Acute Treatments for Episodic Migraine: Surveillance Report 2

Literature Update Period: September 2, 2021, Through December 30, 2021

Background and Purpose

This report is the second surveillance report for the Agency for Healthcare Research and Quality (AHRQ) 2020 report *Acute Treatments for Episodic Migraine*[1] (available at https://effectivehealthcare.ahrq.gov/products/migraine-treatments/research) and covers the time period from September 2, 2021, through December 30, 2021. The original 2020 report examined the evidence on the comparative effectiveness and harms of opioids as well as nonopioid pharmacologic and nonpharmacologic treatments to provide the full range of evidence to inform clinical decision making about the acute treatment of migraine. The objectives of this surveillance report are to identify the latest evidence published since the last surveillance report as of September 2, 2021 (Surveillance Report 1), and to determine how the new evidence impacts the findings of the 2020 report and surveillance report. Another update is planned for June 2022 (based on evidence published from January to March 2022).

Scope

The Key Questions (KQs; available at https://www.ncbi.nlm.nih.gov/books/n/cer239/ch3/#ch3.s2), PICOTS (population, interventions, comparisons, outcomes, timing, and setting; available at https://www.ncbi.nlm.nih.gov/books/NBK566240/table/ch3.tab1/?report=objectonly), and inclusion and exclusion criteria adopted in the original report[1] were used in this surveillance report and are listed in Appendixes A and B. Briefly, the report evaluated acute treatments in adult patients with episodic migraine and addressed the following:

- The comparative effectiveness and harms of opioid therapy versus nonopioid pharmacologic therapy and nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life up to 4 weeks after treatments (KQ 1).
- The comparative effectiveness and harms of nonopioid pharmacologic therapy versus other nonopioid pharmacologic treatments and nonpharmacologic therapy for outcomes related to pain, function, pain relief satisfaction, and quality of life up to 4 weeks after treatments (KQ 2).
- The comparative effectiveness and harms of nonpharmacologic therapy versus sham treatment, waitlist, usual care, attention control, and no treatment up to 4 weeks after treatments (KQ 3).

The original study protocol was developed with input from a six-member Technical Expert Panel and is available on the AHRQ website (https://effectivehealthcare.ahrq.gov/products/migraine-treatments/protocol). The protocol of the report was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020163262).

Methods

For this surveillance report, we searched bibliographic databases, including Embase®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Registrar of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, PsycINFO®, and Scopus from September 2, 2021 to December 30, 2021.We also searched Food and Drug Administration, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency, AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. We performed reference mining of existing systematic reviews/meta-analyses, completed trials identified from clinical trial registries, and relevant primary studies (i.e., randomized clinical trials [RCTs] and observational studies). The same search strategy used in the 2020 report was used for this update (Appendix C); we included RCTs and comparative observational studies published in English on adult patients (18 years and older).

Independent reviewers, working in pairs, screened the titles and abstracts for 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 could not be reached, a third reviewer resolved the difference.

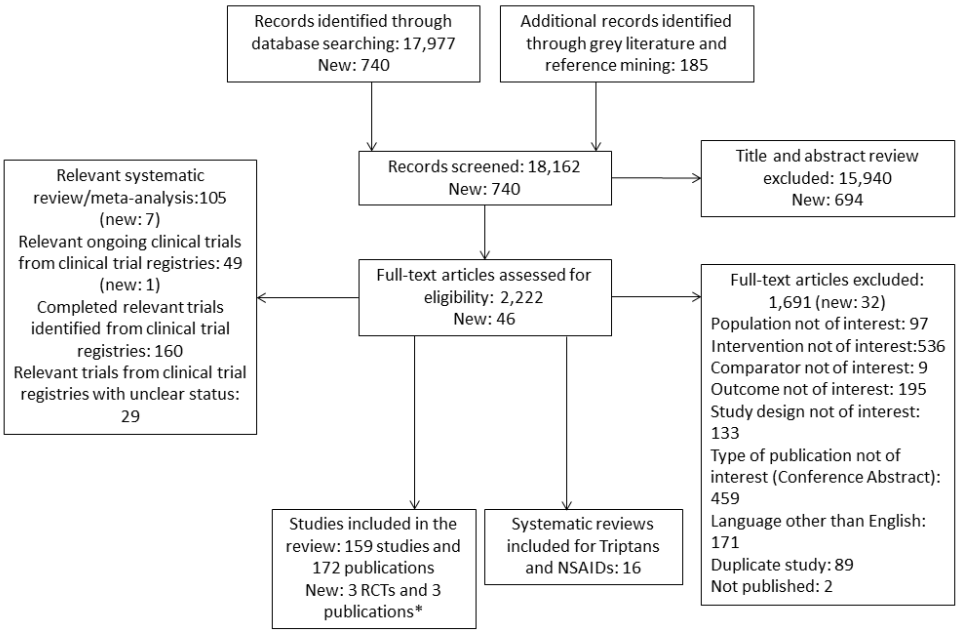
The same standardized data extraction form used in the 2020 report was adopted to extract study characteristics. A second reviewer confirmed the data extraction and resolved conflicts. We contacted authors when important information (e.g., methods and outcomes) was missing. The Cochrane Collaboration's Risk of Bias 2 tool[2] and the Newcastle-Ottawa Scale[3] were used to evaluate risk of bias of the included studies. If newly identified studies were similar in terms of their PICOTS, a meta-analysis will be conducted in the final update, which is scheduled for June 2022.

