

TOPIC BRIEF

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Nonpharmacologic Interventions for Migraine Prevention



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Nonpharmacologic Interventions for Migraine Prevention

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Abstract

Background: Migraine is a common condition that is disabling for many Americans. Although pharmacologic therapies for migraine prevention exist, nonpharmacologic therapies are an important alternative patients may prefer for many reasons, including an inability to tolerate drug side effects or medical comorbidities.

Purpose: To provide an overview of existing randomized controlled trials (RCTs) assessing nonpharmacologic interventions for migraine headache prevention and inform decisions regarding future evidence synthesis and comparative effectiveness research (CER).

Methods: We interviewed stakeholders to identify important nonpharmacologic interventions and performed a rapid scoping review. We searched EMBASE.com, PsycINFO, and PubMed from January 1, 2011 to April 1, 2021, for relevant systematic reviews (SRs) and RCTs. For inclusion, studies had to be randomized trials assessing interventions of interest for migraine prevention, report outcomes of headache frequency and/or Migraine Disability Assessment Test or Headache Impact Test-6, include at least 10 participants per study arm, and have a minimum follow-up duration of ≥ 8 weeks.

We also searched ClinicalTrials.gov for relevant ongoing clinical trials and searched for clinical practice guidelines addressing nonpharmacologic therapies for migraine prevention.

Results: A recent Veterans Affairs/Department of Defense CPG made weak recommendations for aerobic exercise, mindfulness-based therapies, and oral magnesium for migraine prevention and “neither for nor against” recommendations for the following: acupuncture, cognitive behavioral therapy, biofeedback, neurostimulation, and several supplements. We identified no other evidence-based CPG updated within the past 5 years.

Our search identified 164 RCTs, 27 of which were not summarized by relevant SRs. Behavioral interventions had the largest evidence base (52 RCTs), followed by acupuncture (47 RCTs), nutraceuticals/supplements (31 RCTs), noninvasive stimulation (13 RCTs), exercise (12 RCTs), physical therapy (10 RCTs), and education (9 RCTs).

Based on our scoping review of existing guidelines, SRs, and RCTs, we conclude the following:

- Due to limitations of existing SRs or publication of newer trials not captured in existing SRs or clinical practice guidelines, we suggest *new evidence synthesis* for acupuncture, behavioral interventions (particularly mindfulness-based therapy), and yoga. Existing SRs appear to adequately address efficacy for noninvasive neurostimulation, education, aerobic exercise, physical therapy, and nutraceuticals.
- Trials comparing nonpharmacologic versus pharmacologic treatments are relatively sparse. To address evidence gaps, we suggest *trials assessing comparative effectiveness* of acupuncture, mindfulness-based therapy, exercise (eg, aerobic exercise, progressive strength training, yoga), oral magnesium, coenzyme Q, vitamin B2, and supraorbital nerve stimulation. New CER for physical therapy and educational interventions is a low priority at this time.

Conclusion: A substantive evidence base for nonpharmacologic migraine prevention therapies exists. Nonpharmacologic interventions for migraine headache prevention remain an important alternative to pharmacotherapy for patients. Targeted new evidence synthesis and CER of specific interventions can provide important insights on efficacy and address key evidence gaps for patients and clinicians.

Background

Migraine is a common, disabling condition that affected 16% of American adults in 2018; in 2016, migraine accounted for 4 million emergency department visits.¹ Interventions for migraine prevention aim to reduce the number and severity of migraine headaches. A variety of pharmacologic interventions for migraine prevention offer differing (and often modest) degrees of efficacy for decreasing headache frequency.² However, nonpharmacologic therapies offer an important alternative for patients who prefer to avoid pharmacologic therapies or use pharmacologic and nonpharmacologic modalities together. Patients may opt to avoid pharmacotherapy for many reasons, including potential drug side effects or drug-drug interactions. Also, pharmacotherapy may be contraindicated in some patients due to medical comorbidities.

Nonpharmacologic interventions include behavioral therapies (eg, cognitive behavioral therapy [CBT], relaxation, biofeedback, mindfulness), nutraceutical/supplements (eg, vitamins, melatonin, butterbur), acupuncture, exercise, and education/self-management. Other interventions include invasive and noninvasive stimulation (eg, transcranial magnetic stimulation, transcutaneous supraorbital nerve stimulation, invasive occipital nerve stimulation).

This topic brief aims to overview the existing evidence on nonpharmacologic interventions for migraine prevention and inform decisions regarding future comparative effectiveness research (CER) and evidence synthesis. To that end, ECRI performed a rapid scoping review. With input from clinician stakeholders and a patient/patient advocate, we identified key nonpharmacologic interventions. We then summarized existing randomized controlled trials (RCTs) assessing selected nonpharmacologic interventions for migraine prevention by identifying existing clinical practice guidelines, systematic reviews (SRs), and RCTs.

Methods

To identify nonpharmacologic interventions with evidence of efficacy, we interviewed a technical expert panel of stakeholders (3 clinicians with expertise in migraine and 1 patient/patient advocate). Based on this input, we generated a list of nonpharmacologic interventions likely to have been assessed using RCTs and of particular interest to patients and physicians. Given the compressed timeline for this project, we identified a subset of these interventions as high priority for this topic brief. We considered the following interventions out of scope: acupressure, aromatherapy, chiropractic manipulation, and hypnosis. In addition, stakeholders noted other interventions of interest currently considered to have low or unknown efficacy (see Appendix A). Table 1 presents the final list of included interventions for this topic brief.

Table 1. Nonpharmacologic Interventions With Evidence of Efficacy for Migraine Prevention

Intervention category	Specific interventions (where applicable)
Education/self-management strategies	N/A
Exercise	Aerobic exercise Low-impact exercise Moderate-/high-intensity exercise Tai chi Yoga (pranayama breathing, kriya cleansing, ayurveda)
Physical therapy	N/A
Noninvasive neuromodulation	Transcranial magnetic stimulation Transcutaneous supraorbital nerve stimulation Noninvasive vagus nerve stimulation
Acupuncture	Acupuncture Electroacupuncture
Behavioral (often combined modalities)	Biofeedback (thermal biofeedback, electromyography biofeedback, heart rate variability biofeedback), autogenic; eye movement desensitization and reprocessing Cognitive behavioral therapy (in person or delivered via mobile application) Cognitive behavioral therapy for insomnia Acceptance and commitment therapy Dialectical-based therapy Sleep hygiene Mindfulness (mindfulness-based stress reduction, mindfulness-based cognitive therapy ^a) Meditation Neuroscience education therapy (combination therapy) Relaxation (eg, progressive muscle relaxation)

Intervention category	Specific interventions (where applicable)
Nutraceutical/supplements	Alpha lipoic acid Boswellia Butterbur (petasites) Coenzyme Q Feverfew Gingko biloba Magnesium Melatonin Riboflavin (vitamin B2) Vitamin E

Abbreviation: N/A, not applicable.

^aMindfulness-based cognitive therapy appears under both Cognitive Behavioral Therapy and Mindfulness.

Literature Search

We searched EMBASE.com, PsycINFO, and PubMed over the past 10 years (from January 1, 2011 to April 1, 2021) for peer reviewed journal literature. We selected this 10 year timeframe for feasibility given this project’s timeline. We also searched the gray literature for clinical trials and guidelines relating to nonpharmacologic interventions for migraine prevention along with ClinicalTrials.gov to identify relevant ongoing trials. To identify relevant clinical practice guidelines, we searched ECRI Guidelines Trust® and Google and browsed websites of professional organizations, including the American Academy of Neurology, Canadian Headache Society, European Headache Federation, International Headache Society, National Institute for Health and Clinical Excellence, and Veterans Affairs (VA)/Department of Defense (DoD) Clinical Practice Guidelines. The full search strategy is available in Appendix B.

Citation Screening

A single analyst reviewed citations for relevance at the title and abstract level using Distiller SR (Evidence Partners). An experienced systematic reviewer reviewed all full-text articles against prespecified criteria (provided below).

For guidelines, we assessed whether the guidance (1) addressed a relevant intervention; (2) was produced by a medical specialty association, professional medical society, or other relevant clinical practice guidelines development organization; and (3) was based on a verifiable SR of evidence (reporting of databases searched, specific time period covered by literature search, explicit inclusion/exclusion criteria, studies identified by literature search, and evidence analysis [evidence tables, Grading of Recommendations Assessment, Development, and Evaluation tables, or narrative synthesis]). We considered guidelines that met these criteria to be evidence based.

Inclusion/Exclusion Criteria

Although headache frequency is a common primary outcome measure for migraine prevention trials, a 2020 consensus statement by migraine experts recommended that the Migraine Disability Assessment (MIDAS) and Headache Impact Test (HIT-6) be considered along with headache frequency as primary outcome measures in trials of nonpharmacologic interventions.³

We considered the first line of evidence to be published English-language SRs. We selected the most recent, relevant, and comprehensive SR that met the methodologic criteria specified above. If we identified multiple SRs with similar included studies for a given intervention, we chose the most comprehensive (eg, review that included the most studies) and/or the most recent SR. After identifying relevant SRs, we reviewed RCTs identified in our search to identify trials not already captured by included SRs. If these RCTs met inclusion criteria (described below), they were included.

Our technical expert panel provided feedback on key study criteria, including study design, outcome measures, and study duration. To be eligible for inclusion, all SRs were required to meet certain standards for methodologic rigor. Specifically, SRs had to report a comprehensive literature search and explicit inclusion/exclusion criteria and assess individual quality of included studies.

If SRs met these criteria, we then determined (to the extent possible given reported details) whether the review included RCTs that met the following criteria:

- Was an English-language, published full-length article
- Assessed intervention of interest for migraine prevention
- Population was adults ≥ 18 years of age
- Enrolled $N \geq 10$ per treatment arm
- Study design was RCT (or SR including RCTs); we included both comparisons with inactive control and head-to-head trials
- Study duration was ≥ 8 weeks
- Reported on efficacy for migraine prevention using measure of headache frequency (migraines, migraine days per month, headaches, or headache days per month) or patient-oriented outcome for quality of life (MIDAS or HIT-6)

We included SRs with RCTs that met these criteria. Some SRs included both English and non-English studies but did not clearly distinguish these within the review. In such cases, we included all studies that appeared to otherwise meet inclusion criteria. In addition, we reviewed RCTs against the same criteria. If an RCT met inclusion criteria, we then determined whether the study had already been captured within an SR. If not, we included the RCT. In some cases, an SR that did not report on outcomes of interest identified relevant RCTs that were not captured by other SRs or our search of RCTs. To provide the best estimate of all available existing RCTs, we included such SRs

Data Extraction

We extracted study data, including study design, specific comparisons, and whether RCTs compared the intervention against an inactive control or were a head-to-head trial. In addition, for SRs, we extracted the end search date, number of trials included in the review (regardless of whether they met criteria), and author conclusions (as reported in the abstract). For individual RCTs, we extracted the number of patients per trial, study outcomes, and author conclusions (as reported in the abstract).

Results

This section characterizes the existing literature base for nonpharmacologic interventions for migraine prevention. First, we describe relevant clinical practice guidelines; second, we summarize existing SRs and primary research; third, we assess research gaps and the need for future research (including the need for updated evidence synthesis or CER).

Stakeholder Input

Stakeholders confirmed that key categories of nonpharmacologic therapies were represented and refined distinctions among the various intervention modalities. They noted that patient access to behavioral interventions requiring specific expertise was often limited by whether patients were able to identify nearby practitioners. Regarding scoping parameters, stakeholders noted that older trials (eg, published in the 1980s) contribute important evidence that remains applicable. Finally, as previously stated, stakeholders noted that, for nonpharmacologic interventions, both MIDAS and HIT-6 should be considered along with headache frequency as primary outcome measures, given a recent consensus statement.³

Relevant Clinical Practice Guidelines

We identified 3 clinical practice guidelines⁴⁻⁶ addressing nonpharmacologic interventions of interest (Table 2). Further details are available in Appendix C, Table C-1. Only one guideline, the VA/DoD Clinical Practice Guideline for Primary Care Management of Headache,⁴ was published in the past 5 years. This guideline was based on an SR that included both SRs and RCTs published from January 2009 to March 2019 as evidence. Although the full SR was unavailable for review, the guideline provides the supporting evidence base for each recommendation. The authors made weak recommendations for aerobic exercise or progressive strength training, mindfulness-based therapies, and oral magnesium.

Notably, the VA/DoD guideline considered mindfulness-based therapies to include “meditation, relaxation, mindfulness-based stress reduction, mindfulness-based cognitive therapy, acceptance-based approaches, and yoga among others.” This differs from our review, in which we considered yoga a form of exercise, and meditation, relaxation, and acceptance-based approaches as distinct behavioral interventions. The authors acknowledged that confidence in the quality of evidence (for mindfulness-based therapies) was low but concluded that “improved outcomes of headache frequency and other potential benefits outweigh the harms with this relatively low-risk activity.”⁴

The VA/DoD guideline recommended “neither for nor against” acupuncture, cognitive behavioral therapy, biofeedback, neurostimulation, and several supplements (including coenzyme Q, feverfew, melatonin, vitamin B2). For acupuncture, the “neither for nor against” recommendation acknowledged acupuncture’s efficacy for headache frequency but noted inconsistencies in other outcomes (eg, headache days). The authors also considered other factors, such as differences in individual patient preferences, burden of attending treatments, and challenges of access. Regarding supplements (including coenzyme Q, feverfew, melatonin, vitamin B2, omega 3, and vitamin B6), the authors noted, “Evidence suggests small but somewhat inconsistent benefits in reducing migraine frequency, which slightly outweighed potential harms, such as dose variability in supplements, and some specific harms, such as postfeverfew syndrome or vitamin B6 neurotoxicity in high, sustained doses.”⁴

The guideline did not recommend against any nonpharmacologic interventions. Remaining guidelines were nearly a decade old, and one had been retired due to safety concerns regarding butterbur.⁶ Further details regarding other types of guidance identified are available in Appendix C, Table C-1 and C-2.

Table 2. Evidence-Based Clinical Practice Guidelines Addressing Nonpharmacologic Interventions for Migraine Prevention

Guideline	End search date of included literature
Veterans Affairs/Department of Defense Clinical Practice Guideline for Primary Care Management of Headache (2020) ⁴	March 2019
Canadian Headache Society Guideline for Migraine Prophylaxis (2012) ⁵	April 2008
Evidence-Based Guideline Update: Non-steroidal Anti-inflammatory Drugs and Other Complementary Treatments for Episodic Migraine Prevention in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society ^{6a}	May 2009

^aRetired.

Criteria for Recommending Future Evidence Synthesis and CER

The VA/DoD Clinical Practice Guideline was based on an SR with an end search date of March 2019. Since its publication, subsequent trials for migraine prevention have been published, particularly for exercise and behavioral therapies (specifically, acceptance and commitment therapy, biofeedback, mindfulness-based therapy, and progressive muscle relaxation).

We assessed the need for new evidence synthesis or CER based on the following criteria:

- *New Evidence Synthesis*: We assessed the need for new evidence synthesis based on whether new evidence has accumulated since a recent guideline or high-quality SR or the absence of either.
- *CER*: We focused our recommendations on interventions with evidence of efficacy (defined as recommended by recent evidence-based guideline or with a high-quality relevant SR concluding efficacy). We then considered whether trials comparing these interventions versus other interventions with evidence of efficacy exist.

Summary of Interventions With Documented Efficacy in Guidelines or Systematic Reviews

Recommendations from the VA/DoD Clinical Practice Guideline for Primary Care Management of Headache (2020)⁴ suggest some evidence of efficacy exists for aerobic exercise or progressive strength training, mindfulness-based therapies (defined as including meditation, relaxation, mindfulness-based stress reduction [MBSR], mindfulness-based cognitive therapy [MBCT], acceptance-based approaches, and yoga), and oral magnesium. We deemed these interventions higher priority for CER, along with pharmacologic interventions with efficacy summarized in our recent rapid review and evidence map of drugs and devices for migraine prevention.²

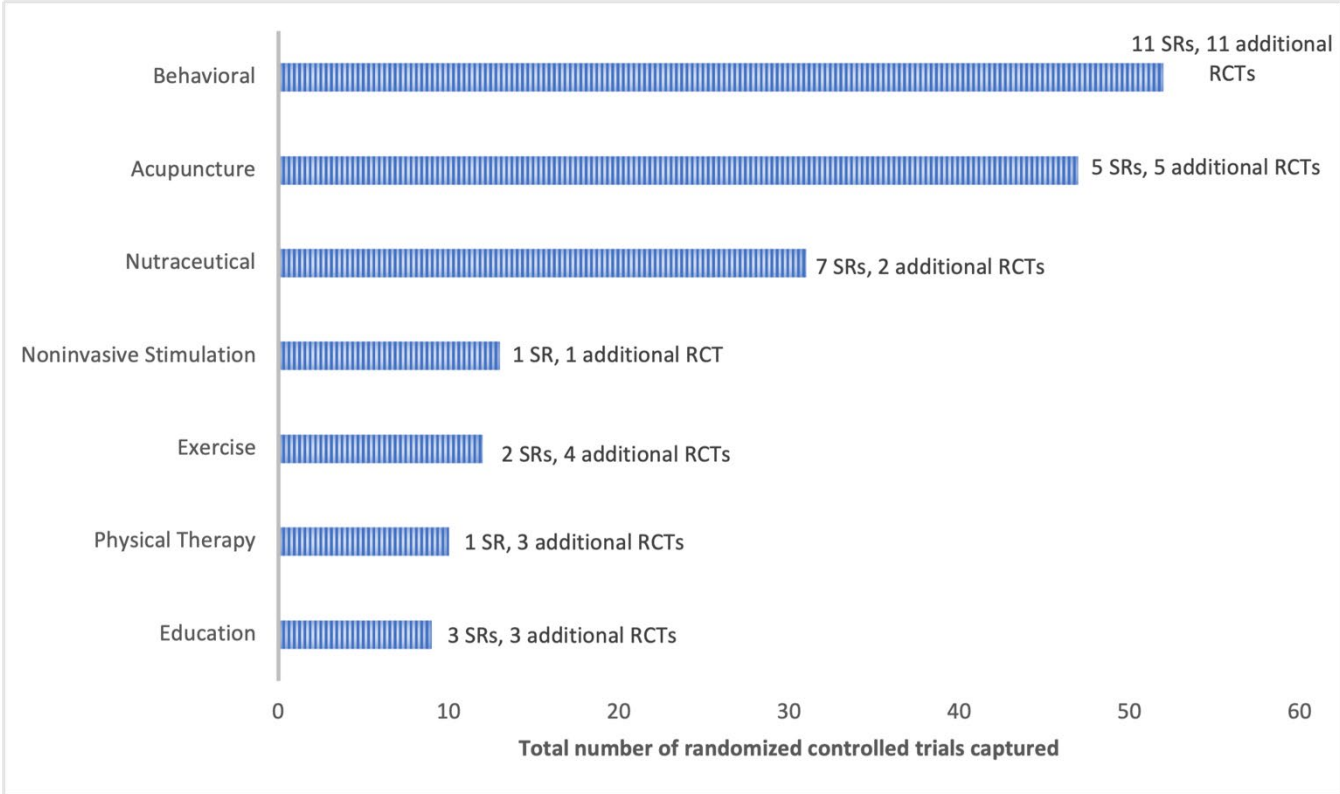
For acupuncture, coenzyme Q, vitamin B2, melatonin, and feverfew, VA/DoD guideline authors acknowledged evidence suggesting that efficacy existed, but a “neither for nor against recommendation” also considered other factors, including conflicting evidence, potential harms, access, and patient preferences. Our scoping review identified SRs suggesting efficacy for acupuncture (Cochrane review focused on episodic migraine⁷), coenzyme Q1,⁸ vitamin B2,⁹ and supraorbital nerve stimulation.¹⁰ All other interventions were deemed of interest but lower priority for CER.

Existing Systematic Reviews/Primary Research and Implications for Future Research

Summary of All Studies

Literature searches identified 1353 potential citations. After screening, we identified 52 studies (25 SRs, 27 RCTs) that met inclusion criteria, representing a total of 164 individual RCTs. Of these trials, 137 were summarized in SRs, with an additional 27 identified as individual RCTs. A flow diagram is provided in Appendix D. Included studies by intervention type are summarized in Figure 1. Table 3 provides number of SRs, additional RCTs, and type of comparisons organized by type of intervention.

Figure 1. Overview of Randomized Controlled Trials Identified by Intervention Type



Note: Both SRs and RCTs may be included in more than one category.

