Systematic Review on Acute Treatments for Episodic Migraine: Surveillance Report 1

Literature Update Period: July 2020 through September 2021

Background and Purpose

This report is the first update for the Agency for Healthcare Research and Quality (AHRQ) 2020 report Acute Treatments for Episodic Migraine (available at https://effectivehealthcare.ahrq.gov/products/migraine-treatments/research)[1] and covers the time period from July 2020 through September 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 objective of this update is to identify the latest evidence published since the 2020 report and to determine how the new evidence impacts the findings of the 2020 report. Subsequent updates are planned for March 2022 (based on evidence published from October to December 2021) and 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 update 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 the current update, we searched bibliographic databases, including Embase®, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE, Cochrane Central Register of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, PsycINFO®, and Scopus from July 2020 to September 2021.We also searched Food and Drug Administration, 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. 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 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 could not be reached, a third reviewer resolved the difference.

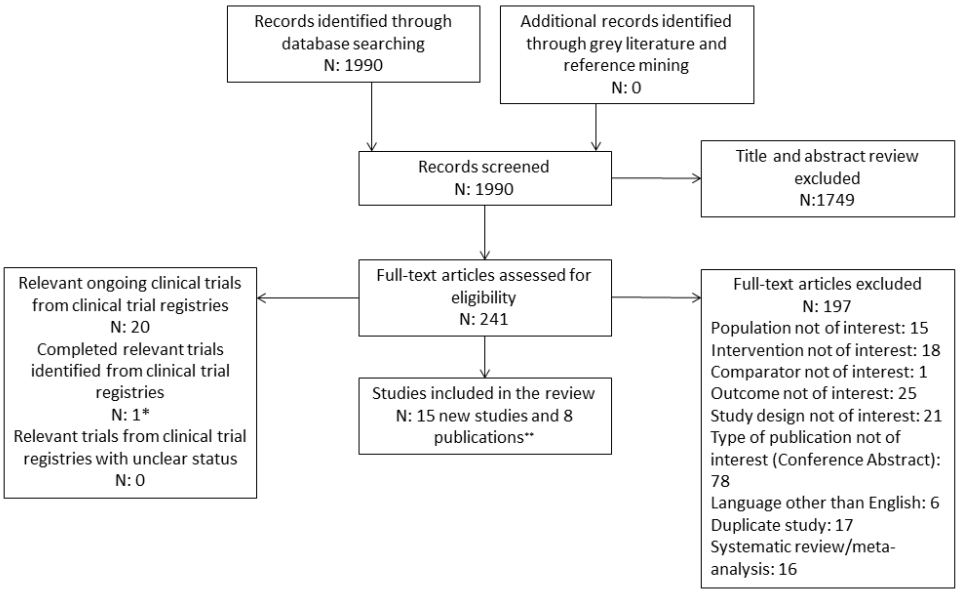
The same standardized data extraction form used in the 2020 report was adopted to extract study characteristics. A second reviewer confirmed data extraction and resolved conflicts. We contacted authors when important information (e.g., methods and outcomes) was missing. The Cochrane Collaboration's Risk 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 update identified 1,990 new citations. No references were identified through reference mining or grey literature search. Fifteen new studies, with a total of 4,859 patients, met the inclusion criteria.[4-18] In addition, we identified eight publications derived from trials previously included in the 2020 report (Figure 1).[19-26] All 15 new studies were RCTs.[4-18] Seven of these studies were conducted in the emergency department (ED),[4, 6, 7, 15-18] and eight were conducted in an outpatient setting.[5, 8-14] Five of these studies were conducted in the United States,[8, 9, 11, 15, 17] two were conducted in Asia,[10, 18] three were conducted in Europe,[4, 7, 13] one was conducted in Brazil,[5] two were conducted in Australia,[6, 16] and two were conducted in multiple countries.[12, 14] The mean followup for these 15 new studies was 10.35 days. Twelve RCTs on pharmacologic therapies were included for KQ 2,[4, 6-10, 12, 14-18] and three on nonpharmacologic interventions were included for KQ 3.[5, 11, 13] No studies of opioids were identified for KQ 1. Details of the interventions used in each study can be found in Appendix D, Table D-1. Findings of the included studies and risk of bias are summarized in Appendix E, Tables E-1 through E-6, and Appendix F, Table F-1, respectively. The list of excluded studies

can be found in Appendix G. Appendix H, Table H-1 lists subgroup analyses. Appendix I includes references listed in the appendixes.

Figure 1. Flow chart



**15 new studies and 8 publications derived from randomized clinical trials already included in the original report.

Evidence Summary

Table 1 summarizes the conclusions from the 2020 report, new evidence from the current update, and the changes to the original conclusions, if any. A few new comparisons of interventions were identified in this update. Compared with placebo, eptinezumab significantly increased the likelihood of freedom from pain at 2 hours and at 1 day, and sustained freedom from pain at 1 day and at 2 days (high strength of evidence [SOE]), and propofol significantly increased pain relief at 2 hours (low SOE). Compared with humidified air, the interventions of dry oxygen, dry air, or humidified oxygen significantly improved pain at 2 hours (low SOE). Compared with supraorbital nerve block alone, the interventions of greater occipital nerve block alone and the combination of greater occipital nerve block and supraorbital nerve block significantly improved pain at 2 hours (low SOE). The evidence is insufficient for the comparison of magnesium sulfate versus metoclopramide, magnesium sulfate versus prochlorperazine, chlorpromazine versus prochlorperazine, mesotherapy (thiocolchicoside plus lidocaine plus tenoxicam) versus dexketoprofen, and greater occipital nerve block versus metoclopramide. There were no changes in 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

Key Question	Conclusions From 2020 Report	Findings From the Update	Assessment of SOE and Conclusion
KQ 2. NSAIDs: Celecoxib vs. Placebo	No study in the original report evaluated this specific NSAID. 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 RCT[9] (n=631) found no significant difference in being pain free at 2 hours. In a subsequent RCT[8] (n=535) of the same group of patients, celecoxib was found to be superior to placebo for the outcomes of pain free, pain relief, function scale at 2 hours and sustained pain free and sustained pain relief at 24 hours.	No change in SOE supporting the effect of NSAID as a drug class vs. placebo on improving pain relief outcomes: SOE remains moderate.
KQ 2. Antiemetic: Magnesium sulfate vs. Metoclopramide	No study in the original report compared these interventions, but in general, compared to placebo, antiemetics including metoclopramide alone and magnesium sulfate alone may resolve pain at 2 hours (low SOE).	One RCT[17] (n=105) found no significant difference on pain scale at 2 hours.	No change in conclusion.
KQ 2. Antiemetic: Magnesium sulfate vs. Prochlorperazine	No study in the original report evaluated this comparison, but compared with placebo, antiemetics including prochlorperazine alone and magnesium sulfate alone may resolve pain at 2 hours (low SOE).	One RCT[17] (n=113) found no significant difference on pain scale at 2 hours.	No change in conclusion.
KQ 2. Antiemetic: Prochlorperazine vs. Metoclopramide	Prochlorperazine was significantly more likely to lead to being pain free and having pain relief at 2 hours compared with metoclopramide (low SOE, based on 2 RCTs). Insufficient evidence for pain scale at 2 hours (based on 2 RCTs).	One small RCT[17] (n=96) found no significant difference on pain scale at 2 hours.	No change in conclusion.
KQ 2. Antiemetic: Metoclopramide plus magnesium sulfate vs. Metoclopramide	Metoclopramide alone was superior to metoclopramide plus magnesium sulfate for pain relief and restored function at 2 hours (low SOE, based on 1 RCT). Insufficient evidence for pain scale at 2 hours (based on 1 RCT).	One small RCT[18] (n=80) found no statistically significant difference on reduction of pain scale at 2 hours.	No change in conclusion.
KQ 2. Antiemetic: Chlorpromazine vs. Prochlorperazine	Chlorpromazine alone was superior to placebo for pain free and pain relief at 2 hours and 1 day (low SOE, based on 2 RCTs). Prochlorperazine alone was superior to placebo for pain free, pain relief, and reduction on pain scale at 2 hours (low SOE based on 1 RCT).	One small RCT[6] (n=88) found no statistically significant difference between chlorpromazine and prochlorperazine on reduction on pain scale at 2 hours.	No change in conclusion.

Key Question	Conclusions From 2020 Report	Findings From the Update	Assessment of SOE and Conclusion
KQ 2. 5-HT1F: Lasmiditan vs. Placebo	Lasmiditan was superior to 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 (moderate to high SOE based on 5 RCTs).	Two RCTs[10, 14] (n=2,459) found lasmiditan was superior to placebo on pain free, pain relief, and restored function at 2 hours, and sustained pain free at 1 day and at 2 days, compared with placebo.	No change in conclusion.
KQ 2. 5-HT1F: Lasmiditan vs. Placebo, subgroup analysis by age	No study in the original report evaluated this subgroup.	Two articles[22, 24] based on two previous RCTs (SAMURAI and SPARTAN) found no significant difference between patients under 65 years and 65 years and over on being pain free at 2 hours or adverse events.	Not applicable.
KQ 2. Other interventions: Propofol vs. Placebo	No study in the original report evaluated this comparison.	One small RCT[16] (n=40) found propofol significantly increased pain relief at 2 hours.	SOE low.
KQ 2. Other interventions: Mesotherapy (thiocolchicoside plus lidocaine plus tenoxicam) vs. Dexketoprofen	No study in the original report evaluated this comparison.	One RCT[4] (n=154) found mesotherapy significantly improved pain scale and pain relief at 2 hours and at 24 hours.	SOE insufficient.
KQ 2. CGRP: Eptinezumab vs. Placebo	No study in the original report evaluated this comparison.	One RCT[12] (n=485) found eptinezumab significantly increased pain free at 2 hours and at 1 day, and sustained pain free at 1 day and at 2 days.	SOE moderate.
KQ 2. Other interventions: Greater occipital nerve block vs. Metoclopramide	No study in the original report evaluated this comparison.	One small RCT[15] (n=99) reported no significant difference between the two groups on pain scale at 2 hours, sustained pain relief and sustained pain free at 2 days, or adverse events.	SOE insufficient.
KQ 2. Other interventions: Greater occipital nerve block vs. Placebo	Insufficient evidence for pain free, pain relief, and pain scale at 2 hours (based on 1 RCT).	One small RCT[7] (n=57) reported significantly more reduction on pain scale at 2 hours with greater occipital nerve block compared with placebo.	No change in conclusion.

Key Question	Conclusions From 2020 Report	Findings From the Update	Assessment of SOE and Conclusion
KQ 2. Other interventions: Greater occipital nerve block vs. Supraorbital nerve block vs. Combination of greater occipital nerve block and supraorbital nerve block vs. Placebo	No study in the original report evaluated this comparison.	One RCT[7] (n=142) reported greater occipital nerve block, supraorbital nerve block, and the combination of these two significantly improved pain scale at 2 hours compared with placebo, while greater occipital nerve block and the combination of greater occipital nerve block and supraorbital nerve block significantly improved pain scale at 2 hours compared with supraorbital nerve block.	SOE low.
KQ 3. Nonpharmacologic therapy: Transcranial alternating current stimulation vs. Sham stimulation	No study in the original report evaluated this comparison.	One small RCT[13] (n=25) found transcranial stimulation significantly improved pain scale at 2 hours and increased the likelihood of being sustained pain free at 1 day and at 2 days compared with those in the sham group.	SOE low.
KQ 3. Nonpharmacologic therapy: External trigeminal nerve stimulation vs. Sham stimulation	External trigeminal nerve stimulation was superior to sham for pain free, pain relief, and pain scale at 2 hours and at 1 day, and for sustained pain free and sustained pain relief at 1 day (low to moderate SOE based on 2 RCTs).	One small RCT[5] (n=77) found external trigeminal nerve stimulation significantly improved pain scale at 2 hours.	No change in conclusion.
KQ 3. Nonpharmacologic therapy: Dry oxygen vs. Dry air vs. Humidified oxygen vs. Humidified air	No study in the original report evaluated this comparison.	One small RCT[11] (n=51) found that patients with dry oxygen, dry air, or humidified oxygen reported a more significant reduction in pain scale at 2 hours than those in the humidified air group, while patients with dry air reported significantly more pain relief at 2 hours than those with humidified air. No significant difference between dry oxygen, dry air, and humidified oxygen was reported on pain scale at 2 hours. No significant adverse events were reported.	SOE low.

Abbreviations: CGRP = calcitonin gene-related peptide; KQ = Key Question; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized clinical trial; SAMURAI = A Study of Two Doses of LAsMiditan (100 mg and 200 mg) Compared to Placebo in the AcUte Treatment of MigRAIne; SOE=strength of evidence; SPARTAN = A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute TReaTment of MigrAiNe.

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

NSAIDS

Since the 2020 report, two separate RCTs[8, 9] evaluated the efficacy of celecoxib versus placebo and reported mixed results. One RCT[9] (n=631) found no significant difference between celecoxib and placebo regarding being pain free at 2 hours or number of adverse events. In a subsequent RCT,[8] the same group of patients who completed the first RCT were re-randomized (n=535). The authors reported that celecoxib was superior to placebo for the outcomes of pain free, pain relief, and function scale at 2 hours, and sustained pain free and sustained pain relief at 24 hours, with again no significant difference in adverse events (Appendix Table E-1). The overall risk of bias was high.

