Comparative Effectiveness Review
Number 209

Effective Health Care Program

Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review

Evidence Summary

Introduction

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.[1,2] Chronic pain is often defined as pain lasting 3 months or longer or persisting past the normal time for tissue healing, though definitions vary.[1,3] Chronic pain affects millions of adults in the United States, with an annual cost in personal and health system expenditures conservatively estimated at $560 billion to $635 billion.[1] 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[2] and 2011 Institute of Medicine (IOM) report1 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 Centers for Disease Control and Prevention (CDC)[4] included

Purpose of Review

To assess which noninvasive nonpharmacological treatments for common chronic pain conditions improve function and pain for at least 1 month after treatment.

Key Messages

- Interventions that improved function and/or pain for at least 1 month when used for—
  - **Chronic low back pain**: Exercise, psychological therapies (primarily cognitive behavioral therapy [CBT]), spinal manipulation, low-level laser therapy, massage, mindfulness-based stress reduction, yoga, acupuncture, multidisciplinary rehabilitation (MDR).
  - **Chronic neck pain**: Exercise, low-level laser, Alexander Technique, acupuncture.
  - **Knee osteoarthritis**: Exercise, ultrasound.
  - **Hip osteoarthritis**: Exercise, manual therapies.
  - **Fibromyalgia**: Exercise, CBT, myofascial release massage, tai chi, qigong, acupuncture, MDR.
  - **Chronic tension headache**: Spinal manipulation.
- Most effects were small. Long-term evidence was sparse.
- There was no evidence suggesting serious harms from any of the interventions studied; data on harms were limited.

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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.[1,5] 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.

This review focuses on noninvasive nonpharmacological treatments for chronic pain including exercise, mind-body practices, psychological therapies, multidisciplinary rehabilitation, mindfulness practices, manual therapies, physical modalities, and acupuncture. 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.

Rationale for This Review

Our review is intended to address some of the needs described in the NPS[2] and IOM[1] reports and others for evidence to inform guidelines and health care policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments as possible alternatives to opioids and other pharmacological treatments. 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:

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, or presence of comorbidities (e.g., emotional or mood disorders) 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, NSAIDS, acetaminophen, antiseizure medications, antidepressants)?

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 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 therapies (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 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 Agency for Healthcare Research & Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[6] See the review protocol (http://effectivehealthcare.ahrq.gov/index.cfm) and the full report of the review for additional details.

Topic Refinement and Review Protocol

The review team developed initial KQs and PICOTS with input from the AHRQ Task Order Officer (TOO), representatives from the CDC and the Office of the Assistant Secretary for Planning and Evaluation (ASPE), and a group of Key Informants. The Evidence-based Practice Center review team considered the public comments received on the provisional Key Questions, PICOTS, and analytic framework (posted on the AHRQ Effective Health Care Web site), along with input from the AHRQ TOO, CDC and ASPE representatives, and a Technical Expert Panel convened for this report. The final version of the protocol for this review was posted on the AHRQ Effective Health Care Program Web site (www.effectivehealthcare.ahrq.gov) and registered in the PROSPERO international database of prospectively registered systematic reviews (CRD42017067729).

Literature Search Strategy

A research librarian conducted searches in Ovid® MEDLINE®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews through November 1, 2017. ClinicalTrials.gov was searched for unpublished trials. A Federal Register notice was posted in an effort to identify unpublished data. No responses were received. Reference lists of included articles and the bibliographies of systematic reviews published since 2010 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 and are detailed in Table 1 of the 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[7,8] and based on methods recommended in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Research.[6] Studies were rated as "good," "fair," or "poor." (See Appendix E).

Data Analysis and Synthesis

Data were synthesized qualitatively (ranges and descriptive analysis) and quantitatively using meta-analysis where appropriate.[9] Duration of followup post-intervention 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.

We categorized the magnitude of effects for function and pain using the system described in our previous reviews.[10-12] We classified effects for measures with a 0-100 scale for pain or function as slight/small (5-10 points), moderate (>10–20 points), or large/substantial (>20 points). The moderate range for functional outcomes roughly corresponds to reported minimum clinically important differences for the measure. Small (slight) 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. 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.[13,14] When all studies for a primary outcome were rated poor quality, we rated the SOE as insufficient (see Appendix G).