Table 3. Inactive and Head-to-Head Comparisons by Intervention Type

Intervention category	Included SRs, additional RCTs	Total RCTs represented (from both SRs and additional RCTs)	Inactive comparison	Head-to-head comparison
Behavioral	11 SRs ¹¹⁻²¹ 11 RCTs ²²⁻³²	52 ²²⁻⁷³	30 ^{22-24, 27, 28, 31-34, 41, 43-45, 47, 49, 52-54, 56, 58, 59, 62-66, 70-73}	18 ^{25, 26, 29, 30, 33, 36-38, 42, 48, 51, 54, 57, 60, 61, 67, 68, 71}
Acupuncture	5 SRs ^{7,10, 74-76} 5 RCTs ⁷⁷⁻⁸¹	47 ⁷⁷⁻¹²³	28 ^{79, 83-85, 88, 89, 91, 93, 95, 97-103, 105, 109-111, 113-116, 118, 120, 121, 123}	20 ^{77, 78, 80-82, 86, 87, 90-92, 94, 96, 104, 106-108, 112, 117, 119, 122}
Nutraceutical	7 SRs ^{8, 9, 124-128} 2 RCTs ^{129,130}	31 ^{80, 129-158}	23 ^{80, 129, 131, 135-145, 147-152, 154, 155, 157}	12 ^{80, 129, 130, 132-134, 146, 151, 153, 155, 156, 158}
Noninvasive stimulation	1 SR ¹⁰ 1 RCT ¹⁵⁹	13 ^{86, 159-170}	8 ^{160-162, 165-167, 169, 170}	5 ^{86, 159, 163, 164, 168}
Exercise	2 SRs ^{171, 172} 4 RCTs ¹⁷³⁻¹⁷⁶	12 ^{61, 173-183}	5 ^{173, 174, 176, 179, 182}	10 ^{61, 174-181, 183}
Physical therapy	1 SR ¹⁵ 3 RCTs ^{176, 184, 185}	10 ^{72, 73, 176, 184-190}	8 ^{72, 73, 176, 186, 188-191}	4 ^{176, 184, 185, 189}
Education	3 SRs ^{13, 17, 171} 3 RCTs ^{30, 192, 193}	9 ^{30, 70, 71, 177, 192-197}	6 ^{70, 71, 192, 194-196}	4 ^{30, 71, 177, 193}
Total	25 SRs, 27 RCTs	164^a		

^aNumbers do not total 164, as 10 trials appear in more than one category. RCTs including both an inactive and head-to-head comparison were counted in both categories. For behavioral interventions, for 7 RCTs identified through SRs, it was not possible to determine from documentation whether comparisons were inactive or head-to-head. These trials were not included in the inactive comparison and head-to-head counts.

Below, we discuss existing evidence for each intervention type. Further details are provided in Appendix E.

Acupuncture

Findings From SRs and Primary Research. We identified 47 RCTs assessing acupuncture for migraine prevention (captured in 5 SRs^{7,10,74-76} and 5 additional individual RCTs⁷⁷⁻⁸¹; see Table 4). Of the 5 SRs, 1 focused specifically on preventing menstrual migraine (Yang 2020⁷⁶). Three SRs (including Yang)⁷⁴⁻⁷⁶ included both English- and Chinese-language articles, and 2 SRs specifically searched Chinese databases. These 3 SRs that included a mix of Chinese- and English-language studies found mixed results for migraine prevention. A fourth SR (Moisset et al 2020)¹⁰ included a single relevant head-to-head trial comparing supraorbital nerve stimulation versus acupuncture.

A fifth SR (Linde et al 2016)⁷ was an older Cochrane review (end search date January 2016) that did not search non-English databases. The authors focused on episodic migraine and included 22 trials with nearly 5000 participants. Most trials (19 of 22) included in this review were relevant for this project. The authors concluded that acupuncture offered a small reduction in headache frequency

compared with either no treatment or sham (although the authors noted significant heterogeneity for sham trials). Also, acupuncture was more effective than was drug prophylaxis after treatment, although this effect was not significant at follow-up. The authors noted that “comparisons with prophylactic drug treatment have to be interpreted with caution due to high dropout rates in two of the trials.”⁷ Notably, this review did not summarize 28 RCTs^{77-81,86,87,89,90,93,97,99,102-108,112,116,117,119,121-123} assessing acupuncture for migraine prevention. Of these trials, 5 RCTs were not captured within any SR; these trials compared acupuncture versus sham (n = 1),⁷⁹ pharmacotherapy (n = 3),^{77,78,81} or feverfew (n = 1).⁸⁰

Twenty RCTs compared acupuncture with another intervention (see Table 5): 17 compared acupuncture with a range of pharmacologic therapies. Of these trials, 9 compared acupuncture with flunarizine, which is not available in the United States. However, 9 trials compared acupuncture with drugs currently used for migraine prevention in the United States (metoprolol, topiramate, valproate, venlafaxine, and Botulinum toxin A) or general pharmacotherapy. Of these trials, 3^{77,87,104} were published after the SR by Linde et al.⁷ In addition, one RCT compared acupuncture with transcutaneous supraorbital stimulation,⁸⁶ which is another modality that has been available for several years and is used in clinical practice. Although review of ClinicalTrials.gov identified 3 RCTs comparing acupuncture with sham, flunarizine, and venlafaxine, these trials are not yet recruiting (see Appendix F).

Table 4. Randomized Controlled Trials Assessing Acupuncture for Migraine Prevention

Intervention	Number of RCTs represented	Source (SR or RCT)
Acupuncture	44	<p>Individual RCTs</p> <p>Ferro et al 2012,⁸⁰ Li et al 2019,⁸¹ Nie et al 2019,⁷⁸ Xu et al 2020,⁷⁹ Giannini et al 2021⁷⁷</p> <p>RCTs captured from SRs</p> <p>Alecrim-Andrade et al 2005,⁸³ Alecrim-Andrade et al 2006,⁸⁴ Alecrim-Andrade et al 2008,⁸⁵ Allais et al 2002,⁸² Bicer 2017,⁸⁷ Ceccherelli et al 1992,⁸⁸ Diener et al 2006,⁹¹ Facco et al 2013,⁹² Linde et al 2005,¹⁰¹ Naderinabi et al 2017,¹⁰⁴ Streng et al 2006,¹⁰⁸ Vincent 1989,¹¹⁰ Wallasch et al 2012,¹¹¹ Wang et al 2015,¹¹³ Yang 2011,¹¹⁷ Zhang et al 2009,^{119b} Zhao et al 2014,¹²⁰ Zhao et al 2017,¹²¹ Zhong 2009^{122b} (from Fan et al 2020⁷⁴)</p> <p>Chang 2013,^{89b,c} Cong et al 2018,^{90b} Foroughipour et al 2014,⁹³ Guan 2019,^{107b,c} Li 2013,^{99b,c} Musil et al 2018,¹⁰³ Qin and Yujie 2019,^{105b} Rezvani et al 2014,¹⁰⁶ Wang et al 2011,¹¹² Wang 2017,^{97b,c} Xu 2018,^{116b,c} Yang 2018^{96b,c} (from Ni et al 2020⁷⁵)</p> <p>Yu and Salmoni 2018¹¹⁸ (from Yang et al 2020⁷⁶)</p> <p>Allais et al 2003⁸⁶ (from Moisset et al 2020¹⁰)</p> <p>Hesse et al 1994,⁹⁴ Jena et al 2008,⁹⁵ Linde et al 2000,¹⁰⁰ Vickers et al 2004,¹⁰⁹ Weinschutz 1993,^{114b} Weinschütz et al 1994^{115b} (from Linde et al 2016⁷)</p>
Electroacupuncture	3	<p>RCTs captured from SRs</p> <p>Li et al 2012⁹⁸ (from Linde et al 2016⁷)</p> <p>Linde et al 2005,¹⁰² Zhou 2018^{123b} (from Yang et al 2020⁷⁶)</p>

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

^aFerro 2012 was not captured by an SR assessing acupuncture; however, the trial compared acupuncture with feverfew and was captured in an SR assessing nutraceuticals. Thus, we included it here as an individual randomized trial, but for nutraceuticals it was considered captured within an SR.

^bForeign-language study.

^cWe noted discrepancies between the author name used in evidence tables and the author name in references for this SR (Ni 2020). We suspect one used the author first name, while the second used the author last name. Given the project timeframe, we were unable to confirm using full text. Here we use the author name described in the SR's evidence tables. This discrepancy was noted in the following studies: Chang 2013 (appears as Xiaorong in SR reference list), Guan 2019 (appears as Shuting in SR reference list), Li 2013 (appears as Haibo in SR reference list), Wang 2017 (appears as Jinzhong in SR reference list), Xu 2018 (appears as Xin in SR reference list), Yang 2018 (appears as Jia in SR reference list).

Table 5. Acupuncture for Migraine Prevention: Head-to-Head Comparisons

Intervention	Pharmacologic	Nonpharmacologic		
		Nutraceutical/supplement	Acupuncture	Supraorbital nerve stimulation
Acupuncture (20 RCTs)	17 studies <ul style="list-style-type: none"> • Flunarizine (9 studies)^{78,81,82,90,96,107,112,119,122} • Metoprolol (2 studies)^{94,108} • Topiramate (1 study)¹¹⁷ • Valproate or botulinum toxin (1 study)¹⁰⁴ • Valproic acid (1 study)⁹² • Venlafaxine (1 study)⁸⁷ • Pharmacotherapy (2 studies)^{77,91} 	1 study (feverfew) ⁸⁰	1 study ¹⁰⁶	1 study ⁸⁶

Table 6. Acupuncture Trials for Migraine Prevention Not Captured in the Cochrane Review by Linde 2016⁷

Comparison	Included in Yang et al 2020 ⁷⁶	Included in Fan et al 2020 ⁷⁴	Included in Ni et al 2020 ⁷⁵	Included in Moisset et al 2020 ¹⁰	Additional RCTs
	3 RCTs (of 13 total)	7 RCTs (of 20 total)	12 RCTs (of 49 total)	1 RCT (of 38 total)	5 RCTs; not yet summarized in SRs
Compared with waitlist			Musil et al 2018 ¹⁰³ (n = 86)		
Compared with sham	Zhou 2018 ^{123a} Yu and Salmoni 2018 ¹¹⁸ (n = 18) Linde et al 2005 ¹⁰² (n = 28)	Zhao et al 2017 ¹²¹ (n = 249)	Qin and Yujie 2019 ^{105a} Chang 2013 ^{89a} Xu 2018 ^{116a} Li 2013 ^{99a} Wang 2017 ^{97a} Foroughipour et al 2014 ⁹³ (n = 100)		Xu et al 2020 ⁷⁹ (n = 150)
Compared with pharmacologic intervention		Zhong 2009 ^{122a} Naderinabi et al 2017 ¹⁰⁴ (n = 150) Zhang et al 2009 ¹¹⁹ (n = 60) Bicer et al 2017 ⁸⁷ (n = 54) Streng et al 2006 ¹⁰⁸ (n = 114) Yang et al 2011 ¹¹⁷ (n = 66)	Guan 2019 ^{107a} Yang 2018 ^{96a} Cong et al 2018 ^{90a}		Giannini et al 2021 ⁷⁷ (n = 148) Nie et al 2019 ⁷⁸ (n = 135) Li et al 2019 ⁸¹ (n = 78)
Compared with other			Rezvani et al 2014 ¹⁰⁶ (scalp acupuncture; n = 80) Wang et al 2011 ¹¹² (flunazarine plus sham; n = 140)	Allais et al 2003 ⁸⁶ (supraorbital stimulation, infrared laser; n = 60)	Ferro et al 2012 ⁸⁰ (feverfew; n = 69)

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

^aDenotes foreign-language study. Note that Yang 2020 was limited to menstrual migraine.

Future Evidence Synthesis. Whether acupuncture is effective for migraine prevention appears conflicting in recent SRs, and the 2020 VA/DoD guideline⁴ made a “neither for nor against” recommendation, suggesting further evaluation of efficacy could be warranted.

Our scoping review identified a total of 47 RCTs, nearly all of which (41 trials) were captured from the 3 most recent/comprehensive SRs.⁷⁴⁻⁷⁶ However, each of these SRs included non-English trials and 2 specifically searched Chinese databases. Although non-English studies can provide important information, results may be less applicable to a US population, particularly for acupuncture, given the importance of specific protocols, provider expertise, and practice. For instance, Chinese acupuncture practitioners may use more frequent sessions and enroll patients who tend to differ from migraine patients receiving acupuncture in the context of Western medicine.⁷

The highest-quality and most recent SR including only English-language studies was a Cochrane review (Linde 2016)⁷ that found a “small, but statistically significant reduction compared over sham” for episodic migraine. Notably, unlike many other reviews, the authors attempted to gauge the quality of acupuncture provided in trials. However, this review captured only studies published before January 2016, was restricted to episodic migraine, and did not include 28 of 47 total trials assessing acupuncture for migraine prevention, of which 17 trials appear to be English language.^{77-81, 86, 87, 102-104, 106, 108, 112, 117, 118, 121}

New evidence synthesis could incorporate evidence from these additional RCTs not captured in the Linde review and determine whether trials support efficacy for chronic migraine (Table 6). Also, 3 RCTs assessed electroacupuncture,^{98,102,123} which is not a typical component of acupuncture as provided in the United States. Other trials may also have included an electroacupuncture component, but it was not feasible to review individual studies to assess. New evidence synthesis could provide insights on efficacy by including newer studies, distinguishing between episodic and chronic migraine, and considering distinctions between forms of acupuncture.

Future CER. As noted, we found mixed conclusions regarding acupuncture’s efficacy. The 2020 VA/DoD guideline recommended “neither for nor against” acupuncture (as described above). However, a 2016 Cochrane review⁷ found that acupuncture was effective compared with sham as well as drug prophylaxis, although the difference compared with drug prophylaxis was no longer statistically significant at follow-up.

Our review identified 20 RCTs, including a head-to-head comparison of acupuncture (see Table 7). Ten of 20 compared acupuncture with therapies used for migraine prevention in the United States: 8 compared acupuncture with various drugs (metoprolol,^{94,108} topiramate,¹¹⁷ valproate,^{92,104} venlafaxine,⁸⁷ and Botulinum toxin A¹⁰⁴) or unspecified pharmacotherapy,^{77,91} 1 trial compared acupuncture with feverfew,⁸⁰ and 1 trial compared acupuncture with supraorbital nerve stimulation.⁸⁰ Three^{77,87,104} of these 10 trials were published after the SR by Linde et al.⁷ Notably, most trials were older (only 3 published in the past 5 years), and no trials compared acupuncture with newer migraine-specific drugs or other nonpharmacologic therapies recommended by the VA/DoD guideline.

Anecdotally, patient interest in acupuncture as an alternative to pharmacologic therapy remains high. The sparse number of recent head-to-head trials suggests that future CER would address important evidence gaps. Specifically, trials should compare acupuncture versus high-priority interventions for CER, such as pharmacologic therapies developed for migraine prevention and nonpharmacologic therapies with some demonstrated efficacy, such as aerobic exercise, mindfulness-based therapies, and oral magnesium. This echoes VA/DoD guideline suggestions that “future research should compare acupuncture for headaches against active controls (i.e., not with sham) . . . Evaluating the role of acupuncture in combination treatment (e.g., along with exercise or behavioral treatments vs. medications) would also help determine its place in headache management.”⁴

Behavioral Interventions

Findings From SRs and Primary Research. We identified 11 SRs¹¹⁻²¹ and 11 additional RCTs²²⁻³² assessing behavioral interventions. Specific types of behavioral interventions are summarized in Table 7 (additional details available in Appendix E, Table E-4). Biofeedback had the most RCTs (n = 9), followed by combined behavioral interventions (n = 6), MBSR/MBCT (n = 8), and cognitive behavioral therapy (n = 6). Other interventions assessed included acceptance and commitment therapy, behavioral training, meditation, progressive muscle relaxation, relaxation, self-management, sleep modification, written emotional disclosure,^{67,68} and sound therapy.⁶⁹ Multiple trials, particularly more recent studies, delivered interventions via telehealth (online) or smartphone app.^{24,31,32}

The most recent SRs^{14,19} were several years old and did not capture 11 additional RCTs.²²⁻³² Furthermore, existing SRs had important limitations. Perhaps the highest-quality SR covering a broad range of behavioral interventions was a Cochrane review by Sharpe et al 2019.¹⁹ The authors noted that patients receiving psychological interventions were “twice as likely to be classified as responders in the short term.” However, the authors concluded there was no evidence of efficacy on medication usage, mood, migraine-related disability, quality of life, or short-/long-term migraine frequency. Notably, SR inclusion criteria differed from our Patients, Interventions, Comparators, Outcomes, Timing (PICOT) criteria in 2 important ways: the authors (1) excluded trials with <15 respondents per arm at follow-up, and (2) included trials with follow-up of only 4 weeks in the analysis. Also, to assess efficacy, the authors appear to have grouped all behavioral intervention types together; however, the VA/DoD guideline recommendations (for mindfulness-based therapy, but neither for nor against biofeedback) suggest important differences in efficacy across behavioral interventions could exist. These differences potentially further limit the applicability of conclusions from this SR.

Two additional SRs (Seo et al 2018¹⁸ and Lee et al 2019¹⁴) contributed relevant RCTs assessing biofeedback, CBT, and progressive muscle relaxation, but included English- and Korean- language studies. Other SRs appeared to use rigorous methodology but focused on only a particular intervention or population (eg, MBSR for chronic headache)¹¹ or included headache types other than migraine.¹²

Table 7. Behavioral Interventions for Migraine Prevention Assessed With Randomized Controlled Trials

Intervention	Number of RCTs represented	Source (SR or RCT)
Acceptance and commitment therapy	2	Individual RCTs Grazzi and Rizzoli 2020, ²² Vasiliou et al 2021 ²³
Behavioral training	2	RCTs captured from SRs Kleiboer et al 2014 ³⁴ (from Lee et al 2019 ¹⁴) Holroyd et al 2010 ³³ (from Sharpe et al 2019 ¹⁹)
Biofeedback	9	Individual RCTs de Tommaso and Delussi 2017, ²⁶ Tehrani et al 2021, ²⁵ Minen et al 2021 ²⁴ RCTs captured from SRs Odawara et al 2015, ³⁹ Pickering et al 2012, ⁴⁰ Blanchard et al 1991, ³⁶ Gauthier et al 1983, ³⁷ Kewman and Roberts 1980 ³⁸ (from Lee et al 2019 ¹⁴) Blanchard et al 1978 ³⁵ (from Seo et al 2018 ¹⁸)
Cognitive behavioral therapy	6	Individual RCTs Martin et al 2015 ²⁷ RCTs captured from SRs Richardson and McGrath 1989, ⁴³ Bromberg et al 2012, ⁴¹ Fritzsche et al 2010 ⁴² (from Sharpe et al 2019 ¹⁹) Smitherman et al 2016 ⁴⁴ (from Sullivan et al 2019 ²¹) Thorn et al 2007 ⁴⁵ (from Sullivan et al 2016 ²⁰)
Combined behavioral interventions	6	RCTs captured from SRs Cousins et al 2015 ⁴⁷ (from Lee et al 2019 ¹⁴) Seng and Holroyd 2010 ⁴⁹ (from Kindelan-Calvo et al 2014 ¹³) Andersson et al 2003, ⁴⁶ Trautmann and Kröner-Herwig 2010 ⁵⁰ (from Minen et al 2016 ¹⁶) Kaushik et al 2005 ⁴⁸ (from Sharpe et al 2019 ¹⁹) Vasudeva et al 2003 ⁵¹ (from Sullivan et al 2016 ²⁰)
Mindfulness-based cognitive therapy/ mindfulness-based stress reduction	8	Individual RCTs Seminowicz et al 2020, ²⁹ Wells et al 2021, ³⁰ Seng et al 2019 ²⁸ RCTs captured from SRs Day et al 2014, ⁵³ Bakshani et al 2015, ⁵² Wells et al 2014 ⁵⁶ (from Anheyer et al 2019 ¹¹) Hedborg and Muhr 2011 ⁵⁴ (from Sharpe et al 2019 ¹⁹) Mansourishad et al 2017 ⁵⁵ (from Lee et al 2019 ¹⁴)
Meditation	1	RCTs captured from SRs Wachholtz and Pargament 2008 ⁵⁷ (from Gu et al 2018 ¹²)
Progressive muscle relaxation	3	Individual RCTs Minen et al 2020, ³¹ Minen et al 2020 ³² RCTs captured from SRs Meyer et al 2016 ⁵⁸ (from Lee et al 2019 ¹⁴)
Relaxation	3	RCTs captured from SRs D'Souza et al 2008 ⁶⁰ (from Lee et al 2019 ¹⁴) Varkey et al 2011, ⁶¹ Devineni and Blanchard 2005 ⁵⁹ (from Sullivan et al 2016 ²⁰)

Intervention	Number of RCTs represented	Source (SR or RCT)
Self-management	4	Individual RCTs Mahmoudzadeh-Zarandi et al 2016, ⁶³ Rashid-Tavalai et al 2015 ⁶⁴ RCTs captured from SRs Kohlenberg and Cahn 1981, ⁶² Rothrock et al 2006 ⁶⁵ (from Sharpe et al 2019 ¹⁹)
Sleep modification	1	RCTs captured from SRs Calhoun and Ford 2007 ⁶⁶ (from Sullivan et al 2019 ²¹)
Other (written emotional disclosure, sound therapy)	3	RCTs captured from SRs Dittrich et al 2008, ⁶⁷ Kraft et al 2008 ⁶⁸ (from Sullivan et al 2016 ²⁰) Trinka et al 2002 ⁶⁹ (from Minen et al 2016 ¹⁶)
Combined modalities (behavioral plus other modality)	4	RCTs captured from SRs Mongini et al 2012, ⁷³ Mongini et al 2008 ⁷² (from Luedtke et al 2016 ¹⁵) Martin et al 2014, ⁷¹ Basler et al 1996 ⁷⁰ (from Probyn et al 2017 ¹⁷)

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Future Evidence Synthesis. Our scoping review suggests updated evidence synthesis of behavioral interventions would be beneficial given the publication of multiple recent RCTs and the limitations of existing SRs. Specifically, we identified 11 recent RCTs²²⁻³² assessing behavioral interventions not captured in SRs, of which only one²⁷ was captured in the recent VA/DoD guideline. Interventions assessed in these recent trials include acceptance and commitment therapy,^{22,23} biofeedback,^{24,25} mindfulness-based therapy,²⁸⁻³⁰ and progressive muscle relaxation.^{31,32}

Increasingly, behavioral interventions may now be delivered via smartphone app, telehealth, or online—delivery modalities not available until the past decade or so. A 2014 scoping review of smartphone applications for chronic pain available for download in the United States found that roughly 10% (n = 21) focused on headache or migraine pain.¹⁹⁸ In addition to addressing the limitations noted above, new evidence synthesis could allow for distinctions between older and newer delivery mechanisms.