Antiemetic and Neuroleptic Medications

Three RCTs[6, 17, 18] have evaluated the efficacy of antiemetic and neuroleptic medications (n=303) for the acute treatment of migraine since the 2020 report. These RCTs studied prochlorperazine, chlorpromazine, and metoclopramide in comparison to each other or magnesium sulfate. Endpoints included the difference in pain scale at 2 hours (Appendix Table E-2). The overall risk of bias was low to moderate.

All the studies (magnesium sulfate vs. prochlorperazine vs. metoclopramide; metoclopramide plus magnesium sulfate vs. metoclopramide; chlorpromazine vs. prochlorperazine) failed to show a significant difference regarding the endpoint (pain scale at 2 hours). Significantly more adverse events were reported in the chlorpromazine group than the prochlorperazine group; otherwise, there were no significant differences in adverse events.

Compared with the results of the 2020 report, there were no changes to conclusions pertaining to the comparisons of prochlorperazine versus metoclopramide or metoclopramide plus magnesium sulfate versus metoclopramide. The strength of evidence was insufficient for the new evidence pertaining to magnesium sulfate versus metoclopramide, magnesium sulfate versus prochlorperazine, and chlorpromazine versus prochlorperazine.

5-HT1F Receptor Agonists

Two RCTs[10, 14] (n=2,459) evaluating the efficacy of the 5-HT1F agonist lasmiditan for the acute treatment of migraine have been published since the 2020 report. The overall risk of bias was low.

These RCTs showed significant improvements of lasmiditan over placebo for the outcomes of being pain free, pain relief, and restored function at 2 hours, and sustained pain free at 1 day and at 2 days (Appendix Table E-3). Significantly more patients treated with 200 mg or 100 mg of lasmiditan reported pain free, pain relief, and improved function at 2 hours, and sustained pain free at 1 day and at 2 days compared with placebo, while significantly more patients reported pain relief at 2 hours with 50 mg of lasmiditan compared with placebo. Lasmiditan was associated with significantly increased risk of adverse events. No serious adverse events, death, or withdrawal due to adverse events were reported.

A subgroup analysis based on two previous RCTs (SAMURAI [A Study of Two Doses of LAsMiditan (100 mg and 200 mg) Compared to Placebo in the AcUte Treatment of MigRAIne] and SPARTAN [A Study of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to Placebo in the Acute TReaTment of MigrAiNe)] found no significant difference between patients under 65 years and 65 years and over with regard to adverse events (Appendix Table H-1).[22, 24]

Based on these additional studies, there is no change to the conclusions of the 2020 report pertaining to lasmiditan.

Calcitonin Gene-Related Peptide Monoclonal Antibodies

Since the 2020 report, there has been one RCT[12] comparing eptinezumab to placebo in the outpatient setting for the acute treatment of migraine. This study, with 241 patients randomized to eptinezumab and 244 patients randomized to placebo, had low risk of bias and reported the drug to be significantly better than placebo with the outcomes of being pain free at 2 hours and 4 hours, and sustained pain free at 1 day and at 2 days (Appendix Table E-4). Eptinezumab was not included in the 2020 report, and these new data provide moderate SOE for this treatment option.

Other Interventions

The use of propofol compared with placebo for the acute treatment of migraine in the ED was evaluated by one RCT[16] that had 40 subjects. The high risk-of-bias study compared the intravenous administration of propofol at a maximum dose of 140 mg over 40 minutes (initial dose of 40 mg followed by up to 5 doses of 20 mg, 5 minutes apart) to placebo infusions at a maximum dose of 14 mL (20% intralipid) over 40 minutes (initial dose of 4 mL followed by up to 5 doses of 2 mL, 5 minutes apart). While more patients in the propofol group experienced pain relief at 2 hours, the study failed to meet its primary outcome of pain free at 1 hour. There was also no difference in terms of sustained pain free at 2 days. More patients in the propofol group experienced adverse events (Appendix Table E-5). While the original report did not include any studies with this comparison, these data provide low SOE for propofol improving pain relief at 2 hours.

Another ED study[4] appraised the use of mesotherapy (thiocolchicoside plus lidocaine plus tenoxicam) versus dexketoprofen, an NSAID, for the acute treatment of migraine, with 77 patients randomized to each arm. This study had an overall high risk of bias. Patients in the mesotherapy group reported significantly more pain relief and reduction of pain scores at 2 hours and at 24 hours. There was no significant difference in adverse events between the two groups (Appendix Table E-5). No studies in the original dataset evaluated mesotherapy; however, this report provides insufficient evidence to permit drawing a conclusion about this potential treatment option.

Two new studies[7, 15] evaluated nerve blocks in the ED setting for the acute treatment of migraine. One RCT[7] with 142 subjects assessed greater occipital nerve blocks against supraorbital nerve blocks or the combination of greater occipital and supraorbital nerve blocks against placebo. This study had an overall low risk of bias. Compared to placebo, patients with either greater occipital nerve block or supraorbital nerve block, alone or in combination, reported a significantly greater reduction on pain scales at 2 hours. Patients who had greater occipital nerve block alone or the combination of nerve blocks reported a significantly greater reduction on pain scales at 2 hours compared with those in the group with supraorbital nerve block alone.

No serious adverse events were reported (Appendix Table E-5). Overall, the SOE is low for nerve blocks.

In the second ED study,[15] 99 subjects were given either greater occipital nerve block or intravenous metoclopramide for the acute treatment of migraine. This RCT had moderate risk of bias and found no significant difference between the two groups' pain scale values at 2 hours, sustained pain relief and sustained pain free at 2 days, or adverse events. These data did not change the conclusion from the 2020 report.

Key Question 3. Nonpharmacologic Therapy

Noninvasive Neuromodulation Devices

There have been two reports on noninvasive neuromodulation devices since the initial 2020 report. One study[13] appraised transcranial alternating current stimulation versus sham stimulation for the acute treatment of migraine. This RCT with 25 patients had moderate overall risk of bias. Patients randomized to transcranial stimulation reported significantly greater pain reduction at 2 hours and sustained pain free at 1 day and at 2 days compared with those in the sham group. No studies in the original report evaluated this comparison, and the SOE for transcranial stimulation is low based on this new evidence.

A second study[5] evaluated external trigeminal nerve stimulation versus sham stimulation, and included 44 subjects in the stimulation group and 33 in the sham group. This study had an overall low risk of bias. The authors found that patients treated by transcutaneous electrical nerve stimulation reported significantly greater reduction on pain scale at 20 minutes compared with sham stimulation. No patients reported adverse events (Appendix Table E-6). The SOE for this treatment option ranged from low to moderate for various outcomes in the 2020 report, and this new study did not change that conclusion.

Other Interventions

One novel study[11] evaluating dry oxygen versus dry air versus humidified oxygen versus humidified air for the acute treatment of migraine was added. This RCT had 51 patients and was found to have moderate risk of bias. The authors found that patients in the dry oxygen, dry air, or humidified oxygen groups reported a significantly greater reduction of their pain scale values at 2 hours than those in the humidified air group. Patients in the dry air group reported significantly greater pain relief at 2 hours than those in the humidified air group. There was no significant difference between dry oxygen, dry air, and humidified oxygen in terms of pain scale at 2 hours. Additionally, no significant adverse events were reported (Appendix Table E-6). No studies in the original report evaluated these options, and there is low SOE for this new evidence.

Conclusions

The findings from this update are consistent with those in the original 2020 report on the comparative effectiveness and harms of opioids, as well as nonopioid pharmacologic and nonpharmacologic treatments, for acute treatments of episodic migraine. The report concluded that, 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. Opioids have low or insufficient strength of evidence for acute treatment of migraine. This update identified weak evidence in support of propofol,

occipital and supraorbital nerve blocks, transcranial stimulations, and inhaled oxygen in acute treatment of episodic migraine. The next surveillance report is scheduled for March 2022.

References

1. Halker Singh RB, VanderPluym JH, Morrow AS et al. Acute Treatments for Episodic Migraine. Comparative Effectiveness Review No. 239. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 290-2015-00013-I.) AHRQ Publication No. 21-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; December 2020. DOI: https://doi.org/10.23970/AHRQEPCCER239. Posted final reports are located on the Effective Health Care Program search page.

2. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.

3. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed 12/17/2021

4. Akbas I, Kocak MB, Kocak AO, et al. Intradermal mesotherapy versus intravenous dexketoprofen for the treatment of migraine headache without aura: a randomized controlled trial. Ann Saudi Med. 2021 May-Jun;41(3):127-34. doi: 10.5144/0256-4947.2021.127. PMID: 34085549.

5. Domingues FS, Gayoso MV, Sikandar S, et al. Analgesic efficacy of a portable, disposable, and self-applied transcutaneous electrical nerve stimulation device during migraine attacks: a real-life randomized controlled trial. Pain Pract. 2021 Nov;21(8):850-8. doi: 10.1111/papr.13042. PMID: 34013542.

6. Hodgson SE, Harding AM, Bourke EM, et al. A prospective, randomized, double-blind trial of intravenous chlorpromazine versus intravenous prochlorperazine for the treatment of acute migraine in adults presenting to the emergency department. Headache. 2021 Apr;61(4):603-11. doi: 10.1111/head.14091. PMID: 33797074.

7. Hokenek NM, Ozer D, Yilmaz E, et al. Comparison of greater occipital nerve and supra orbital nerve blocks methods in the treatment of acute migraine attack: a randomized double-blind controlled trial. Clin Neurol Neurosurg. 2021 Aug;207:106821. doi: 10.1016/j.clineuro.2021.106821. PMID: 34304069.

8. Lipton RB, Munjal S, Dodick DW, et al. Acute treatment of migraine with celecoxib oral solution: results of a randomized, placebo-controlled clinical trial. J Pain Res. 2021;14:549-60. doi: 10.2147/JPR.S287571. PMID: 33658842.

9. Lipton RB, Munjal S, Tepper SJ, et al. A multicenter, randomized, double-blind, placebo-controlled study of the efficacy, tolerability, and safety of celecoxib oral solution (ELYXYB) in acute treatment of episodic migraine with or without aura. J Pain Res. 2021;14:2529-42. doi: 10.2147/JPR.S322292. PMID: 34447267.

10. Sakai F, Takeshima T, Homma G, et al. Phase 2 randomized placebo-controlled study of lasmiditan for the acute treatment of migraine in Japanese patients. Headache. 2021 May;61(5):755-65. doi: 10.1111/head.14122. PMID: 33990951.

11. Shah R, Assis F, Narasimhan B, et al. Trans-nasal high-flow dehumidified air in acute migraine headaches: a randomized controlled trial. Cephalalgia. 2021 Aug;41(9):968-78. doi: 10.1177/0333102421997766. PMID: 33631965.

12. Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. JAMA. 2021 Jun 15;325(23):2348-56. doi: 10.1001/jama.2021.7665. PMID: 34128999.

13. Antal A, Bischoff R, Stephani C, et al. Low intensity, transcranial, alternating current stimulation reduces migraine attack burden in a home application set-up: a double-blinded, randomized feasibility study. Brain Sci. 2020 Nov 21;10(11):21. doi: 10.3390/brainsci10110888. PMID: 33233400.

14. Ashina M, Reuter U, Smith T, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: findings from the CENTURION study. Cephalalgia. 2021 Mar;41(3):294-304. doi: 10.1177/0333102421989232. PMID: 33541117.

15. Friedman BW, Irizarry E, Williams A, et al. A randomized, double-dummy, emergency department-based study of greater occipital nerve block with bupivacaine vs intravenous metoclopramide for treatment of migraine. Headache. 2020 Nov;60(10):2380-8. doi: 10.1111/head.13961. PMID: 32981043.

16. Meek R, Graudins A, McDonald M, et al. Comparing propofol with placebo for early resolution of acute migraine in adult emergency department patients: a double-blind randomised controlled trial. Emerg Med Australas. 2021;33(3):465-72. DOI: 10.1111/1742-6723.13659. PMID: 33070469

17. Kandil M, Jaber S, Desai D, et al. MAGraine: magnesium compared to conventional therapy for treatment of migraines. Am J Emerg Med. 2021 Jan;39:28-33. doi: 10.1016/j.ajem.2020.09.033. PMID: 33041146.

18. Motamed H, Mozafari J, Porozan S, et al. Magnesium sulfate and acute migraine: a randomized clinical trial. Ann Clin Anal Med. 2020 Sep;11(5):369-73. doi: 10.4328/Acam.20072.

19. Brandes JL, Klise S, Krege JH, et al. Long-term safety and efficacy of lasmiditan for acute treatment of migraine: final results of the GLADIATOR study. Cephalalgia Rep. 2020;3(no pagination). doi: 10.1177/2515816320958176.

20. Hutchinson S, Dodick DW, Treppendahl C, et al. Ubrogepant for the acute treatment of migraine: pooled efficacy, safety, and tolerability from the ACHIEVE I and ACHIEVE II phase 3 randomized trials. Neurol Ther. 2021 Jun;10(1):235-49. doi: 10.1007/s40120-021-00234-7. PMID: 33608814.

21. Goadsby PJ, Blumenfeld AM, Lipton RB, et al. Time course of efficacy of ubrogepant for the acute treatment of migraine: clinical implications. Cephalalgia. 2021 Apr;41(5):546-60. doi: 10.1177/0333102420970523. PMID: 33241721.

22. Clemow DB, Baygani SK, Hauck PM, et al. Lasmiditan in patients with common migraine comorbidities: a post hoc efficacy and safety analysis of two phase 3 randomized clinical trials. Curr Med Res Opin. 2020 Nov;36(11):1791-806. doi: 10.1080/03007995.2020.1808780. PMID: 32783644.