Results

The literature search for this surveillance update identified 740 new citations. No additional eligible references were identified through reference mining or grey literature search. Three new original studies with a total of 344 patients met the inclusion criteria.[4-6] Additionally, we identified three publications[7-9] derived from trials[10-12] previously included in the 2020 report (Figure 1).

All three of the new studies were RCTs conducted in the emergency department.[4-6] One of these studies was conducted in the United States[6] and two were conducted in Turkey.[4, 5] The mean followup for these three new RCTs was 8.83 hours. All three RCTs evaluated pharmacologic therapies and were included for KQ 2.[4-6] There were no new studies on opioids for KQ 1 and no new studies on nonpharmacologic therapy for KQ 3. Details of the interventions used in each study can be found in Appendix D, Table D.1. Findings of the included studies are summarized in Appendix E, Tables E.1 and E.2, and risk of bias is summarized in Appendix F, Table F.1. The list of the excluded studies can be found in Appendix G. Appendix H lists findings from subgroup analyses, and Appendix I lists the references used in the appendixes.

Figure 1. Literature flow diagram for Surveillance Report 2



Abbreviations: NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized clinical trial

*Three new RCTs and three publications derived from RCTs already included in the original report.

Summary of Findings

Table 1 summarizes the conclusions from the 2020 report, new evidence from the current surveillance update, and the changes to the original conclusions, if any. The evidence continues to support the conclusions from the original report that triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) improve pain outcomes compared with placebo. Findings from the newly identified studies suggest there was no significant difference between paracetamol (acetaminophen) and zolmitriptan in pain scale at 1 hour, between ibuprofen and placebo in pain free and pain relief outcomes at 2 hours, and between dexketoprofen trometamol and lidocaine in pain scale at 1.5 hours. There were no changes to the overall assessment of the evidence that was already included in the original report.

Table 1. Summary of conclusions and assessments informed by new evidence for Surveillance Report 2

Key Question	Conclusions From the 2020 Report	Findings From This Update	Assessment of SOE and Conclusion
KQ 2. Triptan: Zolmitriptan vs. Paracetamol (acetaminophen)	No study in the original report evaluated this comparison	One RCT[4] (n=200) found no significant difference between zolmitriptan and paracetamol (acetaminophen) in pain scale at 1 hour. No treatment related adverse events were reported.	SOE insufficient
KQ 2. NSAIDs: Ibuprofen vs. Placebo	From the previous report, NSAIDs as a drug class, compared with placebo, resolved pain at 2 hours and 1 day and increased the risk of mild and transient adverse events (moderate SOE).	One underpowered RCT*[,6] (n=44) found no significant difference in pain free at 2 hours, pain relief at 2 hours, sustained pain free at 24 hours, or adverse events. No serious adverse events were observed.	No change in SOE supporting the effect of NSAIDs as a drug class vs. placebo on improving pain relief outcomes. SOE moderate.
KQ 2. NSAIDs: Dexketoprofen trometamol vs. Lidocaine	No study in the original report evaluated this comparison	One RCT[5] (n=100) found no significant difference in pain scale at 1.5 hours.	SOE insufficient
KQ 2. 5-HT1F: Lasmiditan 200 mg vs. Lasmiditan 100 mg vs. Placebo, subgroup analysis by triptan response	No study in the original report evaluated this subgroup.	One sub-group analysis[8] based on three RCTs[10-12] (previously included in the 2020 report) found no significant difference in lasmiditan effectiveness between patients based on previous triptan response (poor/none vs. good), when lasmiditan was compared with placebo or lasmiditan 200 mg compared with lasmiditan 100 mg. For triptan insufficient responders (defined as patients who had poor or very poor treatment efficacy), the study showed that lasmiditan compared with placebo was associated with significantly better pain free and pain relief at 2 hours, and sustained pain free at 24 hours and 48 hours. There was no significant difference between 200 mg and 100 mg lasmiditan. No death was reported.	SOE not assessed for subgroup analyses