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 provided comments and editorial review. The draft report was posted on the AHRQ Web site for 4 weeks for public comment.

Results

Results of Literature Searches

Database searches resulted in 4,996 potentially relevant articles. After dual review of abstracts and titles, 1,193 articles were selected for full-text dual review and 218 publications (202 trials) met inclusion criteria. We included 68 trials (74 publication) on chronic low back pain, 25 trials on chronic neck pain, 53 trials (56 publications) on osteoarthritis, 47 trials (54 publications) on fibromyalgia, and nine trials 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 (59%) were rated fair quality, and 36 percent were rated as poor, with only 5 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 differences were not statistically significant but confidence intervals were close to 0 (continuous outcomes) or 1 (dichotomous outcomes) results were interpreted as showing no clear difference, but favoring one treatment.

Key Question 1: Chronic Low Back Pain

Exercise

- Exercise was associated with slightly greater effects on short-term function than usual care, an attention control or a placebo intervention (6 trials, pooled standardized mean difference [SMD] -0.31, 95% confidence interval [CI] -0.58 to -0.04, I^2=57%); there was no evidence of effects on intermediate-term function (3 trials, pooled SMD -0.15, 95% CI -0.48 to 0.18, I^2=51%) or long-term function (1 trial, difference 0.00 on the 0 to 100 Oswestry Disability Index [ODI], 95% CI -11.4 to 11.4) (SOE: Low).
- Exercise was associated with slightly to moderately greater effects on pain than usual care, an attention control or a placebo intervention at short-term (6 trials, pooled difference -0.81 on a 0 to 10 scale, 95% CI -1.26 to -0.,36, I^2=0%), intermediate-term (3 trials, pooled difference -1.37, 95% CI -2.10 to -0.65, I^2=34%), and long-term (1 trial, difference -1.55, 95% CI -2.378 to -0.32) followup (SOE: Moderate for short term, low for intermediate term and long term).

Psychological Therapies

- Psychological therapy was associated with slightly greater effects on function than usual care or an attention control at short-term (3 trials, pooled SMD -0.25, 95% CI -0.38 to -0.12, I^2=0%), intermediate-term (3 trials, pooled SMD -0.25, 95% CI -0.37 to -0.13, I^2=0%), and long-term followup (3 trials, pooled SMD -0.27, 95% CI -0.39 to -0.15, I^2=0%) (SOE: Moderate).
- Psychological therapy was associated with slightly greater effects on pain than usual care or an attention control at short-term (3 trials, pooled difference -0.76

on a 0 to 10 scale, 95% CI -0.99 to -0.53, I^2=0%), intermediate-term (3 trials, pooled difference -0.71, 95% CI -0.94 to -0.48, I^2=0%), or long-term followup (3 trials, pooled difference -0.53, 95% CI -0.78 to -0.27, I2=0%) (SOE: Moderate).

Physical Modalities

Ultrasound

- No evidence of difference was found between ultrasound versus sham ultrasound in short-term pain (2 trials, SOE: low).

Low-Level Laser Therapy

- •One trial found low-level laser therapy associated with slightly greater effects than sham laser on short-term function (difference -8.2 on the 0 to 100 ODI, 95% CI -13.6 to -2.8) and moderately greater effects on pain (difference -16.0 on a 0 to 100 scale, 95% CI -28.3 to -3.7) (SOE: low).

Traction

- Two trials found no evidence of difference between traction versus sham traction in short-term pain or function (SOE: low).