23. Peres MFP, Vasudeva R, Baygani SK, et al. Lasmiditan efficacy in migraine attacks with mild vs. moderate or severe pain. Curr Med Res Opin. 2021 Jun;37(6):1031-8. doi: 10.1080/03007995.2021.1903846. PMID: 33784930.

24. Martin VT, Ahmed Z, Hochstetler HM, et al. Tolerability and safety of lasmiditan treatment in elderly patients with migraine: post hoc analyses from randomized studies. Clin Ther. 2021 Jun;43(6):1066-78. doi: 10.1016/j.clinthera.2021.04.004. PMID: 34366152.

25. Lipton RB, Baygani SK, Tepper SJ, et al. A close association of freedom from pain, migraine-related functional disability, and other outcomes: results of a post hoc analysis of randomized lasmiditan studies SAMURAI and SPARTAN. J Headache Pain. 2021 Aug 28;22(1):101. doi: 10.1186/s10194-021-01303-w. PMID: 34454420.

26. Clemow DB, Hochstetler HM, Dong Y, et al. Effect of a change in lasmiditan dose on efficacy and safety in patients with migraine. Postgrad Med. 2021 May;133(4):449-59. doi: 10.1080/00325481.2020.1860619. PMID: 33730977.

Authors

Rashmi B. Halker Singh, M.D.
Juliana H. VanderPluym, M.D.
Bashar Hasan, M.D.
Magdoleen H. Farah, M.B.B.S.
Kelly E. Viola, M.P.S.
Samer Saadi, M.D.
Sahrish Shah, M.B.B.S.
Tarek Nayfeh, M.D.
Larry J. Prokop, M.L.S.
M. Hassan Murad, M.D., M.P.H.
Zhen Wang, Ph.D.

Acknowledgments

The authors gratefully acknowledge Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality, for her contributions to this project.

Disclaimers

This report is based on research conducted by the Mayo Clinic Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00005). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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.

AHRQ or U.S. Department of Health and Human Services endorsement of any derivative products that may be developed from this report, such as clinical practice guidelines, other quality enhancement tools, or reimbursement or coverage policies, may not be stated or implied.

AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is the first update report of a living systematic evidence report, Acute Treatments for Episodic Migraine, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

Suggested citation: Halker Singh RB, VanderPluym JH, Hasan B, Farah MH, Viola KE, Saadi S, Shah S, Nayfeh T, Prokop LJ, Murad MH, Wang Z. Acute Treatments for Episodic Migraine: Surveillance Report 1. (Prepared by the Mayo Clinic Evidence-based Practice Center under Contract No. 75Q80120D00005.) AHRQ Publication No. 22-EHC012. Rockville, MD: Agency for Healthcare Research and Quality; February 2022.

DOI: https://doi.org/10.23970/AHRQEPCMIGRAINESURVEILLANCE1. Posted final reports are located on the Effective Health Care Program search page.

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.

David Meyers, M.D.
Acting 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

Craig A. Umscheid, M.D., M.S.
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
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Appendix Contents

Appendix Tables

Appendix A. Key Questions

For Acute Treatment of Patients With Episodic Migraine, the following Key Questions (KQs) were determined based on input from multiple Key Informants.

KQ1. Opioid therapy

KQ2. Nonopioid pharmacologic therapy

KQ3. Nonpharmacologic therapy

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?

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?

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 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/
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/

#	Searches
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/

#	Searches
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/

#	Searches
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/

#	Searches
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.

#	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
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

#	Searches
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
Akbas, 2021[1]	RCT in Turkey, 12/01/2019 to 02/29/2020	ED	Mesotherapy (thiocolchicoside plus lidocaine plus tenoxicam)	Intradermal, first mixture 2 mg thiocolchicoside plus 16.2 mg lidocaine plus 5 mg tenoxicam for the glabella, the area between the eyes and ears and the painful area, second mixture 16.2 mg lidocaine plus 5 mg tenoxicam for the pericarotid region	7 days	77 patients aged 36±17.8 years, 42.1% female, BMI 24.5±1.33
	RCT in Turkey, 12/01/2019 to 02/29/2020	ED	Dexketoprofen	IV, 50 mg, once over 5 minutes	7 days	77 patients aged 36±17 years, 43.1% female, BMI 24.5±1.4
Antal, 2020[2]	RCT in Germany	Outpatient	Transcranial alternating current stimulation	Transcranial stimulation over the visual cortex, 0.4 mA, 140 Hz, for 15 minutes	2 days	16 patients aged 31.1±8.9 years
	RCT in Germany	Outpatient	Sham stimulation	Sham stimulation over the visual cortex, for 15 minutes	2 days	9 patients aged 28.1±10.5 years
Ashina, 2021[3]	RCT in Europe, North America, and Asia	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once for four attacks	2 days	486 patients, aged 42±12 years, 86% female, 77% White
	RCT in Europe, North America, and Asia	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once for four attacks	2 days	485 patients, aged 42±12 years, 83% female, 77% White
	RCT in Europe, North America, and Asia	Outpatient	Placebo	Oral, once for three attacks and lasmiditan 50 mg for either the third or fourth attack	2 days	500 patients, aged 41±12 years, 83% female, 77% White
Domingues, 2021[4]	RCT in Brazil, 11/2017 to 03/2018	Outpatient	External trigeminal nerve stimulation	Transcutaneous electrical nerve stimulation, pulse width 80 µs, frequency 55 Hz, continuous and intermittent (automatic) modes, ramp 2 seconds, pulse train 1 second (continuous), and 3 seconds (intermittent) with mild, moderate, and intense levels that ranged from 16 to 26 volts, over 20 seconds	90 days	44 patients aged 41±10.8 years, 97.7% female, 23% 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
Domingues, 2021[4] (continued)	RCT in Brazil, 11/2017 to 03/2018	Outpatient	Sham stimulation	Electrical current for 30 seconds and no current for the next 15 seconds	90 days	33 patients aged 38±9.7 years, 97% female, 28% White
Friedman, 2020[5]	RCT in United States of America, 11/2017 to 03/2020	ED	Greater occipital nerve block	Adjacent to the greater occipital nerve, total of 6 mL of bupivacaine 0.5% (3 mL each side) once, in addition to an IV drip of normal saline placebo administered over 15 minutes	2 days	51 patients aged 39±11 years, 86% female
	RCT in United States of America, 11/2017 to 03/2020	ED	Metoclopramide	Sham greater occipital nerve block, total of 6 mL of normal saline injected adjacent to the greater occipital nerve bilaterally (3 mL each side), in addition to an IV drip of 10 mg metoclopramide administered over 15 minutes	2 days	48 patients aged 38±11 years, 71% female
Hodgson, 2021[6]	RCT in Australia, 04/01/2018 to 03/01/2020	ED	Chlorpromazine	IV, 12.5 mg once over 30 minutes	2 hours	33 patients aged 36.7±10.7 years, 75% female
	RCT in Australia, 04/01/2018 to 03/01/2020	ED	Prochlorperazine	IV, 12.5 mg once over 30 minutes	2 hours	33 patients aged 42.5±11.8 years, 88% female
Hokenek, 2021[7]	RCT in Turkey, 07/2020 to 03/2021	ED	Greater occipital nerve block	Subcutaneous Injection, 1% lidocaine and 0.9% NaCl, once	2 hours	37 patients aged 36.5±10.37 years, 40% female
	RCT in Turkey, 07/2020 to 03/2021	ED	Supraorbital nerve block	Subcutaneous Injection, 1% lidocaine and 0.9% NaCl, once	2 hours	31 patients aged 36±11.11 years, 67.9% female
	RCT in Turkey, 07/2020 to 03/2021	ED	Combination of greater occipital nerve block plus supraorbital nerve block	Subcutaneous Injection, 1% lidocaine for greater occipital nerve and 1% lidocaine for supraorbital nerve, once	2 hours	43 patients aged 37±9.62 years, 62.8% female
	RCT in Turkey, 07/2020 to 03/2021	ED	Placebo	Subcutaneous Injection, 0.9% NaCl for greater occipital nerve and 0.9% NaCl for supraorbital nerve, once	2 hours	31 patients aged 36±15.55 years, 63% 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
Kandil, 2020[8]	RCT in United States of America, 08/2019 to 03/2020	ED	Magnesium sulfate	IV, 2 g/50 mL dextrose 5% in water, once over 20 minutes	2 hours	61 patients aged 34±15.6 years, 72% female, 49% White, 41% Black, 10% Hispanic, BMI 31.2±7.7
	RCT in United States of America, 08/2019 to 03/2020	ED	Prochlorperazine	IV, 10 mg/50 mL dextrose 5% in water, once over 20 minutes	2 hours	52 patients aged 37.5±15.2 years, 88% female, 27% White, 54% Black, 17% Hispanic, BMI 33.4±7.2
	RCT in United States of America, 08/2019 to 03/2020	ED	Metoclopramide	IV, 10 mg/50 mL dextrose 5% in water, once over 20 minutes	2 hours	44 patients aged 37.5±13.7 years, 75% female, 52% White, 36% Black, 11% Hispanic, BMI 30.1±6.1
Lipton, 2021[9]	RCT in United States of America, 12/13/2016 and 10/06/2017	Outpatient	Celecoxib	Oral, 120 mg, once	1 day	268 patients aged 41±11.96 years, 84% female, 75.8% White, 20.5% Black, 13.1% Hispanic, 1.6% Asian, 2% other, BMI 30.83±8.22
	RCT in United States of America, 12/13/2016 and 10/06/2017	Outpatient	Placebo	Oral, 4.8 mL, once	1 day	267 patients aged 39.6±12.09 years, 90% female, 73.1% White, 21.7% Black, 14.5% Hispanic, 2.4% Asian, 0.4% Native Hawaiian or other Pacific Island,0.4% American Indian or Alaska Native, 2% other, BMI 30.13±7.78
Lipton, 2021[10]	RCT in United States of America, 12/2016 to 10/2017	Outpatient	Celecoxib	Oral, 120 mg, once	2-7 days	316 patients aged 41.4±14 years, 82% female, 74% White, 22.1% Black, 13.8% Hispanic, 0.3% Asian, 3.5% other, BMI 30±7.3
	RCT in United States of America, 12/2016 to 10/2017	Outpatient	Placebo	Oral, 4.8 mL, once	2-7 days	315 patients aged 40.4±13 years, 86.6% female, 73.9% White, 22.3% Black, 14.5% Hispanic, 1.1% Asian, 2.8% other, BMI 30.4±7.4
Meek, 2020[11]	RCT in Australia, 03/01/2016 to 10/31/2018	ED	Propofol	IV, maximum dose 140 mg over 40 minutes (initial dose of 40 mg followed by up to five doses of 20 mg, over 5 minutes apart)	2 days	21 patients, aged 35±9.6 years, 81% female
	RCT in Australia, 03/01/2016 to 10/31/2018	ED	Placebo	IV, maximum dose 14 mL (20% intralipid), over 40 minutes (initial dose of 4 mL followed by up to five doses of 2 mL, over 5 minutes apart)	2 days	19 patients, aged 35±11.9 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
Motamed, 2020[12]	RCT in Iran, 10/2017 to 11/2018	ED	Metoclopramide plus magnesium sulphate	IV, 2 g magnesium sulfate plus 10 mg metoclopramide once	45 minutes	40 patients aged 20-30 years (12.5%), 31-40 years (52.5%), >40 (35%) years, 50% female
	RCT in Iran, 10/2017 to 11/2018	ED	Metoclopramide	IV, 10 mg metoclopramide plus placebo once	45 minutes	40 patients aged 20-30 years (22.5%), 31-40 years (42.5%), >40 (35%) years, 50% female
Sakai, 2021[13]	RCT in Japan, 05/30/2019 and 06/08/2020	Outpatient	Lasmiditan 50 mg	Oral, 50 mg, once	3-28 days	109 patients aged 44.9±10.2 years, 86.2% female, BMI 22.4±3.7
	RCT in Japan, 05/30/2019 and 06/08/2020	Outpatient	Lasmiditan 100 mg	Oral, 100 mg, once	3-28 days	261 patients aged 45.7±9.7 years, 84.6% female, BMI 22.6±3.7
	RCT in Japan, 05/30/2019 and 06/08/2020	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once	3-28 days	218 patients aged 44.7±10.4 years, 79.7% female, BMI 22.7±3.4
	RCT in Japan, 05/30/2019 and 06/08/2020	Outpatient	Placebo	Oral, once	3-28 days	258 patients aged 45.2±9 years, 83.2% female, BMI 22.6±4.1
Shah, 2021[14]	RCT in United States of America, 09/2018 and 09/2019	Outpatient	Dry oxygen	Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops	1 day	12 patients aged 49±15.4 years, 91% female, 92% White
	RCT in United States of America, 09/2018 and 09/2019	Outpatient	Dry air	Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops	1 day	11 patients aged 47±16 years, 82% female, 91% White
	RCT in United States of America, 09/2018 and 09/2019	Outpatient	Humidified oxygen	Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops	1 day	20 patients aged 54±15 years, 80% female, 80% White
	RCT in United States of America, 09/2018 and 09/2019	Outpatient	Humidified air	Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops	1 day	8 patients aged 46±11.3 years, 88% female, 75% 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
Winner, 2021[15]	RCT in United States of America, and Georgia, 11/04/2019 and 07/08/2020	Outpatient	Eptinezumab	IV, 100 mg (total volume of 100 mL with 0.9% saline), once over 30-45 minutes	28 days	241 patients aged 44.9±12 years, 84.9% female, 84% White, 12.6% Black, 12.2% Hispanic, 0.8% Asian, 0.8% American Indian or Alaska native, 0.4% Native Hawaiian or other Pacific Island, 1.3% multiple, BMI 27±4.5
	RCT in United States of America, and Georgia, 11/04/2019 and 07/08/2020	Outpatient	Placebo	IV, total volume of 100 mL with 0.9% saline, once over 30-45 minutes	28 days	244 patients aged 44.1±12.1 years, 83.1% female, 88% White, 7.9% Black, 12.8% Hispanic, 1.2% Asian, 0.4% American Indian or Alaska native, 0.4% Native Hawaiian or other Pacific Island, 1.7% multiple, 0.4% other, BMI 26.6±4.4

Abbreviations: BMI = body mass index; ED = emergency department; g = gram; Hz = hertz; IV = intravenous; L = liter; µs = microsecond; mA = milliampere; mg = milligram; mL = milliliter; NaCl = sodium chloride; RCT = randomized clinical trial

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
Lipton, 2021,[9] RCT	Outpatient	Celecoxib vs. Placebo	Oral, 120 mg, once vs. Oral, 4.8 mL, once	1 day	Celecoxib was superior to placebo for the outcomes of pain free, pain relief, function scale at 2 hours and sustained pain free and sustained pain relief at 24 hours. No significant difference was found on adverse events. No serious adverse events or withdrawal due to adverse events were reported.
Lipton, 2021,[10] RCT	Outpatient	Celecoxib vs. Placebo	Oral, 120 mg, once vs. Oral, 4.8 mL, once	2-7 days	No significant difference was observed on pain free at 2 hours, and number of adverse events.

