# Evidence-based Practice Center Systematic Review Protocol

# Project Title: *Behavioral Interventions for Migraine Prevention*

## I. Background and Objectives for the Systematic Review

### Background

Migraine affects 1 in 6 Americans and globally ranks second among causes of disability, often affecting individuals during critical years of schooling, career development, and child-rearing.[1] Migraine prevention interventions aim to decrease the frequency, severity, and negative life impact of migraine attacks. Behavioral interventions (e.g., cognitive behavioral therapy [CBT], relaxation, mindfulness-based therapies, biofeedback) can offer an important alternative or complement to drug therapies, which can be associated with side effects, drug-drug interactions, contraindications (e.g., pregnancy, cardiac history), and limited efficacy.

Despite interest in behavioral interventions, current guidance from headache societies is limited and requires updating. The most recent clinical practice guidelines from headache societies date from 2012 and do not consider some newer therapies.[2] Consensus statements issued by the American Headache Society (AHS) and American Academy of Family Physicians (AAFP) about nonpharmacologic prevention for migraine were not based on systematic reviews of the evidence and did not fully address the unique treatment needs of children and adolescents.[3-6] A recent topic brief and rapid scoping review of the literature suggested existing systematic reviews on behavioral therapies were outdated.[7] The most recent reviews were published several years ago (2018,2019), and covered psychological interventions, biofeedback, cognitive behavioral therapy, and progressive muscle relaxation for migraine prevention in adults, but did not comprehensively assess all preventive behavioral therapy options.[8-10] Similarly, although a recently published network meta-analysis assessed nonpharmacologic interventions for migraine in children and adolescents, the literature search was completed in 2019.[11]

Given the lack of a recent and comprehensive systematic review and accumulation of newer evidence, we will perform a systematic review to identify and assess evidence for behavioral interventions for migraine prevention in children, adolescents, and adults. This review will address efficacy, comparative effectiveness of migraine-focused behavioral interventions and pharmacotherapy, and harms. In addition, we will also examine the effects of particular non-migraine-focused behavioral interventions. Furthermore, we will examine the extent to which the effects of these interventions vary among individuals characterized by biopsychosocial factors (e.g., sex, socioeconomic status, co-occurring mental health conditions). In this project, we pragmatically define behavioral interventions as nonpharmacologic interventions that aim to improve outcomes through changing behavior and/or ways of thinking.

### Purpose of the Review

The Agency for Healthcare Research and Quality (AHRQ) is collaborating with the American Headache Society (AHS) and Patient-Centered Outcome Research Institute (PCORI) to conduct a systematic evidence review on interventions for behavioral interventions for migraine prevention. The final Research Protocol will be used to guide a systematic review of the evidence by researchers at an Evidence-based Practice Center. The resulting systematic review will form the basis of the AHS clinical practice guidelines on this topic. The intended audience includes guideline developers, health system administrators, and clinicians who provide care to individuals with migraine (e.g., primary care providers, advanced practice practitioners, neurologists, and psychologists).

## II. The Key Questions

This review will be guided by five key questions (KQs). KQs 1 and 2 address the effectiveness and comparative effectiveness of migraine-focused behavioral preventive interventions delivered either in-person or via telehealth. KQ3 addresses the effects of single elements of complex individual behavioral interventions. KQ4 targets the effects of non-migraine-focused behavioral interventions for migraine. KQ5 addresses the extent to which the effectiveness of behavioral interventions might differ depending on patients' characteristics. In addition, two contextual questions (CQs) will address potential benefits of behavioral treatments which include components targeting caregivers (CQ1) and describe patient and provider perceptions of the effects and barriers to engaging with behavioral preventive treatments for migraine (CQ2).

The original questions provided in the request for task orders (RFTO) were revised by the systematic review project team in partnership with the AHS partners, AHRQ Task Order Officer (TOO), PCORI, Key Informants (KIs), and input received while the KQs were posted for public comment.

### Key Questions

**KQ 1:** What are the benefits and harms of behavioral interventions, either alone or in combination with other preventive strategies (including pharmacologic therapy), for migraine prevention compared to inactive control for children and adults?

> **KQ1a:** What are the benefits and harms of behavioral interventions delivered via telehealth and digital health (e/mHealth) technology compared to inactive control?

**KQ 2:** What is the comparative effectiveness and harms of a behavioral intervention for migraine prevention compared to either a) a pharmacologic preventive agent or b) another behavioral intervention for children and adults?

> **KQ2a**: What is the comparative effectiveness and harms of behavioral interventions delivered via telehealth and digital health (e/mHealth) technology compared to a) pharmacologic prevention or b) other behavioral interventions?