Manual Therapies

Spinal Manipulation

- Spinal manipulation was associated with slightly greater effects than sham manipulation, usual care, an attention control, or a placebo intervention in short-term function (3 trials, pooled SMD -0.34, 95% CI -0.63 to -0.05, I^2=61%) and intermediate-term function (3 trials, pooled SMD -0.40, 95% CI -0.69 to -0.11, I^2=76%) (SOE: low)
- There was no evidence of differences between spinal manipulation versus sham manipulation, usual care, an attention control or a placebo intervention in short-term pain (3 trials, pooled difference -0.20 on a 0 to 10 scale, 95% CI -0.66 to 0.26, I^2=58%), but manipulation was associated with slightly greater effects than controls on intermediate-term pain (3 trials, pooled difference -0.64, 95% CI -0.92 to -0.36, I^2=0%) (SOE: low for short term, moderate for intermediate term).

Massage

- Massage was associated with slightly greater effects on short-term function than sham massage or usual care (4 trials, SMD -0.30, 95% CI -0.46 to -0.14, I^2=0%). There was no evidence of differences between massage versus controls in intermediate-term function (3 trials, SMD -0.09, 95% CI -0.24 to 0.06, I2=0%) (SOE: moderate for short term, low for intermediate term).
- Massage was associated with slightly greater effects on short-term pain than sham massage or usual care (4 trials, pooled difference -0.52 on a 0 to 10 scale, 95% CI -0.81 to -0.23, I^2=0%). There was no evidence of differences between massage versus controls in intermediate-term pain (3 trials, difference -0.01, 95% CI -0.40 to 0.38, I^2=0%) (SOE: moderate for short term, low for intermediate term).

Mindfulness-Based Stress Reduction

- There was no evidence of differences between mindfulness-based stress reduction (MBSR) versus usual care or an attention control in short-term function (4 trials, pooled SMD -0.25, 95% CI -0.53 to 0.04, I^2=53%), intermediate-term function (1 trial, SMD -0.20, 95% CI -0.47 to 0.06) or long-term function (1 trial, SMD -0.20, 95% CI -0.47 to 0.06) (SOE: low).
- MBSR was associated with slightly greater effects than usual care or an attention control on short-term pain (3 trials, pooled difference -0.73 on a 0 to 10 scale, 95% CI -1.18 to -0.28, I^2=93%), after excluding two poor-quality trials; MBSR was also associated with small effects on intermediate-term pain (1 trial, difference -0.75, 95% CI -1.17 to -0.33), with no statistically significant effects on long-term pain (1 trial, SMD -0.22, 95% CI -0.64 to 0.20) (SOE: moderate for short term, low for intermediate and long term).

Mind-Body Practices—Yoga

- Yoga was associated with slightly greater effects on function than an attention or waitlist control at short-term (6 trials, pooled SMD -0.50, 95% CI -0.72 to -0.29, I^2=54%) and intermediate-term (3 trials, pooled SMD -0.33, 95% CI -0.49 to -0.16) followup (SOE: moderate for short term, low for intermediate term).
- Yoga was associated with moderately greater effects on pain than an attention or waitlist control at short-term (5 trials, pooled difference -1.10 on a 0 to 10 scale, 95% CI -1.77 to -0.42, I^2=74%) and intermediate-term (2 trials, pooled difference -1.17, 95% CI -1.91 to -0.44, I2=26%) followup (SOE: low for short term, moderate for intermediate term).

Acupuncture

- Acupuncture was associated with slightly greater effects on short-term function than sham acupuncture or usual care (4 trials, pooled SMD -0.22, 95% CI -0.35 to -0.08, I^2=44%). There was no evidence of differences

between acupuncture versus controls in intermediate-term function (3 trials, pooled SMD -0.08, 95% CI -0.36 to 0.20, I^2=75%) or long-term function (1 trial, adjusted difference -3.4 on the 0 to 100 ODI, 95% CI -7.8 to 1.0) (SOE: low).

- Acupuncture was associated with slightly greater effects on short-term pain than sham acupuncture, usual care, an attention control, or a placebo intervention (5 trials, pooled difference -0.55 on a 0 to 10 scale, 95% CI -0.86 to -0.24, I^2=30%). There was no evidence of a difference in intermediate-term pain (5 trials, pooled mean difference -0.25, 95% CI -0.67 to 0.16, I^2=33%); one trial found acupuncture associated with greater effects on long-term pain (mean difference -0.83, 95% CI -1.51 to -0.15) (SOE: moderate for short term, low for intermediate term and long term).

