Comparative Effectiveness Review
Number 227

Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update

Evidence Summary

Introduction

This review focuses on noninvasive nonpharmacological treatment for chronic pain including exercise, mind-body practices, psychological therapies, multidisciplinary rehabilitation, mindfulness practices, manual therapies, physical modalities, and acupuncture, and updates our prior Agency for Healthcare Research and Quality (AHRQ) review.[1] Many trials have examined the impact of these interventions on outcomes during or immediately after the course of treatment reporting improved function and reduced pain. However, given the persistence of chronic pain, understanding whether the benefits are durable would be very helpful for informing selection of therapies. Therefore, this report focuses on durability of treatment effects, defined as at least 1 month following the end of a course of treatment.

Chronic pain substantially impacts physical and mental functioning, productivity, quality of life, and family relationships; it is the leading cause of disability and is often refractory to treatment.[2,3] Chronic pain is often defined as pain lasting 3 months or longer or persisting past the normal time for tissue healing, though definitions vary.[2,4] Chronic pain affects millions of adults in the United States, with an annual

Purpose of Review

To assess noninvasive nonpharmacological treatments for common chronic pain conditions.

Key Messages

- Interventions that improved function and/or pain for ≥1 month:
  - Low back pain: Exercise, psychological therapy, spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, multidisciplinary rehabilitation (MDR)
  - Neck pain: Exercise, low-level laser, mind-body practices, massage, acupuncture
  - Knee osteoarthritis: Exercise, cognitive behavioral therapy (CBT)
  - Hip osteoarthritis: Exercise, manual therapies
  - Fibromyalgia: Exercise, CBT, myofascial release massage, mindfulness practices, tai chi, qigong, acupuncture, MDR
  - Tension headache: Spinal manipulation
- Some interventions did not improve function or pain.
- Serious harms were not observed with the interventions.

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cost in personal and health system expenditures conservatively estimated at $560 billion to $635 billion.[2] The Centers for Disease Control and Prevention (CDC) estimated that 1 in 5 adults in the United States experienced chronic pain in 2016, with 8 percent reporting high-impact chronic pain that limited life or work activities daily or most days in the previous 6 months.[5,6] Chronic pain is multifaceted and is influenced by multiple factors (e.g., genetic, central nervous system, psychological, and environmental factors) and complex interactions, making pain assessment and management a challenge.

Many pharmacological and nonpharmacological treatments are available for management of chronic pain and include a variety of noninvasive as well as surgical and interventional procedures. The National Pain Strategy (NPS) report[3] and 2011 Institute of Medicine (IOM) report[2] describe the need for evidence-based strategies for the management of chronic pain that address the biopsychosocial nature of this problem, including nonpharmacological treatment. Recently, guidelines on opioid use for chronic pain by the CDC[7] included a recommendation on the preferred use of nonopioid treatment over opioid therapy. These initiatives, and others, speak to the importance of understanding current evidence on noninvasive nonpharmacological treatment of chronic pain.

Musculoskeletal pain, particularly related to joints and the back, is the most common type of chronic pain.[2,8] This systematic review thus focuses on five of the most common causes of musculoskeletal pain: chronic low back pain, chronic neck pain, osteoarthritis, fibromyalgia and chronic tension headache.

Rationale for This Review Update

Our 2018 review[1] provided some support for clinical strategies and policies that focus on noninvasive nonpharmacological therapies for chronic pain that have evidence of sustained effectiveness after the completion of therapy, but numerous evidence gaps were identified. Studies published subsequent to our previous review may provide additional evidence to address some of these gaps. This review provides the most current evidence assessment and synthesis to inform clinical practice and health policy. Our review is intended to address some of the needs described in the NPS[3] and IOM[2] reports and others for evidence to inform guidelines and healthcare policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments. It is one of three AHRQ reviews on chronic pain management; the other reviews focus on opioid and nonopioid medications respectively for chronic pain management. This review also aims to provide additional insights into research gaps related to use of noninvasive nonpharmacological alternatives for treating five of the most common chronic pain conditions.

Scope and Key Questions

This Comparative Effectiveness Review focused on noninvasive nonpharmacological therapy, with a Key Question (KQ) for each of five common chronic pain conditions in adults:

KQ 1: Chronic low back pain

KQ 2: Chronic neck pain

KQ 3: Osteoarthritis (knee, hip, hand)

KQ 4: Fibromyalgia

KQ 5: Chronic tension headache

KQ 6: Effects of age, sex, presence of comorbidities (e.g., emotional or mood disorders), or degree of nociplasticity/central sensitization on estimates of benefits and harms

For each condition, we addressed the following subquestions:

a. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?

b. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy (e.g., opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), acetaminophen, antiseizure medications, antidepressants, topical agents, medical cannabis and muscle relaxants)?

c. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise or (for headache) biofeedback?

Exercise was chosen as a common comparator for all conditions except headache, as it is recommended in most guidelines for these conditions and is a frequent comparator in the chronic pain literature. Interventions considered in the review include exercise (including aspects of physical therapy), mind-body practices (yoga, tai chi, qigong), psychological interventions (cognitive behavioral therapy, biofeedback, relaxation techniques, acceptance and commitment therapy), multidisciplinary rehabilitation (including functional restoration), mindfulness practices (meditation, mindfulness-based stress reduction practices), musculoskeletal manipulation (e.g., chiropractic or osteopathic manipulation), and physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation [TENS], low-level laser therapy, interferential therapy, superficial heat or cold, bracing for knee, back or neck, electro-muscular stimulation and magnets), and acupuncture, with a focus on common single active interventions and comparators. We assessed the persistence of effects for therapies at least 1 month following completion of a course of treatment. Studies of combination or adjunctive interventions were excluded. We categorized interventions a priori to provide a framework for the report, realizing that there is some overlap and that other methods for such categorization are possible. We performed stratified analyses to evaluate specific techniques within broader intervention categories (e.g., we looked at different types of psychological therapies or exercise).

Details on the PICOTS (population, interventions, comparators, outcomes, timing, settings) inclusion and exclusion criteria are provided in the full report and in the published protocol.

Methods

The methods for this systematic review follow the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[9] See the review protocol (https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/protocol) and the full report of the review for additional details.

Review Protocol

A multidisciplinary Technical Expert Panel was convened for this update review and provided input into the draft protocol, as did the AHRQ Task Order Officer and representatives from the CDC. The final version of the protocol for this review was posted on the AHRQ Effective Health Care Program website (https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/protocol) and registered in the PROSPERO international database of prospectively registered systematic reviews (CRD42019132457).

Literature Search Strategy

A research librarian conducted searches in Ovid® MEDLINE®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. For the prior report, the searches were conducted from inception through Novmber 1, 2017 and for this update, from September 1, 2017 through September 20, 2019. ClinicalTrials.gov was searched for unpublished trials. A Federal Register notice was posted to request submission of Supplemental Evidence and Data for Systematic Reviews (SEADS) via an AHRQ portal. Responses received were reviewed and suggested citations and other data were compared with the inclusion/exclusion criteria. No new trials eligible for inclusion were identified from these responses. Reference lists of included

articles and the bibliographies of systematic reviews (published since 2010 for the prior report) were reviewed for includable literature.