**KQ 3:** For multicomponent or combined behavioral interventions, what are the effects of individual behavioral intervention components?

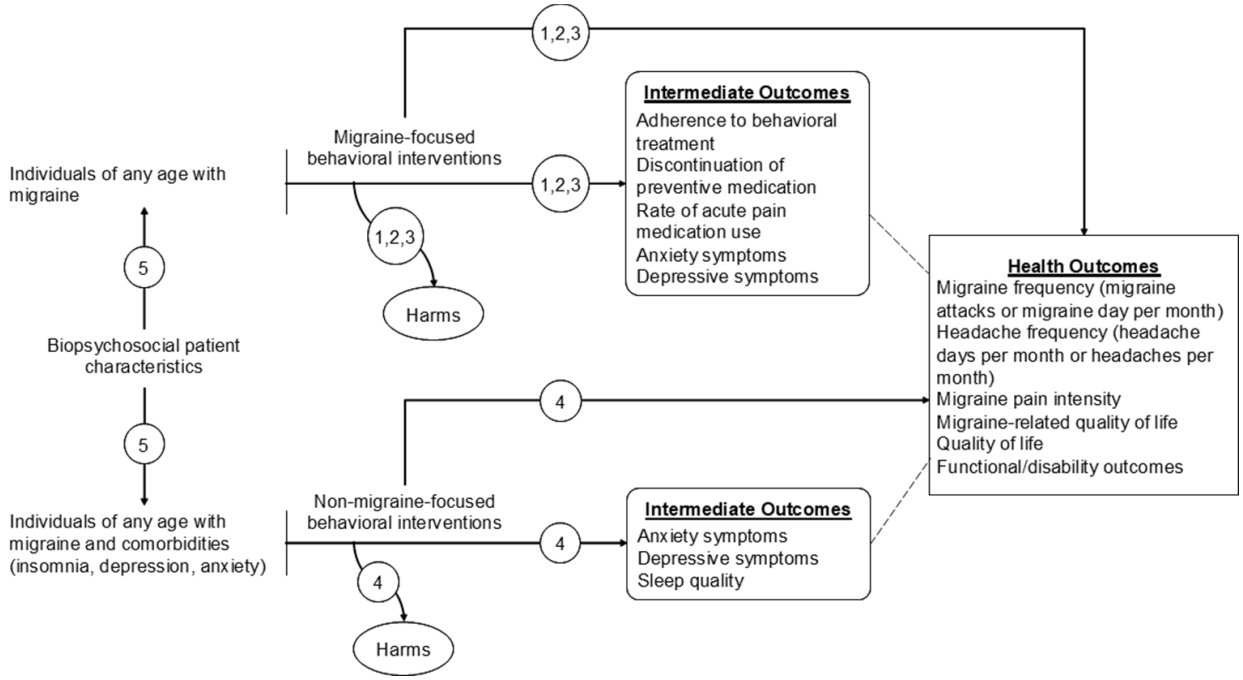
**KQ 4:** What are the benefits and harms of non-headache focused behavioral interventions (e.g., CBT for insomnia, CBT for depression/anxiety, parent training) for migraine prevention in children and adults with migraine?

**KQ 5:** For key questions 1–4, how do the findings vary by baseline biopsychosocial factors (e.g., sex, socioeconomic status, co-occurring mental health conditions)?

**Contextual Questions:**
**CQ 1:** What evidence is available on the benefits of behavioral preventive treatments for children and adults with migraine that include intervention components targeting caregivers (e.g., parents, spouses, and other key support people)?

**CQ 2:** What are patient and provider perceptions of the benefits, harms, and barriers to engaging with behavioral treatments for migraine prevention in children and adults?

## III. Analytic Framework for *Behavioral Interventions for Migraine Prevention*




Circles denote key question numbers.

## IV. Methods

### A. Criteria for Inclusion/Exclusion of Studies in the Review

| PICOTS | Inclusion | Exclusion |
|---|---|---|
| **Patients** | **All KQs:**<br>• Children (age 6 to 11), adolescents (12 to 17), and adults (18 or older) with migraine headache (episodic or chronic) | **All KQs:**<br>Studies conducted exclusively |