Behavioral therapies were often assessed in combination with other intervention types, particularly education, exercise, and physical therapy. For instance, some interventions included components of different modalities: in one trial,⁷¹ the intervention consisted of CBT plus education plus relaxation therapy. Other trials captured in the SR of psychological interventions by Sharpe et al 2019¹⁹ employed interventions that seemed to resemble educational interventions (eg, Orem's self-care, education on migraine biogenesis and management). In the same vein, another trial categorized as a behavioral intervention involved relaxation led by physiotherapist⁶¹; another trial used a multicomponent intervention involving relaxation plus posture correction, exercises, and education for muscle tension release.⁷³ New evidence synthesis of behavioral interventions would benefit from input from clinical experts regarding how best to categorize interventions.

Future CER. Our scoping review identified 18 RCTs with head-to-head comparisons of behavioral interventions (see Table 8). Behavioral interventions were most often compared with other nonpharmacologic interventions (n = 15), such as other behavioral interventions (n = 11), exercise (n = 1), education (n = 1), and other interventions (n = 2). Three of these trials (2 focused on MBSR,^{29,30} 1 on biofeedback²⁵) were published very recently (2020 or 2021), suggesting ongoing interest in this area.

Although 5 RCTs compared behavioral interventions with widely used drugs for migraine prevention (topiramate,^{26,61} beta-blockers,³³ propranolol,⁴⁸ nortriptyline plus gelofen or inderal²⁵), no trials assessed efficacy compared with newer pharmacologic therapies, such as calcitonin gene-related peptide (CGRP) antagonists. As the VA/DoD guideline recommended mindfulness-based therapy for migraine prevention, future research trials should compare this intervention with other high-priority interventions for CER with evidence of efficacy, specifically CGPR antagonists, oral magnesium, aerobic exercise, and progressive strength training. In addition, comparisons with lower-priority interventions for CER (acupuncture, coenzyme Q, vitamin B2) could also be beneficial.

Table 8. Behavioral Interventions for Migraine Prevention: Head-to-Head Comparisons

Behavioral intervention	Total RCTs with head-to-head comparisons ^a	Pharmacologic	Nonpharmacologic				Combined modality
			Behavioral	Exercise	Education	Other	
Behavioral training	1 ³³	1 ³³					
Biofeedback	5 ^{25,26,36-38}	2 ^{25,26}	3 ³⁶⁻³⁸				1 ²⁶
CBT	1 ⁴²		1 ⁴²				
Combined behavioral modalities	2 ^{48,51}	1 ⁴⁸					2 ^{48,51}
MBCT	1 ⁵⁴		1 ⁵⁴				
MBSR	2 ^{29,30}		1 ²⁹		1 ³⁰		
Meditation	1 ⁵⁷		1 ⁵⁷				
Relaxation	2 ^{60,61}	1 ⁶¹	1 ⁶¹	1 ⁶¹		1 ⁶⁰	
Other ^b	2 ^{67,68}		2 ^{67,68}				
Combined modality (CBT plus education plus exposure therapy)	1 ⁷¹						1 ⁷¹
Total	18	5	10	1	1	1	4

Abbreviations: CBT, cognitive behavioral therapy; MBCT, Mindfulness-based cognitive therapy; MBSR, mindfulness-based stress reduction; RCT, randomized controlled trial.

^aFor 7 RCTs captured in SRs, documentation did not allow us to determine whether trials compared interventions with control or active intervention.

^bIntervention was written emotional disclosure plus audiotape relaxation training.

Exercise

Findings From SRs and Primary Research. Two SRs^{171,172} and 4 additional RCTs¹⁷³⁻¹⁷⁶ assessed exercise. Table 9 presents included SRs and RCTs; further details are available in Appendix E, Table E-6.

Types of exercise assessed were aerobic exercise and yoga. One SR¹⁷¹ (with 2 relevant RCTs) and 2 additional RCTs^{173,174} assessed types of aerobic exercise, including endurance training, indoor cycling, strength training, and high- versus moderate-intensity exercise. SR authors¹⁷¹ reported moderate quality evidence that aerobic exercise decreases migraine days (although the SR included 3 RCTs that did not meet our inclusion criteria).

One SR (with 3 relevant RCTs)¹⁷² and 2 additional RCTs^{175,176} assessed yoga. The SR found that yoga reduced migraine frequency, although this finding did not reach statistical significance; however, 2 subsequent RCTs^{175,176} reported positive findings for yoga compared with physical therapy¹⁷⁶ or used as adjunctive treatment in addition to pharmacotherapy.¹⁷⁵

Ten head-to-head trials compared aerobic exercise or yoga with other active comparators (see Table 10). Trials compared aerobic exercise with amitriptyline,¹⁸³ topiramate,⁶¹ education,¹⁷⁷ relaxation,⁶¹ or other exercise regimens.^{174,179} Other trials compared yoga with pharmacotherapy,^{175,180,181} self-care plus medication,¹⁸⁰ or physical therapy.¹⁷⁶

Table 9. Exercise Interventions for Migraine Prevention Assessed With Randomized Controlled Trials

Intervention	Number of RCTs represented	Source (SR or RCT)
Aerobic exercise	4	Individual RCTs Oliveira et al 2019, ¹⁷³ Eslami et al 2021 ¹⁷⁴ RCTs captured from SRs Bond et al 2018, ¹⁷⁷ Varkey et al 2011 ⁶¹ (from Lemmens et al 2019 ¹⁷¹)
Yoga	5	Individual RCTs Kumar et al 2020, ¹⁷⁵ Mehta et al 2021 ¹⁷⁶ RCTs captured from SRs Boroujeni et al 2015, ¹⁷⁸ John et al 2007, ¹⁸⁰ Kisan et al 2014 ¹⁸¹ (from Anheyer et al 2020 ¹⁷²)

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table 10. Exercise for Migraine Prevention: Head-to-Head Trials

RCT	Intervention	Comparison		
		Pharmacologic	Nonpharmacologic	Other
Bond et al 2018 ¹⁷⁷	Aerobic		Exercise, education	
Eslami et al 2021 ¹⁷⁴	Aerobic		Exercise	
Hannsen et al 2018 ¹⁷⁹	Aerobic		High-intensity interval training, moderate continuous training	
Santiago et al 2014 ¹⁸³	Aerobic	Amitriptyline		Aerobic exercise plus amitriptyline
Varkey et al 2011 ⁶¹	Aerobic	Topiramate	Relaxation	
Boroujeni et al 2015 ¹⁷⁸	Yoga plus medication	Medication		
John et al 2007 ¹⁸⁰	Yoga plus medication			Self-care plus medication
Kisan et al 2014 ¹⁸¹	Yoga plus medication	Medication		
Kumar et al 2020 ¹⁷⁵	Yoga plus medication	Medical management		
Mehta et al 2021 ¹⁷⁶	Yoga plus standard therapy		Yoga, physical therapy	

Abbreviation: RCT, randomized controlled trial.

Future Evidence Synthesis. It is unclear whether new evidence synthesis for aerobic exercise/progressive strength training would yield new conclusions in the absence of newer trials. A relatively recent SR (Lemmens et al 2019¹⁷¹) exists. Although 2 additional subsequent RCTs^{173,174} (combined n = 103) reported clinical migraine outcomes, both trials focused on biomarkers as primary end points.

However, new evidence synthesis could be beneficial to explore the efficacy of yoga. A recent SR (Anheyer et al 2020)¹⁷² found that yoga reduced migraine frequency, although this effect was not statistically significant (standardized mean difference: -1.96; 95% CI, -3.9 to 0.05). Our review identified an additional 2 trials^{175,176} that found yoga to be effective for migraine prevention. These studies were performed outside the United States, primarily in India, which may limit the generalizability of these findings. Future RCTs should assess yoga in a US context. However, given the high level of patient interest in this intervention and the VA/DoD guideline recommendation, new evidence synthesis could be beneficial.

Future CER. The VA/DoD guideline made weak recommendations for 3 interventions categorized as exercise in this review: aerobic exercise, progressive strength training, and yoga (which the guideline considered a mindfulness-based therapy). Only 2 trials compared aerobic exercise with standard drugs (amitriptyline¹⁸³ and topiramate⁶¹). Thus, more trials comparing aerobic exercise, progressive strength training, and yoga with other high-priority interventions for CER (eg, newer migraine-specific pharmacologic interventions, mindfulness-based therapy, oral magnesium) are needed. Comparison with acupuncture, along with coenzyme Q and vitamin B2, could also be beneficial.

Physical Therapy

Findings From SRs and Primary Research. One SR (with 7 relevant RCTs)¹⁵ and 3 small additional RCTs^{176,184,185} assessed physical therapy interventions; in addition, 1 RCT (already described above) compared PT with yoga.¹⁷⁶ Types of physical therapy interventions are summarized in Table 11 (additional details available in Appendix E, Table E-8) with head-to-head trials summarized in Table 12. Overall, physical therapy interventions assessed involved exercise (aerobic training, strength training, resistance training), stretching exercises (proprioceptive neuromuscular facilitation and cervical and orofacial treatment), or multicomponent interventions that combined different modalities. For example, Mongini et al 2012⁷³ randomly assigned patients to receive either a combination of relaxation, posture correction, exercises, and education for muscle tension release or keeping a headache diary. Similarly, de Hertogh et al 2009¹⁸⁸ compared a combination of manual therapy, mobilization, and stabilization exercises with treatment as usual.

The sole SR¹⁵ concluded that physiotherapy interventions resulted in a “statistically significant reduction in the intensity, frequency, and duration of migraine” along with other headache types. However, the SR had important limitations: authors included not only migraine but also tension-type and cervicogenic headache patients and did not appear to require a minimum trial duration. The SR also included both English- and German-language studies.

Table 11. Physical Therapy Interventions for Migraine Prevention Assessed by Randomized Controlled Trials

Intervention	Number of RCTs represented	Source (SR or RCT)
Physical therapy (variety of interventions including combined modalities such as strength training, relaxation, posture correction, and exercises)	8	Individual RCTs Mehta et al 2021 ¹⁷⁶ RCTs captured from SRs Lemstra et al 2002, ¹⁹¹ Narin et al 2003, ¹⁹⁰ De Hertogh et al 2009, ¹⁸⁸ Gunreben-Stempfle et al 2009, ¹⁸⁹ Mongini et al 2008, ⁷² Mongini et al 2012, ⁷³ Andersen et al 2011 ¹⁸⁶ (from Luedtke et al 2016 ¹⁵)
Stretching: proprioceptive neuromuscular facilitation	1	Individual RCTs Wanderley et al 2020 ¹⁸⁴
Stretching: craniofacial/orofacial treatment	1	Individual RCTs Garrigós-Pedron et al 2018 ¹⁸⁵

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Future Evidence Synthesis. Although the most recent SR identified was older (end search date 2014),¹⁵ only 3 small, subsequent trials exist.^{176,184,185} Findings from 2^{184,185} of these trials are likely to have limited generalizability because they assessed specific types of stretching interventions in very specific populations (ie, chronic migraine patients with temporomandibular disorders). Thus, at present, new evidence synthesis of physical therapy interventions for migraine prevention does not appear to be warranted. The wide range of interventions considered to be physical therapy could pose challenges for future evidence synthesis efforts.

Future CER. Although the SR by Luedtke et al 2016¹⁵ concluded physical therapy interventions were effective for migraine prevention, as noted, many of these interventions were multicomponent interventions, including aerobic or strength training and stretching, along with behavioral interventions or education. Future CER trials comparing clearly described physical therapy interventions with other interventions with proven efficacy (eg, newer migraine prevention drugs, aerobic exercise, progressive strength training, mindfulness-based therapy, or oral magnesium) could address this evidence gap. However, we suspect the heterogeneity of current interventions is likely to pose challenges for comparisons.

Table 12. Physical Therapy for Migraine Prevention: Head-to-Head Trials

RCT	Intervention	Comparison		
		Pharmacologic	Nonpharmacologic	Other
Gunreben-Stempfle et al 2009 ¹⁸⁹	Multidisciplinary program		Multidisciplinary program	
Garrigós-Pedró et al 2018 ¹⁸⁵	Stretching		Cervical treatment, cervical and orofacial treatment	
Wanderley et al 2020 ¹⁸⁴	Stretching		Static stretching, proprioceptive neuromuscular function	
Mehta et al 2021 ¹⁷⁶	Yoga plus standard therapy		Yoga, physical therapy	

Abbreviation: RCT, randomized controlled trial.

Noninvasive Stimulation

Findings From SRs and Primary Research. We included one SR¹⁰ (with 12 relevant RCTs) and one additional RCT¹⁵⁹ assessing transcranial magnetic stimulation (TMS), transcutaneous supraorbital nerve stimulation, and vagus nerve stimulation. Tables 13 and 14 summarize included intervention types and studies, as well as head-to-head trials. The SR by Moisset et al 2020¹⁰ had a broader scope than ours, including interventions for acute migraine and studies of children, and required only a 4-week follow-up for inclusion. Thus, although the SR included 38 RCTs, only 12 trials met our inclusion criteria. Authors found supraorbital nerve stimulation and TMS (over the primary motor cortex) were effective with “small to medium effect sizes,” while vagus nerve stimulation and TMS performed in different locations were not effective, with high heterogeneity.¹⁰

Eight of 13 overall RCTs compared noninvasive stimulation versus sham: TMS (4 RCTs), vagus nerve stimulation (3 RCTs), and transcutaneous supraorbital nerve stimulation (1 RCT). Conversely, 5 of 13 trials had head-to-head comparisons: TMS was compared with botulinum toxin A¹⁶⁸ and another TMS protocol¹⁶⁴; transcutaneous supraorbital nerve stimulation was compared with acupuncture or infrared laser,⁸⁶ flunarizine or flunarizine plus transcutaneous supraorbital nerve stimulation,¹⁶³ or percutaneous mastoid stimulation.¹⁵⁹

Table 13. Types of Noninvasive Stimulation for Migraine Prevention Assessed by Randomized Controlled Trials

Intervention	Number of RCTs	Source (SR or RCT)
Transcranial magnetic stimulation	6	Individual RCTs Sahu et al 2019, ¹⁶⁶ Kalita et al 2016, ¹⁶⁴ Shehata et al 2016, ¹⁶⁸ Misra et al 2013 ¹⁶⁵ RCTs captured from SRs Amin et al 2020, ¹⁶⁰ Teepker et al 2010 ¹⁷⁰ (from Moisset et al 2020 ¹⁰)
Supraorbital nerve stimulation	4	Individual RCTs Deng et al 2020 ¹⁵⁹ RCTs captured from SRs Jiang et al 2019, ¹⁶³ Schoenen et al 2013, ¹⁶⁷ Allais et al 2003 ⁸⁶ (from Moisset et al 2020 ¹⁰)
Vagus nerve stimulation	3	RCTs captured from SRs Chaudhry et al 2019, ¹⁶¹ Diener et al 2019, ¹⁶² Silberstein et al 2016 ¹⁶⁹ (from Moisset et al 2020 ¹⁰)

Table 14. Noninvasive Stimulation for Migraine Prevention: Head-to-Head Trials

RCT	Intervention	Comparison	
		Pharmacologic	Nonpharmacologic
Allais et al 2003 ⁸⁶	Supraorbital stimulation		Infrared laser, acupuncture
Deng et al 2020 ¹⁵⁹	Supraorbital stimulation		Percutaneous mastoid stimulation
Jiang et al 2019 ¹⁶³	Supraorbital stimulation	Flunarizine	
Kalita et al 2016 ¹⁶⁴	TMS		TMS
Shehata et al 2016 ¹⁶⁸	TMS	Botulinum toxin injection	

Abbreviations: RCT, randomized controlled trial; TMS, transcranial magnetic stimulation.

Future Evidence Synthesis. At present, it is unlikely that noninvasive stimulation modalities included in this review would benefit from new evidence synthesis. Nearly all RCTs that met our inclusion criteria (12 of 13) were captured in a recent SR,¹⁰ which included quantitative synthesis; this review's conclusions regarding effectiveness of supraorbital transcutaneous nerve stimulation and vagus nerve stimulation were congruent with our own recent work.² Waiting for more trials would improve the utility of any evidence synthesis comparing these interventions with control. (An RCT of TMS in episodic migraine is under way in Malaysia; see Appendix F.)

Future CER. Although 5 trials assessed noninvasive stimulation in head-to-head trials, only 2 included comparisons with commonly available therapies (botulinum toxin A¹⁶⁸ and acupuncture⁸⁶). Although the SR by Moisset et al 2020¹⁰ found evidence of benefit for TMS and supraorbital nerve stimulation, the VA/DoD guideline found insufficient evidence to recommend for or against TMS and supraorbital nerve stimulation for headache.⁴ Currently, access to TMS remains challenging for most

patients and is not commonly used for migraine prevention. In contrast, supraorbital nerve stimulation (which is delivered via a small portable device) is more accessible and currently used in practice. Our recent work² suggests evidence of efficacy for supraorbital nerve stimulation (although limited to a single trial), with the need for more RCTs (with comparisons to sham) to confirm findings. Nevertheless, given this evidence of efficacy, high patient interest, favorable side effect profile, and common use, we believe comparative effectiveness trials comparing supraorbital stimulation versus other prevention therapies with evidence of efficacy (CGRP antagonists, other migraine drugs with efficacy, mindfulness-based therapy, aerobic exercise, progressive strength training, or oral magnesium) would address an evidence gap and inform clinical care.

Education

Findings From SRs and Primary Research. We identified 3 SRs^{13,17,171} (including 6 relevant RCTs) and 3 additional RCTs^{30,192,193} assessing education for migraine prevention, for a total of 9 RCTs. Included studies are summarized in Table 15 and head-to-head trials in Table 16.

Of 9 RCTs, 6^{70,71,192,194-196} compared education with inactive control, while 4 trials^{30,71,177,193} included head-to-head comparisons. A 2014 SR (Kindelan-Calvo et al¹³) included 3 RCTs¹⁹⁴⁻¹⁹⁶ assessing therapeutic patient education; the authors concluded that education was effective for migraine. A second SR (Probyn et al 2017)¹⁷ included 2 trials assessing self-management interventions that combined education with other modalities: a 1996 trial⁷⁰ assessed relaxation plus CBT plus education compared with treatment as usual; a 2014 trial⁷¹ assessed multicomponent intervention consisting of CBT plus education plus identification of headache triggers plus managing triggers through avoidance. Authors concluded self-management interventions were effective for reducing headache-related disability but not headache frequency.

Two of 4 head-to-head trials we identified compared education with exercise (Bond et al 2018,¹⁷⁷ captured in Lemmens et al 2019¹⁷¹) and mindfulness-based stress reduction.³⁰ The remaining 2 trials compared education with education plus detoxification programs¹⁹³ and exposure therapy along with other combination modalities (Martin et al 2014,⁷¹ captured in Probyn et al 2017¹⁷).

Table 15. Education for Migraine Prevention: Randomized Controlled Trials

Intervention	Number of RCTs	Source (SR or RCT)
Education	4	Individual RCTs Wells et al 2021, ³⁰ Aguirrezabal et al 2019, ¹⁹² Rossi et al 2013 ¹⁹³ RCTs captured from SRs Bond et al 2018 ¹⁷⁷ (from Lemmens et al 2019 ¹⁷¹)
Self-management (education combined with other modalities)	2	RCTs captured from SRs Basler et al 1996, ⁷⁰ Martin et al 2014 ⁷¹ (from Probyn et al 2017 ¹⁷)
Therapeutic patient education	3	RCTs captured from SRs Matchar et al 2008, ¹⁹⁵ Mérelle et al 2008, ¹⁹⁶ Cady et al 2009 ¹⁹⁴ (from Kindelan-Calvo et al 2014 ¹³)

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table 16. Education for Migraine Prevention: Head-to-Head Trials

RCT	Intervention	Comparison	
		Pharmacologic	Nonpharmacologic
Bond et al 2018 ¹⁷⁷	Education		Exercise
Martin et al 2014 ⁷¹	Education plus identifying headache triggers plus managing triggers through avoidance	Exposure therapy	Combined modality (cognitive behavioral therapy plus education plus exposure therapy)
Wells et al 2021 ³⁰	Education		Mindfulness-based stress reduction
Rossi et al 2013 ¹⁹³	Education		Inpatient detoxification program plus education or outpatient detoxification program plus education

Abbreviation: RCT, randomized controlled trial.

Future Evidence Synthesis. Although the most recent relevant SR for education¹⁷ was older (end search date 2016), we identified only 3 subsequent trials, of which only 1 trial¹⁹² compared education with a control and was primarily focused on inpatient versus outpatient withdrawal programs. Thus, new evidence synthesis of educational interventions does not appear to be warranted at this time.

Future CER. The overall evidence base for educational interventions remains small, and the most recent, relevant SR found educational interventions reduced headache disability but not headache frequency. Therefore, we judged educational interventions as a low priority for new CER trials at this time.

Nutraceuticals/Supplements

Findings From SRs and Primary Research. We identified 31 RCTs assessing nutraceutical/supplements identified in 7 SRs^{8,9,124-128} (including 30 RCTs) and 2 individual RCTs^{129,130} assessing nutraceuticals/supplements for migraine prevention. Twenty-three RCTs compared nutraceuticals/supplements with inactive control; 12 trials included head-to-head comparisons. All SRs and RCTs and head-to-head comparisons are described in Table 17 and Table 18, with additional details provided in Appendix E, Table E-14.