Inclusion and Exclusion Criteria, Study Selection, and Data Abstraction

Inclusion and exclusion criteria were developed a priori based on the Key Questions and PICOTS (populations, interventions, comparators, outcomes, timing, setting, study design) and are detailed in Table 1 of the full report and the published protocol. We focused on randomized controlled trials (RCTs) reporting outcomes at least 1 month following the completion of a course of treatment. Trials comparing interventions with placebo/sham and trials where no active intervention was received (including usual care, waitlist control, minimal intervention) served as one set of comparators. To evaluate comparative effectiveness, exercise was chosen as a common active comparator for all conditions except headache for which biofeedback was considered the common comparator, and we sought trials of intervention compared with pharmacological treatment.

Details regarding process and inclusion/exclusion of studies are provided in the full report and Appendixes B and C. We abstracted data on study characteristics, funding source, populations, interventions, comparators, and results.

Quality Assessment of Individual Studies

Study quality was independently assessed by two investigators using predefined criteria[10,11] and based on methods recommended in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Research.[9] Studies were rated as "good," "fair," or "poor." (See Appendix E).

Data Analysis and Synthesis

Meta-analyses from the 2018 report were updated and new analyses conducted if two or more studies could be combined. Data were synthesized qualitatively (ranges and descriptive analysis) and quantitatively using meta-analysis where appropriate.[12] Duration of followup postintervention was reported and categorized as short term (<6 months), intermediate term (≥6 to <12 months) and long term (≥12 months). Primary outcomes were function and pain.

Analyses were stratified by disease type, intervention, control group (usual care, exercise or pharmacological treatment) and length of followup (short, intermediate, and long term). We performed additional sensitivity and subgroup analyses based on specific interventions (e.g., type of acupuncture, type of exercise, intervention intensity etc.) and control types, and by excluding outlying studies and studies rated poor quality as data permitted.

We categorized the magnitude of effects for function and pain using the system described in our previous reviews.[13-15] We classified effects for measures with a 0 to 10 scale for pain or function as small (0.5 to 1 point), moderate (>1 to 2 points), or large (>2 points). The moderate range for functional outcomes roughly corresponds to reported minimum clinically important differences for the measure. Small effects may not meet standard thresholds for minimal clinically important difference (MCID) but such thresholds may vary between patients and small average effects may be associated with larger effects in some patients. Where data were available, proportions of patients meeting clinically important improvement were reported. In some situations, interventions with small benefits may be warranted (e.g., when harms and costs are small). Additional information is found in the full report and Appendix H.

Grading the Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence (SOE) for each KQ and primary outcome (pain, function) was graded high, moderate, low, or insufficient based on study limitations; consistency of results across studies; the directness of the evidence linking

the interventions with health outcomes; effect estimate precision; and reporting bias.[16,17] When all studies for a primary outcome were rated poor quality, we rated the SOE as insufficient (see Appendix G). Summary strength of evidence tables were updated based on the totality of underlying evidence (i.e., the 2018 systematic review[1] evidence in combination with that newly identified studies), and the impact of new trials on SOE is noted in the summary tables.

Peer Review and Public Commentary

Peer reviewers with expertise in primary care and management of the included chronic pain conditions were invited to provide written comments on the draft report. The AHRQ Task Order Officer and an Evidence-based Practice Center Associate Editor also provided comments and editorial review. The peer-reviewed draft report was posted on the AHRQ website for 4 weeks for public comment.

Results

Results of Literature Searches

The original database searches resulted in 4,996 potentially relevant articles; an additional 3520 were identified for this update. After dual review of abstracts and titles, 1574 articles across searches (381 new to this update) were selected for full-text dual review and 252 (34 new) publications (233 trials; 31 new trials) met inclusion criteria. We included 77 (9 new) trials (83 publications) on chronic low back pain, 27 (2 new) trials (28 publications) on chronic neck pain, 62 (9 new) trials (66 publications) on osteoarthritis, 58 (11 new) trials (66 publications) on fibromyalgia, and nine (0 new) trials (9 publications) on chronic tension headache. The majority of trials compared nonpharmacological interventions with usual care, waitlist, no treatment, attention control, or placebo/sham (93%); few trials employed pharmacological treatments (5%) or exercise (17%). (Note: some trials had more than one comparator group.) Little evidence beyond 12 months was available.

The majority of trials (61%) were rated fair quality, with only 6 percent considered good quality. Attrition was greater than 20 percent in 28 percent of trials. For a number of interventions, providers and patients could not be effectively blinded. Other methodological shortcomings were unclear reporting of randomization or allocation concealment methods. Adherence to interventions was poorly reported.

Key points are presented in the following sections for interventions and outcomes for which there was low or moderate strength of evidence. All outcomes were considered to be direct. Interventions and outcomes with no or insufficient evidence are discussed in the full report. If effect estimates tended to favor one treatment but failed to reach statistical significance with confidence interval crossing the null value of zero or one (perhaps due to sample size), the results are interpreted as showing no clear difference between treatments. If effect estimates are close to zero and not statistically significant, results are interpreted as no difference between groups. Key findings based on the inclusion of new trials are indicated in the bulleted points; otherwise findings are based on evidence included in the prior report.

Key Question 1: Chronic Low Back Pain

Interventions Compared With Usual Care, Waitlist, No Treatment, Attention Control, or Sham

- **Exercise**: Exercise was associated with a small improvement in short-term function compared with usual care, an attention control, or a placebo intervention (10 trials [4 new]); there were no effects on intermediate-term (5 trials [2 new]) or long-term (1 trial) function (SOE: moderate for short term, low for intermediate and long term). For pain, exercise was associated with moderate effects versus usual care, an attention control, or a placebo intervention at short-term (11 trials [5 new]) and long-term (1 trial), and a small effect at intermediate-term (5 trials [2 new]) followup (SOE: low).

- **Psychological Therapies**: Psychological therapy (cognitive behavioral therapy [CBT] primarily) was associated with small improvements in function and pain compared with usual care or an attention control at short-term (3 trials), intermediate-term (3 trials), and long-term (3 trials) followup (SOE: moderate).
- **Physical Modalities**: Two trials found inconsistent effects of ultrasound versus sham ultrasound on short-term function (SOE: insufficient). Two trials found no differences between ultrasound versus sham ultrasound in short-term pain (SOE: low). One new trial found interferential therapy associated with effects on short-term function and pain that were below the threshold for small (statistical significance uncertain) when compared with a placebo therapy (SOE: low). One trial found low-level laser therapy associated with a small improvement compared with sham laser for short-term function and a moderate improvement for short-term pain (SOE: low). Two trials found no difference between traction versus sham traction in short-term function or pain (SOE: low).
- **Manual Therapies**:
  - **Spinal manipulation**. Spinal manipulation was associated with small improvements compared with sham manipulation, usual care, an attention control, or a placebo intervention in short-term (3 trials) and intermediate-term (3 trials) function (SOE: low). There was no difference between spinal manipulation versus sham manipulation, usual care, an attention control, or a placebo intervention in short-term pain (3 trials), but manipulation was associated with a small improvement compared with controls on intermediate-term pain (3 trials) (SOE: low for short term, moderate for intermediate term).
  - **Massage**. Massage was associated with small improvements in short-term function (6 trials [2 new]) and pain (5 trials [1 new]) compared with sham massage or usual care (SOE: moderate). There was no difference between massage versus controls in intermediate-term function or pain (3 trials each) (SOE: low).
- **Mindfulness-Based Stress Reduction (MBSR)**: There was no difference between MBSR versus usual care or attention control in short-term (4 trials), intermediate-term (1 trial), or long-term (1 trial) function (SOE: low). MBSR was associated with a small improvement compared with usual care or an attention control in short-term (3 trials) and intermediate-term (1 trial) pain, but there was no difference between groups in long-term pain (1 trial) (SOE: moderate for short term, low for intermediate and long term).
- **Mind-Body Practices**: Yoga was associated with moderate improvement in function versus an attention or waitlist control at short-term (8 trials [2 new]), and small improvement at intermediate-term (3 trials) followup (SOE: moderate for short term, low for intermediate term). For pain, yoga was associated with a small improvement versus an attention or waitlist control at short-term (7 trials [2 new]), and a moderate improvement at intermediate-term (2 trials) followup (SOE: low for short term, moderate for intermediate term).
- **Acupuncture**: Acupuncture was associated with a small improvement in short-term function compared with sham acupuncture or usual care (4 trials); there was no difference between acupuncture and controls in intermediate-term (3 trials) or long-term (1 trial) function (SOE: low). Acupuncture was associated with small improvements in short-term (5 trials) and long-term (1 trial) pain compared with sham acupuncture, usual care, an attention control, or a placebo intervention but there was no difference in intermediate-term pain (5 trials) (SOE: moderate for short term, low for intermediate term and long term).
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- **Multidisciplinary Rehabilitation**: Multidisciplinary rehabilitation (MDR) was associated with small improvements in function and pain compared with usual care at short term (4 trials each) and intermediate term (4 trials each); there was no difference in long-term function or pain (2 trials each) (SOE: low for function; moderate for short-term and intermediate-term pain and low for long-term pain).