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

Table E-2. 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
Hodgson, 2021,[6] RCT	ED	Chlorpromazine vs. Prochlorperazine	IV, 12.5 mg once over 30 minutes vs. IV, 12.5 mg once over 30 minutes	2 hours	There was no statistically significant difference on reduction of pain scale at 2 hours. Significantly more adverse events were reported in the chlorpromazine group than the prochlorperazine group.
Kandil, 2020,[8] RCT	ED	Magnesium sulfate vs. Prochlorperazine vs. Metoclopramide	IV, 2 g/50 mL dextrose 5% in water, once over 20 minutes vs. IV, 10 mg/50 mL dextrose 5% in water, once over 20 minutes vs. IV, 10 mg/50 mL dextrose 5% in water, once over 20 minutes	2 hours	There was no statistically significant difference on reduction of pain scale at 2 hours and adverse events.
Motamed, 2020,[12] RCT	ED	Metoclopramide plus magnesium sulphate vs. Metoclopramide	IV, 2 g magnesium sulfate plus 10 mg metoclopramide once vs. IV, 10 mg metoclopramide plus placebo once	45 minutes	There was no statistically significant difference on reduction of pain scale at 2 hours. No adverse events were reported in either groups.

Abbreviations: ED = emergency department; g = gram; IV = intravenous; mg = milligram; mL = milliliter; RCT = randomized clinical trial

Table E-3. 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
Ashina, 2021,[3] RCT	Outpatient	Lasmiditan 200 mg vs. Lasmiditan 100 mg vs. Placebo	Oral, 200 mg, once for four attacks vs. Oral, 100 mg, once for four attacks vs. Oral, placebo once for 3 attacks and lasmiditan 50 mg for either the third or fourth attack	2 days	Significantly more patients treated by lasmiditan 200 mg, or 100 mg reported pain free, pain relief and restored function at 2 hours, and sustained pain free at 1 day and 2 days, compared with placebo. Significantly more adverse events were reported in the lasmiditan groups. No death was reported.
Sakai, 2021,[13] RCT	Outpatient	Lasmiditan 50 mg vs. Lasmiditan 100 mg vs. Lasmiditan 200 mg vs. Placebo	Oral, 50 mg, once vs. Oral, 100 mg, once vs. Oral, 200 mg, once vs. Oral, once	3-28 days	Significantly more patients treated by lasmiditan 200 mg, or 100 mg reported pain free, pain relief, and improved function at 2 hours, and sustained pain free at 1 day and 2 days, compared with placebo. Lasmiditan 50 mg reported significantly more patients with pain relief at 2 hours, compared to placebo. Significantly more adverse events were reported in the lasmiditan groups. No serious adverse events, death, and withdrawal due to adverse events were reported.

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

Table E-4. Results from included studies: KQ 2. calcitonin gene-related peptide monoclonal antibodies

Author, Year, Study Design	Study Setting (Outpatient, Inpatient, ED)	Intervention(s) and Comparator	Route of Administration, Dose, and Duration	Length of Followup	Conclusion
Winner, 2021,[15] RCT	Outpatient	Eptinezumab vs. Placebo	IV, 100 mg (total volume of 100 mL with 0.9% saline), once over 30-45 minutes vs. IV, total volume of 100 mL with 0.9% saline, once over 30-45 minutes	28 days	Eptinezumab significantly increased pain free at 2 hours and 1 day, and sustained pain free at 1 day and 2 days.

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

Table E-5. 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
Akbas, 2021,[1] RCT	ED	Mesotherapy (thiocolchicoside plus lidocaine plus tenoxicam) vs. Dexketoprofen	Intradermal, first mixture 2 mg thiocolchicoside plus 16.2 mg lidocaine plus 5 mg tenoxicam for the glabella, the area between the eyes and ears and the painful area, second mixture 16.2 mg lidocaine plus 5 mg tenoxicam for the pericarotid region vs. IV, 50 mg, once over 5 minutes	7 days	Patients in the mesotherapy group reported significantly more pain relief and reduction of pain scores at 2 hours and 24 hours. No significant difference was found in adverse events.
Friedman, 2020,[5] RCT	ED	Greater occipital nerve block vs. Metoclopramide	Adjacent to the greater occipital nerve, total of 6 mL of bupivacaine 0.5% (3 mL each side) once, in addition to an IV drip of normal saline placebo administered over 15 minutes vs. Sham greater occipital nerve block, total of 6 mL of normal saline injected adjacent to the greater occipital nerve bilaterally (3 mL each side), in addition to an IV drip of 10 mg metoclopramide administered over 15 minutes	2 days	There was no significant difference between the two groups on pain scale at 2 hours, sustained pain relief and sustained pain free at 2 days, 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
Hokenek, 2021,[7] RCT	ED	Greater occipital nerve block vs. Supraorbital nerve block vs. Combination of greater occipital nerve block and supraorbital nerve block vs. Placebo	Subcutaneous Injection, 1% lidocaine and 0.9% NaCl, once vs. Subcutaneous Injection, 1% lidocaine and 0.9% NaCl, once vs. Subcutaneous Injection, 1% lidocaine for greater occipital nerve and 1% lidocaine for supraorbital nerve, once vs. Subcutaneous Injection, 0.9% NaCl for greater occipital nerve and 0.9% NaCl for supraorbital nerve, once	2 hours	Patients with greater occipital nerve block, supraorbital nerve block, or the combination of greater occipital nerve block and supraorbital nerve block reported significantly more reduction of pain scales at 2 hours, compared to placebo, while patients with greater occipital nerve block and the combination reported significantly more reduction of pain scales at 2 hours than those in the supraorbital nerve block group. No serious adverse events were reported.
Meek, 2020,[11] RCT	ED	Propofol vs. Placebo	IV, maximum dose 140 mg over 40 minutes (initial dose of 40 mg followed by up to five doses of 20 mg, over 5 minutes apart) vs. IV, maximum dose 14 mL (20% intralipid), over 40 minutes (initial dose of 4 mL followed by up to five doses of 2 mL, over 5 minutes apart)	2 days	Significantly more patients in the propofol group reported pain relief at 40 minutes and adverse events, compared to the placebo group. There was no significant difference in pain free and reduction of pain scale at 40 minutes and sustained pain free at 2 days.

Abbreviations: ED = emergency department; IV = intravenous; KQ = Key Question; mg = milligram; mL = milliliter; NaCl = sodium chloride; RCT = randomized clinical trial

Table E-6. 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
Antal, 2020,[2] RCT	Outpatient	Transcranial alternating current stimulation vs. Sham stimulation	Transcranial stimulation over the visual cortex, 0.4 mA, 140 Hz, for 15 minutes vs. Sham stimulation over the visual cortex, for 15 minutes	2 days	Patients in the transcranial stimulation reported significantly more pain reduction at 2 hours and sustained pain free at 1 day and 2 days, compared to those in the sham group.
Domingues, 2021,[4] RCT	Outpatient	External trigeminal nerve stimulation vs. Sham stimulation	Transcutaneous electrical nerve stimulation, pulse width 80 µs, frequency 55 Hz, continuous and intermittent (automatic) modes, ramp 2 seconds, pulse train 1 second (continuous), and 3 seconds (intermittent) with mild, moderate, and intense levels that ranged from 16 to 26 volts, over 20 seconds vs. Electrical current for 30 seconds and no current for the next 15 seconds	90 days	Patients treated by transcutaneous electrical nerve stimulation reported significantly more reduction of pain scale at 2 hours, compared to sham stimulation. No patients reported adverse events.
Shah, 2021,[14] RCT	Outpatient	Dry oxygen vs. Dry air vs. Humidified oxygen vs. Humidified air	Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops vs. Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops vs. Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops vs. Transnasal, 15 L/minute, once over 15 minutes with nasal saline drops	1 day	Patients with dry oxygen, dry air, or humidified oxygen reported significantly more reduction of pain scale at 2 hours than those in the humidified air group; while patients with dry air reported significantly more pain relief at 2 hours than those with humidified air. No significant difference between dry oxygen, dry air, or humidified oxygen was reported on pain scale at 2 hours. No significant adverse events were reported.

Abbreviations: ED = emergency department; Hz = hertz; KQ = Key Question; L = liter; µs = microsecond; mA = milliampere; mL = milliliter; 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
Akbas, 2021[1]	High risk	Low risk	High risk	Low risk	Moderate risk	Low risk
Antal, 2020[2]	Moderate risk	Low risk	Low risk	Moderate risk	Low risk	Low risk
Ashina, 2021[3]	High risk	Moderate risk	Low risk	High risk	Low risk	Low risk
Domingues, 2021[4]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Friedman, 2020[5]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
Hodgson, 2021[6]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hokenek, 2021[7]	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Kandil, 2020[8]	Moderate risk	Low risk	Low risk	Low risk	Moderate risk	Low risk
Lipton, 2021[9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lipton, 2021[10]	High risk	High risk	Low risk	Low risk	Low risk	Low risk
Meek, 2020[11]	High risk	Low risk	Low risk	High risk	Moderate risk	Moderate risk
Motamed, 2020[12]	Moderate risk	Moderate risk	Low risk	Low risk	Low risk	Low risk
Sakai, 2021[13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shah, 2021[14]	Moderate risk	Low risk	Moderate risk	Low risk	Moderate risk	Low risk
Winner, 2021[15]	Low risk	Low risk	Low risk	Low risk	Moderate risk	Low risk

Abbreviations: ROB = risk of bias

Appendix G. Excluded Studies

1. Ashina M, Cohen JM, Gandhi SK, et al. Reduction in the severity and duration of headache following fremanezumab treatment in patients with episodic and chronic migraine. Headache. 2021 Jun;61(6):916-26. doi: 10.1111/head.14127. PMID: 34115380. [Intervention not of interest]

2. Bagherzadi A, Emani R, Ghavami H, et al. Comparing the effect of heat and cold therapy on the intensity of nitrate induced migraine type headache in cardiac inpatients: a randomized controlled trial. Agri. 2021 Jul;33(3):148-54. doi: 10.14744/agri.2020.00907. PMID: 34318912. [Population not of interest]

3. Bandara SMR, Samita S, Kiridana AM, et al. Effectiveness of paranasal air suction on acute migraine using portable air sucker - a randomized, double blind study. BMC Neurol. 2021 Apr 24;21(1):176. doi: 10.1186/s12883-021-02203-x. PMID: 33892652. [Population not of interest]

4. Beier D, Callesen HE, Carlsen LN, et al. Manual joint mobilisation techniques, supervised physical activity, psychological treatment, acupuncture and patient education in migraine treatment: a systematic review and meta-analysis. Cephalalgia. 2021 Aug 18:3331024211034489. doi: 10.1177/03331024211034489. PMID: 34404258. [Irrelevant systematic review]

5. Cai G, Xia Z, Charvet L, et al. A systematic review and meta-analysis on the efficacy of repeated transcranial direct current stimulation for migraine. J Pain Res. 2021;14:1171-83. doi: 10.2147/JPR.S295704. PMID: 33953607. [Irrelevant systematic review]

6. Citrome L, Sanchez Del Rio M, Dong Y, et al. Benefit-risk assessment of galcanezumab versus placebo for the treatment of episodic and chronic migraine using the metrics of number needed to treat and number needed to harm. Adv Ther. 2021 Aug;38(8):4442-60. doi: 10.1007/s12325-021-01848-x. PMID: 34264500. [Outcomes not of interest]

7. Cohen F, Friedman BW. A randomized study of IV prochlorperazine plus diphenhydramine versus IV hydromorphone for migraine-associated symptoms: a post hoc analysis. Headache. 2021 Sep;61(8):1227-33. doi: 10.1111/head.14185. PMID: 34363617. [Outcomes not of interest]