Two SRs^{124,128} concluded oral magnesium is effective. Recent SRs also found coenzyme Q10 (CoQ10) and vitamin B2 to be effective. Sazali et al 2021⁸ found that CoQ10 had a statistically significant reduction in migraine frequency (mean difference -1.52 ; 95% CI, -2.40 to -0.65) as well as migraine duration. For vitamin B2, Chen et al 2021⁹ found a small, but statistically significant reduction in migraine days and frequency, although the authors included studies with a follow-up of <8 weeks in the analysis. In contrast, evidence for feverfew¹²⁷ and melatonin¹²⁶ was mixed; evidence for butterbur was mostly favorable but limited.¹²⁷ Only a single RCT assessed alpha lipoic acid¹²⁵ and did not find evidence of efficacy.

We noted several limitations in the evidence base. Some individual studies assessed treatments combining multiple supplements (eg, CoQ10 and L-carnitine) or used active substances in the control group (sometimes not used with the intervention), thus potentially confounding impacts of the substance of interest. We also noted variation in the form and dose of herbal substances used in studies, particularly for older individual studies included within SRs. Such studies often used unprocessed materials (eg, dried leaves for feverfew) and may not be applicable to more modern commercially available supplements in pill or capsule form. Furthermore, the variable quality of these substances supplied by a largely unregulated vitamin/supplement market raises more general concerns regarding applicability of findings on supplements.

For SRs performing meta-analyses, we noted considerable variations in the doses and combinations of other supplements in the intervention groups and variations in control group interventions. For instance, in trials of feverfew, the dose ranged from 6.2 to 150 mg per day.¹²⁷ A lack of more selective inclusion criteria may have confounded the analysis of overall effect size.

Table 17. Nutraceutical Interventions for Migraine Prevention Assessed With Randomized Controlled Trials

Intervention	Number of RCTs represented	Source (SR or RCT)
Alpha lipoic acid	1	<i>RCTs captured from SRs</i> Magis et al 2007 ¹³¹ (from de Sousa et al 2019 ¹²⁵)
Vitamin B2 (riboflavin)	4	<i>RCTs captured from SRs</i> Nambiar et al 2011, ¹³² Rahimdel et al 2015, ¹³³ Schoenen et al 1994, ¹³⁴ Schoenen et al 1998 ¹³⁵ (from Chen et al 2021 ⁹)
Butterbur	3	<i>RCTs captured from SRs</i> Diener et al 2004 ¹³⁶ , Grossman and Schmidramsl 2001 ¹⁹⁹ , Lipton et al 2004, ¹³⁷ Oelkers-Ax et al 2008 ¹³⁸ (from Lopresti et al 2020 ¹²⁷)
Coenzyme Q	4	<i>Individual RCTs</i> Parohan et al 2021 ¹²⁹ <i>RCTs captured from SRs</i> Dahri et al 2019 and 2017, ^{139,200} Hajhashemi et al 2019, ¹⁴⁰ Nattagh-Eshtivani et al 2018 ¹⁴¹ (from Sazali et al 2021 ⁸)
Feverfew	5	<i>RCTs captured from SRs</i> De Weerd et al 1996, ¹⁴² Diener et al 2005, ¹⁴³ Ferro et al 2012, ⁸⁰ Murphy et al 1988, ¹⁴⁴ Pfaffenrath et al 2002 ¹⁴⁵ (from Lopresti et al 2020 ¹²⁷)
Magnesium	8	<i>RCTs captured from SRs</i> Pfaffenrath et al 1996, ¹⁵⁰ Taubert 1994, ^{152a} Facchinetti et al 1991, ¹⁴⁷ (from von Luckner and Riederer 2018 ¹²⁸) Bian et al 2013, ^{146a} Köseoglu et al 2008, ¹⁴⁸ Peikert et al 1996, ¹⁴⁹ Yang et al 2005, ^{153a} Tarighat Esfanjani et al 2012 ¹⁵¹ (from Chiu et al 2016 ¹²⁴)
Melatonin	4	<i>Individual RCTs</i> Mohammadyahya et al 2020 ¹³⁰ <i>RCTs captured from SRs</i> Alstadhaug et al 2010, ¹⁵⁴ Ebrahimi-Monfared et al 2017, ¹⁵⁵ Gonçalves et al 2016 ¹⁵⁶ (from Liampas et al 2020 ¹²⁶)
Combination nutraceutical/supplement	2	<i>RCTs captured from SRs</i> Gaul et al 2015 ¹⁵⁷ (from Sazali et al 2021 ⁸) Maizels et al 2004 ¹⁵⁸ (from Chiu et al 2016 ¹²⁴)

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

^aForeign-language study.

Table 18. Nutraceuticals/Supplements for Migraine Prevention: Head-to-Head Trials

RCT	Intervention	Comparison	
		Pharmacologic	Nonpharmacologic
Nambiar et al 2011 ¹³²	B2 (riboflavin)	Propranolol	
Rahimdel et al 2015 ¹³³	B2 (riboflavin)	Sodium valproate	
Schoenen et al 1994 ¹³⁴	B2 (riboflavin)	Aspirin	
Maizels et al 2004 ¹⁵⁸	B2 (riboflavin) plus placebo		B2 (riboflavin), Mg (citrate/oxide) plus feverfew
Parohan et al 2021 ¹²⁹	CoQ10		CoQ10, nano-curcumin, CoQ10 plus nano-curcumin
Bian et al 2013 ^{146a}	Magnesium (K/Mg aspartate plus flunarizine)	Flunarizine	
Tarighat Esfanjani et al 2012 ¹⁵¹	Magnesium		L-carnitine, Mg plus L-carnitine
Yang et al 2005 ^{153a}	Magnesium	Pizotifen	Mg 2-propylvalerate
Ebrahimi-Monfared et al 2017 ¹⁵⁵	Melatonin	Valproate	
Gonçalves et al 2016 ¹⁵⁶	Melatonin	Amitriptyline	
Mohammadyahya et al 2020 ¹³⁰	Melatonin	Naproxen	

Abbreviations: CoQ10: Coenzyme Q10; Mg: Magnesium; RCT, randomized controlled trial.

^aForeign-language study.

Future Evidence Synthesis. The evidence base for nutraceuticals/supplements has expanded over the past decade, with 13 of 32 RCTs published during the past 10 years. However, only 2 of these trials^{129,130} were not already captured in existing reviews. Both trials were published in 2019 or later; one assessed coenzyme Q¹²⁹ and was performed in Iran, while the other compared melatonin with naproxen.¹³⁰ Existing SRs appeared to use adequate methods and with one exception¹²⁵ focused primarily on patients with migraine headache. Thus, it is unlikely that new evidence synthesis would yield new insights at this time.

Future CER. Attempting to reduce migraine frequency with nutraceuticals instead of traditional pharmacologic therapies remains attractive to many patients. Despite evidence of efficacy from the VA/DoD guideline and SRs identified in our review, our review identified only 3 head-to-head trials assessing oral magnesium, only 1 trial¹⁵¹ of which involved a comparator available in the United States. This high-priority evidence gap should be addressed in future CER trials with comparisons against other high- and low-priority interventions.

In addition, coenzyme Q and, to a lesser extent, vitamin B2 are also prevention strategies future CER trials should assess. The 3 existing head-to-head trials of vitamin B2 offer comparisons with propranolol,¹³² valproate,¹³³ and aspirin¹³⁴ but no other high-priority interventions. Similarly, the only head-to-head trial of coenzyme Q¹²⁹ assessed efficacy compared with other supplements (coenzyme Q plus nano-curcumin).

Finally, patients may express interest in using both pharmacologic and nonpharmacologic therapies. Future trials may consider assessing comparative efficacy of nutraceuticals combined with other modalities (ie, nutraceuticals plus pharmacologic or behavioral interventions).

Limitations

We note several important limitations. Given the number of interventions covered in this rapid scoping review, using published recent SRs to identify relevant RCTs facilitated efficient identification of the existing evidence base. This approach prioritized identification of all relevant trials, leveraging both searches from existing SRs along with a *de novo* search for RCTs to maximize identification. While this approach offers increased sensitivity, because some SRs included non-English language studies, we also captured some less-relevant trials.

We relied on data within SRs to characterize interventions, comparators, and follow-up durations. However, given this project's rapid timeline, we were unable to verify whether SRs accurately extracted information from source studies. In some cases, we identified errors in data. For instance, one SR assessing acupuncture for migraine⁷⁴ failed to accurately characterize an included study's¹⁰⁴ botulinum toxin study arm. Although we considered for inclusion only SRs that met a threshold for methodologic rigor, SRs may have had other problematic features that we were unable to adequately assess.

Categorizing various interventions (eg, education/self-management vs particular behavioral interventions) was challenging. Some SRs failed to report how interventions were defined, and many studies assessed interventions with multiple components. Given the accelerated timeline, we did not consider in all cases whether SRs categorized data correctly or seek input from stakeholders as we would for formal evidence synthesis. One challenge of using SRs is the potential for overlap across reviews (ie, one RCT included in multiple SRs). We attempted to avoid this by extracting data at the level of individual RCTs within SRs.

To gauge evidence of efficacy, we relied on conclusions or analysis as stated in RCTs or SRs. Given the timeline, we did not formally appraise the quality of included SRs or RCTs. Also, it was not feasible to obtain or fully consider facets of study design or conduct, or clinical factors that could lower the strength of evidence in a formal appraisal. However, our goal was not to perform new evidence synthesis, but to provide an overview of the evidence base and identify clear evidence gaps and potential opportunities for further evidence synthesis or CER to provide insights.

As noted in the methods, we selected the most recent, comprehensive, or high-quality SR for inclusion; in certain cases, this may have resulted in exclusion of a higher-quality SR with fewer studies. However, relevant SRs (both included and excluded) published in the past 5 years are listed for each intervention category in Appendix E. All excluded studies are provided in Appendix G.

Several SRs included non-English language studies (eg, German, Korean, Chinese); given the time constraints, it was not feasible to determine what proportion of all studies included by reviews were non-English. As is common with rapid reviews, citations were screened by only a single analyst, and data extraction was not independently verified. Our conclusions regarding the need for evidence synthesis or CER considered existing evidence for efficacy, number of relevant trials, types of comparisons, and number of trials not captured in existing reviews. As others might conceivably arrive at alternative conclusions, we provide citation lists for all studies and head-to-head comparisons for review.

Finally, we note that head-to-head comparisons included drugs not currently available in the United States (eg, flunarizine). For this project, we categorized flunarizine as a pharmacologic therapy, but these trials are less relevant for a US population.

Conclusion

A substantive evidence base exists for several nonpharmacologic interventions for migraine prevention. Overall, interventions recommended by recent evidence-based clinical practice guidelines are oral magnesium, aerobic exercise, progressive strength training, and mindfulness-based therapy (including meditation, relaxation, yoga, MBSR, MBCT, and acceptance-based approaches). In addition, SRs suggested efficacy for acupuncture, CoQ10, and vitamin B2.

We suggest new evidence synthesis for acupuncture, behavioral interventions (mind and body interventions such as yoga) due to limitations of existing SRs or identification of newer trials published after existing SRs. Future CER to address key evidence gaps is needed for acupuncture, behavioral interventions (primarily mindfulness-based therapy), aerobic exercise, progressive strength training, yoga, and particular nutraceuticals (eg, oral magnesium, coenzyme Q, vitamin B2). In addition to these interventions, comparators should also include pharmacologic interventions with evidence of efficacy, especially newer drugs such as the CGRP antagonists.

Nonpharmacologic interventions for migraine headache prevention remain an important alternative for patients who cannot tolerate pharmacotherapy due to side effects, drug-drug interactions, or comorbid conditions, or who prefer a perceived more holistic approach. Supporting targeted new evidence synthesis and ongoing head-to-head trials can provide important insights on efficacy and address key evidence gaps.

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Appendix A. Excluded Interventions

Table A-1. Interventions of High Interest to Patients, With Low or Unknown Efficacy

Acupressure
Chinese herbal medicine
Cranial sacral therapy
Cupping
Daith piercing
Diets (eg, elimination, gluten-free, hydration)
Dry needling
Histamines
Massage
Neurobiofeedback
Osteopathic manipulation
Shiatsu

Appendix B. Search Strategy

Bibliographic Database Searches (EMBASE.com, PsycINFO, and PubMed)

We performed bibliographic searches in EMBASE.com (which searches MEDLINE and EMBASE together), PsycINFO, and PubMed (for in-process citations only). Search results were limited to studies published between 2011 and 2021 and added to the databases on or before April 1, 2021.

We developed a specific, peer reviewed search strategy for EMBASE.com based on the interests outlined for the project and under the guidance of ECRI analysts. In Table B-1 we present the strategy in EMBASE.com syntax (using Emtree controlled vocabulary and free-text terms). We translated this strategy into appropriate syntax and search terms for the PsycINFO and PubMed database searches.

Table B-1. Bibliographic Search Strategy Performed in EMBASE.com

Set no.	Topic	Strategy
1	Patients with migraine	migraine/exp OR migrain*:ti,ab
2	General nonpharmacologic interventions	(device* OR 'drug free' OR non-drug OR nondrug OR non-pharmacologic* OR nonpharmacologic* OR 'inter disciplinary' OR interdisciplinary OR 'multi disciplinary' OR multidisciplinary):ti,ab
3	Specific nonpharmacologic interventions Psychotherapy and behavioral interventions	'lifestyle modification'/de OR meditation/exp OR 'psychotherapy'/exp OR 'stress management'/de OR ((acceptance NEXT/2 commitment) OR ((behavior* OR behaviour* OR cognitive) NEXT/1 (intervention* OR modif* OR therap* OR treatment*)) OR autogenic OR bio-feedback OR biofeedback OR breathing OR 'dialectical behav* therapy' OR 'eye movement desensiti*' OR 'guided imagery' OR hypnosis OR hypnotherap* OR meditat* OR mindfulness OR 'music therapy' OR neuro-feedback OR neurofeedback OR relax* OR 'self manag*' OR sleep* OR 'stress management'):ti,ab
4	Exercise, physiotherapy, manipulative medicine	exercise/exp OR kinesiotherapy/exp OR 'oxygen therapy'/de OR 'manipulative medicine'/exp OR 'physical activity'/exp OR physiotherapy/exp OR (acupressure OR aquatherapy OR ayurveda OR ayurvedic OR chiropract* OR exercis* OR massag* OR 'oxygen therapy' OR (manipulat* NEXT/1 (medicine OR therap* OR treatment*)) OR (manual NEXT/2 therapy) OR aerobic* OR exercis* OR kriya OR pranayama OR 'physical* activ*' OR 'physical therapy' OR physiotherapy OR 'qi gong' OR stretch* OR 'tai chi' OR walk* OR 'water therapy' OR 'work* out' OR workout* OR yoga):ti,ab

Set no.	Topic	Strategy
5	Diet, supplements, nutraceuticals	'chinese medicine'/exp OR diet/exp OR 'diet therapy'/exp OR 'herbal medicine'/de OR supplementation/exp OR 'dietary supplement'/de OR 'medicinal plant'/exp OR nutraceutical/de OR 'nutrition supplement'/exp OR 'plant medicinal product'/exp OR vitamin/exp OR ('alpha lipoic acid' OR anti-oxidant* OR antioxidant* OR boswellia OR butterbur OR chamomile OR 'chinese medicine' OR citron OR 'coenzyme Q10' OR coenzymeQ10 OR coriander OR curcumin OR 'damask rose' OR diet OR dietary OR extract OR extracts OR feverfew OR ginger OR 'gingko biloba' OR herb OR herbal OR herbs OR hydrat* OR 'john* wort' OR magnesium OR melatonin OR menthol OR mineral* OR nutraceutical* OR nutrition* OR nutraceutical* OR peppermint OR petadolex* OR petasite* OR phytomedicine* OR plant* OR probiotic* OR riboflavin OR vitamin* OR 'traditional medicine' OR (water NEAR/1 (drink* OR intake)) OR (weight NEAR/2 (control* OR lose OR losing OR loss OR maint* OR manag*)):ti,ab
6	Complementary interventions not addressed elsewhere	'alternative medicine'/exp OR 'integrative medicine'/de OR acupuncture/exp OR (acupunctur* OR ((alternative OR complementary OR integrative) NEXT/3 (approach* OR medicine OR modalit* OR therap* OR treatment*)) OR aromatherapy OR 'craniosacral therapy' OR cupping OR electroacupuncture OR homeopath* OR 'lavender oil' OR 'light therapy' OR mind-body OR mindbody OR piercing* OR reflexology):ti,ab
7	Stimulation	electrotherapy/exp OR neuromodulation/exp OR (cefaly* OR eneura* OR 'electromagnetic fields' OR gammacore* OR 'nerve stimulat*' OR ((occipital OR supraorbital OR trigeminal OR vagal OR vagus) NEXT/3 stimulat*) OR neuromodulat* OR neurostimulat* OR 'percutaneous mastoid electric* stimulat*' OR 'transcranial magnetic stimulat*' OR (transcutaneous NEXT/3 stimulat*)):ti,ab
8	Educational programs and applications	'education program'/de OR 'patient education'/de OR (coaching OR 'education* intervention*' OR 'education* program*' OR 'management program*' OR 'neuroscience education' OR 'patient education'):ti,ab OR program*:ti OR 'self care'/de OR 'self care' OR 'self management' OR 'mobile application'/exp OR (app OR apps OR application* OR digital OR education* OR mobile):ti
9	Combine intervention sets	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10	Combine all sets	1 AND 9
11	Limit to English language and published in the past 10 years	10 AND [english]/lim AND [2011-2021]/py
12	Exclude animal studies	11 NOT ((([animals]/lim NOT [humans]/lim) OR (animal* OR experimental OR (vitro NOT vivo) OR canine OR dog OR dogs OR mouse OR mice OR murine:ti OR pig OR pigs OR piglet* OR porcine OR rabbit* OR rat OR rats OR rodent* OR sheep OR swine):ti)
13	Exclude studies focusing on children	12 NOT ((adolescen* OR boys OR child* OR girls OR juvenile* OR paediatric* OR pediatric* OR preschool* OR school OR schools OR teen* OR toddler* OR youth*) NOT (adult* OR men OR women)):ti

Set no.	Topic	Strategy
14	Exclude undesired publications	13 NOT ('conference paper'/exp OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ('case report' OR book OR editorial OR erratum OR letter OR note OR 'short survey')/de OR (book OR conference OR editorial OR erratum OR letter OR note OR 'short survey'):it OR ('a case' OR 'year old'):ti,ab OR (book OR 'conference proceeding'):pt OR ('case report' OR comment OR ((rationale OR study) NEAR/3 protocol)):ti)
15	Limit to systematic reviews and meta-analyses	14 AND ('meta analysis'/exp OR 'systematic review'/de OR [cochrane review]/lim OR systematic*:ti OR (cochrane OR metaanaly* OR "meta analy*" OR (search* AND (databases OR electronic OR methodolog* OR embase* OR ebsco* OR medline* OR ovid* OR sciencedirect* OR scopus* OR systematic OR web)) OR (systematic* NEAR/2 review*)):ti,ab)
16	Limit to randomized controlled trials	14 AND ('random sample'/de OR 'randomized controlled trial'/de OR randomization/de OR random*:ti,ab)
17	Combine study sets	15 OR 16

Clinical Trials and National Institutes of Health Funding Announcements

We searched ClinicalTrials.gov and the PCORI website (www.pcori.org) to identify PCORI-funded and other ongoing trials in this topic area. Our search included the following terms and concepts: Patient-Centered Research Outcomes Institute, PCORI, migraine, migraines, and migrainous. Results were limited to trials involving adults.

ECRI Guidelines Trust®

We searched ECRI Guidelines Trust® for evidence-based guidelines addressing interventions for migraine prevention in full or in part. We searched using the term *migraine*.

Google Search Engine and Professional Organizations

We searched Google and browsed websites of professional organizations specializing in migraines to identify additional guidelines and similar publications. Organization websites searched included the American Academy of Neurology, Canadian Headache Society, European Headache Federation, International Headache Society, National Institute for Health and Clinical Excellence, and Veterans Affairs/Department of Defense Clinical Practice Guidelines.

Appendix C. Guideline Recommendations

Table C-1. Relevant Recommendations From the VA/DoD Clinical Practice Guideline for Primary Care Management of Headache

VA/DoD Clinical Practice Guideline for Primary Care Management of Headache (2020) ⁴		
End search date, March 2019		
Recommendation level	Intervention	Recommendation text
Weak for	Aerobic exercise or progressive strength training	"We suggest aerobic exercise or progressive strength training for the management of headache."
	Mindfulness-based therapies	"We suggest mindfulness-based therapies for the treatment of headache."
	Oral magnesium	"We suggest oral magnesium for the prevention of migraine."
Neither for nor against	Acupuncture	"There is insufficient evidence to recommend for or against acupuncture for the treatment of headache."
	Cognitive behavioral therapy, biofeedback	"There is insufficient evidence to recommend for or against cognitive behavioral therapy or biofeedback for the treatment of headache."
	Neurostimulation	"There is insufficient evidence to recommend for or against the following for headache <ul style="list-style-type: none"> • Transcranial magnetic stimulation • Transcranial direct current stimulation • External trigeminal nerve stimulation • Supraorbital electrical stimulation."
	Coenzyme Q, feverfew, melatonin, vitamin B2	"There is insufficient evidence to recommend for or against coenzyme Q10, feverfew, melatonin, omega-3, vitamin B2, or vitamin B6 for the prevention of migraine."