Comparative Effectiveness of Interventions

- One trial found no difference between qigong and exercise in short-term function, although intermediate-term results showed a small improvement favoring exercise; for pain, qigong was associated with a small improvement versus exercise at short term, but the difference did not persist at intermediate term (SOE: low).
- Multidisciplinary rehabilitation was associated with a small improvement compared with exercise on function and pain in the short term (6 trials each) and intermediate term (5 trials each); there was no effect on long-term function or pain (2 trials each) (SOE: moderate for short term and intermediate term, low for long term).
- No differences were found between groups for the following interventions compared with exercise:
  - **Low-level laser therapy**. Intermediate-term function or pain (1 trial, SOE: low).
  - **Spinal manipulation**. Function or pain at short term (3 trials each) and intermediate-term (4 trials each) followup (SOE: low).
  - **Massage**. Intermediate-term function or pain (SOE: low).
  - **Yoga**. Short-term (4 trials) or intermediate-term (1 trial) function, short-term (5 trials) or intermediate-term (1 trial) pain (SOE: low).

Key Question 2: Chronic Neck Pain

Interventions Compared With Usual Care, Waitlist, No Treatment, Attention Control, or Sham

- **Exercise**: Across types of exercise, there was no clear improvement in function (3 trials) or pain (3 trials) versus no treatment, waitlist or attention control in the short term, or function (1 trial) or pain (2 trials) versus no intervention or attention control in the intermediate term. Long term, exercise was associated with a small improvement in function (1 trial) but no improvement in pain (3 trials) versus attention control (SOE: low for pain and function at all timepoints). A subgroup of two trials of combination exercises (including 3 of the following 4 exercise categories: muscle performance, mobility, muscle re-education, aerobic) suggests a small benefit in function and pain versus waitlist or attention control over the short term; and function versus attention control in the long term (1 trial) (SOE: low).
- **Psychological Therapies**: No difference was found in function or pain in the short term or intermediate term from one study comparing relaxation training and no intervention (SOE: low for all).
- **Physical Modalities**: Low-level laser therapy was associated with a moderate improvement in short-term function (2 trials) and pain (3 trials) compared with sham (SOE: moderate).
- **Manual Therapies**: The effects of Swedish massage on function (≥5 point improvement on the Neck Disability Index [NDI]) versus self-management attention control were small and not statistically significant in one trial in the short and intermediate term (SOE: low for both time periods). Massage was associated with a small improvement in short-term function compared with attention or waitlist control (2 trials [1 new]) and a moderate improvement

in short-term pain compared with a waitlist control (1 new trial) (SOE: low for function and pain).

- **Mind-Body Practices**: Alexander Technique resulted in a small improvement in function in the short term and intermediate term compared with usual care alone based on one trial (SOE: low).
- **Acupuncture**: Acupuncture was associated with small improvements in short-term (5 trials) and intermediate-term (3 trials) function versus sham acupuncture, a placebo (sham laser), or usual care; one trial reported no difference in function in the long term (SOE: low for all time periods). For pain, there were no differences for acupuncture versus sham acupuncture or placebo interventions in the short (4 trials), intermediate (3 trials), or long (1 trial) term (SOE: low for all time periods).

Comparative Effectiveness of Interventions

- Muscle performance exercise (Pilates) was associated with a small improvement in function and a substantial improvement in pain compared with oral medication (acetaminophen) in the short term in one new trial (SOE: low).
- No clear differences were found between groups for the following interventions compared with exercise:
  - **Physical therapist (PT)-led relaxation training**. Function or pain at short or intermediate term (1 trial, SOE: low for all).
  - **Massage**. Pain at intermediate term (1 trial, SOE: low).
  - **Basic body awareness therapy**. Function at short term (1 trial, SOE: low).

Key Question 3: Osteoarthritis Pain

Interventions Compared With Usual Care, Waitlist, No Treatment, Attention Control, or Sham

Knee Osteoarthritis Pain

- **Exercise**: Exercise was associated with a small improvement in function compared with usual care, no treatment, or sham intervention short term (8 trials [1 new]), moderate improvement intermediate term (11 trials [two new]), and small improvement long term (4 trials [2 new trials]) (SOE: moderate for short term; low for intermediate and long term). One trial found no statistical difference between exercise or sham procedure in the proportion of patients who reported clinically relevant reductions in pain in the short term. Exercise was associated with a small improvement in pain short term (8 trials [1 new]) versus usual care, no treatment, waitlist, or sham intervention (SOE: moderate), a moderate improvement intermediate term (11 trials [2 new]) compared with usual care, an attention control, waitlist, or no treatment (SOE: low), and a small improvement long term (4 trials [2 new]) compared to usual care, attention control, or waitlist (SOE: low).
- **Psychological Therapies**: Two new trials of motivational interviewing and CBT versus usual care and no treatment found no difference between treatment groups in function but a small improvement in pain favoring the psychological treatments compared to controls in the short term (SOE: low for both function and pain). Two trials of pain coping skills training and CBT versus usual care found no difference in function or pain over short-, intermediate-, or long-term followup (SOE: low).
- **Physical Modalities**:
  - **Ultrasound**. No differences were found between ultrasound (continuous or pulsed) and sham for function or pain in the short

term (3 trials [2 new]) or the intermediate term (1 trial) (SOE: low).
  - **TENS**. One trial found no difference between TENS and placebo TENS in intermediate-term function or pain (SOE: low).
  - **Electromagnetic field**. One trial found pulsed electromagnetic fields were associated with small improvements in function and pain versus sham in the short term, but differences may not be clinically significant (SOE: low).