Abbreviations: KQ = Key Question; mg = milligram; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized clinical trial; SOE = strength of evidence

*Due to slow patient enrollment, the study was unable to recruit the prespecified number of patients (n=150) needed to have a power of 0.8 with an alpha error of 0.05.

Evidence Details

Key Question 1. Opioid Pharmacologic Therapy

No new studies addressed the comparative effectiveness or harms of opioid therapy.

Key Question 2. Nonopioid Pharmacologic Therapy

Triptans

Since the previous literature update (Surveillance Report 1) on acute treatments for migraine, one RCT (n=200)[4] evaluated the efficacy of zolmitriptan versus paracetamol (acetaminophen). There was no significant difference noted in pain scale at 1 hour. There were no treatment-related adverse events.

NSAIDS

Since the previous literature update (Surveillance Report 1), two RCTs[5, 6] evaluated NSAIDs. One RCT (n=100)[5] evaluated lidocaine versus dexketoprofen trometamol. Lidocaine showed improvement of the VAS (visual analog scale) at the 20th and 30th minute, but at subsequent time points there was no difference between the two groups. The other RCT (n=44),[6] which was underpowered, evaluated intravenous ibuprofen versus placebo and found no significant difference in pain free at 2 hours, pain relief at 2 hours, sustained pain free at 24 hours, or adverse events; no serious adverse events were observed.[6]

5-HT1F Receptor Agonists

One article[8] based on three previous RCTs (SAMURAI [A Study of Two Doses of LAsMiditan (100 mg and 200 mg) Compared to Placebo in the AcUte Treatment of MigRAIne], SPARTAN [A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute TReaTment of MigrAiNe], and CENTURION [Study of Two Doses of Lasmiditan (100 mg and 200 mg) Compared to either Placebo or Lasmiditan 50 mg in the Acute TReaTment of MigrAiNe attacks]) found no significant differences in lasmiditan effectiveness based on previous triptan response (poor/none vs. good) when lasmiditan was compared with placebo or lasmiditan 200 mg was compared with lasmiditan 100 mg. For triptan insufficient responders, defined as patients who experienced poor or very poor treatment efficacy, the CENTURION study showed that lasmiditan was associated with significantly better pain free and pain relief at 2 hours and sustained pain free at 24 hours and 48 hours compared with placebo. There was no significant difference in effectiveness between 200 mg and 100 mg lasmiditan. For triptan insufficient responders, lasmiditan was associated with significantly more adverse events and withdrawals due to adverse events compared with placebo. There was no significant difference in serious adverse events. No death was reported in any of the study groups.

Key Question 3. Nonpharmacologic Therapy

No new studies addressed the comparative effectiveness or harms of nonpharmacologic therapy.

Conclusions

The findings from this update are consistent with those in the original 2020 report and Surveillance Report 1 on the comparative effectiveness and harms of opioids and nonpharmacologic treatments for acute treatment of episodic migraine. This surveillance update identified three new RCTs evaluating NSAIDs and triptans. Overall, already established effective treatments, such as triptans, NSAIDs, antiemetics, ergot alkaloids, and newer treatments, such as gepants and ditans, are associated with improved pain and functional

outcomes, and different adverse effect profiles. Opioids have low or insufficient strength of evidence for acute treatment of migraine.

The next surveillance update is scheduled for June 2022.

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Disclaimers

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

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Afterword

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this 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. They will be considered in the next version of the report.

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Appendix A. Key Questions

For Acute Treatments for Episodic Migraine, the following Key Questions were determined based on input from multiple Key Informants.