Table C-2. Recommendations From Guidelines Based on a Systematic Review That Include Nonpharmacologic Interventions

Canadian headache society guideline for migraine prophylaxis (2012) ⁵		Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: Report of the quality standards subcommittee of the American Academy of Neurology and the American Headache Society (2012) ^{6a}	
<i>Search ends April 2008</i>		<i>Search ends May 2009</i>	
Recommendation	Intervention	Recommendation	Intervention
Strong recommendation, moderate-quality evidence	Butterbur, feverfew	Level A (established as effective and should be offered for migraine prevention)	Petasides
Strong recommendation, low-quality evidence	Riboflavin, coenzyme Q, magnesium	Level B (probably effective and should be considered for migraine prevention)	Riboflavin, magnesium, feverfew, histamines, fenoprofen, ibuprofen, ketoprofen, naproxen, naproxen sodium
		Level C (possibly effective and may be considered for migraine prevention)	Coenzyme Q, estrogen, cryptoheptadine, flurbiprofen, mefenamic acid
		Level U (evidence is inadequate or conflicting to support or refute use)	Omega-3, hyperbaric oxygen, aspirin, indomethacin
		Level B (negative—following therapy probably ineffective and should not be considered for migraine prevention)	Montelukast

^aRetired due to safety concerns regarding butterbur.

We identified 3 interventional procedure guidance documents from the National Institute for Health and Care Excellence (NICE). These are not clinical practice guidelines; the guidelines state they are “based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.”²⁰¹⁻²⁰³

Table C-3. Interventional Procedures Guidance Documents Developed by NICE

Publication and review date	Guidance title (Last search date, web address)	Relevant guidance
NICE 2016 (reviewed May 2019)	Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine ²⁰¹ Search updated July 2015 Available at https://www.nice.org.uk/guidance/ipg559	“Current evidence on transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine raises no major safety concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”
NICE 2016 (review date NR)	Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine ²⁰² Search updated November 2015 Available at http://www.nice.org.uk/guidance/ipg552	“Current evidence on the safety of transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine raises no major concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.”
NICE 2014 (review date NR)	Transcranial magnetic stimulation for treating and preventing migraine ²⁰³ Search updated March 2013 Available at http://www.nice.org.uk/guidance/ipg477	“Evidence on the efficacy of TMS for the treatment of migraine is limited in quantity and for the prevention of migraine is limited in both quality and quantity. Evidence on its safety in the short and medium term is adequate but there is uncertainty about the safety of long-term or frequent use of TMS. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research.” “NICE encourages further research on TMS for treating and preventing migraine. Data should be collected for all patients not entered into controlled trials. Studies should describe clearly whether its use is for treatment or prevention. They should report details of patient selection and the dose and frequency of use. Outcome measures should include the number and severity of migraine episodes, and quality of life in both the short and long term. The development of any neurological disorders (such as epilepsy) in the short or longer term after starting treatment should be documented.”

Abbreviations: NICE, National Institute for Health and Care Excellence; NR: Not reported

We also identified several additional documents from professional organizations that did not appear to meet criteria for an evidence-based guideline (based on review of publicly available documentation) but are provided below.

Table C-4. Additional Guidance

Organization (year)	Guideline title
American Family Physicians (2019)	Migraine Headache Prophylaxis ²⁰⁴
American Headache Society (2018)	The American Headache Society Position Statement on Integrating New Migraine Treatments Into Clinical Practice ²⁰⁵
German Migraine and Headache Society (2019)	Treatment of Migraine Attacks and Prevention of Migraine: Guidelines by the German Migraine and Headache Society and the German Society of Neurology ²⁰⁶
Institute for Clinical Systems Improvement (2013)	Diagnosis and Treatment of Headache. Health Care Guideline ^{207a}
Italian Society for the Study of Headaches (2012)	Italian Guidelines for Primary Headaches: 2012 Revised Version ²⁰⁸
Kaiser Permanente (2018)	Migraine and Tension Headache Guideline ²⁰⁹

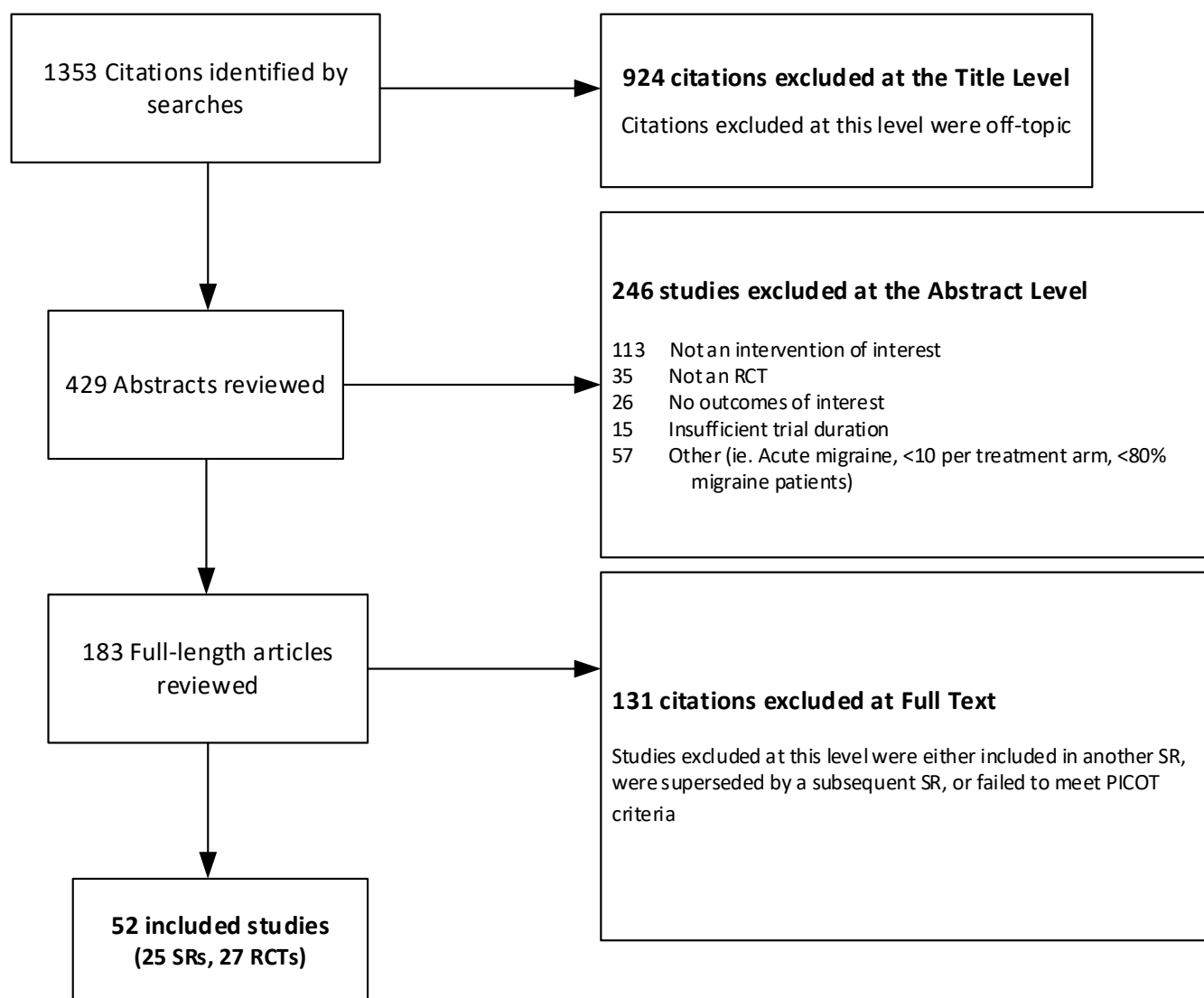
^aNo longer appears on organizational website; may be retired or being updated.

We also identified several additional documents from professional organizations that did not appear to meet criteria for an evidence-based guideline (based on review of publicly available documentation) but are provided below.

We identified additional papers offering guidance, but which focused on interventions not prioritized for this topic brief (eg, transcranial direct current stimulation,²¹⁰ chiropractic care²¹¹).

Appendix D. Flow Diagram, Additional Interventions

Figure D-1. Flow Diagram



Appendix E. Additional Evidence Tables

Acupuncture

Table E-1. Acupuncture: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Fan et al 2020 ⁷⁴	Giovanardi et al 2020 ²¹²
Linde et al 2016 ⁷	Jiang et al 2018 ²¹³
Moisset et al 2020 ¹⁰	Shen et al 2019 ²¹⁴
Ni et al 2020 ⁷⁵	Xu et al 2018 ²¹⁵
Yang et al 2020 ⁷⁶	Yang et al 2016 ²¹⁶

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-2. Systematic Reviews and Randomized Controlled Trials of Acupuncture for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Fan et al 2020 ⁷⁴	Efficacy of Acupuncture for Migraine Prophylaxis: ^a Trial Sequential Meta-analysis	SR (20 RCTs) April 2020	"Acupuncture can reduce migraine episodes compared to sham one and can be an alternative and safe prophylactic treatment for conventional drugs therapy, but it should be further verified through more RCTs. Available studies suggested acupuncture was superior to sham acupuncture and conventional drugs in terms of responder rate as verified by TSA [trial sequential analysis]."	Search included English and Chinese studies; search included <i>electroacupuncture</i> in addition to <i>acupuncture</i> Includes 19 RCTs that meet PICOT criteria

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Ni et al 2020 ⁷⁵	Acupuncture Versus Various Control Treatments in the Treatment of Migraine: A Review of Randomized Controlled Trials From the Past 10 Years	SR (49 RCTs) December 2019	"The present review evaluated the current research on the use of acupuncture for migraine, compared with various control treatments. The evidence for the effectiveness of acupuncture in controlling migraine is still limited due to the low quality of the published studies."	Search included 4 Chinese databases; authors assessed efficacy for acute migraine as well as migraine prevention Only 12 of 49 studies relevant; SR included crossover trials and all trials regardless of follow-up duration; authors noted poor quality of individual trials but did not perform sensitivity analysis restricted to higher-quality trials
Yang et al 2020 ⁷⁶	Acupuncture for Menstrual Migraine: A Systematic Review	SR (13 RCTs) May 2019	"There is no convincing evidence to support the use of acupuncture in treating menstrual migraine. Acupuncture cannot yet be recommended to patients with menstrual migraine until more solid evidence is produced."	Search included Chinese databases Menstrual migraine patients only; includes electroacupuncture
Moisset et al 2020 ¹⁰	Neuromodulation Techniques for Acute and Preventive Migraine Treatment: A Systematic Review and Meta-analysis of Randomized Controlled Trials	SR (38 RCTs [28 addressing prevention included in quantitative synthesis]) July 2020	"Remote electrical neuromodulation (REN) was effective for acute treatment. Data were insufficient to draw conclusions for any other techniques (single studies). Invasive occipital nerve stimulation (ONS) was effective for migraine prevention, with a large effect size but considerable heterogeneity, whereas supra-orbital transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and high-frequency repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) were effective, with small to medium effect sizes. Vagus-nerve stimulation, left prefrontal cortex rTMS, and cathodal transcranial direct current stimulation (tDCS) over the M1 had no significant effect and heterogeneity was high."	Addressed acute and preventive migraine treatment; also included invasive neurostimulation interventions; included children; required follow-up for only 4 weeks Included one relevant RCT (Allais et al 2003 ⁸⁶) comparing acupuncture with transcutaneous supraorbital nerve stimulation

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Linde et al 2016 ⁷	Acupuncture for the Prevention of Episodic Migraine	SR (22 RCTs) January 2016	<p>"Acupuncture was associated with a moderate reduction of headache frequency over no acupuncture after treatment (four trials, 2199 participants; standardized mean difference (SMD): -0.56; 95% CI: -0.65 to -0.48); findings were statistically heterogeneous ($I^2 = 57\%$; moderate quality evidence)." "Both after treatment (12 trials, 1646 participants) and at follow-up (10 trials, 1534 participants), acupuncture was associated with a small but statistically significant frequency reduction over sham (moderate quality evidence)." "Acupuncture reduced migraine frequency significantly more than drug prophylaxis after treatment (SMD: -0.25; 95% CI: -0.39 to -0.10; 3 trials, 739 participants), but the significance was not maintained at follow-up (SMD: -0.13; 95% CI: -0.28 to 0.01; 3 trials, 744 participants; moderate quality evidence). After three months headache frequency at least halved in 57% of participants receiving acupuncture and 46% receiving prophylactic drugs (pooled RR: 1.24; 95% CI: 1.08 to 1.44) and after six months in 59% and 54%, respectively (pooled RR: 1.11; 95% CI: 0.97 to 1.26; moderate quality evidence."</p>	<p>Cochrane review focused on episodic migraine (22 trials included 4985 participants) Did not search Chinese or Korean databases</p>
Additional RCTs not captured in SRs				
Giannini et al 2021 ⁷⁷	A Randomized Clinical Trial on Acupuncture Versus Best Medical Therapy in Episodic Migraine Prophylaxis: The ACUMIGRAN Study	RCT (n = 148) Acupuncture vs pharmacotherapy	<p>Outcomes: Headache frequency, headache days, 50% reduction "Our trial is the first one comparing acupuncture with the more appropriate pharmacological treatment for migraine prophylaxis. Data suggested that acupuncture could be adopted as migraine prophylaxis and seem to be slightly superior to pharmacological treatment in compliance and rate of adverse events."</p>	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Nie et al 2019 ⁷⁸	The Effectiveness of Acupuncture Combined With Tuina Therapy in Patients With Migraine	RCT (n = 135) Acupuncture plus tuina vs acupuncture vs flunarizine hydrochloride	Outcomes: Frequency of attacks, severity of pain, duration of migraine, associated symptoms, patient-reported outcome scores, frequency of analgesic consumption "Acupuncture combined with tuina could significantly increase the therapeutic effect of acupuncture in migraine treatment."	
Xu et al 2020 ⁷⁹	Manual Acupuncture Versus Sham Acupuncture and Usual Care for Prophylaxis of Episodic Migraine Without Aura: Multicentre, Randomised Clinical Trial	RCT (n = 150) Acupuncture vs sham	Outcomes: Change in migraine days and migraine attacks per 4 weeks during weeks 1 to 20 "Twenty sessions of manual acupuncture was superior to sham acupuncture and usual care for the prophylaxis of episodic migraine without aura. These results support the use of manual acupuncture in patients who are reluctant to use prophylactic drugs or when prophylactic drugs are ineffective, and it should be considered in future guidelines."	
Ferro et al 2012 ⁸⁰	The Combined Effect of Acupuncture and Tanacetum Parthenium on Quality of Life in Women With Headache: Randomised Study	RCT (n = 69) Acupuncture plus feverfew vs acupuncture vs feverfew	Outcomes: Short-Form 36 quality of life assessment score; Migraine Disability Assessment and Visual Analogue Scale score "The present work shows an improvement of the quality of life and better analgesic effect of acupuncture combined with TAN [tanacetum] treatment on migraine pain in women when compared with acupuncture or TAN [tanacetum] alone."	RCT is also captured under nutraceutical/ supplements

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Li et al 2019 ⁸¹	Analysis of Clinical Efficacy Levels of Sibelium Combined With Acupuncture in the Treatment of Migraines	RCT (n = 78) Acupuncture plus flunarizine vs flunarizine	Outcomes: Migraine attack duration and frequency, visual analogue scale "After treatment, fifteen patients in the acupuncture group were cured. A total of 21 patients showed effective treatment, while 3 patients showed ineffective treatment. Compared with the control group, differences were statistically significant ($P < 0.05$). In terms of concomitant symptoms of migraine attacks during treatment, the number of patients with symptoms, including nausea, vomiting, photophobia, and phonophobia, in the acupuncture group was significantly lower than that in the control group ($P < 0.05$). Conclusion: Sibelium combined with acupuncture can effectively alleviate clinical symptoms of migraine attacks. This method is superior to Sibelium monotherapy in terms of clinical efficacy. Therefore, it is worthy of promotion in clinic practice."	

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Note: All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; all SRs include at least one relevant RCT that meets these criteria.

Behavioral Interventions

Table E-3. Behavioral: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Anheyer et al 2019 ¹¹	Buhrman et al 2016 ²¹⁷
Gu et al 2018 ¹²	Mukhtar et al 2021 ²¹⁸
Kindelan-Calvo et al 2014 ¹³	Pei et al 2021 ²¹⁹
Lee et al 2019 ¹⁴	
Luedtke et al 2016 ¹⁵	
Minen et al 2016 ¹⁶	
Probyn et al 2017 ¹⁷	
Seo et al 2018 ¹⁸	
Sharpe et al 2019 ¹⁹	
Sullivan et al 2016 ²⁰	
Sullivan et al 2019 ²¹	

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-4. Systematic Reviews and Randomized Controlled Trials of Behavioral Interventions for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Acceptance and commitment therapy				
Grazzi and Rizzoli 2020 ²²	Acceptance and Commitment Therapy (ACT) vs Erenumab for High Frequency Episodic Migraine Without Aura: Time to Take the Gloves Off!	RCT (n = 24) ACT vs treatment as usual	Outcomes: Migraine days per month No abstract. "The future is now: perhaps in addition to the new era of monoclonal antibodies, there should also be a renewed focus on potentially effective nonpharmacologic migraine management. Considering both the high cost of the new drugs, and the possibility of individualizing therapies and to best utilize resources, combination management should be aggressively investigated."	Trial described in editorial
Vasiliou et al 2021 ²³	Acceptance and Commitment Therapy for Primary Headache Sufferers: A Randomized Controlled Trial of Efficacy	RCT (n = 94) ACT vs treatment as usual	Outcomes: Disability, distress, medical utilization, functioning, quality of life "Results (intent to treat analyses corroborated by linear mixed model analyses) showed substantial improvements in favor of ACT compared to control, on disability, quality of life, functional status, and depression at 3-, 6-, and 12-month follow-up. Improvements were maintained in the ACT group at 6- and 12-month follow-up. At 3-month follow-up, clinical improvement occurred in headache-related disability (63%) and 65% in quality of life in ACT versus 37% and 35% in control. These findings offer new evidence for the utility and efficacy of ACT in localized pain conditions and yields evidence for both statistical and clinical improvements over a years' period."	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Behavioral training				
Sharpe et al 2019 ¹⁹	Psychological Therapies for the Prevention of Migraine in Adults	SR (21 RCTs) July 2018	“This review identified 21 studies of psychological interventions for the management of migraine. We did not find evidence that psychological interventions affected migraine frequency, a result based on four studies of primarily brief treatments. Those who received psychological interventions were twice as likely to be classified as responders in the short term, but this was based on very low-quality evidence and there was no evidence of an effect of psychological intervention compared to control at follow-up. There was no evidence of an effect of psychological interventions on medication usage, mood, migraine-related disability or quality of life. There was no evidence of an effect of psychological interventions on migraine frequency in the short-term or long-term. In terms of adverse events, we were unable to draw conclusions as there was insufficient evidence. High and unclear risk of bias in study design and reporting, small numbers of participants, performance and detection bias meant that we rated all evidence as very low quality. Therefore, we conclude that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults and we are uncertain whether there is any difference between psychological therapies and controls.”	A Cochrane review including trials for episodic or chronic migraine 21 RCTs (with 2482 participants) Included studies with follow up duration >4 weeks; also excluded studies with <15 respondents at follow-up per arm Only 10 of 21 included RCTs meet PICOT criteria Only one relevant RCT (Kleiboer et al 2014 ³⁴) for behavioral training