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| | We will not require studies to only include individuals with an International Classification of Headache Disorders diagnosis of migraine headache.<br><br>• ≥80% of study participants had migraine headache, or the study reports a subgroup analysis comprised of at least 80% migraine patients<br>• We will include studies with participants with other headache types (e.g., medication overuse headache, tension type headache, cluster headache, etc.) in addition to migraine, as long as ≥80% of participants have migraine | • Among individuals in institutions (e.g., psychiatric inpatients, long-term care facilities, incarcerated populations)<br>• Parents, for studies with interventions targeting children and adolescents<br>• Individuals with psychotic disorders |
| **Interventions** | **KQs 1–3**<br>Migraine-focused behavioral interventions used for prevention, administered either alone or with pharmacotherapy, delivered in-person, via telehealth, or with e- or mHealth<br>1. CBT<br>• Cognitive behavioral therapy<br>• Cognitive therapy<br>• Behavioral therapy<br>• Stress management training (SMT)<br>• Coping skills training<br>• "Learning to cope with triggers" (LCT)<br>• Parent/caregiver operant training (parent or caregiver reinforces coping behaviors)<br>• Problem-solving training<br><br>2. Biofeedback<br>• Thermal/temperature biofeedback (Handwarming/Thermal biofeedback) (often feedback of skin temperature from finger)<br>• Electromyographic (EMG) biofeedback (feedback of electrical activity from muscles of scalp, neck, or upper body)<br>• Heart rate variability biofeedback<br>• Electrocardio biofeedback<br>• Pulse<br>• Blood Volume Pulse | We will exclude studies focused solely on the following interventions:<br>• Physical therapy<br>• Exercise<br>• Catharsis therapy (e.g., written emotional disclosure)<br>• Occupational therapy<br>• Creative arts therapy (art therapy, music therapy, dance therapy) |

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| | • Respiratory<br>• Electroencephalography (EEG)/Neurofeedback<br><br>3. Relaxation<br>• Diaphragmatic Breathing<br>• Progressive muscle relaxation (alternatively tensing/relaxing selected muscles)<br>• Autogenic feedback (use of calm, self-soothing statements to promote a state of deep relaxation)<br>• Autogenic training<br><br>4. Mindfulness based stress reduction<br>• Meditation (use of silently repeated word or sound to promote mental calm and relaxation)<br>• Transcendental meditation<br>• Guided imagery/Guided visual imagery<br><br>5. Third wave CBT<br>• Acceptance and commitment therapy<br><br>6. Education<br>• Education (skills, lifestyle, exercise, nutrition, hydration, stress management, sleep hygiene)<br>• Neuroscience education therapy<br>• Healthy lifestyle counseling<br>• Sleep counseling<br>• Trigger avoidance<br>• Weight management (informational)<br>• Diary/tracking<br><br>7. Hypnotherapy<br>8. Trauma-informed therapy<br>• Eye movement desensitization and reprocessing (EMDR)<br>• Trauma-focused therapy<br><br>9. Dialectical behavioral therapy (DBT)<br>10. Motivational interviewing and stages of change<br>11. Professionally led support groups/peer support<br>12. Combination therapies<br><br>**KQ1a and KQ2a:** The above interventions delivered via telehealth or with e- or mHealth. | |

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| | **KQ 4**<br>Non-headache focused behavioral interventions, e.g.,<br>• CBT for insomnia or depression/anxiety<br>• Sleep hygiene counseling<br>• Parent/caregiver operant training (parent or caregiver reinforces adaptive sleep behaviors)<br>• Healthy lifestyle counseling<br><br>**KQ5** Interventions included for KQs 1–4 | |
| **Comparisons** | **KQs 1**<br>• No intervention (e.g., waitlist, usual care)<br>• Minimal intervention (e.g., educational materials without skills training)<br>• Most active: Attention control, sham, or placebo<br><br>**KQs 2–4**<br>A different eligible behavioral intervention<br><br>**KQ 2–4**<br>Medications from the following drug classes (see Table 2):<br>• Alpha agonists<br>• Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers<br>• Antiepileptics<br>• Antihistamines (for child and adolescents only)<br>• Beta-blockers<br>• Botulinum toxin type A<br>• Calcitonin gene–related peptide antagonists<br>• Calcium channel blockers<br>• Other antidepressants<br>• Serotonin norepinephrine reuptake inhibitors (SNRIs)<br>• Tricyclic antidepressants<br><br>**KQ5** Comparators in KQs 1–4 | Comparators not listed as included. |
| **Outcomes** | **All KQs** | |