Multidisciplinary Rehabilitation

- Multidisciplinary rehabilitation was associated with slightly greater effects on function than usual care at short-term followup (4 trials, pooled SMD -0.31, 95% CI -0.57 to -0.05, I^2=70%) and intermediate-term followup (4 trials, pooled SMD -0.37, 95% CI -0.64 to -0.10, I^2=50%); there was no evidence of differences in long-term function (2 trials, pooled SMD -0.04, 95% CI -0.31 to 0.24, I2=35%) (SOE: low).
- Multidisciplinary rehabilitation was associated with slightly greater effects on pain than usual care at short-term followup (4 trials, pooled difference -0.51 on a 0 to 10 scale, 95% CI -0.89 to -0.13, I^2=23%) and intermediate-term followup (4 trials, pooled difference -0.63, 95% CI -1.04 to -0.22, I^2=0%); the long-term difference was smaller and not statistically significant (2 trials, pooled difference -0.34, 95% CI -0.86 to 0.18, I^2=0%) (SOE: moderate for short term and intermediate term, low for long term).

Comparative Effectiveness of Interventions

- One trial found no differences between low-level laser therapy versus exercise therapy in intermediate-term function or pain (SOE: low).
- There was no evidence of difference between spinal manipulation versus exercise in short-term function (3 trials, pooled SMD 0.01, 95% CI -0.22 to 0.25; I^2=62%) or intermediate-term function (4 trials, pooled SMD 0.02, 95% CI -0.13 to 0.18; I^2=48%) (SOE: low).
- There was no evidence of difference between spinal manipulation versus exercise in short-term pain (3 trials, pooled difference 0.31 on a 0 to 10 scale, 95% CI -0.30 to 0.92; I2=60%) or intermediate-term pain (4 trials, pooled difference 0.22, 95% CI -0.09 to 0.52, I^2=9.4%) (SOE: low).
- One trial found no differences between massage versus exercise in intermediate-term or function or pain (SOE: low).
- There was no statistically significant difference between yoga versus exercise in short-term or intermediate-term function or pain (SOE: low).
- One trial found no evidence of differences between qigong versus exercise in short-term function (difference 0.9 on the RRoland-Morris Disability Questionnaire, 95% CI -0.1 to 2.0), although intermediate-term results slightly favored exercise (difference 1.2, 95% CI 0.1 to 2.3) (SOE: low).
- One trial found qigong associated with slightly lower effects on pain versus exercise at short-term followup (difference 7.7 on a 0 to 100 scale, 95% CI 0.7 to 14.7), but the difference at intermediate-term was not statistically significant (difference 7.1, 95% CI -1.0 to 15.2) (SOE: low).
- Multidisciplinary rehabilitation was associated with slightly greater effects than exercise on short-term function (6 trials, pooled SMD -0.28, 95% CI -0.54 to -0.01, I^2=39%) and intermediate-term function (5 trials [excluding outlier trial], pooled SMD -0.22, 95% CI -0.40 to -0.03, I^2=0%); there was no effect on long-term function (2 trials [excluding outlier trial], pooled SMD -0.06, 95% CI -0.36 to 0.25, I^2=0%) (SOE: moderate for short term and intermediate term, low for long term).
- Multidisciplinary rehabilitation was associated with slightly greater effects than exercise on short-term pain (6 trials, pooled difference -0.75 on a 0 to 10 scale, 95% CI -1.18 to -0.31, I^2=0%) and intermediate-term pain (5 trials [excluding outlier trial], pooled difference -0.55, 95% CI -0.95 to -0.15, I^2=0%); there was no effect on long-term pain (2 trials [excluding outlier trial], pooled difference 0.00, 95% CI -0.94 to 0.95) (SOE: moderate for short term and intermediate term, low for long term).

Key Question 2: Chronic Neck Pain

Exercise

- Across types of exercise, there was no clear improvement in function (3 trials [excluding outlier trial], pooled SMD -0.23, 95% CI -0.71 to 0.15) or pain

(3 trials [excluding outlier trial], pooled SMD -0.72, 95% CI -1.49 to 0.06) versus no treatment or advice alone in the short-term (SOE: low).