Key Question 1. Opioid Therapy

a. 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?

b. 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?

c. 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)?

d. 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?

e. 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)?

f. 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?

g. 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?

h. 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?

Key Question 2. Nonopioid Pharmacologic Therapy

a. 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?

b. 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?

c. 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)?

d. 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?

Key Question 3. Nonpharmacologic Therapy

a. 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?

b. 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?

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

d. 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?

Appendix B. Population, Interventions, Comparisons, Outcomes, Timing, and Setting

The related population, interventions, comparisons, outcomes, timing, and setting (PICOTS) are listed in Table B.1.

Table B.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	KQ1 a-e: Any systemic opioid abortive therapy, including: 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 KQ1 f-g: Instruments and genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose 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 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 KQ3: Any non-invasive nonpharmacologic abortive therapy, including: Exercise Cognitive behavioral therapy Acupuncture And others	For all KQs, exclude invasive treatments (surgical interventions, etc.), and preventive (prophylactic) treatment For KQ2, exclude NSAIDs vs placebo and triptans vs placebo
Comparators	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	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, overdose, medication overuse headache). 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, harms/adverse events KQ3: Noninvasive nonpharmacological therapy: Pain, function, pain relief satisfaction, 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

Abbreviations: ED = emergency department; KQ = Key Question; NSAID = nonsteroidal anti-inflammatory drugs; PICOTS = population, interventions, comparisons, outcomes, timing, and setting; RCT = randomized clinical trial

Appendix C. Search Strategy

Ovid

Database(s): APA PsycInfo 1806 to December Week 4 2021, EBM Reviews - Cochrane Central Register of Controlled Trials November 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 28, 2021, Embase 1974 to 2021 December 30, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to December 30, 2021
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/
5	(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 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/
11	(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).ti,ab,hw,kw.

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 indolylethylamine* or meksamine* or methoxydimethyltryptamine* or methoxytryptamine* or methylbufotenin or mexamine* or Serotonin or triptan* or tryptamine*).ti,ab,hw,kw.

15 exp Ergot Alkaloids/

16 (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.

17 exp Analgesics/

18 (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 brivoligide 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 davasaicin or deacetyllappaconitine 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.

19 exp Muscle Relaxants, Central/

20 exp muscle relaxant agent/

21 (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).ti,ab,hw,kw.

22 exp Antiemetics/

23 exp Nausea/dt [Drug Therapy]

24 exp Vomiting/dt [Drug Therapy]

25 (((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 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 meclozine 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/

27 exp cannabinoid/

28 exp "cannabis use"/

29 exp Marijuana Smoking/

30 exp Cannabinoids/

31 exp Cannabidiol/

32 ("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 hemps 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/

34 ("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 "psychophysiologic feedback*").ti,ab,hw,kw.

35 Electric Stimulation Therapy/

36 exp neuromodulation/

37 (((Electric* or electro or galvano or Transcutaneous*) adj3 (stimulat* or stimulus)) or 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/
46 (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).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.
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/

77 ((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 referrent 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.

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

88 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]

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 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)

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 indolylethylamine* 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 brivoligide 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 davasaicin or deacetyllappaconitine 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)

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 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 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 meclozine 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)

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 hemps 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 "psychophysiologic 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 referrent 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 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
Arikan, 2021[1]	RCT in Turkey, 01/2016 to 12/2016	ED	Paracetamol (acetaminophen)	Oral, 1000 mg, once	1 hour	100 patients aged 29.5±10.3 years, 73.7% female.
	RCT in Turkey, 01/2016 to 12/2016	ED	Zolmitriptan	Oral, 2.5 mg, once	1 hour	100 patients aged 32.2±10.6 years, 72.2% female.
Gur, 2021[2]	RCT in Turkey	ED	Lidocaine	IV, 1.5 mg/kg as an intravenous bolus, followed by a 1 mg/kg/h infusion over the first 30 minutes + 100 ml saline and a 0.5 mg/kg/h infusion over the second 30 minutes, once	1.5 hour	50 patients aged 43±16.3 years, 62% female.
	RCT in Turkey	ED	Dexketoprofen trometamol	IV, normal saline at the same bolus volume as the other group, and then were administered 50 mg dexketoprofen in 100 ml saline and a saline infusion at the same volume as lidocaine over the first 30 minutes. For the second 30 minutes, the patients received normal saline at the same bolus volume as in the lidocaine group, once.	1.5 hour	50 patients aged 37±15.6 years, 54% female.
Yuan, 2021[3]	RCT in the USA, 06/2011 to 05/2017	ED	Ibuprofen	IV, 800 mg diluted in 250 ml of normal saline, once over 7-10 minutes.	24 hours	23 patients aged 42.8±10.5 years, 70% female.
	RCT in the USA, 06/2011 to 05/2017	ED	Placebo	IV, 250 ml of normal saline, once over 7-10 minutes.	24 hours	21 patients aged 40.3±12.1 years, 81% female.