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| | Migraine/Headache frequency:<br>• Migraine / headache count: Migraine days per month, migraine attacks per month, headache days per month, or headaches per month.<br>• Responder rate: 50% or more reduction in one of the above quantities<br><br>Functional Status/Disability<br>• MIDAS, PedMIDAS, HANA, MIBS, FIS, FDI (Parent form), FDI-(child and adolescent), IMPAC)<br><br>Quality of Life (QOL)<br>• Migraine Specific: HIT-6, MSQoL v2.1, MSQ<br>• General: SF-36, EQ-5, SF-12, PedsQL<br><br>Adverse effects such as dropout and any reported<br><br>Emotional Status<br>• Anxiety symptoms (e.g., GAD-7, PROMIS Pediatric – Anxiety, HADS)<br>• Depression symptoms (e.g., PHQ4, PHQ 9, CDI, PROMIS Pediatric-Depression, HADS)<br><br>Other:<br>• Most bothersome symptoms<br>• Headache pain intensity (VAS, NRS)<br>• Acute headache medication use<br>• Discontinuation of preventive medication<br><br>**KQ 4. Additional outcomes:**<br>• Anxiety (e.g., GAD-7, PROMIS Pediatric - Anxiety)<br>• Depression (e.g., PHQ 4, PHQ 9, CDI, PROMIS Pediatric-Depression)<br>• Sleep outcomes (sleep onset latency, wake after sleep onset, total sleep time, sleep efficiency) | |
| **Study Design Criteria** | **All KQs:** | **All KQs:** |

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| | • Randomized controlled trials reporting outcomes for ≥ 10 participants per treatment arm<br>• Period 1 data from crossover RCTs<br>• Published in English-language<br>• Published 1975 or after<br><br>For KQ1-4, we will require studies to report at least one of four primary outcomes: Migraine/Headache frequency, migraine-related disability, migraine-specific quality of life, and/or adverse events. | • Exclude crossover trials not reporting period 1 data separately<br>• Exclude reviews, letters, guidelines, position statements and commentaries<br>• Exclude single arm or non-randomized controlled studies<br><br>SRs will only be used to identify potential RCTs for inclusion |
| **Setting** | • Any non-inpatient setting<br>• Trials conducted in countries rated as "very high" on the 2022 Human Development Index (as defined by the United Nations Development Programme) | Hospitalized patients |
| **Timing** | Studies must report a primary outcome at 4 weeks or longer after treatment initiation | |

CDI = Children's Depression Inventory, EQ-5D = EuroQol-5D, FDI-Child Form = Functional Disability Inventory - Child and Adolescent Form, FDI-Parent Form = Functional Disability Inventory - Parent Form, FIS = Fatigue Impact Scale, GAD-7 = General Anxiety Disorder-7, HADS = Hospital Anxiety and Depression Scale, HANA = HeAdache Needs Assessment, HIT–6™ = Headache Impact Test, IMPAC = Impact of Migraine on Partners and Adolescent Children, MIBS = Migraine Interictal Burden Scale, MIDAS = Migraine Disability Assessment, MSQ = Migraine Specific Quality of Life Questionnaire v. 2.1, NRS = Numeric Rating Scale, PedMIDAS = Pediatric Migraine-Specific Disability Assessment, PedsQL = Pediatric Quality of Life Inventory, PHQ = Patient Health Questionnaire–Depression, PQ-LES-Q = Pediatric quality of life enjoyment and satisfaction , SF-12 = 12-Item Short Form Survey, SF-36 = 36-Item Short Form Survey, VAS = Visual Analogue Scale

**Table 1. Migraine Prevention Medications**

| Intervention Class | Specific interventions |
|---|---|
| Alpha agonists | Clonidine, guanfacine |
| Angiotensin-converting enzyme inhibitors/Angiotensin receptor blockers | Candesartan, captopril, enalapril, lisinopril, telmisartan |
| Antiepileptics | Carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid, zonisamide |
| Antihistamines (for children and adolescents only) | Cyproheptadine |
| Beta-blockers | Acebutolol, atenolol, bisoprolol, metoprolol, nadolol, nebivolol, propranolol, timolol |

| Intervention Class | Specific interventions |
|---|---|
| Botulinum toxin type A | AbobotulinumtoxinA, incobutulinumtoxinA, onabotulinumtoxinA |
| Calcitonin gene–related peptide antagonists | Atogepant, rimegepant, eptinezumab, erenumab, fremanezumab, galcanezumab |
| Calcium channel blockers | Nicardipine, nifedipine, nimodipine, verapamil |
| Other antidepressants | Citalopram, escitalopram, fluoxetine, fluvoxamine |
| Serotonin norepinephrine reuptake inhibitors (SNRIs) | Venlafaxine, duloxetine |
| Tricyclic antidepressants | Amitriptyline, clomipramine, nortriptyline, protriptyline |

**B. Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

A research librarian will develop a comprehensive search strategy. The research librarian will search MEDLINE and EMBASE (via EMBASE.com), PsycINFO, PubMed (publisher-supplied records only), and the Cochrane Database of Systematic Reviews for randomized controlled trials, systematic reviews, and meta-analyses published from 1975 to the present (**Appendix A**). We chose 1975 because recent systematic reviews covering adult and pediatric populations did not identify any relevant studies published before 1975.[10,11] The search strategy will be independently peer-reviewed by a second librarian using the PRESS Checklist.[12] The proposed search strategy for EMBASE and Medline (via EMBASE.com) is included in Appendix A. Additionally, we will review reference lists of other systematic reviews for inclusion in the current review.