- **Acupuncture**: No differences were seen between acupuncture and control interventions (sham acupuncture, waitlist, or usual care) for function in the short term (4 trials) or the intermediate term (4 trials) (SOE: low for short term; moderate for intermediate term). Stratified analysis showed no differences between acupuncture and sham treatments (4 trials) but moderate improvement in function compared with usual care (2 trials) short term. For pain, there were no differences between acupuncture versus control interventions in the short term (6 trials) or clinically meaningful differences in the intermediate term (4 trials) (SOE: low for short term; moderate for intermediate term). Short-term differences in pain were significant for acupuncture versus usual care but not for acupuncture versus sham acupuncture.

Hip Osteoarthritis Pain

- **Exercise**: Exercise was associated with a small improvement in function versus usual care in the short term (3 trials) and intermediate term (2 trials) (SOE: low for short and intermediate term). Exercise tended toward a small improvement in short-term pain compared with usual care (3 trials), but the results were no longer significant at intermediate term (2 trials) (SOE: low for short and intermediate term).

Hand Osteoarthritis Pain

- **Physical Modalities**: One trial of low-level laser treatment versus sham demonstrated no improvement in function or pain in the short term (SOE: low).
- **Multidisciplinary Rehabilitation**: One trial of MDR versus waitlist control found no differences between groups over the short term in function or pain, or with regard to the proportion of responders to Osteoarthritis Research Society International Outcome Measures in Rheumatology (SOE: low for all outcomes).

Comparative Effectiveness of Interventions

Knee Osteoarthritis Pain

- One new trial found that more patients who received exercise versus pharmacological therapy (analgesics and anti-inflammatory drugs) achieved a clinically important improvement in function in the intermediate term, although the difference did not reach statistical significance. There were no differences between the groups across all other function and pain outcomes measured (SOE: low).
- One trial of pain coping skills training versus strengthening exercises found no differences in function or pain at short term and intermediate term (SOE: low).

Hip Osteoarthritis Pain

- Manual therapy was associated with small improvements in short-term and intermediate-term function, and in short-term pain versus exercise (SOE: low).

Key Question 4: Fibromyalgia

Interventions Compared With Usual Care, Waitlist, No Treatment, Attention Control, or Sham

- **Exercise**: Exercise was associated with a small improvement in function compared with attention control, no treatment, or usual care in the short term (7 trials; SOE: low) and intermediate term (8 trials; SOE: moderate). There were no clear effects in the long term (3 trials; SOE: low). Exercise was associated with a small improvement in pain compared with usual care, attention control, or no treatment short term (6 trials) and intermediate term (8 trials[1 new]) but no effect long term (4 trials) (SOE: moderate for all time frames).
- **Psychological Therapies**: There was no clear difference between CBT versus usual care or waitlist in short-term function (3 trials [1 new]) (SOE: low). At intermediate term, CBT was associated with a moderate improvement in function (3 trials [1 new]) versus waitlist or usual care and versus an attention control (1 additional trial) (SOE: low). CBT was associated with a small improvement in pain compared with usual care or waitlist in the short term (4 trials [1 new]) but not at intermediate term (6 trials [4 new]). There was no difference in clinically important improvement in pain at intermediate term between CBT or emotional awareness and expression therapy\\ and usual care in one new trial (SOE: low for short term and intermediate term).
- **Physical Modalities**: One parallel trial found no differences between magnetic mattress pads compared with sham or usual care in intermediate-term function or pain (SOE: low).
- **Manual Therapies**: Myofascial release therapy was associated with a small improvement in intermediate-term function, but not long-term function, compared with sham in one trial (SOE: low). Myofascial release therapy was associated with a small improvement in long-term pain compared with sham based on the sensory and evaluative domains of the McGill Pain Questionnaire (MPQ) in one trial; there were no differences for the affective domain of the MPQ or for Visual Analog Scale pain (SOE: low).
- **Mindfulness Practices**: No clear short-term effects of MBSR were seen on function compared with waitlist or attention control in two trials; clinically meaningful improvement in function was not different for MBSR versus either comparator. No clear short-term effects of MBSR on pain were seen compared with waitlist or attention control in two trials (SOE: moderate for function and pain). In one new trial, meditation awareness training was associated with small improvements in function and pain at intermediate term versus attention control (SOE: low).
- **Mind-Body Practices**: Over the short term, small improvements in function were seen for qigong compared with waitlist (1 trial) and for tai chi compared with attention control (1 trial). Qigong and tai chi were associated with a moderately greater improvement in pain compared with waitlist and attention control in the short term (2 trials). Significantly more participants in the tai chi group also showed clinically meaningful improvement in both function and pain consistent with a small effect (SOE: low for all).
- **Acupuncture**: Acupuncture was associated with a small improvement in function compared with sham acupuncture at short-term (3 trials [1 new]) and intermediate-term (2 trials) followup (SOE: moderate). There was no effect for acupuncture versus sham acupuncture on pain in the short term (4 trials [1 new]) or intermediate term (3 trials) (SOE: low) or based on pooled estimates across control conditions (sham or attention control, 5 trials [2 new]) SOE: low).

- **Multidisciplinary Rehabilitation**: More MDR participants experienced a clinically meaningful improvement in function compared with usual care at short, intermediate, and long term in one trial. MDR was associated with a small improvement in function versus usual care or waitlist in the short term (3 trials), and versus usual care at intermediate-term (3 trials) and long-term (2 trials) followup (SOE: low for all function). MDR was associated with a small improvement in pain compared with usual care or waitlist at intermediate term (3 trials); there were no clear differences compared with usual care or waitlist in the short term (2 trials) or with usual care in the long term (2 trials) (SOE: low for all pain).

Comparative Effectiveness of Interventions

- CBT was associated with a small improvement in intermediate-term function versus pregabalin (plus duloxetine as needed) in two trials [1 new]; differing effect size magnitudes for the trials resulted in substantial heterogeneity for the pooled effect estimate making it unreliable (SOE: low). There was no difference across these same trials for pain at intermediate-term followup (SOE: low).
- In one new trial, compared with aerobic exercise, tai chi was associated with a small improvement in function over short to intermediate-term followup, but the effect did not persist to longer term (SOE: low). Analyses confined to two 60-minute sessions of tai chi per week for 24 weeks versus comparable sessions per weeks of aerobic exercise suggest moderate functional improvement at intermediate term that was sustained long term.
- There was no difference between multidisciplinary treatment versus aerobic exercise for function or pain at long term in one trial (SOE: low).

Key Question 5: Chronic Tension Headache

Interventions Compared With Usual Care, Waitlist, No Treatment, Attention Control, or Sham

- **Manual Therapies**: Spinal manipulation therapy was associated with small improvements in function and moderate improvements in pain compared with usual care over the short term in one trial (SOE: low). Approximately a quarter of the patients had comorbid migraine.
- **Acupuncture**: Laser acupuncture was associated with small, short-term improvements in pain intensity and in the number of headache days per month versus sham in one trial (SOE: low).

Comparative Effectiveness of Interventions

- No studies compared the interventions of interest to biofeedback and evidence from comparisons with pharmacological interventions was insufficient.

Key Question 6: Differential Efficacy

Evidence was insufficient to determine whether factors such as age, sex, comorbidities or degree of nociplasticity/central sensitization modify the effects of treatment.