Abbreviations: ED = emergency department; IV = intravenous; mg = milligram; mg/kg = milligram/kilogram, mg/kg/h = milligram/kilogram/hour; ml = milliliter; RCT = randomized clinical trial; USA = United States of America

Appendix E. Results From Included Studies

Table E.1. Results from included studies: KQ 2, nonsteroidal anti-inflammatory drugs

Author, Year, Study Design	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose, and Duration	Length of Followup	Conclusion
Gur, 2021[2], RCT	ED	Dexketoprofen trometamol vs. Lidocaine	IV, normal saline at the same bolus volume as the other group, and then were administered 50 mg dexketoprofen in 100 ml saline and a saline infusion at the same volume as lidocaine over the first 30 minutes. For the second 30 minutes, the patients received normal saline at the same bolus volume as in the lidocaine group, once vs. IV, 1.5 mg/kg as an intravenous bolus, followed by a 1 mg/kg/h infusion over the first 30 minutes + 100 ml saline and a 0.5 mg/kg/h infusion over the second 30 minutes, once	1.5 hour	There was no significant difference in pain scale at 1.5 hours.
Yuan, 2021[3], RCT	ED	Ibuprofen vs. Placebo	IV, 800 mg diluted in 250 ml of normal saline, once over 7-10 minutes vs. IV, 250 ml of normal saline, once over 7-10 minutes	24 hours	There was no significant difference in pain free at 2 hours, pain relief at 2 hours, sustained pain free at 24 hours, or adverse events. No serious adverse events were observed.

Abbreviations: ED = emergency department; IV = intravenous; KQ = Key Question; mg = milligram; mg/kg = milligram/kilogram; mg/kg/h = milligram/kilogram/hour; ml = milliliter; RCT = randomized clinical trial; USA = United States of America

Table E.2. Results from included studies: KQ 2, triptans

Author, Year, Study Design	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose and Duration	Length of Followup	Conclusion
Arikan, 2021[1], RCT	ED	Zolmitriptan vs. Paracetamol (acetaminophen)	Oral, 1000 mg, once vs Oral, 2.5 mg, once	1 hour	There was no significant difference between zolmitriptan and paracetamol (acetaminophen) in pain scale at 1 hour. No treatment related adverse events were reported.

Abbreviations: ED = emergency department; KQ = Key Question; mg = milligram; RCT = randomized clinical trial

Appendix F. Risk of Bias

Table F.1. Risk of bias (Cochrane ROB tool) for included randomized clinical 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
Arikan, 2021[1]	Moderate risk	Low risk	Moderate risk	Low risk	Low risk	Moderate risk
Gur, 2021[2]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
Yuan, 2021[3]	Moderate risk	Moderate risk	Low risk	Low risk	Moderate risk	Low risk