- 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 slight benefit in function and pain versus no treatment or advice alone over the short term and function in the long term (SOE: low).

Psychological

- No evidence of differences in function (Neck Disability Index, 0-80 scale) or pain (Visual Analog Scale for Pain [VAS], 0-10 scale) in the short term (adjusted difference 0.1, 95% CI 2.9 to 3.2 and 0.2, 95% CI 0.4 to 0.8, respectively) or intermediate term (adjusted difference 0.2, 95% CI 2.8 to 3.1 and 0.2, 95% CI 0.3 to 0.8, respectively) from one trial comparing relaxation training and no intervention or exercise (SOE: low for all).

Physical Modalities

- Low-level laser therapy was associated with a moderate improvement in short-term function (2 trials, pooled difference -14.98 , 95% CI -23.88 to -6.07, I^2=39%, 0-100 scale) and pain (3 trials, pooled difference -1.81 on a 0-10 scale, 95% CI -3.35 to -0.27, I^2=75%) compared with sham (SOE: moderate for function and pain).

Manual Therapies

- The effects of massage on function versus self-management attention control were slight and not statistically significant in one trial (N=64) in the short term (≥5 point improvement on the Neck Disability Index, 39% versus 14%, relative risk [RR] 2.7, 95% CI 0.99 to 7.5) and intermediate term (57% versus 31%, RR 1.8, 95% CI 0.97 to 3.5) (SOE: low for both time periods).

Mind-Body Practices

- Alexander Technique resulted in a slight improvement in function in the short term (difference -5.56 on a 0-100% scale, 95% CI -8.33 to -2.78) and intermediate term (difference -3.92, 95% CI -6.87 to -0.97) compared with usual care alone based on one trial (SOE: low).

Acupuncture

- Acupuncture was associated with slightly greater effects on short-term and intermediate-term function versus sham acupuncture, placebo (sham laser) or usual care (short term, 5 trials, pooled SMD -0.40, 95% CI -0.64 to -0.17, I^2=67.7%; intermediate term, 3 trials, pooled SMD -0.19, 95% CI -0.35 to -0.02). One trial reported no difference in function in the long term (SMD -0.23, 95% CI -0.61 to 0.16) (SOE: low for all time periods). A sham comparator was used in all but one trial.
- There was no evidence of differences in pain comparing acupuncture with sham acupuncture, or placebo interventions in the short term (4 trials [excluding outlier trial], pooled difference -0.2 on a 0-10 scale, 95% CI -0.59 to 0.05, I^2=2%), intermediate term (3 trials, pooled difference 0.45, 95% CI -0.34 to 1.25, I2=59%) or long term (1 trial, difference -1.8, 95% CI -1.34 to 0.64). (SOE: low for all time periods).

Comparative Effectiveness of Interventions for Chronic Neck Pain

- There was no clear evidence that massage improved pain in the intermediate term versus exercise (P>0.05, data not reported) in one trial (SOE: low).
- No clear evidence that basic body awareness therapy improved function in the short term versus exercise in one trial (SOE: low).

Key Question 3: Osteoarthritis

Exercise (Knee)

- Exercise was associated with slightly greater improvement in function than usual care, no treatment or sham intervention short term (7 trials, pooled SMD -0.25, 95% CI -0.4 to -0.09, I^2=0%), at intermediate term (9 trials [excluding outlier trial] pooled SMD -0.78, 95%CI -1.37 to -0.19, I^2=91.4%), and long term (2 trials, pooled SMD -0.24, 95%CI -0.37 to -0.11 I^2=0%) (SOE: moderate for short term; low for intermediate and long term).
- Exercise was associated with a slight improvement in pain short term (7 trials, pooled difference -0.44 on a 0 to 10 scale, 95% CI -0.82 to -0.05, I^2=35%) versus usual care, no treatment or sham intervention (SOE: moderate), and with moderately greater effect on pain in the intermediate term (9 trials, pooled difference -1.61 on a 0 to 10 scale, 95% CI -2.51 to -0.72, I^2=91%) compared with usual care, an attention control, or no treatment (SOE: low). Long term, there was no clear difference between exercise and improvement in pain but data were limited (2 trials, difference -0.24, 95% CI -0.72 to 0.24) (SOE: low).