8. Dudman DC, Tauqeer F, Kaur M, et al. A systematic review and meta-analyses on the prevalence of pregnancy outcomes in migraine treated patients: a contribution from the IMI2 ConcePTION project. J Neurol. 2021 Apr 1;01:01. doi: 10.1007/s00415-021-10534-5. PMID: 33792783. [Irrelevant systematic review]

9. Frank F, Ulmer H, Sidoroff V, et al. CGRP-antibodies, topiramate and botulinum toxin type A in episodic and chronic migraine: a systematic review and meta-analysis. Cephalalgia. 2021 Oct;41(11-12):1222-39. doi: 10.1177/03331024211018137. PMID: 34130525. [Irrelevant systematic review]

10. Ghanizada H, Al-Karagholi MA, Arngrim N, et al. Effect of adrenomedullin on migraine-like attacks in patients with migraine: a randomized crossover study. Neurology. 2021 May 18;96(20):e2488-e99. doi: 10.1212/WNL.0000000000011930. PMID: 33827963. [Intervention not of interest]

11. Hershey AD, Irwin S, Rabany L, et al. Comparison of remote electrical neuromodulation (REN) and standard-care medications for acute treatment of migraine in adolescents: a post-hoc analysis. Pain Med. 2021 Jun 29;29:29. doi: 10.1093/pm/pnab197. PMID: 34185084. [Population not of interest]

12. Hershey AD, Lin T, Gruper Y, et al. Remote electrical neuromodulation for acute treatment of migraine in adolescents. Headache. 2021 Feb;61(2):310-7. doi: 10.1111/head.14042. PMID: 33349920. [Population not of interest]

13. Ingvaldsen SH, Tronvik E, Brenner E, et al. A biofeedback app for migraine: development and usability study. JMIR Form Res. 2021 Jul 28;5(7):e23229. doi: 10.2196/23229. PMID: 34319243. [Outcomes not of interest]

14. Lim C, Singh M. Subcutaneous sumatriptans for acute migraine attacks in adults. Acad Emerg Med. 2021 Jul;28(7):814-5. doi: 10.1111/acem.14208. PMID: 33426737. [Study design not of interest]

15. Nahas SJ, Hindiyeh N, Friedman DI, et al. Long term safety, tolerability, and efficacy of intracutaneous zolmitriptan (M207) in the acute treatment of migraine. J Headache Pain. 2021 May 17;22(1):37. doi: 10.1186/s10194-021-01249-z. PMID: 34001002. [Study design not of interest]

16. Navarro-Perez MP, Ballesta-Martinez S, Rodriguez-Montolio J, et al. Acute migraine

management in the emergency department: experience from a large Spanish tertiary hospital. Intern Emerg Med. 2021 Nov;16(8):2243-9. doi: 10.1007/s11739-021-02698-9. PMID: 33712966. [Outcomes not of interest]

17. Nierenburg H, Rabany L, Lin T, et al. Remote electrical neuromodulation (REN) for the acute treatment of menstrual migraine: a retrospective survey study of effectiveness and tolerability. Pain Ther. 2021 Dec;10(2):1245-53. doi: 10.1007/s40122-021-00276-7. PMID: 34138449. [Study design not of interest]

18. Pellesi L, Al-Karagholi MA, De Icco R, et al. Effect of vasoactive intestinal polypeptide on development of migraine headaches: a randomized clinical trial. JAMA Netw Open. 2021 Aug 2;4(8):e2118543. doi: 10.1001/jamanetworkopen.2021.18543. PMID: 34357396. [Intervention not of interest]

19. Peres MFP, Vasudeva R, Baygani SK, et al. Lasmiditan efficacy in migraine attacks with mild vs. moderate or severe pain. Curr Med Res Opin. 2021 Jun;37(6):1031-8. doi: 10.1080/03007995.2021.1903846. PMID: 33784930. [Duplicate]

20. Pozo-Rosich P, Samaan KH, Schwedt TJ, et al. Galcanezumab provides consistent efficacy throughout the dosing interval among patients with episodic and chronic migraine: a post hoc analysis. Adv Ther. 2021 Jun;38(6):3154-65. doi: 10.1007/s12325-021-01708-8. PMID: 33950375. [Population not of interest]

21. Scuteri D, Corasaniti MT, Tonin P, et al. Role of CGRP pathway polymorphisms in migraine: a systematic review and impact on CGRP mAbs migraine therapy. J Headache Pain. 2021 Jul 30;22(1):87. doi: 10.1186/s10194-021-01295-7. PMID: 34330208. [Irrelevant systematic review]

22. Shi M, Guo J, Li Z, et al. Network meta-analysis on efficacy and safety of different anti-CGRP monoclonal antibody regimens for prophylaxis and treatment of episodic migraine. Neurol Res. 2021 Nov;43(11):932-49. doi: 10.1080/01616412.2021.1940672. PMID: 34281473. [Irrelevant systematic review]

23. Smith TR, Spierings ELH, Cady R, et al. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. J Headache Pain. 2021 Mar 30;22(1):16. doi: 10.1186/s10194-021-01227-5. PMID: 33781209. [Outcomes not of interest]

24. Wang X, Chen Y, Song J, et al. Efficacy and safety of monoclonal antibody against calcitonin gene-related peptide or its receptor for migraine: a systematic review and network meta-analysis. Front Pharmacol. 2021;12:649143. doi: 10.3389/fphar.2021.649143. PMID: 33867991. [Irrelevant systematic review]

25. Xu Z, Chen L, Jin S, et al. The efficacy of memantine for the treatment of migraine: a meta-analysis of randomized controlled studies. Clin Neuropharmacol. 2021 May-Jun 01;44(3):94-8. doi: 10.1097/WNF.0000000000000425. PMID: 33961371. [Intervention not of interest]

26. Yan Z, Xue T, Chen S, et al. Different dosage regimens of eptinezumab for the treatment of migraine: a meta-analysis from randomized controlled trials. J Headache Pain. 2021 Mar 6;22(1):10. doi: 10.1186/s10194-021-01220-y. PMID: 33676408. [Irrelevant systematic review]

27. Ailani J, Andrews J, Tockhorn-Heidenreich A, et al. Total pain burden in patients with treatment-resistant migraine: effects of galcanezumab in the CONQUER Phase 3b trial. Eur J Neurol. 2021 June;28 (SUPPL 1):272. doi: http://dx.doi.org/10.1111/ene.14974. PMID: 635426815. [Population not of interest]

28. Ashina M, Krikke-Workel J, Krege J, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: consistency findings. Cephalalgia. 2020 Oct;40:14-5. doi: http://dx.doi.org/10.1177/0333102420962311. PMID: n/a. [Type of publication (Conference abstract)]

29. Beauchene JK, Levien TL. Lasmiditan: Acute migraine treatment without vasoconstriction. A Review. J Pharm Technol. 2021 Oct;37(5):244-53. doi: 10.1177/87551225211024630. PMID: 34752575. [Study design not of interest]

30. Cevoli S, Pensato U, Favoni V. Moving closer to the ideal migraine acute treatment. Neurol Sci. 2020 Dec;41(Suppl 2):381-2. doi: 10.1007/s10072-020-04650-9. PMID: 32885392. [Study design not of interest]

31. Chowdhury D, Chaudhuri J, Ghosh P, et al. Efficacy and safety of erenumab in indian episodic migraine population: india subanalysis of Global EMPOwER study. Eur J Neurol. 2021 Jun;28:704-. doi: http://dx.doi.org/10.1111/ene.14975. PMID: n/a. [Type of publication (Conference abstract)]

32. Cosslett T, Mitchell C. The use of calcitonin gene related peptide monoclonal antibodies in the

difficult to treat migraine population. J Neurol. 2021 Feb;268(2):734-6. doi: 10.1007/s00415-020-10392-7. PMID: 33439329. [Study design not of interest]

33. Croop R, Madonia J, Conway CM, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

34. Fang X, Chiang C, Serrano D. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

35. Franklin M, Druyts E. ICER's assessment of lasmiditan, rimegepant, and ubrogepant for acute migraine. J Manag Care Spec Pharm. 2020 Nov;26(11):1464-6. doi: 10.18553/jmcp.2020.26.11.1464. PMID: 33119438. [Commentary]

36. Iaconangelo C, Serrano D, Manack Adams A, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

37. Iaconangelo C, Serrano D, Manack Adams A, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

38. Jankowska A, Pogoda A, Staszewski J. Intravenous sodium valproate for acute migraine: a meta-analysis. Eur J Neurol. 2021 Jun;28:226-. doi: http://dx.doi.org/10.1111/ene.14974. PMID: n/a. [Type of publication (Conference abstract)]

39. Johnston KM, Powell L, Popoff E, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

40. Jones A, O'Gorman C, Tabuteau H. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

41. Jones A, O'Gorman C, Tepper SJ, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

42. Joshi S, Aurora SK, Wang S, et al. PND7 assessing the comparative efficacy of INP104 for acute treatment of migraine attacks: a matching-adjusted indirect comparison. Value in Health. 2021 June;24:S159. doi: 10.1016/j.jval.2021.04.791. PMID: n/a. [Type of publication (Conference abstract)]

43. Joshi S, Aurora SK, Wang S, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

44. Krikke-Workel J, Krege J, Ashina M, et al. PAINWeek Abstract Book 2020. Postgrad Med. 2020;132(sup1):1-76. doi: 10.1080/00325481.2020.1824967. PMID: 634270843. [Type of publication (Conference abstract)]

45. Lipton RB, Blumenfeld AM, Jensen CM, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

46. Lipton RB, Contreras-De Lama J, Serrano D, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

47. Lipton RB, Dodick DW, Goadsby PJ, et al. Migraine Trust Virtual 2020 – Oral presentations. Cephalalgia. 2020 October;40(1_suppl):3-17. doi: 10.1177/0333102420962311. PMID: 634192764. [Type of publication (Conference abstract)]

48. Lipton RB, Dodick DW, Goadsby PJ, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

49. Lombard LA, Reuter U, Krege JH, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

50. Loo LS, Lipton R, Tepper S, et al. PAINWeek Abstract Book 2020. Postgrad Med. 2020;132(sup1):1-76. doi:

10.1080/00325481.2020.1824967. PMID: 634270829. [Type of publication (Conference abstract)]

51. MacGregor E, Komori M, Krege JH, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

52. McAllister P, Winner PK, Chakhava G, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

53. Nahas SJ, Cohen JM, Ramirez Campos V, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

54. O'Gorman C, Jones A, Lipton RB, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

55. Pavlovic J, Ailani J, Hutchinson S, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

56. Polavieja P, Belger M, Kumar Venkata S, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

57. Rabany L, Buse DC. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

58. Rosen N, Mathew P, Buchanan A, et al. PAINWeek Abstract Book 2020. Postgrad Med. 2020;132(sup1):1-76. doi: 10.1080/00325481.2020.1824967. PMID: 634270792. [Type of publication (Conference abstract)]

59. Schobel VR. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

60. Smith TR, Aurora SK, Hocevar-Trnka J, et al. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

61. Tassorelli C, Bragg S, Krege J, et al. Abstracts of the 7(th) Congress of the European Academy of Neurology, Virtual 2021. Eur J Neurol. 2021 Jun;28 Suppl 1:1-921. doi: 10.1111/ene.14968. PMID: 34143923. [Type of publication (Conference abstract)]

62. Tepper SJ, Sharon R. 63rd Annual Scientific Meeting American Headache Society((R)). Headache. 2021 Jun;61 Suppl 1:1-178. doi: 10.1111/head.14130. PMID: 34081778. [Type of publication (Conference abstract)]

63. Torres-Ferrus M, Gallardo VJ, Alpuente A, et al. The impact of anti-CGRP monoclonal antibodies in resistant migraine patients: a real-world evidence observational study. J Neurol. 2021 Oct;268(10):3789-98. doi: 10.1007/s00415-021-10523-8. PMID: 33772636. [Intervention not of interest]

64. Tuta-Quintero E, Zuleta-Sánchez N, Guerron-Gómez G, et al. Revisión de ensayos clínicos y estudios de cohorte para el tratamiento de la migraña con acupuntura. Revista Internacional de Acupuntura. 2021 01 Apr;15(2):51-9. doi: 10.1016/j.acu.2021.02.005. PMID: 2013160876. [Foreign language]

65. Vernieri F, Altamura C, Aurilia C, et al. Effectiveness, safety, and tolerability of galcanezumab in a real-life setting in patients with migraine in Italy (the GARLIT study). Neurol Sci. 2020 Dec;41(Suppl 2):487-8. doi: 10.1007/s10072-020-04669-y. PMID: 32845481. [Brief communication]

66. Wang PR, Lopez R, Seballos SS, et al. 2021 Annual Meeting Supplement. Acad Emerg Med. 2021 May;28 Suppl 1:S9-S418. doi: 10.1111/acem.14249. PMID: 33945187. [Type of publication (Conference abstract)]

67. Winner P, McAllister P, Chakhava G, et al. Efficacy and safety of eptinezumab initiated during a migraine attack: results from the RELIEF study. Eur J Neurol. 2021 Jun;28:271-. doi:

http://dx.doi.org/10.1111/ene.14974. PMID: n/a. [Type of publication (Conference abstract)]