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	"Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed."	English- and Korean-language articles; included primary headache and medication overuse headache; only 10 of 27 RCTs appear to meet PICOT criteria Only one relevant RCT (Holroyd et al 2010 ³³) for behavioral training
Biofeedback				
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	"Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed."	English- and Korean-language articles; included primary headache and medication overuse headache Only 3 relevant RCTs (Blanchard et al 1991 ³⁶ , Gauthier et al 1983 ³⁷ , Kewman and Roberts 1980 ³⁸) for biofeedback
Seo et al 2018 ¹⁸	Effectiveness of Autogenic Training on Headache: A Systematic Review	6 RCTs December 2016	"The small number of studies retrieved in this review, with their variations in autogenic training [AT]interventions used, in AT training/ practice time, and headache measures used, did not facilitate rigorous evaluation of the effectiveness of specific AT approaches nor of the optimum length of AT practice for reduction of headache. More research is needed on the effectiveness of AT-only for headache, the most effective duration of autogenic training and practice, and the type(s) of headache for which it is most effective."	English and Korean studies; included 1 RCT not captured elsewhere (Blanchard 1978 ³⁵ ; biofeedback)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Additional RCTs not captured in SRs				
Minen et al 2021 ²⁴	Heartrate Variability Biofeedback for Migraine Using a Smartphone Application and Sensor: A Randomized Controlled Trial	RCT (n = 52) Heartrate variability biofeedback (smartphone) vs waitlist	Outcomes: Feasibility/acceptability (number and duration of sessions, satisfaction, barriers, adverse events) Primary clinical outcome: Migraine-Specific Quality of Life Questionnaire "App-based HRV [heart rate variability] biofeedback was feasible and acceptable on a time-limited basis for people with migraine. Changes in the primary clinical outcome did not differ between biofeedback and control; however, high users of the app reported more benefit than low users."	
Tehrani et al 2021 ²⁵	Biofeedback: An Effective Add-On Treatment for Migraine Headache Alongside Medication Therapy	RCT (n = 86) Biofeedback plus pharmacotherapy vs nortriptyline plus gelofen or inderal	Outcomes: Medication use, frequency and severity of attack, MIDAS "It can be concluded that the combination of biofeedback treatment and medication therapy provides a more rapid response than pharmacological treatment alone. Therefore, biofeedback is an effective add-on therapy, which can be taken into consideration for diminishing all aspects of migraine headache attacks."	RCT performed in Iran
de Tommaso and Delussi 2017 ²⁶	Nociceptive Blink Reflex Habituation Biofeedback in Migraine	RCT (n = 33) Nociceptive blink reflex (NBR) habituation biofeedback vs nociceptive blink reflex biofeedback plus topiramate vs topiramate	Outcomes: Frequency of headache and disability changes, anxiety, depression, sleep, fatigue, quality of life, allodynia and pericranial tenderness "NBR biofeedback reduced the R2 area, without improving R2 habituation. However, it reduced the frequency of headache and disability, similarly to the combined treatment and topiramate alone. Reduced habituation of the NBR is a stable neurophysiological pattern, scarcely modifiable by learning procedures. Training methods able to act on stress-related responses may modulate cortical mechanisms inducing migraine onset and trigeminal activation under stressful trigger factors."	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Cognitive behavioral therapy				
Sharpe et al 2019 ¹⁹	Psychological Therapies for the Prevention of Migraine in Adults	SR (21 RCTs) July 2018	“This review identified 21 studies of psychological interventions for the management of migraine. We did not find evidence that psychological interventions affected migraine frequency, a result based on four studies of primarily brief treatments. Those who received psychological interventions were twice as likely to be classified as responders in the short term, but this was based on very low-quality evidence and there was no evidence of an effect of psychological intervention compared to control at follow-up. There was no evidence of an effect of psychological interventions on medication usage, mood, migraine-related disability or quality of life. There was no evidence of an effect of psychological interventions on migraine frequency in the short-term or long-term. In terms of adverse events, we were unable to draw conclusions as there was insufficient evidence. High and unclear risk of bias in study design and reporting, small numbers of participants, performance and detection bias meant that we rated all evidence as very low quality. Therefore, we conclude that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults and we are uncertain whether there is any difference between psychological therapies and controls.”	Cochrane review; included studies with f/u duration >4 weeks; also excluded studies with <15 respondents at follow-up per arm Only 10 of 21 included RCTs meet PICOT criteria 3 RCTs addressed CBT (Richardson and McGrath 1989, ⁴³ Bromberg et al 2012, ⁴¹ Fritzsche et al 2010 ⁴²)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Sullivan et al 2019 ²¹	Psychological Sleep Interventions for Migraine and Tension-Type Headache: A Systematic Review and Meta-analysis	2 RCTs, 2 pre- post studies NR	"The effects of psychological sleep interventions (and in one study, combined with drug therapy) significantly reduced headache frequency and headache intensity. Three studies improved various sleep outcomes such as duration, efficiency, and excessive sleepiness. Psychological sleep interventions improve headache frequency and sleep, however there is conflicting evidence for the effect on headache intensity between studies. Limitations include the small number of studies conducted to date. Despite this, the notable improvements in headaches and sleep achieved after psychological sleep interventions indicates further research on this promising topic is warranted."	Included one relevant RCT not captured elsewhere (Smitherman et al 2016 ⁴⁴)
Sullivan et al 2016 ²⁰	Psychological Interventions for Migraine: A Systematic Review	24 RCTs 2014 (month NR)	"We conclude that evidence supports the efficacy of psychological interventions in migraine. Over half of the studies were from the USA, which did not provide universal health care at the time of the study, so it is difficult to generalise results to typical populations in receipt of publically funded health services. We agree with the NICE recommendation that high quality pragmatic randomised controlled trials are needed in the UK."	Includes migraine and migraine plus tension-type headache patients Included one relevant RCT assessing group CBT not captured elsewhere (Thorn et al 2007 ⁴⁵)
Additional RCTs not captured in SRs				
Martin et al 2015 ²⁷	Cognitive Behavior Therapy for Comorbid Migraine and/or Tension-Type Headache and Major Depressive Disorder: An Exploratory Randomized Controlled Trial	RCT (n = 66) CBT vs treatment as usual	Outcomes: Measures of headaches, depression, anxiety, quality of life "Participants in the treatment group improved significantly more than participants in the control group from pre-to post-treatment on measures of headaches, depression, anxiety, and quality of life. Improvements achieved with treatment were maintained at four-month follow-up. Comorbid anxiety disorders were not a predictor of response to treatment, and the only significant predictor was gender (men improved more than women). The new integrated treatment program appears promising and worthy of further investigation."	Patients with migraine and/or tension-type headache and depression

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Mindfulness-based stress reduction/mindfulness-based cognitive therapy				
Sharpe et al 2019 ¹⁹	Psychological Therapies for the Prevention of Migraine in Adults	SR (21 RCTs) July 2018	"This review identified 21 studies of psychological interventions for the management of migraine. We did not find evidence that psychological interventions affected migraine frequency, a result based on four studies of primarily brief treatments. Those who received psychological interventions were twice as likely to be classified as responders in the short term, but this was based on very low-quality evidence and there was no evidence of an effect of psychological intervention compared to control at follow-up. There was no evidence of an effect of psychological interventions on medication usage, mood, migraine-related disability or quality of life. There was no evidence of an effect of psychological interventions on migraine frequency in the short-term or long-term. In terms of adverse events, we were unable to draw conclusions as there was insufficient evidence. High and unclear risk of bias in study design and reporting, small numbers of participants, performance and detection bias meant that we rated all evidence as very low quality. Therefore, we conclude that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults and we are uncertain whether there is any difference between psychological therapies and controls."	Cochrane review; included studies with f/u duration >4 weeks; also excluded studies with <15 respondents at follow-up per arm Only 10 of 21 included RCTs meet PICOT criteria Includes one relevant RCT (Hedborg and Muhr 2011 ⁵⁴)
Anheyer et al 2019 ¹¹	Mindfulness-Based Stress Reduction for Treating Chronic Headache: A Systematic Review and Meta-analysis	SR (5 RCTs) June 2017	"Due to the low number, small scale and often high or unclear risk of bias of included randomized controlled trials, the results are imprecise; this may be consistent with either an important or negligible effect. Therefore, more rigorous trials with larger sample sizes are needed."	Mixture of tension-type and migraine patients Includes 3 relevant RCTs (Day et al 2014, ⁵³ Bakshani et al 2015, ⁵² Wells et al 2014 ⁵⁶)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	"Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed."	English- and Korean-language articles; included primary headache and medication overuse headache; only 10 of 27 RCTs appear to meet PICOT criteria One relevant RCT (Mansourishad et al 2017 ⁵⁵)
RCTs published subsequent to SRs				
Seng et al 2019 ²⁸	Does Mindfulness-Based Cognitive Therapy for Migraine Reduce Migraine-Related Disability in People With Episodic and Chronic Migraine? A Phase 2b Pilot Randomized Clinical Trial	RCT (n = 60) Mindfulness-based cognitive therapy vs treatment as usual	Outcomes: Headache days, pain intensity, Migraine Disability Index, Headache Disability Inventory "Mindfulness-Based Cognitive Therapy for Migraine demonstrated efficacy to reduce headache-related disability and attack-level migraine-related disability. Mindfulness-Based Cognitive Therapy for Migraine is a promising emerging treatment for addressing migraine-related disability."	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Seminowicz et al 2020 ²⁹	Enhanced Mindfulness-Based Stress Reduction in Episodic Migraine: A Randomized Clinical trial With Magnetic Resonance Imaging Outcomes	RCT (n = 98) Mindfulness-based stress reduction vs stress reduction	<p>Outcomes: Magnetic resonance imaging (MRI) outcomes included activity of left dorsolateral prefrontal cortex (DLPFC) and cognitive task network during cognitive challenge; resting state connectivity of right dorsal anterior insula to DLPFC and cognitive task network; gray matter volume of DLPFC, dorsal anterior insula, and anterior midcingulate. Secondary outcomes were headache-related disability, pain severity, response to treatment, migraine days, and MRI whole-brain analyses.</p> <p>“Reduction in headache days from baseline to 20 weeks was greater for MBSR+ [enhanced mindfulness-based stress reduction] (7.8 [95% CI: 6.9 to 8.8] to 4.6 [95% CI: 3.7 to 5.6]) than for SMH[stress management for headaches] (7.7 [95% CI: 6.7 to 8.7] to 6.0 [95% CI: 4.9 to 7.0]) (P5 0.04). Fifty-two percent of the MBSR+ group showed a response to treatment (50% reduction in headache days) compared with 23% in the SMH group (P5 0.004). Reduction in headache-related disability was greater for MBSR+(59.6 [95% CI: 57.9 to 61.3] to 54.6 [95% CI: 52.9 to 56.4]) than SMH (59.6 [95% CI: 57.7 to 61.5] to 57.5 [95% CI: 55.5 to 59.4]) (P 5 0.02). There were no differences in clinical outcomes at 52 weeks or MRI outcomes at 20 weeks, although changes related to cognitive networks with MBSR+ were observed. Enhanced mindfulness-based stress reduction is an effective treatment option for episodic migraine.”</p>	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Wells et al 2021 ³⁰	Effectiveness of Mindfulness Meditation vs Headache Education for Adults With Migraine: A Randomized Clinical Trial	RCT (n = 89) Mindfulness-based stress reduction vs education	Outcomes: Change in migraine day frequency (baseline to 12 weeks); changes in disability, quality of life, self-efficacy, pain catastrophizing, depression scores, and experimentally induced pain intensity and unpleasantness (baseline to 12, 24, and 36 weeks) “Mindfulness-based stress reduction did not improve migraine frequency more than headache education, as both groups had similar decreases; however, MBSR improved disability, quality of life, self-efficacy, pain catastrophizing, and depression out to 36 weeks, with decreased experimentally induced pain suggesting a potential shift in pain appraisal. In conclusion, MBSR may help treat total migraine burden, but a larger, more definitive study is needed to further investigate these results.”	
Meditation				
Gu et al 2018 ¹²	Mindfulness Meditation for Primary Headache Pain: A Meta-analysis	10 RCTs, 1 controlled trial November 2016	“Mindfulness meditation may reduce pain intensity and is a promising treatment option for patients. Clinicians may consider mindfulness meditation as a viable complementary and alternative medical option for primary headache.”	Includes only one relevant RCT (Wachholtz and Pargament 2008 ⁵⁷)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Progressive muscle relaxation				
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	"Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed."	English- and Korean-language articles; included primary headache and medication overuse headache; only 10 of 27 RCTs appear to meet PICOT criteria One relevant RCT for PMR [progressive muscle relaxation](Meyer et al 2016 ⁵⁸)
Additional RCTs not captured in SRs				
Minen et al 2020 ³¹	Smartphone-Delivered Progressive Muscle Relaxation for the Treatment of Migraine in Primary Care: A Randomized Controlled Trial	RCT (n = 139) Progressive muscle relaxation (delivered via app) vs app tracking headaches alone	Outcomes: Feasibility (adherence to the intervention and diary entries during the 90-day interval) and acceptability (satisfaction levels); change in Migraine Disability Assessment Scale scores or change in headache days "Smartphone-delivered PMR [progressive muscle relaxation] may be an acceptable, accessible form of therapy for migraine. Mean effects show a small-moderate mean effect size in disability scores."	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Minen et al 2020 ³²	Smartphone Based Behavioral Therapy for Pain in Multiple Sclerosis (MS) Patients: A Feasibility Acceptability Randomized Controlled Study for the Treatment of Comorbid Migraine and MS Pain	RCT (n = 62) Smartphone app delivering progressive muscle relaxation vs smartphone app alone	Outcomes: Recruitment, retention, engagement, and adherence to RELAXaHEAD; migraine disability (MIDAS) and MS pain (PES [Pain effects scale]) “There was interest in scalable accessible forms of behavioral therapy to treat migraine and MS-related pain in patients with MS and comorbid migraine. Similar to prior studies, a significant minority were willing to practice the PMR at least twice weekly. In the societal shift from telephone to more text and internet-based interactions, follow up was challenging, but those reached indicated that they appreciated the PMR and would recommend it to others. Future work should focus on engagement and efficacy.”	Pilot feasibility and acceptability study of the RELAXaHEAD app in patients with MS and comorbid migraine and to assess whether any change in migraine disability and MS pain-related disability occurred
Relaxation				
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	“Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed.”	Includes 1 RCT (D’Souza et al 2008 ⁶⁰), comparing relaxation to written emotional disclosure
Sullivan et al 2016 ²⁰	Psychological Interventions for Migraine: A Systematic Review	SR (24 RCTs) 2014	“We conclude that evidence supports the efficacy of psychological interventions in migraine. Over half of the studies were from the USA, which did not provide universal health care at the time of the study, so it is difficult to generalise results to typical populations in receipt of publically funded health services. We agree with the NICE recommendation that high quality pragmatic randomised controlled trials are needed in the UK.”	Includes migraine and migraine plus tension-type headache patients Included 2 relevant RCTs (Varkey et al 2011, ⁶¹ Devineni and Blanchard 2005 ⁵⁹)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Self-management				
Sharpe et al 2019 ¹⁹	Psychological Therapies for the Prevention of Migraine in Adults	SR (21 RCTs) July 2018	<p>"This review identified 21 studies of psychological interventions for the management of migraine. We did not find evidence that psychological interventions affected migraine frequency, a result based on four studies of primarily brief treatments. Those who received psychological interventions were twice as likely to be classified as responders in the short term, but this was based on very low-quality evidence and there was no evidence of an effect of psychological intervention compared to control at follow-up. There was no evidence of an effect of psychological interventions on medication usage, mood, migraine-related disability, or quality of life. There was no evidence of an effect of psychological interventions on migraine frequency in the short-term or long-term. In terms of adverse events, we were unable to draw conclusions as there was insufficient evidence. High and unclear risk of bias in study design and reporting, small numbers of participants, performance and detection bias meant that we rated all evidence as very low quality. Therefore, we conclude that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults and we are uncertain whether there is any difference between psychological therapies and controls."</p>	<p>Cochrane review; included studies with f/u duration >4 weeks; also excluded studies with <15 respondents at follow-up per arm Only 10 of 21 included RCTs meet PICOT criteria Four RCTs appear to specifically address self-management</p>

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Sleep modification				
Sullivan et al 2019 ²¹	Psychological Sleep Interventions for Migraine and Tension-Type Headache: A Systematic Review and Meta-analysis	SR (2 RCTs, 2 pre-post studies) NR	"The effects of psychological sleep interventions (and in one study, combined with drug therapy) significantly reduced headache frequency and headache intensity. Three studies improved various sleep outcomes such as duration, efficiency, and excessive sleepiness. Psychological sleep interventions improve headache frequency and sleep, however there is conflicting evidence for the effect on headache intensity between studies. Limitations include the small number of studies conducted to date. Despite this, the notable improvements in headaches and sleep achieved after psychological sleep interventions indicates further research on this promising topic is warranted."	Includes one relevant RCT (Calhoun and Ford 2007 ⁶⁶)
Other behavioral interventions				
Sullivan et al 2016 ²⁰	Psychological Interventions for Migraine: A Systematic Review	24 RCTs 2014 (month not reported)	"We conclude that evidence supports the efficacy of psychological interventions in migraine. Over half of the studies were from the USA, which did not provide universal health care at the time of the study, so it is difficult to generalise results to typical populations in receipt of publically funded health services. We agree with the NICE recommendation that high quality pragmatic randomised controlled trials are needed in the UK."	Includes 2 RCTs assessing written emotional disclosure or audiotape relaxation training (Dittrich et al 2008, ⁶⁷ Kraft et al 2008 ⁶⁸)
Minen et al 2016 ^{16a}	Electronic Behavioral Interventions for Headache: A Systematic Review	SR (23 studies) December 2015	"Despite the move toward individualized medicine and mHealth, the current literature shows that most studies using electronic behavioral intervention for the treatment of headache did not use mobile devices. The studies examining mobile devices showed that the behavioral interventions that employed them were acceptable to patients. Data are limited on the dose required, long term efficacy, and issues related to the security and privacy of this health data."	Includes one relevant RCT (Trinka et al 2002 ⁶⁹ ; assessing sound therapy)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Combined behavioral interventions				
Sharpe et al 2019 ¹⁹	Psychological Therapies for the Prevention of Migraine in Adults	SR (21 RCTs) July 2018	<p>"This review identified 21 studies of psychological interventions for the management of migraine. We did not find evidence that psychological interventions affected migraine frequency, a result based on four studies of primarily brief treatments. Those who received psychological interventions were twice as likely to be classified as responders in the short term, but this was based on very low-quality evidence and there was no evidence of an effect of psychological intervention compared to control at follow-up. There was no evidence of an effect of psychological interventions on medication usage, mood, migraine-related disability or quality of life. There was no evidence of an effect of psychological interventions on migraine frequency in the short-term or long-term. In terms of adverse events, we were unable to draw conclusions as there was insufficient evidence. High and unclear risk of bias in study design and reporting, small numbers of participants, performance and detection bias meant that we rated all evidence as very low quality. Therefore, we conclude that there is an absence of high-quality evidence to determine whether psychological interventions are effective in managing migraine in adults and we are uncertain whether there is any difference between psychological therapies and controls."</p>	<p>Cochrane review; included studies with f/u duration >4 weeks; also excluded studies with <15 respondents at follow-up per arm Only 10 of 21 included RCTs meet PICOT criteria Included one RCT (Kaushik et al 2005⁴⁸) assessing biofeedback plus relaxation</p>

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Lee et al 2019 ¹⁴	Efficacy of Psychological Treatment for Headache Disorder: A Systematic Review and Meta-analysis	SR (27 RCTs) March 2018	"Psychological treatments for primary headache disorder reduced headache frequency and the headache index. Future research using standardized outcome measures and strategies for reducing bias is needed."	Includes one RCT (Cousins et al 2015 ⁴⁷) assessing CBT plus relaxation
Minen et al 2016 ^{16a}	Electronic Behavioral Interventions for Headache: A Systematic Review	SR (23 studies) December 2015	Despite the move toward individualized medicine and mHealth[mobile health], the current literature shows that most studies using electronic behavioral intervention for the treatment of headache did not use mobile devices. The studies examining mobile devices showed that the behavioral interventions that employed them were acceptable to patients. Data are limited on the dose required, long-term efficacy, and issues related to the security and privacy of these health data.	Describes 3 RCTs not included elsewhere 2 RCTs assessed combination of 2 behavioral modalities (CBT plus relaxation or progressive muscle relaxation); one RCT assessed sound therapy Unclear if these were inactive or head-to-head comparisons
Sullivan et al 2016 ²⁰	Psychological Interventions for Migraine: A Systematic Review	SR (24 RCTs) 2014 (month NR)	"We conclude that evidence supports the efficacy of psychological interventions in migraine. Over half of the studies were from the USA, which did not provide universal health care at the time of the study, so it is difficult to generalise results to typical populations in receipt of publically funded health services. We agree with the NICE recommendation that high quality pragmatic randomised controlled trials are needed in the UK."	Includes one RCT not captured elsewhere (Vasudeva et al 2003 ⁵¹) comparing biofeedback assisted relaxation vs self-relaxation
Kindelan-Calvo et al 2014 ¹³	Effectiveness of Therapeutic Patient Education for Adults With Migraine. A Systematic Review and Meta-analysis of Randomized Controlled Trials	SR (14 RCTs) May 2013	"This systematic review revealed strong-moderate evidence for intermediate-term effectiveness of therapeutic patient education for migraine. Further high-quality RCTs are required for conclusive determination of its effectiveness."	Includes one RCT not captured elsewhere (Seng and Holroyd 2010 ⁴⁹) comparing behavioral migraine management (including biofeedback and relaxation) vs control

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Combined modalities (behavioral plus other modality)				
Luedtke et al 2016 ¹⁵	Efficacy of Interventions Used by Physiotherapists for Patients With Headache and Migraine—Systematic Review and Meta-analysis	SR (20 RCTs) August 2014	“Results suggest a statistically significant reduction in the intensity, frequency and duration of migraine, TTH [tension type headache], and CGH [cervicogenic headache]. Pain reduction and reduction in CGH frequency do not reach clinically relevant effect sizes. Small sample sizes, inadequate use of headache classification, and other methodological shortcomings reduce the confidence in these results. Methodologically sound, randomized controlled trials with adequate sample sizes are required to provide information on whether and which physiotherapy approach is effective. According to Grading of Recommendations Assessment, Development and Evaluation (GRADE), the current level of evidence is low.”	English- or German-language studies Includes 2 relevant RCTs (Mongini et al 2012, ⁷³ Mongini et al 2008 ⁷²), which assess a combined modality intervention of relaxation, posture correction, and exercises; another combines these modalities with education
Probyn et al 2017 ¹⁷	Non-pharmacological Self-management for People Living With Migraine or Tension-Type Headache: A Systematic Review Including Analysis of Intervention Components	SR (16 RCTs) June 2016	“Overall, we found that self-management interventions for migraine and tension-type headache are more effective than usual care in reducing pain intensity, mood and headache-related disability, but have no effect on headache frequency. Preliminary findings also suggest that including CBT, mindfulness and educational components in interventions, and delivery in groups may increase effectiveness.”	Included adults with either tension type or migraine headache Included 2 relevant RCTs (Martin et al 2014, ⁷¹ Basler et al 1996 ⁷⁰) not captured elsewhere that assess combination of education with other modalities (eg, exercise, cognitive behavioral therapy)

Abbreviations: NR, Not reported; RCT, randomized controlled trial; SR, systematic review.

^aThis SR (Minen 2016¹⁶) did not assess outcomes of interest but was included because it identified RCTs that met inclusion criteria and were not captured elsewhere (ie, not captured by other SRs or our search of RCTs).

Note: All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; with the exception of Minden 2016¹⁶, all SRs include at least one relevant RCT that met these criteria.