Psychological Therapy (Knee)

- Two trials of pain coping skills training and cognitive behavioral training versus usual care found no evidence of differences in function (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] physical function, 0-100) or pain (WOMAC pain, 0-100); treatment effects were averaged over short term to intermediate term (difference -0.3, 95% CI -8.3 to 7.8 for function and -3.9, 95% CI -1.8 to 4.0 for pain) and intermediate term to long term (mean 35.2, 95% CI 31.8 to 38.6 vs. mean 37.5, 95% CI 33.9 to 41.2, and mean 34.5, 95% CI 30.8 to 38.2 vs. mean 38.0, 95% CI 34.1 to 41.8), respectively (SOE: low).

Physical Modalities (Knee)

Ultrasound

- One trial found continuous and pulsed ultrasound was associated with better short-term function (difference of -6.2, 95% CI -8.36 to -4.20, and -5.71, 95% CI -7.72 to -3.70 on a 0-24 scale) and short-term pain intensity (difference -3.3, 95% CI -4.64 to -1.96, and -3.37, 95% CI -4.73 to -2.01 on a 0-10 scale) (SOE: low).
- One trial found no evidence of differences between continuous and pulsed ultrasound versus sham in intermediate-term function (difference -2.9, 95% CI -9.19 to 3.39 and 1.6, 95% CI -3.01 to 6.22, on a 0-68 scale) or pain (difference -1.6, 95% CI -3.26 to 0.06 and 0.2, 95% CI -1.34 to 1.74, on a 0-20 scale). There was also no evidence of difference between groups for VAS pain during rest or on movement (SOE: low).

Transcutaneous Electrical Nerve Stimulation

- There was no evidence of difference from one trial between transcutaneous electrical nerve stimulation (TENS) and placebo TENS in intermediate-term function as measured by the WOMAC function subscale (proportion of patients who achieved MCID (≥9.1), 38% vs. 39%, RR 1.2 (95% CI 0.6 to 2.2); and difference -1.9 (95% CI -9.7 to 5.9) on a 0-100 scale) or intermediate-term pain (proportion of patients who achieved MCID (≥20) in VAS pain, 56% vs 44%, RR 1.3 (95% CI 0.8 to 2.0); and mean difference -5.6 (95% CI -14.9 to 3.6) on the 0-100 WOMAC pain subscale) (SOE: low for function and pain).

Electromagnetic Field

- One trial found pulsed electromagnetic fields were associated with slight improvements in function (difference -3.48, 95% CI -4.44 to -2.51 on a 0-85 WOMAC Activities of Daily Living subscale) and pain (difference -0.84, 95% CI -1.10 to -0.58 on a 0-25 WOMAC pain subscale) versus sham short-term but differences may not be clinically significant (SOE: low).

Acupuncture (Knee)

- There was no evidence of differences between acupuncture versus control interventions (sham acupuncture, waitlist or usual care) on function in the short term (4 trials [excluding outlier trial], pooled SMD -0.05, 95% CI -0.32 to 0.38) or the intermediate term (4 trials, pooled SMD -0.15, 95% CI -0.31 to 0.02, I^2=0%) (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.
- There was no evidence of differences between acupuncture versus control interventions (sham acupuncture, waitlist, or usual care) on pain in the short term (6 trials, pooled SMD -0.27, 95% CI -0.56 to 0.02, I^2=75%) or clinically meaningful differences in the intermediate term (4 trials, pooled SMD -0.16, 95% CI -0.31 to 0.02, I^2=0%); no individual trial was statistically significant. (SOE: low for short term; moderate for intermediate term). Short-term differences were significant for acupuncture versus usual care but not for acupuncture versus sham acupuncture.