The research librarian will also conduct a grey literature search of relevant stakeholder organizations (e.g., American Headache Society, American Academy of Neurology), clinical trial registries (e.g., ClinicalTrials.gov), government agencies (e.g., NIH, AHRQ), PCORI, and other resources identified by the other team members, KI's, and TEP. We will update our literature search during the peer review of the draft report.

To inform the contextual questions, we will search the last five years for pertinent survey and qualitative studies; we will also include any pertinent data identified from search results addressing the Key Questions. Contextual questions will be addressed in the review's Discussion section.

We will use prespecified criteria to guide study selection. Citations will be screened in DistillerSR (DistillerSR Inc., Ottawa, Canada). Two reviewers will independently screen abstracts and full-text articles. Discrepancies will be resolved by discussion and consensus among the review team.

For screening, we will employ the capabilities of Microsoft Excel and DistillerSR to maximize efficiency. In MS Excel, we will use text formulas applied to titles and abstracts to accelerate the exclusion of obviously irrelevant articles. To accelerate screening efficiency, we will utilize results from a recent topic brief, Nonpharmacologic Treatments for Migraine Prevention[7], which identified 52 potentially relevant RCTs in adults. We will screen these trials first to facilitate early identification of trials with a high probability of inclusion. Prioritizing these trials for

screening will also support "training" of DistillerSR's Re-Rank tool in title and abstract screening allowing for more accurate prioritization of references for screening and acceleration of full-text ordering of articles for potential inclusion. We will also consider modifying the screening approach from dual to single screening by experienced reviewers once the tool estimates that 95% of relevant references have progressed to full-text screening.

### D. Data Abstraction and Data Management

One reviewer will extract data into a standardized data abstraction form in DistillerSR. A second analyst will perform a quality check of 10% of extracted data for accuracy. For each included trial, we will abstract general study characteristics (e.g., author, year of publication, design, authors, purpose, country), patients' characteristics and settings (e.g., age, sex, gender identification, race/ethnicity, socioeconomic status, comorbidities, setting, country, funding source), migraine characteristics (migraine subtype, diagnostic criteria used for migraine, concomitant migraine prevention treatments including medications, devices, or other treatments; co-morbid headache disorders); intervention and comparator details (e.g., type, intensity, dose, delivery method), and study results (health and intermediate outcomes).

### E. Assessment of Methodological Risk of Bias of Individual Studies

We define risk of bias as the risk that a study's point estimate of the effect size is inaccurate. We will assess the risk of bias in each study included for a KQ. We will assess randomized trials for Key Questions 1 and 2 using the Cochrane Risk of Bias 2 (ROB2) tool.[13] The five domains of ROB2 are:

- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

Two reviewers will independently evaluate each to-be-graded outcome reported by each study and assign a risk of bias rating of "high," "some concerns," and "low" for each of the above domains and for the overall risk of bias. Discrepancies will be resolved by discussion and consensus among the review team. Although we will assess selective outcome reporting, we will not incorporate it in the overall risk of bias rating because the EPC SOE system places it in the Reporting Bias domain (along with publication bias).

### F. Data Synthesis

The data will be synthesized separately for each KQ. We will summarize the evidence both qualitatively and quantitatively (e.g., meta-analysis, network meta-analysis) when possible. Decisions about whether a quantitative synthesis is appropriate will be based on the number of studies, our judgment regarding population, research design, and outcome measures heterogeneity across the included studies.

To address clinical heterogeneity, we plan to conduct separate analyses for adult and pediatric populations, as well as for episodic and chronic migraine populations. To assess whether pairwise meta-analysis will be appropriate, we will consider population factors, including treatment history, intervention factors such as similarity in intervention definitions, and whether outcomes are the same or address the same concept (e.g., frequency measures such as monthly headache days and monthly migraine days are suitable for combining across studies, but headache index, which includes both frequency and severity, would not be combined with these).

No widespread consensus regarding a minimally important difference (MID) for headache outcomes exist. However, given recent thresholds used for approval of newer migraine specific drugs or thresholds for powering trials, for headache frequency, we will use a difference of 1 migraine day/month as the MID for between group comparisons (i.e., intervention vs. control or another intervention).[14-17]

In considering network meta-analysis, we will evaluate how these factors are distributed across direct comparisons, as well as systematic differences in intervention implementation based on the comparator (e.g., whether CBT is implemented similarly in trials with an inactive comparator to those with an active control).