Harms

Although data on harms were limited, no evidence suggested serious harms (e.g., death, disability, or need for intensive medical attention) for the interventions included in the review. Many trials did not report harms, withdrawals due to adverse events, or differences between compared interventions in risk of harms or withdrawals. Reported harms varied in scope and specification. Results were considered insufficient for many interventions. Trials that did report such data generally found infrequent occurrences of nonserious treatment-related adverse events (e.g.,

discomfort, soreness, bruising, increased pain, worsening of symptoms), few withdrawals from nonpharmacological treatments due to adverse events, and no differences between comparison groups in frequency of intervention-related adverse events or withdrawals. Table 64 in the full report summarizes reported adverse events for each intervention.

Discussion

Key Findings and Strength of Evidence

This report updates the prior 2018 AHRQ report. The key findings of this update, including SOE ratings, are summarized for each chronic pain condition in the Results and evidence summary Tables A–O and reflect the totality of evidence from the 2018 review combined with new evidence from this update. Changes to effect size or SOE based on integration of new trials with the 2018 evidence base are footnoted in the tables. Interventions and comparators with insufficient evidence or no evidence (no RCTs meeting inclusion criteria) for either function or pain outcomes are not shown but are available in the full report. Domains used to determine the overall SOE are shown in Appendix G of the full report. All outcomes were considered direct.

The SOE was low (limited confidence in the estimates) or insufficient (no confidence in the estimated effects) for many interventions and was limited by small numbers of trials for specific comparisons at our specified time frames, particularly for long-term followup. We focused on evaluating the persistence of effects for therapies at least 1 month beyond the course of treatment, using the following definitions for postintervention followup: short term (1 to <6 months), intermediate term (≥6 to <12 months) and long term (≥12 months). Evidence was particularly limited on long-term outcome; only two new trials contributed additional long-term data.

No trials in pregnant or breastfeeding women with pre-existing chronic pain or new trials comparing interventions with topical agents, medical cannabis or muscle relaxants were identified. No data were available to evaluate nociplasticity as a modifier to treatment effectiveness or safety.

The majority of trials compared interventions with usual care and very few trials employed pharmacological treatments or exercise as comparators, with only three new trials of interventions versus active comparators identified. In general, effect sizes for most interventions remained small, based on mean differences. Few trials reported on patients meeting clinically important differences. There tended to be more evidence for the effects of interventions on pain than for function and effects on function were generally smaller or not clearly present. Information on adherence to interventions was not well-reported; poor adherence may have impacted some of our findings.

No trials directly compared interventions with opioids and few trials, reported effects of interventions on opioid use. In our concurrent review on opioid medications for chronic pain management, opioids were associated with small effects on function and pain during treatment (effects would not be expected to persist) compared with placebo; evidence was primarily from short-term (≤3 month) trials.[13,14,18] There were no differences in pain, function or other outcomes for opioid compared with nonopioid medications.

Harms were poorly reported across interventions. No serious intervention-related adverse events leading to death or disability or requiring intensive medical attention were identified; reported adverse events were generally minor (e.g., muscle soreness or increased pain with exercise, bruising with acupuncture) and time-limited (e.g., temporary worsening of pain). Evidence was moderate for no differences between treatment groups for author-defined serious adverse events for spinal manipulation versus exercise (low back pain,

7 RCTs) or acupuncture versus sham, placebo, usual care (neck pain 6 RCTs, knee osteoarthritis 9 trials, fibromyalgia 4 trials). Evidence was low or insufficient for other adverse events. Detail is provided in the full report.

Table A. Chronic low back pain: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist[a]

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Exercise	small[b] ++	none +	none +	moderate[c] +	small +	moderate +
Psychological Therapies: CBT Primarily	small ++	small ++	small ++	small ++	small ++	small ++
Physical Modalities: Ultrasound	insufficient evidence	no evidence	no evidence	none +	no evidence	no evidence
Physical Modalities: Interferential Therapy[d]	none +	no evidence	no evidence	none +	no evidence	no evidence
Physical Modalities: Low-Level Laser Therapy	small +	none +	no evidence	moderate +	none +	no evidence
Manual Therapies: Spinal Manipulation	small +	small +	no evidence	none +	small ++	no evidence
Manual Therapies: Massage	small ++	none +	no evidence	small ++	none +	no evidence
Manual Therapies: Traction	none +	no evidence	no evidence	none +	no evidence	no evidence
Mindfulness Practices: MBSR	none +	none +	none +	small ++	small +	none +
Mind-Body Practices: Yoga	moderate[e] ++	small +	no evidence	small[f] +	moderate ++	no evidence
Acupuncture	small +	none +	none +	small ++	none +	small +
Multidisciplinary Rehabilitation	small +	small +	none +	small ++	small ++	none +

Table A. Chronic low back pain: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist[a] (continued)

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

CBT = cognitive-behavioral therapy; MBSR = mindfulness-based stress reduction; none = no effect/no statistically significant effect; SOE = strength of evidence.

[a] SOE and effect size based on totality of evidence from prior report and new trials.

[b] SOE upgraded one level from prior report.

[c] Effect size upgraded one level from prior report and SOE downgraded one level.

[d] No interferential therapy trials were in the prior review.

[e] Effect size upgraded one level from prior report.

[f] Effect size downgraded one level from prior report

Table B. Chronic low back pain: summary of effects of nonpharmacological interventions compared with exercise

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Physical Modalities: Low-Level Laser Therapy	no evidence	none +	no evidence	no evidence	small +	no evidence
Manual Therapies: Spinal Manipulation	none +	none +	no evidence	none +	small +	no evidence
Manual Therapies: Massage	no evidence	none +	no evidence	no evidence	none +	no evidence
Mind-Body Practices: Yoga	none +	none +	no evidence	small +	none +	no evidence
Mind-Body Practices: Qigong	none +	small favoring exercise +	no evidence	small favoring exercise +	none +	no evidence
Multidisciplinary Rehabilitation	small ++	small ++	none +	small ++	small ++	none

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

none = no effect/no statistically significant effect; SOE = strength of evidence.

Table C. Chronic neck pain: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist[a]

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Exercise	none +	none +	small +	none +	none +	none +
Psychological Therapies: PT-Led Relaxation Training	none +	none +	no evidence	none +	none +	no evidence
Physical Modalities: Low-Level Laser Therapy	moderate ++	no evidence	no evidence	moderate ++	no evidence	no evidence
Manual Therapies: Massage	small[b] +	none +	no evidence	moderate[c] +	no evidence	no evidence
Mind-Body Practices: Alexander Technique	small +	small +	no evidence	no evidence	no evidence	no evidence
Acupuncture	small +	small +	none +	none +	none +	none +

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
none = no effect/no statistically significant effect; PT = physical therapist; SOE = strength of evidence.

[a] SOE and effect size based on totality of evidence from prior report and new trials

[b] Effect size upgraded one level from prior AHRQ report.

[c] There was no evidence for short-term pain in the prior AHRQ report.

Table D. Chronic neck pain: summary of effects of nonpharmacological interventions compared with pharmacological treatments[a]

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Exercise (Pilates): Versus Acetaminophen[b]	small +	no evidence	no evidence	large +	no evidence	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

none = no effect/no statistically significant effect; SOE = strength of evidence.

[a] SOE and effect size based on totality of evidence from prior report and new trials.

[b] New trial of exercise versus pharmacological intervention with short-term followup only; evidence was insufficient from trials in the prior AHRQ report (data are in full report).