Exercise for Osteoarthritis of the Hip

- Exercise was associated with a slight improvement in function versus usual care in the short term (3 trials, pooled SMD -0.33, 95% CI, -0.53 to -0.12, I^2=0.0%) and intermediate term (2 trials, pooled SMD -0.28, 95% CI -0.50 to -0.05, I^2=0.0%). (SOE: low for short and intermediate term).
- Exercise tended toward slightly greater improvement in short-term pain compared with usual care (3 trials, pooled SMD -0.34, 95% CI, -0.63 to -0.04, I2=48.2%), but the results were no longer significant at intermediate term (2 trials, pooled SMD -0.14, 95% CI -0.37 to 0.08, I^2=0%) (SOE: low for short and intermediate term).

Physical Modalities for Osteoarthritis of the Hand

- One trial of low-level laser treatment versus sham demonstrated no improvement in terms of function (difference 0.2, 95% CI -0.2 to 0.6) or pain (difference 0.1, 95% CI -0.3 to 0.5) in the short term (SOE: low).

Multidisciplinary Rehabilitation for Osteoarthritis of the Hand

- One trial of multidisciplinary rehabilitation versus waitlist control demonstrated no short-term differences between groups in function (adjusted difference 0.49, 95% CI, -0.09 to 0.37 on 0-36 scale), pain (adjusted difference 0.40, 95% CI, -0.5 to 1.3 on a 0-20 scale), or with regard to the proportion of Osteoarthritis Research Society International Outcome Measures in Rheumatology responders (odds ratio [OR] 0.82, 95% CI, 0.42 to 1.61) (SOE: low for all outcomes).

Comparative Effectiveness of Interventions for Osteoarthritis

- Knee Osteoarthritis: One trial of pain coping skills training versus strengthening exercises found no evidence of differences in WOMAC physical function scores (0-68 scale) at short term (mean difference 2.0, 95% CI -2.4 to 6.4) or intermediate term (mean difference 3.2, 95% CI -0.6 to 7.0) or in WOMAC pain scores (0-20 scale) at short term (mean difference -0.1, 95% CI -1.2 to 1.0) or intermediate term (mean difference 0.4, 95% CI -0.8 to 1.6) (SOE low).
- Hip Osteoarthritis: Manual therapy was associated with slight improvements in short-term (mean difference 11.1, 95% CI 4.0 to 18.6, 0-100 scale Harris Hip Score) and intermediate-term (mean difference 9.7, 95% CI, 1.5 to 17.9) function, and in short-term pain (mean differences of -0.72, 95% CI -1.38 to -0.05 for pain at rest; and -1.21, 95% CI -2.29 to -0.25 for pain walking) versus exercise (SOE: low for both function and pain).

Key Question 4: Fibromyalgia

Exercise

- Exercise was associated with slightly greater effects on function compared with an attention control, no treatment, or usual care in the short term (7 trials, pooled mean difference -7.61 on a 0 to 100 scale, 95% CI, -12.78 to -2.43, I^2=59.9%) (SOE: low) and intermediate-term (8 trials, pooled mean difference, -6.04, 95% CI –9.05 to -3.03, I^2=0%) (SOE: moderate). There were no clear effects long term (3 trials, pooled mean difference -4.33, 95% CI -10.18 to 1.52, I^2=0%) (SOE: low).
- Exercise had a slightly greater effect on VAS pain (0-10 scale) compared with usual care, an attention control or no treatment short term (6 trials [excluding outlier trial] pooled mean difference -0.89, 95% CI -1.32 to -0.46, I^2=0%) but there were no clear effects at intermediate term (7 trials, pooled mean difference -0.41, 95% CI -0.87 to 0.05, I2=9.5%) or long term (4 trials, pooled mean difference -0.18, 95% CI -0.77 to 0.42, I2=0%) (SOE: moderate for all time frames).