For Key Question 5, which addresses possible associations between patient factors and treatment effectiveness, we will prioritize any pertinent subgroup analyses reported by each study. For example, some studies might report that the post-treatment migraine difference between CBT and usual care was higher for patients with concomitant anxiety than for other patients. In the absence of such subgroup analyses, we will consider meta-regression as a secondary method for assessing whether the KQ1–4 results vary by patient factors (e.g., did CBT vs. usual care studies with a higher enrolled percentage of patients with anxiety observe larger between-group differences in outcomes than other CBT vs. usual care studies).

### G. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the SOE for the following outcomes:

- Migraine/Headache Frequency (most often reported in days per month or 28 days)
- Functional Status/Disability
- Quality of Life (Migraine specific)
- Adverse effects

We will grade the SOE according to EPC Methods Guide recommendations. The primary domains assessed include risk of bias, directness, consistency, precision, and reporting bias. Additional domains may be used when appropriate, including dose-response association, strength of association, and the possibility that controlling for plausible confounders would increase the effect size. The output is a rating of the SOE: high, moderate, low, or insufficient. This rating is made separately for each outcome of each comparison of each KQ.

We will assign a rating of Insufficient when the evidence does not permit a conclusion for the outcome of interest for that KQ (for example, when a difference is not statistically significant, and the 95% confidence is too wide to permit a conclusion that there is no important difference

[based on the MID]). If the evidence is sufficient to permit a conclusion, the rating is deemed high, moderate, or low. Below, we discuss the primary domains and how we will assess them:

**Risk of bias** (see the above section entitled *Assessment of Methodological Risk of Bias of Individual Studies*). This concerns internal validity: the extent to which post-treatment outcomes can be attributed to the treatments themselves rather than other factors. If the evidence permits a conclusion, then, all else being equal, a set of studies at low risk of bias yields a higher SOE rating than a set of studies at moderate or high risk of bias.

**Directness.** Directness relates to (a) whether evidence links interventions directly to a health outcome of specific importance for the review and (b) for comparative studies, whether the comparisons are based on head-to-head studies.

**Consistency.** Consistency is the degree to which included studies find either the same direction or similar magnitude of effect.

**Precision.** Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome, based on the width of confidence intervals relative to a clinically important effect estimate, sufficiency of sample size, and number of events.

**Reporting bias**. Reporting bias will be addressed by examining the funding source of included studies, the direction and magnitude of effects identified in included studies, possible selective outcome reporting, and noting the presence of abstracts or ClinicalTrials.gov entries describing studies that did not subsequently appear as full-length published articles.

### H. Applicability

Several factors may limit the applicability of findings, including the extent to which the results from included studies may or may not apply to the full spectrum of patients, interventions, and comparators for this clinical area. Based on EPC guidance, the SOE rating will be uninfluenced by these factors. Instead, we will discuss applicability in a separate section, using PICOTS as a guiding framework to ensure that we consider several components of applicability.

## V. References


1. Steiner TJ, Stovner LJ, Jensen R, et al. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain. 2020 Dec;21(1):137. doi: 10.1186/s10194-020-01208-0. PMID: 33267788.
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## VI. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe each change and give the rationale in this section.

## VII. Review of Key Questions

The Agency for Healthcare Research and Quality (AHRQ) posted the Key Questions on the AHRQ Effective Health Care Website for public comment. The Evidence-based Practice Center (EPC) refined and finalized them after reviewing the public comments and seeking input from Key Informants (KIs).

## VIII. Key Informants

Key Informants are the end-users of research; they can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into the decisional dilemmas and help keep the focus on Key Questions that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for the systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## IX. Technical Expert Panel (TEP)

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel is selected to

provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts.

Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism. Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

## X. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

## XI. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

## XII. Role of the Funder

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## XIII. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

**Appendix A. Search strategies**

Embase.com Strategy: (Combines Medline and EMBASE)
*Syntax*
* = truncation
/exp = explode to include all terms in the tree
/mj = limit to terms indexed as major concepts
/de = search term without exploding
:ti = search in the title field
:kw = search in the author keywords field
:ab = search in the abstract field
NEAR/# - search the terms within # of each other in any order
NEXT/# - search terms within # of each other in the specified order

1 'migraine'/exp OR migrain*:ti,ab,kw OR headache*:ti

2 ('drug free' OR non-drug OR nondrug OR non-pharmacologic* OR nonpharmacologic* OR collaborative OR 'inter disciplinary' OR interdisciplinary OR 'multi disciplinary' OR multidisciplinary OR psych* OR behav* OR cognitive):ti