Exercise

Table E-5. Exercise: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Anheyer et al 2020 ¹⁷²	LaTouche et al 2020 ²²⁰
Lemmens et al 2019 ¹⁷¹	

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-6. Systematic Reviews and Randomized Controlled Trials of Exercise for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Aerobic exercise				
Lemmens et al 2019 ¹⁷¹	The Effect of Aerobic Exercise on the Number of Migraine Days, Duration and Pain Intensity in Migraine: A Systematic Literature Review and Meta-analysis	SR (5 RCTs, 1 controlled trial) February 2018	"There is moderate quality evidence that in patients with migraine aerobic exercise therapy can decrease the number of migraine days. No conclusion for pain intensity or duration of attacks can be drawn. Effect sizes are small due to a lack of uniformity. For future studies, we recommend standardized outcome measures and sufficiently intense training programs."	Search only from 2004 forward Types of aerobic exercise included endurance training, indoor cycling, strength training Identified 2 relevant RCTs (Bond et al 2018, ¹⁷⁷ Varkey et al 2011 ⁶¹)
Additional RCTs not captured in SRs				
Oliveira et al 2019 ¹⁷³	Anandamide Is Related to Clinical and Cardiorespiratory Benefits of Aerobic Exercise Training in Migraine Patients: A Randomized Controlled Clinical Trial	RCT (n = 58) Aerobic exercise vs waitlist	Outcomes: Changes in plasma anandamide; secondary outcome was number of days with migraine/month; other clinical variables, mood scores, and cardiorespiratory fitness; headache-free days "This study suggests that peripheral AEA[N-arachidonoyl-ethanolamine] metabolism may be partly linked to the clinical and cardiorespiratory benefits of regular aerobic exercise in migraine patients."	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Eslami et al 2021 ¹⁷⁴	The Effects of Two Different Intensities of Aerobic Training Protocols on Pain and Serum Neuro-biomarkers in Women Migraineurs: A Randomized Controlled Trial	RCT (n = 45) High-intensity exercise vs moderate-intensity exercise vs control	Outcomes: Body composition factors, migraine pain indexes, VO2max [maximal oxygen consumption], and serum adenylate-cyclase activating polypeptide and substance P were measured; study also reports reduced headache intensity, frequency, and duration “Our results demonstrated that either moderate-intensity aerobic training (MOD-T) or high-intensity aerobic training (HIGH T) could modify migraine pain indices but neither MOD T nor HIGH T could not alter the serum Adenylate-Cyclase Activating Polypeptide and Substance P contents in women with migraine.”	
Yoga				
Anheyer et al 2020 ¹⁷²	Yoga for Treating Headaches: A Systematic Review and Meta-analysis	SR (6 RCTs) May 2019	“Despite discussed limitations, this review found preliminary evidence of short-term efficacy of yoga in improving headache frequency, headache duration, and pain intensity in patients suffering from tension-type headaches. Further studies are urgently needed to draw deeper conclusions from the available results.”	Included both tension-type and migraine headaches Includes 3 RCTs that met PICOT assessing yoga (Boroujeni et al 2015, ¹⁷⁸ John et al 2007, ¹⁸⁰ Kisan et al 2014 ¹⁸¹); of note, these trials were performed in India or Iran Authors found yoga reduced migraine frequency, but this finding was not statistically significant

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Additional RCTs not captured in SRs				
Kumar et al 2020 ¹⁷⁵	Effect of Yoga as Add-on Therapy in Migraine (CONTAIN): A Randomized Clinical Trial	RCT (n = 160) Yoga plus pharmacotherapy vs pharmacotherapy	Outcomes: Headache frequency, headache intensity, and Headache Impact Test-6 score; Migraine Disability Assessment score, pill count, and proportion of headache-free patients "Yoga as an add-on therapy in migraine is superior to medical therapy alone. It may be useful to integrate a cost-effective and safe intervention like yoga into the management of migraine."	Episodic migraine patients only; performed in India
Mehta et al 2021 ¹⁷⁶	Study of Additive Effect of Yoga and Physical Therapies to Standard Pharmacologic Treatment in Migraine	RCT (n = 61) Yoga vs physical therapy vs treatment as usual	Outcomes: Headache frequency, Short-Form McGill Pain Questionnaire, and Headache Impact Test-6 at recruitment and once every month for 3 months "Either physical or yoga therapy as an adjuvant to standard pharmacologic treatment may further improve the quality of life and reduce headache frequency in patients with migraine."	Note: Although listed here, this trial also assesses physical therapy. Performed in India

Abbreviations: RCT, randomized controlled trial; SR, systematic Review.

Note: All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; all SRs included in this report include at least one relevant RCT that meets these criteria.

Physical Therapy

Table E-7. Physical Therapy: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years
Luedtke et al 2016 ¹⁵	None

Abbreviation: SR, systematic review.

Table E-8. Systematic Reviews and Randomized Controlled Trials of Physical Therapy for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Physical therapy				
Luedtke et al 2016 ¹⁵	Efficacy of Interventions Used by Physiotherapists for Patients With Headache and Migraine—Systematic Review and Meta-analysis	SR (20 RCTs) August 2014	“Results suggest a statistically significant reduction in the intensity, frequency and duration of migraine, TTH [tension type headache] and CGH [cervicogenic headache]. Pain reduction and reduction in CGH frequency do not reach clinically relevant effect sizes. Small sample sizes, inadequate use of headache classification, and other methodological shortcomings reduce the confidence in these results. Methodologically sound, randomized controlled trials with adequate sample sizes are required to provide information on whether and which physiotherapy approach is effective. According to Grading of Recommendations Assessment, Development and Evaluation (GRADE), the current level of evidence is low.”	English- or German-language studies Includes 7 RCTs that met PICOT criteria (Lemstra et al 2002, ¹⁹¹ Narin et al 2003, ¹⁹⁰ De Hertogh et al 2009, ¹⁸⁸ Gunreben-Stempfle et al 2009, ¹⁸⁹ Mongini et al 2008, ⁷² Mongini et al 2012, ⁷³ Andersen et al 2011 ¹⁸⁶) Interventions include combined modalities (eg, strength training, relaxation, posture correction, exercises)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Additional RCTs not captured in SRs				
Wanderley et al 2020 ¹⁸⁴	Contract-Relax Technique Compared to Static Stretching in Treating Migraine in Women: A Randomized Pilot Trial	RCT (n = 30) Proprioceptive neuromuscular facilitation (PNF) vs static stretching	Outcomes: Medication intake, severity of migraine-related disability, neck disability, cervical mobility, pressure pain threshold, adverse effects and global perception of change “This is a feasible pilot trial. The PNF contract-relax technique was no more effective than static stretching for treating migraine, but both techniques improved the headache, the severity of migraine-related disability and the satisfaction after treatment.”	
Garrigós-Pedron et al 2018 ¹⁸⁵	Effects of a Physical Therapy Protocol in Patients With Chronic Migraine and Temporomandibular Disorders: A Randomized, Single-Blinded, Clinical Trial	RCT (n = 45) Cervical treatment vs cervical and orofacial treatment	Outcomes: Craniofacial Pain and Disability Inventory (CF-PDI), Headache Impact Test (HIT-6); Tampa Scale for Kinesiophobia (TSK-11), Visual Analog Scale, pressure pain thresholds (PPTs) in the temporal, masseter (2 points, M1 and M2), and extratrigeminal (wrist) regions, and maximal mouth opening (MMO) “Both groups reported a significant improvement in CF-PDI, HIT-6, and pain intensity. Cervical and orofacial treatment was more effective than cervical treatment alone for increasing PPTs in the trigeminal region and producing pain-free MMO. Physical therapy alone was not effective for increasing the PPTs in the extratrigeminal region (wrist) or decreasing the level of TSK-11.”	

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Mehta et al 2021 ¹⁷⁶	Study of Additive Effect of Yoga and Physical Therapies to Standard Pharmacologic Treatment in Migraine	RCT (n = 61) Yoga vs physical therapy vs treatment as usual	Outcomes: Headache frequency, Short-Form McGill Pain Questionnaire, and Headache Impact Test-6 at recruitment and once every month for 3 months "Either physical or yoga therapy as an adjuvant to standard pharmacologic treatment may further improve the quality of life and reduce headache frequency in patients with migraine."	Note: This also appears above under yoga Performed in India

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Note: All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; all SRs include at least one relevant RCT that meets these criteria.

Noninvasive Stimulation

Table E-9. Noninvasive Stimulation: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Moisset et al 2020 ¹⁰	Cadalso et al 2018 ²²¹
	Feng et al 2019 ²²²
	Hulla and Liegey-Dougall 2019 ²²³
	Lan et al 2017 ²²⁴
	Reuter et al 2019 ²²⁵
	Tao et al 2018 ²²⁶

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-10. Summary of Systematic Reviews and Randomized Controlled Trials of Noninvasive Stimulation for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Moisset et al 2020 ¹⁰	Neuromodulation Techniques for Acute and Preventive Migraine Treatment: A Systematic Review and Meta-analysis of Randomized Controlled Trials	SR (38 RCTs; 28 addressing prevention included in quantitative synthesis) July 2020	“Remote electrical neuromodulation (REN) was effective for acute treatment. Data were insufficient to draw conclusions for any other techniques (single studies). Invasive occipital nerve stimulation (ONS) was effective for migraine prevention, with a large effect size but considerable heterogeneity, whereas supra-orbital transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS), and high-frequency repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) were effective, with small to medium effect sizes. Vagus-nerve stimulation, left prefrontal cortex rTMS, and cathodal transcranial direct current stimulation (tDCS) over the M1 had no significant effect and heterogeneity was high.”	Addressed acute and preventive migraine treatment; also included invasive neurostimulation interventions; included children; required follow-up for only 4 weeks RCTs that met PICOT criteria: Transcranial magnetic stimulation (6 RCTs) Supraorbital nerve stimulation (3 RCTs) Vagus nerve stimulation (3 RCTs)
Additional RCTs not captured in SRs				
Deng et al 2020 ¹⁵⁹	A Head-to-Head Comparison of Percutaneous Mastoid Electrical Stimulator and Supraorbital Transcutaneous Stimulator in the Prevention of Migraine: A Prospective, Randomized Controlled Study	RCT (n = 90) Transcutaneous supraorbital nerve stimulation vs percutaneous mastoid stimulation	Outcomes: Monthly migraine days and the 50% response rate “Percutaneous Mastoid Electrical Stimulator (PMES) and Supraorbital Transcutaneous Stimulator (STS) treatment were both effective in migraine prevention. The safety and efficacy of PMES and STS were comparable.”	

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Note: All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; all SRs include at least one relevant RCT that meets these criteria.

Education

Table E-11. Education: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Kindelan-Calvo et al 2014 ¹³	Joypaul et al 2019 ²²⁷
Probyn et al 2017 ¹⁷	
Lemmens et al 2019 ¹⁷¹	

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-12. Summary of Systematic Reviews and Randomized Controlled Trials of Education for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Lemmens et al 2019 ¹⁷¹	The Effect of Aerobic Exercise on the Number of Migraine Days, Duration and Pain Intensity in Migraine: A Systematic Literature Review and Meta-analysis	SR (5 RCTs, 1 controlled trial) February 2018	"There is moderate quality evidence that in patients with migraine aerobic exercise therapy can decrease the number of migraine days. No conclusion for pain intensity or duration of attacks can be drawn. Effect sizes are small due to a lack of uniformity. For future studies, we recommend standardized outcome measures and sufficiently intense training programs."	Search from only 2004 forward Identified one relevant RCT (Bond et al 2018 ¹⁷⁷) comparing exercise vs headache education
Probyn et al 2017 ¹⁷	Non-pharmacological Self-management for People Living With Migraine or Tension-Type Headache: A Systematic Review Including Analysis of Intervention Components	SR (16 RCTs) June 2016	"Overall, we found that self-management interventions for migraine and tension-type headache are more effective than usual care in reducing pain intensity, mood, and headache-related disability, but have no effect on headache frequency. Preliminary findings also suggest that including CBT, mindfulness, and educational components in interventions, and delivery in groups may increase effectiveness."	Included adults with either tension-type or migraine headaches Included 2 relevant RCTs not captured elsewhere (Basler et al 1996, ⁷⁰ Martin et al 2014 ⁷¹), which assessed combination of education with other modalities (eg, exercise, cognitive behavioral therapy)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Kindelan-Calvo et al 2014 ¹³	Effectiveness of Therapeutic Patient Education for Adults With Migraine. A Systematic Review and Meta-analysis of Randomized Controlled Trials	SR (14 RCTs) May 2013	"This systematic review revealed strong-moderate evidence for intermediate-term effectiveness of therapeutic patient education for migraine. Further high-quality RCTs are required for conclusive determination of its effectiveness."	Adults with migraine; included English- and Spanish-language studies Includes 3 relevant RCTs (Matchar et al 2008, ¹⁹⁵ Mérelle et al 2008, ¹⁹⁶ Cady et al 2009 ¹⁹⁴)
Additional RCTs not captured in SRs				
Wells et al 2020 ³⁰	Effectiveness of Mindfulness Meditation vs Headache Education for Adults With Migraine: A Randomized Clinical Trial	RCT (n = 89) Mindfulness-based stress reduction vs education	Outcomes: Change in migraine day frequency (baseline to 12 weeks); changes in disability, quality of life, self-efficacy, pain catastrophizing, depression scores, and experimentally induced pain intensity and unpleasantness (baseline to 12, 24, and 36 weeks). "Mindfulness-based stress reduction did not improve migraine frequency more than headache education, as both groups had similar decreases; however, MBSR improved disability, quality of life, self-efficacy, pain catastrophizing, and depression out to 36 weeks, with decreased experimentally induced pain suggesting a potential shift in pain appraisal. In conclusion, MBSR may help treat total migraine burden, but a larger, more definitive study is needed to further investigate these results."	
Aguirrezabal et al 2019 ¹⁹²	Effectiveness of a Primary Care-Based Group Educational Intervention in the Management of Patients With Migraine: A Randomized Controlled Trial	RCT (n = 116) Inpatient detoxification program plus education vs outpatient detoxification plus education vs education	Outcomes: Reduction in days lost due to migraine-related disability according to the Migraine Disability Assessment Test score; intensity and frequency of the pain and the number of analgesic drugs taken in the previous 3 months "The provision of suitable information through a group educational intervention delivered in primary care appears to be effective in preventing migraine attacks. Moreover, the intervention could offer a new cost-effective management alternative that seems to reduce the need for pharmacological treatment in patients with migraine."	Conducted in 5 primary health care clinics in Spain Education covered current concepts of pain neuroscience applied to migraine and migraine management

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Rossi et al 2013 ¹⁹³	Advice Alone Versus Structured Detoxification Programmes for Complicated Medication Overuse Headache (MOH): A Prospective, Randomized, Open-Label Trial	RCT (n = 137) Education vs treatment as usual	Outcomes: Lower analgesic use "Inpatient withdrawal is significantly more effective than advice alone or an outpatient strategy in complicated MOH patients."	Study goal was to assess educational strategy (advice to withdraw the overused medication[s]) with that of 2 structured pharmacological detoxification programs in patients with complicated medication overuse headache plus migraine

Abbreviations: MOH, medication overuse headache; RCT, randomized controlled trial; SR, systematic review.

Nutraceuticals/Supplements

Table E-13. Nutraceuticals/Supplements: Systematic Reviews Published in the Past 5 Years

Included SRs	Other potentially relevant SRs published in the past 5 years ^a
Chen et al 2021 ⁹	Okoli et al 2019 ²²⁸
Chiu et al 2016 ¹²⁴	Namazi et al 2015 ²²⁹
de Sousa et al 2019 ¹²⁵	Nierenburg et al 2015 ²³⁰
Liampas et al 2020 ¹²⁶	Parohan et al 2020 ²³¹
Lopresti et al 2020 ¹²⁷	Rehman et al 2019 ²³²
Sazali et al 2021 ⁸	Thompson and Saluja 2017 ²³³
von Luckner and Riederer 2018 ¹²⁸	Tseng et al 2020 ²³⁴
	Zeng et al 2019 ²³⁵

Abbreviation: SR, systematic review.

^aThese SRs were considered for inclusion but another more recent, relevant, high-quality SR was included instead.

Table E-14. Summary of Systematic Reviews and Randomized Controlled Trials of Nutraceuticals/Supplements for Migraine Prevention

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Alpha lipoic acid				
de Sousa et al 2019 ¹²⁵	Alpha-Lipoic Acid in the Treatment of Psychiatric and Neurological Disorders: A Systematic Review	SR (32 studies) June 2018	"In neurological disorders, ALA [alpha-lipoic acid] as a supplement was effective in the prevention of Alzheimer disease progression. For stroke, the use of the supplement ALAnerv® (containing 300 mg ALA) presented important results, since it was observed a reversal of clinical parameters and oxidative imbalance in these patients. For other neurological conditions, such as encephalopathy, multiple sclerosis, traumatic brain injury, mitochondrial disorders, and migraine, the results are still preliminary. Overall, there is a need of well-designed clinical trials to enhance the clinical evidences of ALA effects for the treatment of neurological and psychiatric conditions."	Not restricted to migraine patients Includes one relevant RCT (Magis et al 2007 ¹³¹)
Vitamin B2 (riboflavin)				
Chen et al 2021 ⁹	Effect of Vitamin B2 Supplementation on Migraine Prophylaxis: A Systematic Review and Meta-analysis	SR (8 RCTs, 1 controlled trial) March 2019	"A pooled analysis of available randomized controlled clinical trials demonstrated that Vitamin B2 400 mg/day for 3 months supplementation had significant effect on days, duration, frequency, and pain score of migraine attacks."	Includes 4 relevant RCTs (Nambiar et al 2011, ¹³² Rahimdel et al 2015, ¹³³ Schoenen et al 1994, ¹³⁴ Schoenen et al 1998 ¹³⁵)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Butterbur				
Lopresti et al 2020 ¹²⁷	Herbal Treatments for Migraine: A Systematic Review of Randomised-Controlled Studies	SR (19 RCTs) March 2020	“Overall, findings on the efficacy of feverfew were mixed and there was positive, albeit limited evidence for butterbur. There were positive, preliminary findings on curcumin, citron, and coriander as a prophylactic treatment for migraine, and the use of menthol and chamomile as an acute treatment. However, the risk of bias was high for many studies. The results of this systematic review suggest that several herbal medicines, via their multifactorial physiological influences, present as potential options to enhance the treatment of migraine. However, further high-quality research is essential to examine their efficacy and safety as a treatment for migraine.”	SR included adults and children Includes 3 relevant RCTs (in 4 publications: Diener et al 2004 ¹³⁶ (data also reported in Grossman and Schmidramsl 2001 ¹⁹⁹) Lipton et al 2004, ¹³⁷ Oelkers-Ax et al 2008 ¹³⁸)
Coenzyme Q				
Sazali et al 2021 ⁸	Coenzyme Q10 Supplementation for Prophylaxis in Adult Patients With Migraine—A Meta-analysis	SR (6 RCTs) December 2019	“CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.”	Includes 3 relevant RCTs (Dahri et al 2019 and 2017, ^{139,200} Hajhashemi et al 2019, ¹⁴⁰ Nattagh-Eshtivani et al 2018 ¹⁴¹)
Additional RCTs not captured in SRs				
Parohan et al 2021 ¹²⁹	The Synergistic Effects of Nano-curcumin and Coenzyme Q10 Supplementation in Migraine Prophylaxis: A Randomized, Placebo-Controlled, Double-Blind Trial	RCT (n = 100) CoQ10 vs CoQ10 plus nano-curcumin vs nano-curcumin vs placebo	Outcomes: Frequency, severity, and duration of headache attacks; headache diary results; headache disability based on migraine-specific questionnaires “These findings suggest a possible synergistic effect of nano-curcumin and CoQ10 on clinical features of migraine.”	Episodic migraine only Performed in Iran

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Feverfew				
Lopresti et al 2020 ¹²⁷	Herbal Treatments for Migraine: A Systematic Review of Randomised-Controlled Studies	SR (19 RCTs) March 2020	"Overall, findings on the efficacy of feverfew were mixed and there was positive, albeit limited evidence for butterbur. There were positive, preliminary findings on curcumin, citron, and coriander as a prophylactic treatment for migraine, and the use of menthol and chamomile as an acute treatment. However, the risk of bias was high for many studies. The results of this systematic review suggest that several herbal medicines, via their multifactorial physiological influences, present as potential options to enhance the treatment of migraine. However, further high-quality research is essential to examine their efficacy and safety as a treatment for migraine."	5 relevant RCTs (De Weerd et al 1996, ¹⁴² Diener et al 2005, ¹⁴³ Ferro et al 2012, ⁸⁰ Murphy et al 1988, ¹⁴⁴ Pfaffenrath et al 2002 ¹⁴⁵)
Magnesium				
von Luckner et al 2018 ¹²⁸	Magnesium in Migraine Prophylaxis—Is There an Evidence-Based Rationale? A Systematic Review	SR (5 RCTs) Second quarter of 2016	"This systematic review provides Grade C (possibly effective) evidence for prevention of migraine with magnesium. Prophylactic treatment of migraine by means of high levels of magnesium dicitrate (600 mg) seems to be a safe and cost efficient strategy in clinical use."	Includes 3 relevant RCTs not captured elsewhere (Pfaffenrath et al 1996, ¹⁵⁰ Taubert 1994, ^{152a} Facchinetti et al 1991 ¹⁴⁷)
Chiu et al 2016 ¹²⁴	Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials	SR (21 RCTs) February 2015	"Intravenous magnesium reduces acute migraine attacks within 15–45 minutes, 120 minutes, and 24 hours after the initial infusion and oral magnesium alleviates the frequency and intensity of migraine. Intravenous and oral magnesium should be adapted as parts of multimodal approach to reduce migraine."	Included 5 relevant RCTs assessing a form of oral magnesium, sometimes combined with other interventions (Bian et al 2013, ^{146a} Köseoglu et al 2008, ¹⁴⁸ Peikert et al 1996, ¹⁴⁹ Yang et al 2005, ^{153a} Tarighat Esfanjani et al 2012 ¹⁵¹)