Table E. Chronic neck pain: summary of effects of nonpharmacological interventions compared with exercise

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Psychological Therapies: PT-Led Relaxation Training	none +	none +	no evidence	none +	none +	no evidence
Manual Therapies: Massage	no evidence	no evidence	no evidence	no evidence	none +	no evidence
Mind-Body Practices: Body Awareness Therapy	none +	no evidence	no evidence	no evidence	no evidence	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

none = no effect/no statistically significant effect; PT = physical therapist; SOE = strength of evidence.

Table F. Osteoarthritis knee pain: effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist[a]

Intervention	Function Short-Term Effect Size SOE	Function Intermediate-Term Effect Size SOE	Function Long-Term Effect Size SOE	Pain Short-Term Effect Size SOE	Pain Intermediate-Term Effect Size SOE	Pain Long-Term Effect Size SOE
Exercise	small ++	moderate[b] +	small +	small ++	moderate +	small[b] +
Psychological Therapies: Pain Coping, CBT	none +	none +	none +	small[b] +	none +	none +
Physical Modalities: Ultrasound	none[c] +	none +	no evidence	none[c] +	none +	no evidence
Physical Modalities: TENS	no evidence	none +	no evidence	no evidence	none +	no evidence
Physical Modalities: Electromagnetic Field	none +	no evidence	no evidence	none +	no evidence	no evidence
Acupuncture	none +	none ++	no evidence	none +	none ++	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

CBT = cognitive-behavioral therapy; none = no effect/no statistically significant effect; TENS = transcutaneous electrical nerve stimulation; SOE = strength of evidence

[a] SOE and effect size based on totality of evidence from prior report and new trials.

[b] Effect size upgraded one level from prior AHRQ report.

[c] Effect size downgraded one level from prior AHRQ report.

Table G. Osteoarthritis knee pain: summary of effects of nonpharmacological interventions compared with pharmacological treatments

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain Short-Term Effect Size SOE	Pain Intermediate-Term Effect Size SOE	Pain Long-Term Effect Size SOE
Exercise: Versus Acetaminophen and NSAIDs[a]	no evidence	none +	no evidence	no evidence	none +	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

none = no effect/no statistically significant effect; NSAIDS = nonsteroidal anti-inflammatory drugs; SOE = strength of evidence.

[a] No trials comparing nonpharmacological interventions with pharmacological treatments were in the prior review.

Table H. Osteoarthritis knee pain: summary of effects of nonpharmacological interventions compared with exercise

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Psychological Therapies: Pain Coping	none +	none +	no evidence	none +	none +	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

none = no effect/no statistically significant effect; SOE = strength of evidence

Table I. Osteoarthritis hip pain: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist

Intervention	Function Short-Term Effect Size SOE	Function Intermediate-Term Effect Size SOE	Function Long-Term Effect Size SOE	Pain Short-Term Effect Size SOE	Pain Intermediate-Term Effect Size SOE	Pain Long-Term Effect Size SOE
Exercise	small +	small +	insufficient evidence	small +	none +	insufficient evidence

Table J. Osteoarthritis hip pain: summary of effects of nonpharmacological interventions compared with exercise

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Manual Therapies	small +	small +	no evidence	small +	insufficient evidence	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
SOE = strength of evidence

Table K. Osteoarthritis hand pain: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Physical Modalities: Low-Level Laser Therapy	none +	no evidence	no evidence	none +	no evidence	no evidence
Multidisciplinary Rehabilitation	none +	no evidence	no evidence	none +	no evidence	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
none = no effect/no statistically significant effect; SOE = strength of evidence.

Table L. Fibromyalgia: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist[a]

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Exercise	small +	small ++	none +	small ++	small[c] ++	none ++
Psychological Therapies: CBT	none[b] +	moderate[c] +	insufficient evidence	small[d] +	none +	insufficient evidence
Physical Modalities: Magnetic Pads	insufficient evidence	none +	no evidence	insufficient evidence	none +	no evidence
Manual Therapies: Massage (Myofascial Release)	no evidence	small +	none +	insufficient evidence	insufficient evidence	small +
Mindfulness Practices: MBSR, MAT	none ++	small[e] +	no evidence	none ++	small[e] +	no evidence
Mind-Body Practices: Qigong, Tai Chi	small +	no evidence	no evidence	moderate +	no evidence	no evidence
Acupuncture	small[d] ++	small ++	no evidence	none[d] +	none +	no evidence
Multidisciplinary Rehabilitation	small +	small +	small +	none +	small +	none +

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months

Effect Size: none, small, moderate, or large improvement

Strength of Evidence: + = low, ++ = moderate, +++ = high

CBT = cognitive-behavioral therapy; MAT = meditation awareness training; MBSR = mindfulness-based stress reduction; none = no effect/no statistically significant effect; SOE = strength of evidence

[a] SOE and effect size based on totality of evidence from prior report and new trials

[b] Effect size downgraded one level from prior report

[c] Effect size upgraded one level from prior report

[d] New trial(s) did not change effect size or SOE

[e] New trial reporting intermediate-term effects

Table M. Fibromyalgia: summary of effects of nonpharmacological interventions compared with pharmacological treatments[a]

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
CBT: Versus Pregabalin; Duloxetine	no evidence	small[b] +	no evidence	no evidence	none[b] +	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
CBT = cognitive-behavioral therapy; none = no effect/no statistically significant effect; SOE = strength of evidence
[a] SOE and effect size based on totality of evidence from prior report and new trials
[b] New trial did not change effect size or SOE

Table N. Fibromyalgia: summary of effects of nonpharmacological interventions compared with exercise

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Mind-Body Therapies: Yang Style Tai Chi[a]	small +	small +	none +	no evidence	no evidence	no evidence
Multidisciplinary Rehabilitation	no evidence	no evidence	none +	no evidence	no evidence	none +

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
None = no effect/no statistically significant effect; SOE = strength of evidence
[a] No trials of mind-body interventions versus exercise were in prior report.

Table O. Chronic tension headache: summary of effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist

Intervention	Function *Short-Term* Effect Size SOE	Function *Intermediate-Term* Effect Size SOE	Function *Long-Term* Effect Size SOE	Pain *Short-Term* Effect Size SOE	Pain *Intermediate-Term* Effect Size SOE	Pain *Long-Term* Effect Size SOE
Manual Therapies: Spinal Manipulation	small +	no evidence	no evidence	moderate +	no evidence	no evidence
Acupuncture	no evidence	no evidence	no evidence	small + (laser) insufficient evidence (needle)	insufficient evidence (needle)	insufficient evidence (needle)

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
SOE = strength of evidence

Findings in Relationship to What Is Already Known

The updated evidence in this systematic review provides some additional support for the effectiveness of selected nonpharmacological treatments presented in the 2018 review. New trials filled evidence gaps identified in the previous report in a few areas. There is now evidence for benefits of massage therapy on short-term pain and for exercise versus acetaminophen on function and pain for chronic neck pain, for CBT on short-term pain in knee osteoarthritis, and for mindfulness practices on intermediate-term function and pain and for tai chi versus exercise on short- and intermediate-term function in persons with fibromyalgia. Conclusions regarding effect sizes and SOE remained the same for the addition of trials for many interventions. As noted in the summary tables, some additions led to changes in effect size. For example, new trials of exercise versus nonactive comparators in chronic low back pain and knee osteoarthritis resulted in different conclusions in some instances. For chronic low back pain, short-term SOE was upgraded from low to moderate for small improvement in function and for pain improvement the effect size was upgraded to moderate, but the strength of evidence downgraded to low. For knee OA, effect sizes were upgraded for functional improvement to moderate at intermediate-term function and the addition of the only two trials with long-term data led to upgrading effect size to small where no difference was noted in the previous report; however, SOE remained low.