3 Psychotherapy/exp OR 'psychological care'/mj/exp OR 'behavior therapy'/exp OR 'cognitive therapy'/exp OR 'cognitive behavioral therapy'/exp OR 'stress management'/de OR 'coping behavior'/exp OR 'caregiver support'/de OR 'parent counseling'/de OR 'problem solving'/de OR 'problem-focused coping'/exp OR ((behav* OR cognitive) NEAR/2 (intervention* OR modif* OR therap* OR treatment* OR manag*)):ti,ab,kw OR (manag* NEAR/2 stress):ti,ab,kw OR coping:ti,ab,kw OR (cope NEAR/3 trigger*):ti,ab,kw OR ((caregiver* OR mother* OR father* OR parent*) NEAR/4 (behav* OR counsel* OR educat* OR intervention* OR mediated OR support* OR train* OR operant* OR therapy)):ti,ab,kw OR ('parent child interaction therapy' OR PCIT OR 'supportive care'):ti,ab,kw OR (problem NEXT/3 (solving OR coping)):ti,ab,kw OR psychotherap*:ti,ab,kw

4 'biofeedback'/exp OR 'neurofeedback'/de OR 'biofeedback system (device)'/de OR 'biofeedback software (device)'/de OR (biofeedback OR 'bio feedback' OR neurofeedback OR 'neuro feedback' OR neurobiofeedback* OR neurotherapy*):ti,ab,kw OR (Handwarming OR 'hand warming'):ti,ab,kw OR (feedback NEAR/5 (thermal OR temperature OR EMG OR electromyograph* OR 'heart rate' OR electrocardiogra* OR pulse OR "blood volume" OR respiratory OR respiration OR breathing OR electroencephalogra* OR EEG OR ECG OR BVP)):ti,ab,kw OR (finger* NEAR/3 temp*):ti,ab,kw OR (skin NEAR/3 conduct*):ti,ab,kw

5 'relaxation training'/de OR 'muscle relaxation'/de OR 'autogenic training'/exp OR 'breathing exercise'/exp OR 'guided imagery'/exp OR (Autogenic NEAR/3 (feedback OR training OR exercise)):ti,ab,kw OR ('AFTE' OR 'progressive muscle relaxation'):ti,ab,kw OR (relaxation NEXT/2 (techniques OR therapy OR training)):ti,ab,kw OR breathing:ti OR relaxation:ti,ab,kw OR (Breathing NEAR/4 (exercise* OR deep OR guided OR diaphragm* OR paced OR belly)):ti,ab,kw OR ((guided OR visual) NEXT/3 imagery):ti,ab,kw

6 meditation/exp OR 'mindfulness-based stress reduction'/exp OR 'mindfulness based cognitive therapy'/exp OR (mindfulness* OR 'mind body' OR MBSR OR MBCT OR meditat*):ti,ab,kw

7 'acceptance and commitment therapy'/de OR (acceptance NEXT/2 commitment):ti,ab,kw

8 'dialectical behavior therapy'/de OR 'dialectical behav* therapy'

9 'motivational interviewing'/de OR 'transtheoretical model'/de OR (motivational NEXT/2 (enhancement OR interview*)) OR 'stages of change' OR (transtheoretical NEXT/2 model*)

10 'education program'/de OR 'patient education'/de OR 'patient guidance'/de OR 'patient counseling'/exp OR 'nutritional counseling'/de OR 'counseling'/de OR 'lifestyle modification'/de OR 'self care'/de OR coaching:ti,ab,kw OR counseling:ti,ab,kw OR counselling:ti,ab,kw OR (((education* OR management* OR training) NEXT/3 (intervention* OR program*)):ti,ab,kw) OR (((weight OR nutrition* OR lifestyle OR neuroscience OR sleep* OR diet* OR exercis* OR hydrat*) NEAR/3 (education* OR training* OR coaching OR counseling OR counselling)):ti,ab,kw) OR 'self care':ti,ab,kw OR 'self management':ti,ab,kw OR ((trigger* NEAR/3 avoid*):ti,ab,kw) OR motivation*:ti,ab,kw OR ((goal* NEAR/3 set*):ti,ab,kw) OR diary:ti,ab,kw OR diaries:ti,ab,kw OR journaling:ti,ab,kw OR (((keep* OR record*) NEXT/2 journal*):ti,ab,kw)

11 'hypnosis'/de OR (hypnosis OR hypnotherap*):ti,ab,kw

12 'eye movement desensitization and reprocessing'/de OR EDMR OR 'eye movement desensiti*' OR (trauma NEXT/3 (informed OR focused)):ti,ab,kw

13 'group therapy'/exp OR 'support group'/exp OR ((group OR peer* OR 'self help') NEAR/2 (counseling OR meeting* OR therap* OR support*)):ti,ab,kw OR ((mutual OR community OR peer) NEAR/2 (help OR group* OR meeting* OR 'self help' OR support* OR aided OR led OR assist*)):ti,ab,kw