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Melatonin				
Liampas et al 2020 ¹²⁶	Endogenous Melatonin Levels and Therapeutic Use of Exogenous Melatonin in Migraine: Systematic Review and Meta-analysis	SR (7 RCTs, 9 nonrandomized trials) January 2020	"Overall, melatonin was more efficacious and equally safe with placebo in the prevention of migraine in adults (3 of 4 RCTs provided superior efficacy results for melatonin, 1 RCT revealed no difference regarding Headache Frequency -HF-), while there are limited data for children (1 RCT revealed no difference against placebo regarding HF). Additionally, no difference was revealed between melatonin and amitriptyline (1 RCT), sodium valproate (1 RCT) or propranolol (1 non-randomized study) with respect to their efficacy in adults with migraine, while melatonin was more effective than pizotifen (1 RCT)."	Includes 3 relevant RCTs (Alstadhaug et al 2010, ¹⁵⁴ Ebrahimi-Monfared et al 2017, ¹⁵⁵ Gonçalves et al 2016 ¹⁵⁶)
Additional RCTs not captured in SRs				
Mohammadyahya et al 2020 ¹³⁰	Melatonin as a Potential Prophylactic Therapy for Menstrual-Related Migraine Headache: A Randomized Clinical Trial	RCT (n = 56) Melatonin vs naproxen	Outcomes: Migraine diary, Visual Analog Scale for pain, Berlin questionnaire "We showed the beneficial role of melatonin in reducing the attack frequency and severity in migraine patients with menstrual-related headaches. Preventive therapy with melatonin also showed a significant reduction in the number of sedative drug use during attacks and improved the patients' sleep quality when compared to naproxen."	Prevention of menstrual migraine Performed in Iran

Reviews published in the past 5 years	Title	Study type, end search date (comparison for RCTs)	Author conclusions	Comments
Combination nutraceutical/supplement				
Sazali et al 2021 ⁸	Coenzyme Q10 Supplementation for Prophylaxis in Adult Patients With Migraine—A Meta-analysis	SR (6 RCTs) December 2019	“CoQ10 appears to have beneficial effects in reducing duration and frequency of migraine attack.”	Includes one RCT (Gaul et al 2015 ¹⁵⁷) assessing proprietary combination of riboflavin, magnesium, and CoQ10
Chiu et al 2016 ¹²⁴	Effects of Intravenous and Oral Magnesium on Reducing Migraine: A Meta-analysis of Randomized Controlled Trials	SR (21 RCTs) February 2015	“Intravenous magnesium reduces acute migraine attacks within 15–45 minutes, 120 minutes, and 24 hours after the initial infusion and oral magnesium alleviates the frequency and intensity of migraine. Intravenous and oral magnesium should be adapted as parts of multimodal approach to reduce migraine.”	Includes one RCT (Maizels et al 2004 ¹⁵⁸) assessing combination of riboflavin, magnesium, and feverfew

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Note All RCTs assessed treatments of interest in adults with migraine and measured outcomes of interest (headache frequency or quality of life measure) with a minimum follow-up of 8 weeks; all SRs include at least one relevant RCT that meets these criteria.

^aForeign-language study.

Appendix F. Ongoing Clinical Trials

Table F-1. Clinical Trials of Nonpharmacologic Interventions for Migraine Prevention

Status	Title and NCT	Interventions	Enrollment	Completion date	Location
Acupuncture					
Not yet recruiting	Brain Connectome for Acupuncture-Treated Migraine Patients NCT04157192	Acupuncture vs sham	40	June 2021	France
Not yet recruiting	A Randomized Controlled Trial of Acupuncture in Treating Migraine NCT04766762	Acupuncture plus placebo vs sham plus flunarizine hydrochloride	96	February 2023	China
Not yet recruiting	Acupuncture for Prophylaxis of Vestibular Migraine NCT04664088	Acupuncture vs venlafaxine	72	December 2023	China
Behavioral interventions					
Recruiting	Introvision for Migraine and Headaches NCT03507400	Introvision: mental and emotional self-regulation vs wait list	80	May 2020	Germany
Recruiting	Study on 30 Outpatients With Chronic Migraine Treated With Well-being Therapy or With a Control Therapy NCT03404336	Well-being therapy vs education-based on lifestyle and well-being National Institute for Health and Care Excellence guidelines	30	December 2020	Italy
Active, not recruiting	Feasibility and Effectiveness of Acceptance and Commitment Therapy (ACT) for High Frequency Episodic Migraine Without Aura NCT03461874	ACT plus treatment as usual vs treatment as usual	64	December 2022	Italy
Recruiting	Improving Health Outcomes of Migraine Patients Who Present to the Emergency Department NCT04281030	Progressive muscle relaxation therapy smartphone app vs monitored usual care	85	December 2022	United States

Status	Title and NCT	Interventions	Enrollment	Completion date	Location
Not yet recruiting	Effectiveness of a Dialogue-Based Online Intervention Against A) Tension-Type Headache and B) Migraine NCT04276142	Ceprica (online cognitive behavioral therapy for pain management) vs information on headache and migraine	520 ^a	October 2022	Not provided
Recruiting	TelemEdiciNe-bAsed Cognitive Therapy for Migraines NCT04613362	Cognitive behavioral therapy (TENACITY) via telehealth plus education vs cognitive behavioral therapy (face to face) plus education	150	June 2023	United States
Recruiting	Mindfulness Therapy for Chronic Migraine NCT03671681	Mindfulness-based therapy plus education plus standard pharmacological treatment vs education plus standard pharmacological treatment	170	November 2023	Italy
Education/self-management					
Recruiting	Clinical Decision Support for Patient Migraine Management NCT03706794	Education (tailored education provided via a smartphone app) vs nontailored education (provided via a smartphone app)	120	July 2021	United States
Not yet recruiting	Effectiveness of a Health Education Programme for Prevention of Chronic Migraine: A Randomized Clinical Trial NCT04788667	Education program delivered via telerehabilitation platform plus fremanezumab or erenumab vs general education plus fremanezumab or erenumab	182	April 2023	Not provided
Not yet recruiting	Healthy Living Partnerships for Veterans With Migraine NCT04373330	Intensive lifestyle intervention (including education component describing the links between lifestyle behaviors, including physical activity and migraine activity) vs usual care	24	December 2021	United States

Status	Title and NCT	Interventions	Enrollment	Completion date	Location
Noninvasive stimulation					
Active, not recruiting	Transcranial Magnetic Stimulation in Episodic Migraine (Magnet-EM) NCT03556722	Repetitive transcranial magnetic stimulation (rTMS) vs sham rTMS	76	January 2021	Malaysia
Recruiting	Vagus Nerve Stimulation and Stress Reduction Training for Migraine NCT03592329	tVNS + stress reduction training "A" (SRT A) vs tVNS plus SRT B vs sham plus SRT A vs sham plus SRT B	150	July 2024	United States

ACT: Acceptance and Commitment Therapy; NCT: National clinical trial; rTMS: Repetitive transcranial magnetic stimulation; SRT: Stress reduction training; tVNS: Transcutaneous vagus nerve stimulation;

Note: For all trials, study participants were adults with migraine.

^aTrial is divided between tension-type headache and migraine headache patients.

Appendix G. Excluded Studies

Table G-1. Excluded Studies: Acupuncture

Study type	Author, year	Reasons for exclusion
SR	Chen et al 2020 ²³⁶	Indirect treatment comparison meta-analysis.
SR	Giovanardi et al 2020 ²¹²	All relevant studies already captured in other included SRs.
SR	Jiang et al 2018 ²¹³	Superseded by subsequent SRs.
SR	Li et al 2019 ²³⁷	Follow-up duration not reported; studies reporting outcomes of interest not of requisite trial duration.
SR	Ou et al 2020 ²³⁸	Not restricted to RCTs; includes trials published in all languages.
SR	Shen et al 2019 ²¹⁴	All included studies captured in other SRs.
SR	Trinh et al 2019 ²³⁹	Does not report comparison of interest (includes only drug studies; only indirect comparison to acupuncture).
SR	Xu et al 2018 ²¹⁵	Superseded by subsequent SRs.
SR	Yang et al 2016 ²¹⁶	Superseded by subsequent SRs.
SR	Zheng et al 2021 ²⁴⁰	Not comparison of interest; network meta-analysis that includes indirect comparisons.
RCT	Bicer et al 2017 ⁸⁷	Included in Fan SR. ⁷⁴
RCT	Ceccherelli et al 2012 ^{241a}	Already included in Fan SR. ⁷⁴
RCT	Foroughipour et al 2014 ⁹³	Already included in Ni SR. ⁷⁵
RCT	Li et al 2012 ⁹⁸	Already included in Fan SR. ⁷⁴
RCT	Mayrink et al 2018 ²⁴²	Not a population of interest (<80% migraine patients).
RCT	Musil et al 2018 ¹⁰³	Already included in Ni SR. ⁷⁵
RCT	Naderinabi et al 2017 ¹⁰⁴	Included in Fan SR. ⁷⁴
RCT	Wallasch et al 2012 ¹¹¹	Already included in Fan SR. ⁷⁴
RCT	Wang et al 2015 ¹¹³	Already included in Fan SR. ⁷⁴
RCT	Yang et al 2011 ¹¹⁷	Already included in Fan SR. ⁷⁴
RCT	Yu and Salmoni 2018 ¹¹⁸	<10 patients per group.

Study type	Author, year	Reasons for exclusion
RCT	Zhao et al 2014 ¹²⁰	Already included in Fan SR. ⁷⁴
RCT	Zhao et al 2017 ¹²¹	Already included in Fan SR. ⁷⁴

Abbreviation: RCT, randomized controlled trial.

^aForeign language.

Table G-2. Excluded Studies: Behavioral Interventions

Study type	Author, year	Reasons for exclusion
SR	Buhrman et al 2016 ²¹⁷	Other more recent SRs identified.
SR	Eccleston et al 2014 ²⁴³	Adequate SRs within 5 years identified (also, no additional studies in this review).
SR	Harris et al 2015 ²⁴⁴	Other adequate SRs published within the past 5 years already identified.
SR	Huguet et al 2014 ²⁴⁵	Adequate SRs within 5 years addressed this question.
SR	McCombie et al 2015 ²⁴⁶	Other adequate SRs identified within 5 years.
SR	Mukhtar et al 2021 ²¹⁸	All relevant studies already captured in other included SRs.
SR	Pei et al 2021 ²¹⁹	Includes only 2 migraine-specific studies, which are already included in Anheyer SR ¹¹ and Lee SR. ¹⁴
SR	Roy et al 2020 ²⁴⁷	No migraine-specific studies.
RCT	Bakhshani et al 2015 ⁵²	Already included in Anheyer SR. ¹¹
RCT	Cousins et al 2015 ⁴⁷	Already included in Lee et al 2019. ¹⁴
RCT	Hedborg and Muhr 2011 ⁵⁴	Already included in Minen et al 2016. ¹⁶
RCT	Kleiboer et al 2014 ³⁴	Included in Lee SR. ¹⁴
RCT	Mansourishad et al 2017 ⁵⁵	Already included in Lee SR. ¹⁴
RCT	Martin et al 2014 ⁷¹	Already included for education in Probyn SR. ¹⁷
RCT	Meyer et al 2016 ⁵⁸	Already included in Lee et al 2019. ¹⁴
RCT	Mo'tamedi et al 2012 ²⁴⁸	Only 33% migraine (mostly tension-type headache).

Study type	Author, year	Reasons for exclusion
RCT	Odawara et al 2015 ³⁹	Already included in Lee SR. ¹⁴
RCT	Smitherman et al 2016 ⁴⁴	Already included in Sullivan SR. ²¹
RCT	Sorbi et al 2015 ²⁴⁹	Secondary analysis of Kleiboer et al 2014 ³⁴ included in Lee SR. ¹⁴
RCT	Varkey et al 2011 ⁶¹	Already included in Sullivan SR. ²⁰
RCT	Wachholtz et al 2019 ²⁵⁰	Secondary analysis of data from Wachholtz and Pargament 2008 ⁵⁷ included in Gu SR. ¹²
RCT	Wells et al 2014 ⁵⁶	Already included in Anheyer SR. ¹¹

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table G-3. Excluded Studies: Noninvasive Stimulation

Study type	Author, year	Reasons for exclusion
SR	Cadalso et al 2018 ²²¹	Includes invasive implanted devices.
SR	Chen et al 2015 ²⁵¹	Studies of implanted devices.
SR	Deer et al 2014 ²⁵²	Not an SR; expert panel recommendations.
SR	Feng et al 2019 ²²²	Relevant studies captured in Lan SR. ²²⁴
SR	Fregni et al 2021 ²⁵³	Guideline.
SR	Hofmeister et al 2020 ²⁵⁴	Not specific to migraine patients; chronic pain.
SR	Hulla et al 2019 ²²³	Most studies not of sufficient duration.
SR	Lan et al 2017 ²²⁴	Includes relevant RCTs (Shehata et al 2016, ¹⁶⁸ Misra et al 2013 ¹⁶⁵) already included in Moisset SR ¹⁰ ; additional RCTs have n < 10 per arm or examine effect on acute migraine (not migraine prevention).
SR	Reuter et al 2019 ²²⁵	Includes nonpublished studies; narrative review.
SR	Stilling et al 2019 ²⁵⁵	Not specific to migraine patients.
SR	Tajti et al 2019 ²⁵⁶	Narrative review; no risk of bias or strength of evidence analysis.
SR	Tao et al 2018 ²²⁶	Only 2 of 4 studies have interventions of interest.

Study type	Author, year	Reasons for exclusion
SR	Xu et al 2021 ²⁵⁷	Covers invasive devices; narrative review.
SR	Yang and Chang 2020 ²⁵⁸	Narrative review; not specific to migraine.
SR	Yang et al 2016 ²⁵⁹	Not an intervention of interest; invasive device.
RCT	Belvís et al 2020 ²⁶⁰	Guideline; narrative-style review.
RCT	Sahu et al 2019 ¹⁶⁶	Included in Moisset SR. ¹⁰
RCT	Antal et al 2011 ²⁶¹	Not intervention of interest (transcranial direct current stimulation of visual cortex).
RCT	Auvichayapat et al 2012 ²⁶²	Not intervention of interest (transcranial direct current stimulation of motor cortex).
RCT	Bono et al 2015 ²⁶³	Not intervention of interest (noninvasive occipital nerve stimulation).
RCT	Conforto et al 2014 ²⁶⁴	Included in Lan SR. ²²⁴
RCT	Dasilva et al 2012 ²⁶⁵	No outcomes of interest.
RCT	Diener et al 2019 ¹⁶²	Included in Moisset SR. ¹⁰
RCT	Dodick et al 2015 ²⁶⁶	Open-label extension of RCT. ²⁶⁷
RCT	Gandolfi et al 2018 ²⁶⁸	Not interventions of interest: (transcutaneous electrical nerve stimulation of trapezius vs acupuncture).
RCT	Granato et al 2019 ²⁶⁹	Not population of interest (mixture of migraine and medication overuse headache).
RCT	Grazzi et al 2020 ²⁷⁰	Not intervention of interest (motor cortex direct current electrical stimulation).
RCT	Juan et al 2017 ²⁷¹	Not intervention of interest (percutaneous mastoid electrical stimulation vs sham).
RCT	Kalita et al 2016 ¹⁶⁴	Included in Moisset SR. ¹⁰
RCT	Li and Xu 2017 ²⁷²	Not intervention of interest (invasive device).
RCT	Liu et al 2017 ²⁷³	Not intervention of interest (noninvasive occipital nerve stimulation).
RCT	Mekhail et al 2017 ²⁷⁴	Single-center subanalysis of larger RCT. ²⁶⁷
RCT	Pohl et al 2020 ²⁷⁵	Not intervention of interest (visual cortex stimulation).
RCT	Przeklasa-Muszyska et al 2017 ²⁷⁶	Not intervention of interest (DCS [direct current stimulation] of motor cortex plus pharmacologic vs pharmacologic).

Study type	Author, year	Reasons for exclusion
RCT	Rahimi et al 2020 ²⁷⁷	Not intervention of interest (transcranial DCS at motor or sensory cortex vs sham).
RCT	Rapinesi et al 2016 ²⁷⁸	Only n = 7 per group.
RCT	Rocha et al 2015 ²⁷⁹	Only n = 9 in control group.
RCT	Saper et al 2011 ²⁸⁰	Invasive device.
RCT	Schoenen et al 2013 ¹⁶⁷	Included in Moisset SR. ¹⁰
RCT	Shehata et al 2016 ¹⁶⁸	Included in Moisset SR. ¹⁰
RCT	Silberstein et al 2016 ¹⁶⁹	Included in Lai SR. ²⁸¹
RCT	Silberstein et al 2012 ²⁶⁷	Invasive device.

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table G-4. Excluded Studies: Education

Study type	Author, year	Reasons for exclusion
SR	Joypaul et al 2019 ²²⁷	Includes only one migraine-specific RCT, which is included in Kindelan-Calvo SR. ¹³
SR	Wallace and Dhingrha 2014 ¹⁹⁸	Does not report outcome of interest (does not address efficacy).
RCT	Bromberg et al 2012 ⁴¹	Included in Minen SR. ¹⁶
RCT	Mahmoudzadeh-Zarandi et al 2016 ⁶³	Included in Sharpe SR ¹⁹ and Probyn SR. ¹⁷
RCT	Smelt et al 2012 ²⁸²	Not intervention of interest (education directed at physicians, not patients).

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table G-5. Excluded Studies: Exercise and Physical Therapy

Study type	Author, year	Reasons for exclusion
SR	Baillie et al 2014 ²⁸³	Relevant RCT already included in Kindelan-Calvo SR. ¹³
SR	LaTouche et al 2020 ²²⁰	RCTs included here also included in Lemmens SR. ¹⁷¹
SR	Machado-Oliveira et al 2020 ²⁸⁴	Fails to specify if trials were RCTs.
RCT	Bond et al 2018 ¹⁷⁷	Included in Lemmens SR. ¹⁷¹
RCT	Hanssen et al 2017 ²⁸⁵	Data already reported in another trial included in Lemmens SR. ¹⁷¹
RCT	Hanssen et al 2018 ¹⁷⁹	Included in Lemmens SR. ¹⁷¹
RCT	Kroll et al 2018 ¹⁸²	Included in Lemmens SR. ¹⁷¹
RCT	Santiago et al 2014 ¹⁸³	Included in Lemmens SR. ¹⁷¹
RCT	Varkey et al 2011 ⁶¹	Included in Lemmens SR. ¹⁷¹

Abbreviations: RCT, randomized controlled trial; SR, systematic review.

Table G-6. Excluded Studies: Nutraceuticals

Study type	Author, year	Reasons for exclusion
SR	Ghorbani et al 2019 ²⁸⁶	Vitamin D not intervention of interest.
SR	Liampas et al 2020 ²⁸⁷	Not intervention of interest.
SR	Namazi et al 2015 ²²⁹	Narrative review.
SR	Nattagh-Eshstivani et al 2018 ²⁸⁸	Narrative review; literature search and risk of bias analysis not reported.
SR	Nierenburg et al 2015 ²³⁰	Narrative review; most interventions not of interest.
SR	Okoli et al 2019 ²²⁸	Mixed interventions; covered in other reviews.
SR	Park et al 2020 ²⁸⁹	Narrative review not specific to migraine; Okoli et al 2019 ²²⁸ and Chiu et al 2016 ¹²⁴ cover more studies.
SR	Parohan et al 2020 ²³¹	Superseded by Sazali SR. ⁸

Study type	Author, year	Reasons for exclusion
SR	Rehman et al 2019 ²³²	Most interventions of interest covered in other SRs and individual studies.
SR	Thompson and Saluja 2017 ²³³	Narrative review; also superseded by Chen. ⁹
SR	Tseng et al 2020 ²³⁴	Only 2 studies of interest; more direct comparisons covered in Liampas et al 2020. ¹²⁶
SR	Zeng et al 2019 ²³⁵	Superseded by Sazali et al 2021. ⁸
RCT	Pringsheim et al 2012 ⁵	Guideline.
RCT	Dahri et al 2017 ²⁰⁰	Already included in Sazali SR. ⁸
RCT	Dahri et al 2019 ¹³⁹	Already included in Sazali SR. ⁸
RCT	Gaul et al 2015 ¹⁵⁷	Already included in Sazali SR. ⁸
RCT	Gazerani et al 2019 ²⁹⁰	Vitamin D not intervention of interest.
RCT	Ghorbani et al 2020 ²⁹¹	Vitamin D not intervention of interest.
RCT	Gonçalves et al 2016 ¹⁵⁶	Already included in Liampas SR. ¹²⁶
RCT	Hajhashemi et al 2019 ¹⁴⁰	Already included in Sazali SR. ⁸
RCT	Mottaghi et al 2015 ²⁹²	Vitamin D not intervention of interest.
RCT	Nattagh-Eshtivani et al 2018 ¹⁴¹	Already included in Sazali SR. ⁸
RCT	Rahimdel et al 2015 ¹³³	Already included in Chen SR. ⁹
RCT	Tarighat Esfanjani et al 2012 ¹⁵¹	Already included in Chiu SR. ¹²⁴

Abbreviations: RCT, randomized controlled trial; SR, systematic review.