Many previous reviews have addressed the effects of interventions for chronic pain management during or immediately following treatments. We focused on evaluating the sustainability of effects for at least 1 month postintervention.

This review provides additional updates to our previous review on low back pain.[13]

Consistent with the prior review, we again found exercise, yoga, various psychological therapies, acupuncture, spinal manipulation, and low-level laser therapy associated with small to moderate effects on function and/or pain. This report differs from the prior review on low back pain by focusing on durability of treatment effects 1 month or longer after completion of a course of treatment, basing estimates on meta-analyses when poolable data were available, and conducting stratified and sensitivity analyses to evaluate sources of heterogeneity and robustness of findings. Although we found some evidence that beneficial effects of some nonpharmacological therapies persist for up to 12 months following the end of a course of a treatment, data on longer-term (>12 months) outcomes were very sparse in previous reports and remain so.

Our findings indicate that a number of nonpharmacological treatments improve pain and/or function for specific chronic pain conditions included in this review. This is consistent with other reviews including a recent Institute for Clinical and Economic Review review on chronic low back pain and neck pain,[19] an AHRQ report on knee osteoarthritis treatment[20] and with recent reviews that included a variety of chronic pain conditions which examined exercise,[21] acupuncture,[22] and complementary health approaches[23] for chronic pain management, as well as a review of chronic pain treatment guidelines on the use of manual and physical therapies.[24]

Applicability

New trials included for this update did not provide additional clarity on applicability. The applicability of our findings continues to be impacted by a number of factors. Symptom duration, clinical characteristics, comorbid conditions, the presence of overlapping chronic pain conditions or psychosocial factors, and concomitant treatments were rarely reported. In addition, with the exception of fibromyalgia, information regarding diagnostic criteria for the pain condition of interest was limited. Information related to centralization of pain was not described. Thus, it is difficult to evaluate the extent to which populations represented in the included RCTs are reflective of those in primary care clinical practice. The majority of trial participants were female. The age of included populations generally reflected the ages impacted by the conditions. Our review did not include children or adolescents or people with chronic pain conditions other than those specified in our population criteria. Evidence to evaluate how effectiveness varies by age was limited. Duration of chronic pain, severity of pain (most trials enrolled patients with at least moderate pain at baseline), as well as other factors, (e.g., use of medications, medical and psychological comorbidities) varied across trials. Our findings are generally most applicable to persons without comorbidities who have moderate or severe intensity pain that has persisted for >1 year. The heterogeneity in populations across included trials likely is consistent with the heterogeneity seen in clinical practice, so our findings may be applicable to most primary care clinical settings.

Heterogeneity in interventions, comparators, and cointerventions may impact applicability. Substantial variability in the numbers of sessions, length of sessions, duration of treatment, methods of delivering the interventions and the experience and training of those providing the interventions present a challenge to assessing applicability. To address heterogeneity within intervention categories we abstracted details of techniques or methods used (e.g., specific type of psychological intervention or yoga) and attempted to stratify by them; however, in most cases, data were insufficient to do so. We stratified by comparator where possible (e.g., sham acupuncture, usual care). In general, there were no clear differences in effects based on intervention factors or comparators; however, analyses were quite limited by small numbers of trials. In clinical practice, most chronic pain patients likely use a combination of therapies

and patients may continue to receive therapies if benefit is perceived. Our report focuses on single interventions. It is unclear to what extent our findings represent conditions under which the various interventions are currently delivered.

Implications for Clinical and Policy Decision Making

Our review provides updated evidence that an array of nonpharmacological treatments provide small to moderate benefits in function and/or pain that are durable for more than 1 month for five chronic pain conditions addressed in this review. Musculoskeletal pain, particularly back and joint pain, is the most common single type of chronic pain. Age-adjusted rates of adults reporting pain in the last 3 months were highest for low back pain (28%), neck pain (15%), knee pain (19.5%), and severe headache or migraine (16%).[2,8] The evidence synthesized in this review may help inform guidelines and healthcare policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments, and inform policy decisions regarding funding priorities for future research.

Recent guidelines from the CDC[7] in the United States and the Canadian Guidelines for Opioid Use in Chronic Non-Cancer Pain[24] recommend nonopioid treatment as preferred treatment for chronic pain. Further, American College of Physicians guidelines recommend nonpharmacological therapies over medications for chronic back pain.[15] Our findings support the feasibility of such guidelines by presenting evidence of sustained effectiveness after the completion of therapy for a number of nonpharmacological treatments. Importantly, interventions such as exercise, multidisciplinary rehabilitation, mind-body interventions, cognitive behavioral therapy, and some complementary and integrative medicine therapies such as acupuncture and spinal manipulation were associated with some sustained effects on function, although evidence beyond 12 months remains sparse. At the same time, there was no evidence suggesting serious harms, although data on harms were limited.

Evidence reviewed in our report may also help inform decisions regarding prioritization of nonpharmacological therapies by clinicians selecting therapy and facilitate provider/patient shared decision making. Exercise and CBT are considered routine first-line treatments in many guidelines, with many of the nonpharmacological treatments in this review including spinal manipulation, acupuncture, mindfulness practices, and multidisciplinary rehabilitation considered adjunctive or second line treatment for chronic low back pain.[25] Our report provides indirect support for the adoption of integrated, multimodal management of chronic pain. While the CDC guidelines suggest use of a multimodal approach to pain management, data on clinical pathways and optimal integration of nonpharmacological pain management as well as utilization are sparse, contributing to challenges on how to best implement evidence-based strategies into practice.[25,26] Consistent with a biopsychosocial understanding of chronic pain,[2,3] evidence was somewhat more robust for "active" interventions that engage patients in movement and address psychological contributors to pain, particularly at longer-term followup, versus more "passive" treatments focused on symptom relief such as massage. Active interventions include exercise, multidisciplinary rehabilitation, psychological interventions (particularly CBT), and mind-body interventions. This provides some support for clinical strategies that focus on "active" interventions as primary therapies, with "passive" interventions used in a more adjunctive or supplementary role. Research is needed to compare "active" versus "passive" strategies.

Our review also has policy implications related to treatment access and reimbursement. Given heterogeneity in chronic pain, variability in patient preferences for treatments, and differential responses to specific therapies in patients with a given chronic pain condition, policies that

broaden access to a broader array of effective nonpharmacological treatments may have greater impact than those that focus on one or a few therapies. Several considerations could inform policy decisions regarding access to and coverage of nonpharmacological therapies. Efforts could prioritize access to interventions with evidence of persistent effectiveness across different pain conditions, such as exercise, multidisciplinary rehabilitation, psychological interventions, mind-body interventions, and acupuncture. Because the level of supporting evidence varies from condition to condition, policy makers may need to consider the degree to which evidence may be reasonably extrapolated across conditions (e.g., effectiveness of psychological therapies for chronic back pain may not necessarily be extrapolated to osteoarthritis pain). There is substantial variability in reimbursement, and authorization procedures remain a potential barrier.[25-27] Although evidence supports the use of multidisciplinary rehabilitation over exercise therapy or usual care, primarily for low back pain, cost and availability remain important barriers, particularly in rural areas. Our report suggests that less-intensive multidisciplinary rehabilitation may be similarly effective to high-intensity multidisciplinary rehabilitation, which could inform decisions about more efficient methods for delivering this intervention. Not all patients may require multidisciplinary rehabilitation.[28] Policy efforts that focus on use of multidisciplinary rehabilitation in persons more likely to benefit (e.g., severe functional deficits, failure to improve on standard nonmultidisciplinary therapies, significant psychosocial contributors to pain) could also inform efforts to deliver this modality efficiently.