Abbreviations: ROB = risk of bias

Appendix G. Excluded Studies

1. Alanya Alaaddin Keykubat University. Comparison of osteopathic manipulative therapy and myofacial relaxation techniques in people diagnosed with migraine. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://clinicaltrials.gov/ct2/show/NCT04976725. Identifier: NCT04976725 [Population not of interest]
2. Allergan. Observational study to assess adverse events when adult female participants are treated with Ubrelvy (ubrogepant) during pregnancy. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05158894. Identifier: NCT05158894. [Outcomes not of interest]
3. Ashina M, Krikke-Workel J, Krege J, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: consistency findings (1825). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021 Neurology. 2021 Apr 13;96(15 Supplement):1825. [Type of publication (Conference abstract)]
4. Aurora S, Smith T, Jeleva M, et al. A long-term, open label safety and tolerability study of precision olfactory delivery of DHE in acute migraine treatment (STOP 301): exploratory efficacy results (2490). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):2490. [Type of publication (Conference abstract)]
5. Barreto T. Acute treatments for episodic migraine in adults. Am Fam Physician. 2021 Nov 1;104(5):509-12. PMID: 34783486. [Study design not of interest]
6. Blumenfeld AM, Knievel K, Manack Adams A, et al. Ubrogepant is safe and efficacious in participants taking concomitant preventive medication for migraine: a pooled analysis of phase 3 trials. Adv Ther. 2021 Dec 7 [Epub ahead of print]. doi: 10.1007/s12325-021-01923-3. PMID: 34874514. [Intervention not of interest]
7. Bnai Zion Medical Center. Migraine abortive treatment. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05048914. Identifier: NCT05048914. [Population not of interest]
8. Deighton A, Johnston K, Harris L, et al. Acute migraine medication and medication overuse headache: a systematic literature review. Neurology (4505). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):4505. [Type of publication (Conference abstract)]
9. Eli Lilly Company. A study of galcanezumab (LY2951742) in adult participants with episodic migraine. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05127486. Identifier: NCT05127486 . [Intervention not of interest]
10. Ezzati A, Fanning K, Buse D, et al. Use of predictive modeling to determine treatment-response to OTC medications in acute migraine: results from the American migraine prevalence and prevention study (AMPP) (1587). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):1587. [Type of publication (Conference abstract)]
11. Fayoum University. Management of migraine using enerumab and traditional therapy at the time of COVID-19. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05052008. Identifier: NCT05052008. [Population not of interest]

12. H. Lundbeck A/S. A study with Lu AG09222 in adults with migraine who have not been helped by prior preventive treatments. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05133323. Identifier: NCT05133323. [Intervention not of interest]

13. Hagan JC 3rd. Systematic review and meta-analysis of acute treatments for episodic migraine in adults. JAMA. 2021 Oct 26;326(16):1636. doi: 10.1001/jama.2021.14060. PMID: 34698791. [Type of publication (Editorial letter)]

14. Jones A, O'Gorman C, Lipton RB, et al. Efficacy and safety of AXS-07 (MoSEIC meloxicam-rizatriptan) for the acute treatment of migraine: results from the INTERCEPT phase 3, randomized, double-blind, placebo-controlled trial. [abstract] The International Headache Congress – IHS and EHF Joint Congress 2021, 8-12 September 2021. J Headache Pain 2021;22(103):P0276. https://doi.org/10.1186/s10194-021-01293-9 [Type of publication (Conference abstract)]

15. Kellerman D, Engels J. Comparison of efficacy outcomes in trials using a M207 in the acute treatment of a single migraine or multiple migraines (2136). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):2136. [Type of publication (Conference abstract)]

16. Kou RZ, Yang F, Lin Q, et al. [Clinical observation on horizontal penetration needling combined with rizatriptan monobenzoate tablets for migraine without aura in acute stage]. Zhongguo Zhen Jiu. 2021 Sep 12;41(9):993-6. doi: 10.13703/j.0255-2930.20201203-k0007. PMID: 34491648. [Foreign language]

17. Kuruvilla D, Starling A, Tepper SJ, et al. A phase 3 randomized, double-blind, sham-controlled trial of e-TNS for the acute treatment of migraine (TEAM). [abstract] The International Headache Congress – IHS and EHF Joint Congress 2021, 8-12 September 2021. J Headache Pain 2021;22(103):AL059. https://doi.org/10.1186/s10194-021-01293-9 [Type of publication (Conference abstract)]

18. Li M, Wang W, Gao W, et al. Comparison of acupuncture and sham acupuncture in migraine treatment: an overview of systematic reviews. Neurology. 2021 Nov 26. [Epub ahead of print]. doi: 10.1097/NRL.0000000000000386. PMID: 34842579. [Population not of interest]

19. Lipton RB, Blumenfeld AM, Jensen CM, et al. Rimegepant for the acute treatment of migraine: subgroup analyses from 3 phase 3 clinical trials by number of triptans previously tried and failed (P-161). [abstract] 63rd Annual Scientific Meeting American Headache Society® Headache. 2021;61(SUPPL 1):144-5. [Type of publication (Conference abstract)]

20. Marmura M, Cohen JM, Ning X, et al. Time gained with long-term fremanezumab treatment in patients with chronic and episodic migraine. [abstract] International Headache Congress 8-12 September 2021. Cephalalgia. 2021 Sep;41(1_suppl):P0323. doi: 10.1177/03331024211034005. PMID: 34492213. [Type of publication (Conference abstract)]