68. Barchakh Z, Mardani Valandani Z, Khorvash F. The effectiveness of compassion-focused therapy for improving emotional control and reducing the severity of pain in migraine patients. Practice in Clinical Psychology. 2021 Win;9(1):51-60. doi: 10.32598/jpcp.9.1.740.1. PMID: n/a. [Population not of interest]

69. Huang L, Zhou PY, Cao ZH. Observation of efficacy of transcranial magnetic stimulation combined with ibuprofen in treatment of migraine patients and its influence on VAS scores. Basic & Clinical Pharmacology & Toxicology. 2020 Nov;127(SUPPL 3):112-. PMID: n/a. [Type of publication (Conference abstract)]

70. Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory controlled study of the migraine-suppressing effects of psilocybin. Neurother. 2021 Jan;18(1):534-43. doi: 10.1007/s13311-020-00962-y. PMID: 33184743. [Intervention not of interest]

71. Goadsby PJ, Blumenfeld AM, Lipton RB, et al. Time course of efficacy of ubrogepant for the acute treatment of migraine: clinical implications. Cephalalgia. 2021 Apr;41(5):546-60. doi: 10.1177/0333102420970523. PMID: 33241721. [Duplicate]

72. Clemow DB, Hochstetler HM, Dong Y, et al. Effect of a change in lasmiditan dose on efficacy and safety in patients with migraine. Postgrad Med. 2021 May;133(4):449-59. doi: 10.1080/00325481.2020.1860619. PMID: 33730977. [Duplicate]

73. Bandara SMR, Samita S, Kiridana AM, et al. Effectiveness of paranasal air suction on acute migraine using portable air sucker - a randomized, double blind study. BMC Neurol. 2021 Apr 24;21(1):9. doi: ARTN 17610.1186/s12883-021-02203-x. PMID: n/a. [Population not of interest]

74. Ghanizada H, Al-Karagholi MA, Arngrim N, et al. Effect of adrenomedullin on migraine-like attacks in patients with migraine: a randomized crossover study. Neurology. 2021 May 18;96(20):e2488-e99. doi: 10.1212/WNL.0000000000011930. PMID: 33827963. [Intervention not of interest]

75. Irct20161203031212N. The effect of alpha-lipoic acid on migraine. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=IRCT20161203031212N3. 2020. PMID: n/a. [Intervention not of interest]

76. Irct20170316033099N. The effectiveness of melatonin on migraine headaches. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=IRCT20170316033099N12. 2021. PMID: n/a. [Intervention not of interest]

77. Nct. A randomized controlled trial of acupuncture in treating migraine. https://clinicaltrialsgov/show/NCT04766762. 2021. PMID: n/a. [Intervention not of interest]

78. Nct. Eptinezumab in adults with migraine and medication overuse headache. https://clinicaltrialsgov/show/NCT04772742. 2021. PMID: n/a. [Intervention not of interest]

79. Shahsavani S, Mashhadi A, Bigdeli I. The effect of group emotional schema therapy on cognitive emotion strategies in women with migraine headaches: a pilot study. International journal of cognitive therapy. 2020;13(4):328-40. PMID: n/a. [Population not of interest]

80. Smith TR, Spierings ELH, Cady R, et al. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. Journal of headache and pain. 2021;22(1):11. PMID: n/a. [Intervention not of interest]

81. Herranz-Gómez A, García-Pascual I, Montero-Iniesta P, et al. Effectiveness of exercise and manual therapy as treatment for patients with migraine, tension-type headache or cervicogenic headache: an umbrella and mapping review with meta-meta-analysis. Applied Sciences. 2021;11(15). doi: 10.3390/app11156856. [Population not of interest]

82. Jie G, Mi-mi X, Ya-ying P. Clinical observation of electroacupuncture with different frequencies for migraine without aura. J Acupunct Tuina Sci. 2021;19(2):129-32. doi: 10.1007/s11726-021-1236-x. [Outcomes not of interest]

83. Zhang D, Tang X, Jiang W, et al. Clinical study of high-frequency repetitive transcranial magnetic stimulation in treatment of migraine without aura. Chinese J Neuromedicine. 2021;20(7):711-5. doi: 10.3760/cma.j.cn115354-20210409-00234. [Foreign language]

84. A/S HL. Eptinezumab in adults with migraine and medication overuse headache. https://ClinicalTrials.gov/show/NCT04772742; 2021. PMID: n/a. [Intervention not of interest]

85. Allergan. Study to assess adverse events and drug to drug interaction of oral tablet atogepant

and ubrogepant in adult participants with a history of migraine. https://ClinicalTrials.gov/show/NCT04818515; 2021. PMID: n/a. [Population not of interest]

86. Amgen. A study to evaluate treatment satisfaction with erenumab in participants with migraine. https://ClinicalTrials.gov/show/NCT04825678; 2021. PMID: n/a. [Intervention not of interest]

87. Brigham, Hospital Ws, Technology MIo. ACT for high frequency migraine; a virtual mindfulness intervention. https://ClinicalTrials.gov/show/NCT05003362; 2020. PMID: n/a. [Intervention not of interest]

88. St. Luke's Hospital P. Osteopathic manipulative treatment and migraine headaches. https://ClinicalTrials.gov/show/NCT04976985; 2022. PMID: n/a. [Intervention not of interest]

89. Theranica, University G, Clinic M. Real-world data analysis of REN treatment in migraine patients. https://ClinicalTrials.gov/show/NCT04992897; 2021. PMID: n/a. [Population not of interest]

90. University AAK. Comparison of osteopathic manipulative therapy and myofacial relaxation techniques in people diagnosed with migraine. https://ClinicalTrials.gov/show/NCT04976725; 2021. PMID: n/a. [Population not of interest]

91. Abu-Zaid A, AlBatati SK, AlHossan AM, et al. Galcanezumab for the management of migraine: a systematic review and meta-analysis of randomized placebo-controlled trials. Cureus. 2020 Nov 22;12(11):e11621. doi: 10.7759/cureus.11621. PMID: 33376635. [Outcomes not of interest]

92. Akerman S, Romero-Reyes M, Karsan N, et al. Therapeutic targeting of nitroglycerin-mediated trigeminovascular neuronal hypersensitivity predicts clinical outcomes of migraine abortives. Pain. 2021 May 1;162(5):1567-77. doi: 10.1097/j.pain.0000000000002142. PMID: 33181579. [Population not of interest]

93. de Tommaso M, Delussi M, Gentile E, et al. Effect of single dose erenumab on cortical responses evoked by cutaneous a-delta fibers: a pilot study in migraine patients. Cephalalgia. 2021 Aug;41(9):1004-14. doi: 10.1177/0333102421996345. PMID: 33593077. [Outcomes not of interest]

94. Hokenek NM, Erdogan MO, Hokenek UD, et al. Treatment of migraine attacks by transcutaneous electrical nerve stimulation in emergency department: a randomize controlled trial. Am J Emerg Med. 2021 Jan;39:80-5. doi: 10.1016/j.ajem.2020.01.024. PMID: 31983598. [Duplicate]

95. Kandil M, Jaber S, Desai D, et al. MAGraine: magnesium compared to conventional therapy for treatment of migraines. Am J Emerg Med. 2021 Jan;39:28-33. doi: 10.1016/j.ajem.2020.09.033. PMID: 33041146. [Duplicate]

96. Kurian A, Reghunadhan I, Thilak P, et al. Short-term efficacy and safety of topical beta-blockers (timolol maleate ophthalmic solution, 0.5%) in acute migraine: a randomized crossover trial. JAMA Ophthalmol. 2020 Nov 1;138(11):1160-6. doi: 10.1001/jamaophthalmol.2020.3676. PMID: 33001159. [Population not of interest]

97. Lin L, Min J, Yun-Ling Z, et al. [Systematic review and meta-analysis on efficacy and safety of yangxue qingnao granules in treatment of migraine]. Zhongguo Zhong Yao Za Zhi. 2020 Nov;45(21):5093-102. doi: 10.19540/j.cnki.cjcmm.20200729.501. PMID: 33350224. [Foreign language]

98. Min J, Yun-Ling Z, Yan LU, et al. [Systematic review and meta-analysis on randomized controlled trial of efficacy and safety for acupuncture versus flunarizine in treatment of migraine]. Zhongguo Zhong Yao Za Zhi. 2020 Nov;45(21):5083-92. doi: 10.19540/j.cnki.cjcmm.20200521.502. PMID: 33350223. [Foreign language]

99. Ou MQ, Fan WH, Sun FR, et al. A systematic review and meta-analysis of the therapeutic effect of acupuncture on migraine. Front Neurol. 2020;11:596. doi: 10.3389/fneur.2020.00596. PMID: 32714268. [Outcomes not of interest]

100. Rezaeian T, Mosallanezhad Z, Nourbakhsh MR, et al. Effects of dry needling technique into trigger points of the sternocleidomastoid muscle in migraine headache: a randomized controlled trial. Am J Phys Med Rehabil. 2020 Dec;99(12):1129-37. doi: 10.1097/PHM.0000000000001504. PMID: 32544109. [Outcomes not of interest]

101. Shao Q, Rascati KL, Lawson KA, et al. Impact of emergency department opioid use on future health resource utilization among patients with migraine. Headache. 2021 Feb;61(2):287-99.

doi: 10.1111/head.14071. PMID: 33599982. [Outcomes not of interest]

102. Wu B, Rao H, Yang S, et al. Efficacy and safety of the classic Chinese herbal prescription sanpian decoction on migraine: a meta-analysis. Explore (NY). 2020 Sep - Oct;16(5):318-27. doi: 10.1016/j.explore.2020.05.006. PMID: 32505521. [Intervention not of interest]

103. Ailani J, Blumenfeld A, Klein B, et al. An optional second dose of ubrogepant is effective in achieving 2-hour pain freedom in the acute treatment of migraine. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

104. Ashina M, Goadsby PJ, Dodick DW, et al. Cardiovascular safety of erenumab in patients with migraine with or without a history of aura. European Journal of Neurology. 2020 May;27 (Supplement 1):12. PMID: n/a. [Type of publication (Conference abstract)]

105. Ashina M, Goadsby PJ, Dodick DW, et al. Cardiovascular safety of erenumab in patients with migraine and aura. Headache. 2020 June;60 (Supplement 1):101-2. PMID: n/a. [Type of publication (Conference abstract)]

106. Clemow DB, Baygani SK, Hauck PM, et al. Lasmiditan in patients with common migraine comorbidities: a post hoc efficacy and safety analysis of two phase 3 randomized clinical trials. Curr Med Res Opin. 2020 Nov;36(11):1791-806. doi: 10.1080/03007995.2020.1808780. PMID: 32783644. [Type of publication (Conference abstract)]

107. Croop R, Berman G, Kudrow D, et al. Long-term safety of rimegepant 75 mg for the acute treatment of migraine (Study 201). Headache. 2020 June;60 (Supplement 1):111-2. PMID: n/a. [Type of publication (Conference abstract)]

108. Croop R, Jensen C, Thiry A, et al. Rimegepant is effective for the acute treatment of migraine in patients who have discontinued or currently use triptans: results from 3 phase 3 clinical trials. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement). PMID: n/a. [Type of publication (Conference abstract)]

109. DeFalco AP, Lazim R, Cope NE. Rimegepant orally disintegrating tablet for acute migraine treatment: a review. Ann Pharmacother. 2021 May;55(5):650-7. doi: 10.1177/1060028020954800. PMID: 32909437. [Study design not of interest]

110. Deighton A, Johnston KM, Dabirvaziri P, et al. Acute migraine medication and medication overuse headache: a systematic literature review. Headache. 2020 Jun;60:59-60. PMID: n/a. [Type of publication (Conference abstract)]

111. Dodick D, Goadsby P, Lu KF, et al. Ubrogepant achieves onset of pain relief at 1 hour for the acute treatment of migraine. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

112. Friedman BW, Irizarry E, Williams A, et al. 17 A randomized study of greater occipital nerve block with bupivacaine versus intravenous metoclopramide for acute migraine. Annals of Emergency Medicine. 2020 October;76 (4 Supplement):S7. PMID: n/a. [Type of publication (Conference abstract)]

113. Ghorbani Z, Togha M, Rafiee P, et al. Vitamin D3 might protect against inflammation in migraine: post hoc analysis of a randomized clinical trial. Cephalalgia Reports. 2020 January-December;3:3. PMID: n/a. [Type of publication (Conference abstract)]

114. Hutchinson S, Dodick DW, Treppendahl C, et al. Ubrogepant for the acute treatment of migraine: pooled efficacy from ACHIEVE I and ACHIEVE II phase 3 trials. Headache. 2020 Jun;60:93-. PMID: n/a. [Type of publication (Conference abstract)]

115. Hutchinson S, Dodick DW, Treppendahl C, et al. Ubrogepant for the acute treatment of migraine: pooled safety and tolerability from ACHIEVE I and ACHIEVE II phase 3 studies. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

116. Jakate A, Boinpally R, Butler M, et al. Safety and tolerability of ubrogepant for the acute treatment of migraine following co-administration with preventive monoclonal antibody treatment. Headache. 2020 Jun;60:124-. PMID: n/a. [Type of publication (Conference abstract)]

117. Johnston K, Popoff E, Deighton A, et al. Comparative efficacy and safety of rimegepant versus ubrogepant and lasmiditan for acute treatment of migraine: a network metaanalysis (NMA). Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement). PMID: n/a. [Type of publication (Conference abstract)]