14 'sleep hygiene'/de OR chronotherapy/de OR ((sleep OR insomnia*) NEAR/2 (behav* OR educat* OR habit* OR health OR hygiene OR quality OR specialist* OR therap* OR intervention*)):ti,ab,kw OR (CBTi OR chronotherap*):ti,ab,kw

15 bluetooth/mj OR 'e therapy'/mj OR 'internet'/mj OR 'mobile application'/exp OR 'mobile phone'/exp OR 'short message service'/mj OR 'social media'/mj OR 'tablet computer'/mj OR 'teleconsultation'/exp OR 'telehealth'/mj OR 'telemedicine'/mj OR 'telemonitoring'/mj OR 'telephone'/mj OR 'telepsychiatry'/mj OR 'telepsychology'/mj OR 'telepsychotherapy'/mj OR 'teletherapy'/mj OR 'text messaging'/mj OR 'web-based intervention'/mj OR 'wireless communication'/mj OR 'video consultation'/mj OR 'videoconferencing'/mj OR bluetooth:ti OR 'blue tooth':ti OR (((distance OR mobile OR remote OR tele* OR virtual) NEAR/3 (care OR counseling OR counselor* OR consult* OR health OR medical OR medicine OR monitor* OR psychiatr* OR psycholog* OR psychotherap* OR therapy OR visit*)):ti) OR android*:ti OR app:ti OR apps:ti OR asynchronous*:ti OR cellphone*:ti OR 'computer based':ti OR cyber*:ti OR digital:ti OR 'e health*':ti OR ehealth*:ti OR 'e therapy':ti OR etherapy:ti OR facebook:ti OR facetime:ti OR internet:ti OR ipad:ti OR iphone:ti OR 'lap top*':ti OR laptop*:ti OR 'm health*':ti OR mhealth*:ti OR (((mobil* OR portab*) NEXT/1 (computer* OR device* OR health OR tablet*)):ti) OR 'on line':ti OR online:ti OR phone:ti OR phones:ti OR samsung:ti OR 'short messag* service*':ti OR smartphone*:ti OR (((sms OR text) NEXT/2 messag*):ti) OR ((social NEXT/1 (media OR network* OR platform*)):ti) OR

| | |
|---|---|
| | software:ti OR synchronous*:ti OR teleconsult*:ti OR telecounsel*:ti OR telehealth*:ti OR telemed*:ti OR telemonitor*:ti OR telephone*:ti OR telepsych*:ti OR teletherapy:ti OR televisit*:ti OR texting*:ti OR video*:ti OR web:ti OR website*:ti OR zoom:ti |
| 16 | 1 AND (2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15) |
| 17 | 16 NOT (([animals]/lim NOT [humans]/lim) OR ((animal OR animals OR canine* OR dog OR dogs OR feline OR hamster* OR lamb OR lambs OR mice OR monkey OR monkeys OR mouse OR murine OR pig OR piglet* OR pigs OR porcine OR primate* OR rabbit* OR rat OR rats OR rodent* OR sheep* OR swine OR veterinar* OR (vitro NOT vivo)) NOT (human* OR patient*)):ti) |
| 18 | 17 NOT ('book'/de OR 'case report'/de OR 'conference paper'/exp OR 'editorial'/de OR 'letter'/de OR (book OR chapter OR conference OR editorial OR letter):it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR (abstract OR annual OR conference OR congress OR meeting OR proceedings OR sessions OR symposium):nc OR ((book NOT series) OR 'conference proceeding'):pt OR ('case report' OR comment* OR editorial OR letter OR news):ti OR ((protocol AND (study OR trial)) NOT ('therapy protocol*' OR 'treatment protocol*')):ti) |
| 19 | 18 AND [english]/lim |
| 20 | 19 AND (('meta analysis'/exp OR 'systematic review'/de OR cochrane:jt OR [cochrane review]/lim OR systematic*:ti OR (cochrane* OR metaanaly* OR 'meta analy*' OR (search* AND (cinahl* OR databases OR ebsco* OR embase* OR psychinfo* OR psycinfo* OR 'science direct*' OR sciencedirect* OR scopus* OR systematic* OR 'web of knowledge*' OR 'web of science')) OR (systematic* NEAR/3 review*)):ti,ab) NOT ((protocol NEXT/3 review) OR 'review protocol'):ti) |
| 21 | 19 AND ('random sample'/de OR 'randomization'/de OR 'randomized controlled trial'/exp OR ('phase 3' OR 'phase iii' OR random* OR rct):ti,ab) |
| 22 | 22 OR 23 |
| 23 | 22 AND [1975-2023]/py |