21. Patel K, Batchu S, Wang R, et al. The use of electrical nerve stimulation to treat migraines: a systematic review. Cureus. 2021 Aug;13(8):e17554. doi: 10.7759/cureus.17554. PMID: 34646611. [Population not of interest]

22. RDC Clinical Pty Ltd A study evaluating the effectiveness of PEA compared to placebo for reducing pain severity and duration of migraines. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://clinicaltrials.gov/ct2/show/NCT05046522. Identifier: NCT05046522 . [Duplicate]

23. Reuter U, Lombard L, Krege J, et al. Lasmiditan is effective in the acute treatment of migraine in patients with insufficient response to triptans: findings from the modified-parallel, placebo-controlled, double-blind, phase 3 consistency CENTURION study. [abstract] The International Headache Congress – IHS and EHF joint congress 2021. J Headache Pain 2021;22(103):P0387. https://doi.org/10.1186/s10194-021-01293-9 [Type of publication (Conference abstract)]

24. Rezaeian T, Ahmadi M, Mosallanezhad Z, et al. The impact of myofascial release and stretching techniques on the clinical outcomes of migraine headache: a randomized controlled trial. J Res Med Sci. 2021;26:45. doi: 10.4103/jrms.JRMS_745_18. PMID: 34484377. [Population not of interest]

25. Schim J, Hutchinson S, Lipton R, et al. Rimegepant is safe and tolerable for the acute treatment of migraine in patients using preventive migraine medications: results from a long-term open-label safety study (2370). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):2370. [Type of publication (Conference abstract)]

26. Seydi P, Bagheri-Nesami M, Mohammadpour-Tahamtan RA, et al. Efficacy of acupressure on intensity of acute migraine in patients attending an emergency department: a randomized clinical trial. [Persian]. Journal of Mazandaran University of Medical Sciences. 2021 December;31(203):83-94. [Foreign language]

27. Smith T, Krikke-Workel J, Krege J, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: first attack findings (1791). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):1791. PMID: n/a. [Type of publication (Conference abstract)]

28. Swiat Zdrowia, Wroclaw Medical University. Migraine in Poland - a web-based cross-sectional survey. In: ClinicalTrials.gov. Bethesda, MD: National Library of Medicine (US); 2000- [cited 2021]. https://ClinicalTrials.gov/show/NCT05087420. Identifier: NCT05087420 [Intervention not of interest]

29. Tavakoli F, Tafakhori A, Zebardast J, et al. A new technique employing direct tactile pressure on the common carotid artery to relieve acute episode attack of migraine headache: a single-arm interventional study. Front Emerg Med. 2021 Feb;5(1):e7. [Study design not of interest]

30. Tepper SJ, Ashina M, Reuter U, et al. Reduction in acute migraine-specific and non-specific medication use in patients treated with erenumab: post-hoc analyses of episodic and chronic migraine clinical trials. J Headache Pain. 2021 Jul 23;22(1):81. doi: 10.1186/s10194-021-01292-w. PMID: 34301173. [Intervention not of interest]

31. Varangot-Reille C, Suso-Marti L, Romero-Palau M, et al. Effects of different therapeutic exercise modalities on migraine or tension-type headache: a systematic review and meta-analysis with a replicability analysis. J Pain. 2021 Dec 17 [Epub ahead of print]. doi: 10.1016/j.jpain.2021.12.003. PMID: 34929374. [Intervention not of interest]

32. Vincent M, Peres M, Vasudeva R, et al. Lasmiditan efficacy in mild versus moderate or severe migraine headaches (1811). [abstract] 73rd AAN Annual Meeting, April 17-22, 2021. Neurology. 2021 Apr 13;96(15 Supplement):1811. [Type of publication (Conference abstract)]

Appendix H. Subgroup Analysis

Table H.1. Subgroup analysis by prior triptan response for 5-HT1F receptor agonist