Limitations of the Evidence Base and the Systematic Review Process

Evidence remains sparse for most interventions, particularly long term. There were also limited data on outcomes other than pain and function and particularly for harms. The Visual Analog Scale for pain was the most commonly reported pain measure and does not adequately characterize or categorize pain. In addition, mean changes in outcomes measures between treatment groups describe how groups respond to treatment on average, but do not capture individuals' response or achievement of clinically important differences which may be more clinically intuitive. Few trials directly compared an included intervention versus pharmacological therapy or the specified active comparator (exercise or biofeedback). Only 5 percent of included trials across conditions were considered to be of good quality; the majority were considered fair (61%).

There were limitations to the systematic review process. We did not include trials of patients with chronic pain conditions other than those specified and excluded trials of patients with diffuse or mixed pain conditions. Some noninvasive nonpharmacological interventions (e.g., self-management education) were excluded, and we did not address invasive therapies. The strict definition of chronic tension headache may have limited the number of trials identified. Trials that evaluated active comparators other than biofeedback (for headache) or exercise (all other conditions) or interventions as adjunctive treatment were excluded. Some meta-analyses were based on two or three trials; findings based on such meta-analyses must be interpreted with caution.

The frequency and scope of harms was poorly reported in included RCTs. RCTs may not be adequately powered or have sufficient length of followup to identify rare or long-term adverse events. RCTs assess benefits and harms under ideal circumstances in homogenous populations and

specific settings which may limit the applicability of harms reported to more wide-spread use in general clinical practice.[29] Intervention-related serious adverse events resulting in death, disability or requiring intensive medical intensive attention were not seen across included RCTs; no differences between interventions and comparators were identified for serious events. Most reported events were minor and transient and SOE was low or insufficient for most. In general, serious adverse events are considered very rare for the interventions evaluated in this report and likely depend on patient factors (e.g., comorbid conditions) and provider skill and qualifications as well as characteristics of the intervention and how it is delivered.[21,30-35] Serious adverse events reported in the general literature may or may not be applicable to the interventions as applied in included studies or patient populations studied in this review.

Research Recommendations

Although new RCTs published subsequent to our 2018 report[1] provided additional support for many nonpharmacological interventions, evidence remains sparse for a number of interventions, particularly long term, and additional methodologic work is needed. New trials provided limited evidence to fill the gaps which continue to be many across the common conditions we included (Table P). Four primary issues relate to the need (1) to understand the longer-term sustainability of intervention effects; (2) for standardization of interventions for future trials; (3) for standardization of research protocols for collection and reporting of outcomes including harms; and (4) for comparisons of interventions with pharmacological interventions. For many of these areas, future research would benefit from considering recommendations from organizations such as the Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials,[36] the Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks,[37] the Report of the Task Force on Research Standards for Chronic Low Back Pain for the National Institutes of Health Pain Consortium[38] and the research priorities outlined in the recent Federal Pain Research Strategy.[39] Changes in conceptualization and terminology related to pain that reflect newer understandings of pain mechanisms are needed in future research. In addition, further research to evaluate differential effectiveness and safety of chronic pain treatments based on pain type/mechanism (e.g., nociplastic pain), age, and social determinants of health are needed, as are studies in pregnant and breastfeeding women with chronic pain. Evaluation of optimal delivery and integration of nonpharmacological strategies for chronic pain management is needed. Research funding for methodologically sound trials of nonpharmacological interventions is needed.

Table P. Summary of evidence gaps and research recommendations

Research Component	Evidence Gap	Future Research Recommendation
Study design methods and reporting	Evidence on the sustainability of effects was sparse. There was limited information on adherence and need to maximize retention.	Traditional (explanatory) and pragmatic trials with long-term followup and use of methods to enhance recruitment, retention and adherence are needed as are documentation of adherence and studies with sufficient sample size designed to evaluate differential effectiveness and safety of treatments in subpopulations of interest are needed. Consider recommendations from IMMPACT,[36] ACTTION,[37] NIH Research Standards for Chronic Low Back Pain[38] and Federal Pain Research Strategy.[39]
Patient populations	Information on overlapping chronic pain conditions or psychosocial factors was generally not provided in included trials. There is a lack of evidence related to treatment of chronic pain in pregnant or breastfeeding women and on the extent to which patients with nociplastic pain may respond differently than those with nociceptive pain.	Documentation of coexisting conditions and factors in trials with sufficient sample-size to evaluate the differential impact of conditions and factors is needed. Studies in pregnant and breastfeeding women with chronic pain are needed as is the comparison of treatment effects between patients with nociplastic pain and those with other types of pain.
Interventions and comparators	There is a lack of information on optimal techniques, duration and frequency of treatment and lack of evidence comparing interventions to pharmacological agents or other active controls.	Research leading to standardization of techniques and their delivery to be used in future trials and understanding best combinations of interventions is needed. Pragmatic trials may provide valuable information. Trials comparing interventions with pharmacological treatments are needed.

Table P. Summary of evidence gaps and research recommendations (continued)

Research Component	Evidence Gap	Future Research Recommendation
Outcomes measures	There is a lack of consistency in types outcomes measures used for function and pain across trials which makes it challenging to compare results across trials. Commonly used VAS or NRS for pain do not capture the impact of pain or allow for accurate classification or evaluation of changes in chronic pain. Common or known harms are not routinely collected.	Standardized protocols for types of outcomes to be assessed (including harms) would facilitate evaluation and comparison across studies. Use of measures that incorporate understanding of pathophysiological mechanisms and address multiple domains of pain is important. Reporting of the proportions of patients achieving a clinically meaningful improvement for measures of pain and function (i.e., responders) as well as outcomes related to change in use of opioids, healthcare utilization and quality of life are needed. Consider recommendations from IMMPACT,[36] ACTTION,[37] NIH Research Standards for Chronic Low Back Pain[38] and Federal Pain Research Strategy.[39]

ACTTION = Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks; IMMPACT = Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials; NIH = National Institutes of Health; NRS = Numeric Rating Scale; VAS = Visual Analog Scale.

Conclusions

Our prior AHRQ report found evidence of persistent effects for a number of nonpharmacological, noninvasive treatments for specific chronic pain conditions. Findings in this update are largely consistent with those in the prior report. Across trials in the prior report and this update, exercise, multidisciplinary rehabilitation, acupuncture, cognitive behavioral therapy, mindfulness, and mind-body practices were most consistently associated with durable small to moderate improvements in function and pain for specific chronic pain conditions, although the data were sparse for many interventions. Our findings provided some support for clinical strategies that focus on use of nonpharmacological therapies for specific chronic pain conditions. Additional comparative research on sustainability of effects beyond the immediate post-treatment period is needed, particularly for conditions other than low back pain.

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Full Report

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