
Lasmiditan 100 mg vs. Placebo	Pain free at 2 hours	$\geq 30 \text{ kg/m}^2$	OR: 2.04; 95% CI: 1.51 to 2.75; $I^2=N/A$
	Pain free at 2 hours	$< 30 \text{ kg/m}^2$	OR: 1.79; 95% CI: 1.38 to 2.34; $I^2=N/A$
Lasmiditan 200 mg vs. Placebo	Pain free at 2 hours	$\geq 30 \text{ kg/m}^2$	OR: 2.66; 95% CI: 1.98 to 3.60; $I^2=N/A$
	Pain free at 2 hours	$< 30 \text{ kg/m}^2$	OR: 2.30; 95% CI: 1.77 to 3.00; $I^2=N/A$

CI = confidence interval; kg = kilograms; mg = milligrams;  $\text{m}^2$  = square meters; N/A = not applicable; OR = odds ratio

\* Tepper et al.<sup>159</sup> reported OR instead of RR. No conversion to RR was made.

## Appendix L. Sensitivity Analysis

**Table L-1. Sensitivity analysis by excluding studies with high risk of bias for ergot alkaloids**

Comparison	Outcome	Risk of Bias	Findings
Dihydroergotamine vs. Placebo	Pain Free 2 hours	Low/Moderate ROB	RR: 2.82; 95% CI: 2.01 to 2.95; I <sup>2</sup> =N/A
	Pain Free 2 hours	Overall	RR: 2.89; 95% CI: 2.07 to 4.03; I <sup>2</sup> =0.00%
	Pain Relief 2 hours	Low/Moderate ROB	RR: 1.70; 95% CI: 1.44 to 2.01; I <sup>2</sup> =N/A
	Pain Relief 2 hours	Overall	RR: 1.83; 95% CI: 1.58 to 2.13; I <sup>2</sup> =0.00%
	Sustained Pain Free 1 day	Low/Moderate ROB	RR: 3.48; 95% CI: 2.30 to 5.28; I <sup>2</sup> =N/A
	Sustained Pain Free 1 day	Overall	RR: 3.51; 95% CI: 2.33 to 5.28; I <sup>2</sup> =0.00%
	Sustained Pain Free 1 week	Low/Moderate ROB	RR: 2.93; 95% CI: 1.86 to 4.62; I <sup>2</sup> =N/A
	Sustained Pain Free 1 week	Overall	RR: 2.96; 95% CI: 1.90 to 4.62; I <sup>2</sup> =0.00%
	Sustained Pain Relief 1 day	Low/Moderate ROB	RR: 2.21; 95% CI: 1.74 to 2.81; I <sup>2</sup> =N/A
	Sustained Pain Relief 1 day	Overall	RR: 2.23; 95% CI: 1.76 to 2.81; I <sup>2</sup> =N/A
	Sustained Pain Relief 1 week	Low/Moderate ROB	RR: 2.09; 95% CI: 1.59 to 2.75; I <sup>2</sup> =N/A
	Sustained Pain Relief 1 week	Overall	RR: 2.11; 95% CI: 1.62 to 2.76; I <sup>2</sup> =N/A

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias

**Table L-2. Sensitivity analysis by excluding studies with high risk of bias for antiemetic**

<b>Comparison</b>	<b>Outcome</b>	<b>Risk of Bias</b>	<b>Findings</b>
Metoclopramide vs. Saline	Pain Scale 2 hours	Low/Moderate ROB	SMD: -0.38; 95% CI: -0.70 to 0.96; I <sup>2</sup> =N/A
	Pain Scale 2 hours	Overall	SMD: -0.12; 95% CI: -0.40 to 0.17; I <sup>2</sup> =90.46%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias; SMD = standardized mean difference

**Table L-3. Sensitivity analysis by excluding studies with high risk of bias for calcitonin gene-related peptide receptor antagonists**

<b>Comparison</b>	<b>Outcome</b>	<b>Risk of Bias</b>	<b>Findings</b>
Rimegepant vs. Placebo	Pain Free 2 hours	Low/Moderate ROB	RR: 1.64; 95% CI: 1.22 to 2.18; I <sup>2</sup> =N/A
	Pain Free 2 hours	Overall	RR: 1.80; 95% CI: 1.52 to 2.13; I <sup>2</sup> =0.00%
	Restored Function 2 hours	Low/Moderate ROB	RR: 1.40; 95% CI: 1.14 to 1.70; I <sup>2</sup> =N/A
	Restored Function 2 hours	Overall	RR: 1.43; 95% CI: 1.26 to 1.62; I <sup>2</sup> =0.00%
	Sustained Pain Free 1 day	Low/Moderate ROB	RR: 1.73; 95% CI: 1.18 to 2.54; I <sup>2</sup> =N/A
	Sustained Pain Free 1 day	Overall	RR: 2.24; 95% CI: 1.65 to 3.05; I <sup>2</sup> =70.86%
	Sustained Pain Free 1 week	Low/Moderate ROB	RR: 1.65; 95% CI: 1.08 to 2.52; I <sup>2</sup> =N/A
	Sustained Pain Free 1 week	Overall	RR: 2.23; 95% CI: 1.60 to 3.09; I <sup>2</sup> =71.31%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias

**Table L-4. Sensitivity analysis by excluding studies with high risk of bias for other interventions**

<b>Comparison</b>	<b>Outcome</b>	<b>Risk of Bias</b>	<b>Findings</b>
Lidocaine vs. Placebo	Pain Scale 2 hours	Low/Moderate ROB	SMD: 0.46; 95% CI: 0.10 to 0.82; I <sup>2</sup> =72.62%
	Pain Scale 2 hours	Overall	SMD:0.02; 95% CI: -0.21 to 0.26; I <sup>2</sup> =85.02%
Valproate vs. Dexamethasone	Pain Scale 1 day	Low/Moderate ROB	SMD: -0.49; 95% CI: -0.84 to 0.04; I <sup>2</sup> =N/A
	Pain Scale 1 day	Overall	SMD: -0.15; 95% CI:-0.51 to 0.22; I <sup>2</sup> =73.59%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias; SMD = standardized mean difference



**Table L-5. Sensitivity analysis by excluding studies with high risk of bias for nonpharmacologic therapy**

<b>Comparison</b>	<b>Outcome</b>	<b>Risk of Bias</b>	<b>Findings</b>
External trigeminal nerve stimulation vs. Sham	Pain Scale 2 hours	Low/Moderate ROB	SMD: 0.52; 95% CI: 0.13 to 0.91; I <sup>2</sup> = N/A
	Pain Scale 2 hours	Overall	SMD: 1.25; 95% CI: 0.90 to 1.60; I <sup>2</sup> = 98.65%

CI = confidence interval; ROB = risk of bias; SMD = standardized mean difference

## Appendix M. Appendix References

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