118. Johnston KM, Popoff E, Deighton A, et al. Comparative efficacy and safety of rimegepant vs ubrogepant and lasmiditan for acute treatment of migraine: a network meta-analysis (NMA). Headache. 2020 Jun;60:65-6. PMID: n/a. [Type of publication (Conference abstract)]

119. Jurgens TP, Ning X, Kessler Y, et al. Pooled analysis of cardiovascular safety with fremanezumab treatment in patients with migraine by number of cardiovascular or cerebrovascular risk factors. Headache. 2020 June;60 (Supplement 1):3-4. PMID: n/a. [Type of publication (Conference abstract)]

120. Kessing R. ACHIEVE II trial: Ubrogepant compared to placebo for migraine attacks. [German]. Fortschritte der Neurologie Psychiatrie. 2020 01 Aug;88(8):486-7. PMID: n/a. [Foreign language]

121. L'Italien G, Croop R, Stock E, et al. Acute treatment with oral rimegepant 75mg reduces migraine-related disability: results from a one year, open-label safety study (BHV3000-201). Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

122. Levin M, Buse D, Blumenfeld A, et al. Rimegepant 75 mg is effective for the acute treatment of migraine regardless of attack frequency: results from 3 phase 3 trials. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

123. Lipton R, Dodick D, Goadsby P, et al. Ubrogepant is effective in the acute treatment of migraine with mild pain. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement). PMID: n/a. [Type of publication (Conference abstract)]

124. Lipton RB, Blumenfeld AM, Croop R, et al. Rimegepant is effective for the acute treatment of migraine in subjects who have discontinued or currently use triptans: results from 3 phase 3 clinical trials. Headache. 2020 June;60 (Supplement 1):122. PMID: 632639034. [Type of publication (Conference abstract)]

125. Lipton RB, Dodick DW, Goadsby PJ, et al. Ubrogepant is effective in the acute treatment of migraine with mild pain. Headache. 2020 June;60 (Supplement 1):126. PMID: n/a. [Type of publication (Conference abstract)]

126. Lipton RB, Singh RBH, Revicki DA, et al. Improved functionality, satisfaction, and global impression of change with ubrogepant for the acute treatment of migraine in triptan insufficient responders. Headache. 2020 Jun;60:95-. PMID: n/a. [Type of publication (Conference abstract)]

127. Loo L, Lipton RB, Tepper SJ, et al. A close association of pain freedom with freedom from most bothersome symptom and from migraine-related functional disability in lasmiditan studies samurai and spartan. Headache. 2020 June;60 (Supplement 1):97. PMID: n/a. [Type of publication (Conference abstract)]

128. Loo LS, Buse D, Lombard L, et al. Trajectory of migraine-related disability over 12 months with lasmiditan for acute treatment of migraine in the GLADIATOR study. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

129. Martin VT, Ahmed Z, Buchanan AS, et al. Tolerability of lasmiditan in elderly patients with migraine. Headache. 2020 June;60 (Supplement 1):125. PMID: n/a. [Type of publication (Conference abstract)]

130. McAllister P, Berman G, Kudrow D, et al. Rimegepant 75 mg demonstrates superiority to placebo on nausea freedom: results from a post hoc pooled analysis of 3 phase 3 trials in the acute treatment of migraine. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

131. McAllister P, Ning X, Cohen JM, et al. Improvements in quality-of-life, productivity, and satisfaction with fremanezumab in migraine patients >=60 years of age: pooled results of 3 randomised, double-blind, placebocontrolled phase 3 studies. European Journal of Neurology. 2020 May;27 (Supplement 1):301. PMID: 632534616. [Type of publication (Conference abstract)]

132. McCurry R, Krashin D, Schorn M, et al. Effectiveness of erenumab-aooe, fremanezumab-vfrm and galcanezumab-gnlm in migraine patients at tertiary headache clinic with emphasis on high-frequency migraine patients. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

133. Paget MA, Tockhorn-Heidenreich A, Belger M, et al. Generalisability of the CONQUER trial results to routine clinical practice: galcanezumab versus placebo in patients with inadequately controlled migraine. European Journal of Neurology. 2020 May;27:1082-. PMID: n/a. [Type of publication (Conference abstract)]

134. Pavlovic J, Dodick D, Friedman D, et al. Rimegepant 75 mg provides early and sustained relief of migraine with a single dose: results from 3 phase 3 clinical trials. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement). PMID: n/a. [Type of publication (Conference abstract)]

135. Pavlovic J, Dodick D, Newman L, et al. Rimegepant is effective for the acute treatment of migraine in subjects taking concurrent preventive medication: results from 3 phase 3 trials. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

136. Pavlovic J, Dodick DW, Friedman D, et al. Rimegepant 75 mg provides early and sustained relief of migraine with a single oral dose: results from 3 phase 3 clinical trials. Headache. 2020 Jun;60:96-. PMID: n/a. [Type of publication (Conference abstract)]

137. Popoff E, Johnston KM, Croop R, et al. Matching-adjusted indirect comparisons of intermittent oral rimegepant vs placebo and injectable anti-CGRP-targeted monoclonal antibodies examining monthly migraine days in the treatment of migraine. Headache. 2020 Jun;60:73-4. PMID: n/a. [Type of publication (Conference abstract)]

138. Rapoport AM, Strom S, Kollins J, et al. Safety of dihydroergotamine for acute migraine treatment: reality vs perception. Headache. 2020 Jun;60:24-. PMID: n/a. [Type of publication (Conference abstract)]

139. Rosen NL, Mathew PG, Buchanan AS, et al. Long-term cardiovascular safety of lasmiditan for the acute treatment of migraine for up to one year: interim results of an open-label phase 3 study (Gladiator). Headache. 2020 June;60 (Supplement 1):111. PMID: n/a. [Type of publication (Conference abstract)]

140. Smith TR, McAllister P, Berman G, et al. Low rates of rescue medication usage in subjects treated with a single dose of rimegepant 75 mg for the acute treatment of migraine: results from 3 phase 3 clinical trials. Headache. 2020 Jun;60:112-3. PMID: n/a. [Type of publication (Conference abstract)]

141. Strom S, Kollins J, Albrecht D. The efficacy of dihydroergotamine vs emerging acute migraine medications. Headache. 2020 Jun;60:26-7. PMID: n/a. [Type of publication (Conference abstract)]

142. Tehrani MRH, Kalhor L, Khosravi A, et al. .. Journal of Advances in Medical and Biomedical Research. 2021;29(132):14-20. PMID: n/a. [Outcomes not of interest]

143. Tepper SJ, Ailani J, Ford JH, et al. Effects of galcanezumab on health-related quality of life in patients with treatment-resistant migraine: results from CONQUER study. European Journal of Neurology. 2020 May;27 (Supplement 1):445. PMID: n/a. [Type of publication (Conference abstract)]

144. Tepper SJ, Lin T, Montal T, et al. Real-world experience with remote electrical neuromodulation in the acute treatment of migraine. Pain Med. 2020 Dec 25;21(12):3522-9. doi: 10.1093/pm/pnaa299. PMID: 32935848. [Outcomes not of interest]

145. Terwindt G, Nagy AJ, Doty EG, et al. Characterization of treatment emergent adverse events in headache pain-free patients after lasmiditan dosing for the acute treatment of a single migraine attack. European Journal of Neurology. 2020 May;27:163-. PMID: n/a. [Type of publication (Conference abstract)]

146. Tfelt-Hansen P, Ashina M, Diener H, et al. Effect of erenumab on monthly migraine days and monthly migraine attacks in patients with episodic migraine. Headache. 2020 Jun;60:103-. PMID: n/a. [Outcomes not of interest]

147. Trugman JM, Ailani J, Hutchinson S, et al. Efficacy is maintained with long-term intermittent use of ubrogepant for the acute treatment of migraine. Neurology. 2020 Apr 14;94(15). PMID: n/a. [Type of publication (Conference abstract)]

148. Turner I, Buse D, Blumenfeld A, et al. Rimegepant 75 mg is more effective for migraine than nonsteroidal anti-inflammatory drugs: post hoc analysis of data from 2 phase 3 trials. Neurology Conference: 72nd Annual Meeting of the American Academy of Neurology, AAN. 2020;94(15 Supplement). PMID: n/a. [Type of publication (Conference abstract)]

149. Vargas BB, Baygani SK, Hauck P, et al. A close association of pain freedom with freedom from most bothersome symptom and from migraine-related functional disability in lasmiditan studies Samurai and Spartan. Annals of Neurology. 2020 Oct;88:S151-S2. PMID: n/a. [Type of publication (Conference abstract)]

150. von Mentzer B, Russo AF, Zhang Z, et al. A CGRP receptor antagonist peptide formulated for nasal administration to treat migraine. J Pharm

Pharmacol. 2020 Oct;72(10):1352-60. doi: 10.1111/jphp.13317. PMID: 32588458. [Study design not of interest]

151. Wang YF, Chen YT, Shia BC, et al. PND116 treatment pattern and medication usage for patients with migraine in Taiwan. Value in Health. 2020 December;23 (Supplement 2):S643. PMID: n/a. [Type of publication (Conference abstract)]

152. Wei J, Liang X, Fu G, et al. Guidelines concerning pharmacological intervention for migraine in adults: a systematic review. [Chinese]. Chinese Journal of Evidence-Based Medicine. 2020;20(11):1316-25. PMID: n/a. [Foreign language]

153. Yang M, Du T, Liang F, et al. The efficacy of acupuncture for treating menstrual migraine: a systematic review. Integrative Medicine Research. 2020;Conference: KIOM-SAR 2020 International Research Conference. South Korea. 9(Supplement 1). PMID: n/a. [Type of publication (Conference abstract)]

154. Stauffer VL, Wang S, Bonner J, et al. Evaluation of injection-site-related adverse events with galcanezumab: a post hoc analysis of phase 3 studies in participants with migraine. BMC Neurol. 2020 May 19;20(1):194. doi: 10.1186/s12883-020-01775-4. PMID: 32429851. [Intervention not of interest]

155. Tepper SJ, Vasudeva R, Krege JH, et al. Evaluation of 2-hour post-dose efficacy of lasmiditan for the acute treatment of difficult-to-treat migraine attacks. Headache. 2020 Sep;60(8):1601-15. doi: 10.1111/head.13897. PMID: 32634275. [Duplicate]

156. Erratum: effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial (JAMA - Journal of the American Medical Association (2019) 322: 19 (1887-1898) DOI: 10.1001/jama.2019.16711). JAMA - journal of the american medical association. 2020;323(13):1318-. PMID: n/a. [Study design not of interest]

157. Hokenek NM, Erdogan MO, Hokenek UD, et al. Treatment of migraine attacks by transcutaneous electrical nerve stimulation in emergency department: a randomize controlled trial. Am J Emerg Med. 2021 Jan;39:80-5. doi: 10.1016/j.ajem.2020.01.024. PMID: 31983598. [Duplicate]

158. A randomized controlled trial of a[Euro sign]oeuplifting yang and dispersing stagnation, activating the channel and alleviating paina[Euro sign] acupuncture therapy for migraine. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=ChiCTR2000032308. 2020. PMID: n/a. [Outcomes not of interest]

159. Qi X, Fan G, Jia H. The probiotic lactobacillus casei shirota attenuates symptoms of vestibular migraine: a randomised placebo-controlled double-blind clinical trial. Beneficial Microbes. 2020;11(5):469-76. doi: 10.3920/Bm2020.0058. PMID: n/a. [Outcomes not of interest]

160. Clemow DB, Baygani SK, Hauck PM, et al. Lasmiditan in patients with common migraine comorbidities: a post hoc efficacy and safety analysis of two phase 3 randomized clinical trials. Curr Med Res Opin. 2020 Nov;36(11):1791-806. doi: 10.1080/03007995.2020.1808780. PMID: 32783644. [Duplicate]

161. Effect of craniosacral therapy in the management of migraine. http://wwwwhoint/trialsearch/Trial2aspx?TrialID=CTRI. 2020;07(026360). PMID: n/a. [Outcomes not of interest]

162. Acupuncture in migraine without aura patients. https://clinicaltrialsgov/show/NCT04542811. 2020. PMID: n/a. [Outcomes not of interest]

163. A study of LY3451838 in participants with migraine. https://clinicaltrialsgov/show/NCT04498910. 2020. PMID: n/a. [Outcomes not of interest]

164. Study to evaluate oral ubrogepant in the acute treatment of migraine during the prodrome in adult participants. 2020 August 21. PMID: n/a. [Duplicate]

165. Biohaven Pharmaceuticals I. Randomized trial in adult subjects with acute migraines. 2020 October 27. PMID: n/a. [Duplicate]

166. Biohaven Pharmaceuticals I. Safety and efficacy trial of BHV3000 (rimegepant) 75 mg for the acute treatment of migraine. 2020 October 22. PMID: n/a. [Duplicate]

167. Efficacy of onabotulinumtoxinA in migraine. 2020 March 13. PMID: n/a. [Study design not of interest]

168. Scripps H, Kaneka C. Effects of a multispecies probiotic on migraine. 2021 April 1. PMID: n/a. [Outcomes not of interest]

169. Eli Lilly C. A study of LY3451838 in participants with migraine. 2020 November 16. PMID: n/a. [Duplicate]

170. Herbacure N. Improvement of migraine severity and frequency with Migraineguard ™ supplement a randomized, placebo-controlled, double-blind, trial. 2020 April 1. PMID: n/a. [Outcomes not of interest]

171. Nocira LLC. Automated variable pattern insufflator device (AVPI) for the acute treatment of migraine. 2020 March 9. PMID: n/a. [Duplicate]