Comparisons	Outcome	Subgroups	Findings
Lasmiditan 200 mg vs. Lasmiditan 100 mg	Pain free at 2 hours	Poor/None	RR: 1.78; 95% CI: 1.58 to 2.00; I^2 =N/A
	Pain free at 2 hours	Good	RR: 1.89; 95% CI: 1.69 to 2.11; I^2 =N/A
Lasmiditan 200 mg vs. Placebo	Pain free at 2 hours	Poor/None	RR: 4.93; 95% CI: 4.12 to 5.91; I^2 =N/A
	Pain free at 2 hours	Good	RR: 4.02; 95% CI: 3.43 to 4.72; I^2 =N/A
Lasmiditan 100 mg vs. Placebo	Pain free at 2 hours	Poor/None	RR: 4.93; 95% CI: 4.12 to 5.90; I^2 =N/A
	Pain free at 2 hours	Good	RR: 4.02; 95% CI: 3.41 to 4.74; I^2 =N/A

Abbreviations: CI = confidence interval; mg = milligram; N/A = not applicable; RR = relative risk.

Table H.2. Subgroup analysis of triptan insufficient responder* for 5-HT1F receptor agonist

Comparisons	Outcome	Findings
Lasmiditan 200 mg vs. Lasmiditan 100 mg	Disability free 2 hours	RR: 1.32; 95% CI: 0.83 to 2.08; I^2 =N/A
	Disability free 24 hours	RR: 0.94; 95% CI: 0.54 to 1.63; I^2 =N/A
	Pain free 2 hours	RR: 1.07; 95% CI: 0.75 to 1.51; I^2 =N/A
	Pain relief 2 hours	RR: 1.07; 95% CI: 0.92 to 1.26; I^2 =N/A
	Patients with adverse events	RR: 1.10; 95% CI: 0.95 to 1.28; I^2 =N/A
	Serious adverse event	RR: 0.75; 95% CI: 0.21 to 2.76; I^2 =N/A
	Sustained pain freedom 24 hours	RR: 1.04; 95% CI: 0.64 to 1.69; I^2 =N/A
	Sustained pain freedom 48 hours	RR: 1.40; 95% CI: 0.80 to 2.45; I^2 =N/A
	Withdrawals due to adverse events	RR: 0.89; 95% CI: 0.46 to 1.71; I^2 =N/A
Lasmiditan 200 mg vs. Placebo	Disability free 2 hours	RR: 1.90; 95% CI: 1.14 to 3.18; I^2 =N/A
	Disability free 24 hours	RR: 1.37; 95% CI: 0.75 to 2.51; I^2 =N/A
	Pain free 2 hours	RR: 2.91; 95% CI: 1.75 to 4.85; I^2 =N/A
	Pain relief 2 hours	RR: 1.62; 95% CI: 1.32 to 1.98; I^2 =N/A
	Patients with adverse events	RR: 2.67; 95% CI: 2.07 to 3.44; I^2 =N/A
	Serious adverse event	RR: 1.93; 95% CI: 0.36 to 10.41; I^2 =N/A
	Sustain pain freedom 24 hours	RR: 4.08; 95% CI: 1.83 to 9.06; I^2 =N/A
	Sustain pain freedom 48 hours	RR: 2.66; 95% CI: 1.33 to 5.33; I^2 =N/A
	Withdrawals due to adverse events	RR: 5.14; 95% CI: 1.52 to 17.38; I^2 =N/A
Lasmiditan 100 mg vs. Placebo	Disability free 2 hours	RR: 1.44; 95% CI: 0.83 to 2.52; I^2 =N/A
	Disability free 24 hours	RR: 1.45; 95% CI: 0.79 to 2.67; I^2 =N/A
	Pain free 2 hours	RR: 2.73; 95% CI: 1.62 to 4.60; I^2 =N/A
	Pain relief 2 hours	RR: 1.51; 95% CI: 1.22 to 1.86; I^2 =N/A
	Patients with adverse events	RR: 2.42; 95% CI: 1.87 to 3.15; I^2 =N/A
	Serious adverse event	RR: 2.56; 95% CI: 0.50 to 13.05; I^2 =N/A
	Sustained pain freedom 24 hours	RR: 3.92; 95% CI: 1.74 to 8.80; I^2 =N/A
	Sustained pain freedom 48 hours	RR: 1.90; 95% CI: 0.90 to 4.00; I^2 =N/A
	Withdrawals due to adverse events	RR: 5.81; 95% CI: 1.73 to 19.51; I^2 =N/A

Abbreviations: CI = confidence interval; mg = milligram; N/A = not applicable; RR = relative risk.

* Triptan insufficient responders are defined as patients having poor or very poor treatment efficacy.

Appendix I. Appendix References

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