172. Efficacy and safety of nerivio for the acute treatment of menstrual migraine. 2020 September 9. PMID: n/a. [Outcomes not of interest]

173. Dr. Lutfi Kirdar Kartal T, Research H. Comparison of great occipital nerve and supraorbital nerve blockade methods at treatment of acute migraine attack in the emergency department. 2020 August 15. PMID: n/a. [Duplicate]

174. Ataturk U. Acupuncture in migraine without aura patients. 2020 March 1. PMID: n/a. [Outcomes not of interest]

175. Ataturk U. Mesotherapy versus systemic therapyin treatment of migraine headache. 2020 December 1. PMID: n/a. [Duplicate]

176. Lund University B. Nasal cavity cooling for the symptomatic relief of migraine headache - a pilot study. 2021 March. PMID: n/a. [Study design not of interest]

177. The Third Affiliated hospital of Zhejiang Chinese Medical U. A randomized controlled trial of acupuncture in treating migraine. 2021 March 1. PMID: n/a. [Outcomes not of interest]

178. Seo J, Chu H, Kim C-H, et al. Cupping therapy for migraine: a PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med. 2021;2021:7582581. doi: https://dx.doi.org/10.1155/2021/7582581. PMID: 33833822. [Outcomes not of interest]

179. Soni P, Chawla E. Quality of life related to functional disability in migraine patients: a systematic review and network-meta analysis. Clin J Pain. 2021 Aug 23;23:23. doi: https://dx.doi.org/10.1097/AJP.0000000000000972. PMID: 34419975. [Outcomes not of interest]

180. Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: a meta-analysis of randomized controlled studies. Am J Emerg Med. 2021 Aug;46:567-71. doi: 10.1016/j.ajem.2020.11.030. PMID: 33293189. [Systematic review]

181. Ha DK, Kim MJ, Han N, et al. Comparative efficacy of oral calcitonin-gene-related peptide antagonists for the treatment of acute migraine: updated meta-analysis. Clin Drug Investig. 2021 Feb;41(2):119-32. doi: 10.1007/s40261-020-00997-1. PMID: 33426614. [Systematic review]

182. Houts CR, McGinley JS, Nishida TK, et al. Systematic review of outcomes and endpoints in acute migraine clinical trials. Headache. 2021 Feb;61(2):263-75. doi: 10.1111/head.14067. PMID: 33611818. [Systematic review]

183. Moisset X, Pereira B, Ciampi de Andrade D, et al. Neuromodulation techniques for acute and preventive migraine treatment: a systematic review and meta-analysis of randomized controlled trials. J Headache Pain. 2020 Dec 10;21(1):142. doi: 10.1186/s10194-020-01204-4. PMID: 33302882. [Systematic review]

184. Wang F, Zhang H, Wang L, et al. Intravenous sodium valproate for acute migraine in the emergency department: a meta-analysis. Acta Neurol Scand. 2020 Dec;142(6):521-30. doi: 10.1111/ane.13325. PMID: 32740903. [Systematic review]

185. Yang Y, Sun Y, Gao B, et al. Lasmiditan for acute treatment of migraine in adults: a systematic review and meta-analysis of randomized controlled trials. CNS Drugs. 2020 Oct;34(10):1015-24. doi: 10.1007/s40263-020-00753-1. PMID: 32857291. [Systematic review]

186. Zhu H, Tang Y, Zhou T, et al. The efficacy of lasmiditan for the treatment of migraine: a meta-analysis of randomized controlled studies. Clin Neuropharmacol. 2020 Nov/Dec;43(6):191-5. doi: 10.1097/WNF.0000000000000417. PMID: 32969971. [Systematic review]

187. Gao B, Yang Y, Wang Z, et al. Efficacy and safety of rimegepant for the acute treatment of migraine: evidence from randomized controlled trials. Front Pharmacol. 2019;10:1577. doi: 10.3389/fphar.2019.01577. PMID: 32038251. [Systematic review]

188. Basutkar RS, Vinod CE, Saju SJ, et al. Optimal dosing of lasmiditan in the management of acute migraine attack: a systematic review and meta-analysis. Ann. 2021 Mar-Apr;24(2):155-63. doi:

https://dx.doi.org/10.4103/aian.AIAN_1223_20. PMID: 34220057. [Systematic review]

189. Chen L, Cai Z. The efficacy of ginger for the treatment of migraine: a meta-analysis of randomized controlled studies. Am J Emerg Med. 2021 08;46:567-71. doi: https://dx.doi.org/10.1016/j.ajem.2020.11.030. PMID: 33293189. [Systematic review]

190. Johnston K, Popoff E, Deighton A, et al. Comparative efficacy and safety of rimegepant, ubrogepant, and lasmiditan for acute treatment of migraine: a network meta-analysis. Expert rev. 2021 Jul 02:1-12. doi: https://dx.doi.org/10.1080/14737167.2021.1945444. PMID: 34148501. [Systematic review]

191. Joyner KR, Morgan KW. Novel therapies in acute migraine management: small-molecule calcitonin gene-receptor antagonists and serotonin 1F receptor agonist. Ann Pharmacother. 2021 06;55(6):745-59. doi: https://dx.doi.org/10.1177/1060028020963574. PMID: 32993366. [Systematic review]

192. Nedd M, Garland S, Falk N, et al. Ubrogepant: an oral calcitonin gene-related peptide (CGRP) receptor antagonist for abortive migraine treatment. Ann Pharmacother. 2021 Jun 10:10600280211023810. doi: https://dx.doi.org/10.1177/10600280211023810. PMID: 34109839. [Systematic review]

193. VanderPluym JH, Halker Singh RB, Urtecho M, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. Jama. 2021 06 15;325(23):2357-69. doi: https://dx.doi.org/10.1001/jama.2021.7939. PMID: 34128998. [Systematic review]

194. Zhang Z, Shu Y, Diao Y, et al. Calcitonin gene-related peptide receptor antagonist ubrogepant for the treatment of acute migraine: a meta-analysis. Medicine (Baltimore). 2021 Feb 26;100(8):e24741. doi: https://dx.doi.org/10.1097/MD.0000000000024741. PMID: 33663087. [Systematic review]

195. Viau JA, Patel D, Cheng W, et al. Sodium valproate vs dopamine antagonists for acute migraine in the emergency department: a systematic review. Canadian Journal of Neurological Sciences. 2021. doi: http://dx.doi.org/10.1017/cjn.2021.195. PMID: 34382533. [Systematic review]

196. Hutchinson S, Dodick DW, Treppendahl C, et al. Ubrogepant for the acute treatment of migraine: pooled efficacy, safety, and tolerability from the ACHIEVE I and ACHIEVE II phase 3 randomized trials. Neurol Ther. 2021 Jun;10(1):235-49. doi: 10.1007/s40120-021-00234-7. PMID: 33608814. [Duplicate]

197. Goadsby PJ, Blumenfeld AM, Lipton RB, et al. Time course of efficacy of ubrogepant for the acute treatment of migraine: clinical implications. Cephalalgia. 2021 Apr;41(5):546-60. doi: 10.1177/0333102420970523. PMID: 33241721. [Duplicate]

Appendix H. Subgroup Analysis

Table H-1. Subgroup analysis by age for 5-HT1F receptor agonist

Comparisons	Outcome	Subgroups	Findings
Lasmiditan (50 mg, 100 mg, 200 mg) vs. Placebo[16]	SAE	<65 years	RR: 0.66; 95% CI: 0.16 to 2.76; I^2=N/A
	SAE	≥65 years	RR: 2.90; 95% CI: 0.15 to 55.11; I^2=N/A
Lasmiditan (50 mg, 100 mg, 200 mg) >=65 years vs. Lasmiditan (50 mg, 100 mg, 200 mg) <65 years[16]	SAE	≥65 years vs. <65 years	RR: 13.84; 95% CI: 3.34 to 57.30; I^2=N/A
Lasmiditan (50 mg, 100 mg, 200 mg) vs. Placebo[16]	Any AE	<65 years	RR: 2.57; 95% CI: 2.22 to 2.98; I^2=N/A
	Any AE	≥65 years	RR: 3.72; 95% CI: 1.68 to 8.25; I^2=N/A
Lasmiditan (50 mg, 100 mg, 200 mg) >=65 years vs. Lasmiditan (50 mg, 100 mg, 200 mg) <65 years[16]	Any AE	≥65 years vs. <65 years	RR: 0.98; 95% CI: 0.77 to 1.24; I^2=N/A

Abbreviations: AE = adverse event; CI = confidence interval; mg = milligram; N/A = not applicable; RR = relative risk; SAE = serious adverse event

Appendix I. Appendix References

1. Akbas I, Kocak MB, Kocak AO, et al. Intradermal mesotherapy versus intravenous dexketoprofen for the treatment of migraine headache without aura: a randomized controlled trial. Ann Saudi Med. 2021 May-Jun;41(3):127-34. doi: 10.5144/0256-4947.2021.127. PMID: 34085549.

2. Antal A, Bischoff R, Stephani C, et al. Low intensity, transcranial, alternating current stimulation reduces migraine attack burden in a home application set-up: a double-blinded, randomized feasibility study. Brain Sci. 2020 Nov 21;10(11):21. doi: 10.3390/brainsci10110888. PMID: 33233400.

3. Ashina M, Reuter U, Smith T, et al. Randomized, controlled trial of lasmiditan over four migraine attacks: findings from the CENTURION study. Cephalalgia. 2021 Mar;41(3):294-304. doi: 10.1177/0333102421989232. PMID: 33541117.

4. Domingues FS, Gayoso MV, Sikandar S, et al. Analgesic efficacy of a portable, disposable, and self-applied transcutaneous electrical nerve stimulation device during migraine attacks: a real-life randomized controlled trial. Pain Pract. 2021 Nov;21(8):850-8. doi: 10.1111/papr.13042. PMID: 34013542.

5. Friedman BW, Irizarry E, Williams A, et al. A randomized, double-dummy, emergency department-based study of greater occipital nerve block with bupivacaine vs intravenous metoclopramide for treatment of migraine. Headache. 2020 Nov;60(10):2380-8. doi: 10.1111/head.13961. PMID: 32981043.

6. Hodgson SE, Harding AM, Bourke EM, et al. A prospective, randomized, double-blind trial of intravenous chlorpromazine versus intravenous prochlorperazine for the treatment of acute migraine in adults presenting to the emergency department. Headache. 2021 Apr;61(4):603-11. doi: 10.1111/head.14091. PMID: 33797074.

7. Hokenek NM, Ozer D, Yilmaz E, et al. Comparison of greater occipital nerve and supra orbital nerve blocks methods in the treatment of acute migraine attack: a randomized double-blind controlled trial. Clin Neurol Neurosurg. 2021 Aug;207:106821. doi: 10.1016/j.clineuro.2021.106821. PMID: 34304069.

8. Kandil M, Jaber S, Desai D, et al. MAGraine: magnesium compared to conventional therapy for treatment of migraines. Am J Emerg Med. 2021 Jan;39:28-33. doi: 10.1016/j.ajem.2020.09.033. PMID: 33041146.

9. Lipton RB, Munjal S, Dodick DW, et al. Acute treatment of migraine with celecoxib oral solution: results of a randomized, placebo-controlled clinical trial. J Pain Res. 2021;14:549-60. doi: 10.2147/JPR.S287571. PMID: 33658842.

10. Lipton RB, Munjal S, Tepper SJ, et al. A multicenter, randomized, double-blind, placebo-controlled study of the efficacy, tolerability, and safety of celecoxib oral solution (ELYXYB) in acute treatment of episodic migraine with or without aura. J Pain Res. 2021;14:2529-42. doi: 10.2147/JPR.S322292. PMID: 34447267.

11. Meek R, Graudins A, McDonald M, et al. Comparing propofol with placebo for early resolution of acute migraine in adult emergency department patients: a double-blind randomised controlled trial. Emerg Med Australas. 2021;33(3):465-72. PMID: 33070469 DOI: 10.1111/1742-6723.13659

12. Motamed H, Mozafari J, Porozan S, et al. Magnesium sulfate and acute migraine: a randomized clinical trial. Ann Clin Anal Med. 2020 Sep;11(5):369-73. doi: 10.4328/Acam.20072.

13. Sakai F, Takeshima T, Homma G, et al. Phase 2 randomized placebo-controlled study of lasmiditan for the acute treatment of migraine in Japanese patients. Headache. 2021 May;61(5):755-65. doi: 10.1111/head.14122. PMID: 33990951.

14. Shah R, Assis F, Narasimhan B, et al. Trans-nasal high-flow dehumidified air in acute migraine headaches: a randomized controlled trial. Cephalalgia. 2021 Aug;41(9):968-78. doi:

10.1177/0333102421997766. PMID: 33631965.

15. Winner PK, McAllister P, Chakhava G, et al. Effects of intravenous eptinezumab vs placebo on headache pain and most bothersome symptom when initiated during a migraine attack: a randomized clinical trial. JAMA. 2021 Jun 15;325(23):2348-56. doi: 10.1001/jama.2021.7665. PMID: 34128999.

16. Martin VT, Ahmed Z, Hochstetler HM, et al. Tolerability and safety of lasmiditan treatment in elderly patients with migraine: post hoc analyses from randomized studies. Clin Ther. 2021 Jun;43(6):1066-78. doi: 10.1016/j.clinthera.2021.04.004. PMID: 34366152.