Psychological Therapies

- Cognitive behavioral therapy (CBT) was associated with a slightly greater effect on the Fibromyalgia Impact Questionnaire (FIQ) Total Score than usual care or waitlist in the short-term (2 trials, pooled mean difference -10.67, 95% CI -17 to -4.30, I2=0%, 0-100 scale). The pooled estimate at intermediate term was not statistically significant due to heterogeneity, however individual trials showed a greater effect than usual care and a third trial using the 0 to 10 FIQ Physical Impairment Scale showed a greater effect of CBT than an attention control (mean difference -1.8, 95% CI -2.9 to -0.70) (SOE: low for short term and intermediate term).
- CBT was associated with a slight improvement in pain (on a 0-10 scale) compared with usual care or waitlist in the short term (3 trials, pooled mean difference -0.78, 95% CI -1.30 to -0.17) but not in the intermediate term (2 trials, pooled mean difference -0.44, 95% CI -1.30 to 0.01) (SOE: low for short term and intermediate term).

Physical Modalities

- One parallel trial showed no differences between magnetic mattress pads compared with sham or usual care in intermediate-term function (difference on the 0-80 scale FIQ -5.0, 95% CI -14.1 to 4.1 vs. sham and -5.5, 95% CI -14.4 to 3.4 vs. usual care) or pain (difference -0.6, 95% CI -1.9 to 0.7 and -1.0, 95% CI -2.2 to 0.2, respectively on a 0-10 scale) (SOE: low).

Manual Therapies

- Myofascial release therapy was associated with a slightly greater effect on intermediate-term function as measured by the FIQ (mean 58.6 ± 16.3 vs. 64.1 ± 18.1 on a 100 point scale, P=0.048 for group by repeated measures [analysis of variance] ANOVA), but not long-term function (mean 62.8 ± 20.1 vs. 65.0 ± 19.8 on the FIQ, 0-100 scale, P=0.329), compared with sham in one trial (SOE: low).
- Myofascial release therapy was associated with slightly greater effects on long-term pain based on the sensory (mean 18.2 ± 8.3 vs. 21.2 ± 7.9 on a 0-33 scale, P=0.038 for group by repeated measures ANOVA) and evaluative (mean 23.2 ± 7.6 vs. 26.7 ± 6.9 on a 0-42 scale, P=0.036) domains of the McGill

Pain Questionnaire (MPQ) in one trial; there were no differences for the affective domain of the MPQ or for VAS pain (SOE: low).

Mindfulness-Based Stress Reduction Therapy

- No clear short-term effects of MBSR were seen on function compared with waitlist or an attention control (mean difference 0 to 0.06 on a 0-10 scale) in two trials (SOE: moderate).
- No clear short-term effects of MBSR on pain (mean difference 0.1 on a 0-100 VAS pain scale in one trial; mean difference -1.38 to -1.59 on the affective and -0.28 to -0.71 on the sensory dimension [scales not reported] of the Pain Perception Scale in one trial) compared with waitlist or an attention control in two trials (SOE: moderate). Intermediate and long-term outcomes were not reported.

Mind-Body Practices

- Over the short term, two trials of mind-body practices reported a slight improvement in function for qigong compared with waitlist (mean difference -7.5, 95% CI -13.3 to -1.68) and a large improvement for tai chi compared with attention control (mean difference -23.5, 95% CI -30 to -17) based on 0-100 scale total FIQ score; heterogeneity may be explained by duration and intensity of intervention and control condition. Significantly more participants in the tai chi group also showed clinically meaningful improvement on total FIQ (RR 1.6, 95% CI 1.1 to 2.3) consistent with a slight effect (SOE: low).
- Qigong and tai chi were associated with moderately greater improvement in pain (0-10 scale) compared with waitlist and an attention control in the short term (2 trials, pooled mean difference -1.54, 95% CI -2.67, -0.41, I^2=75%). Significantly more participants in the tai chi group also showed clinically meaningful improvement on VAS pain (RR 2.0, 95% CI 1.1 to 3.8) consistent with a slight effect (SOE: low).

Acupuncture

- Acupuncture was associated with slightly greater effects on function based on 0-100 FIQ Total Score in patients with fibromyalgia than sham acupuncture in the short-term (2 trials, pooled difference -8.63, 95% CI =12.12 to -5.13, I^2=0%) and intermediate-term (2 trials, pooled mean difference -9.41, 95% CI -13.96 to -4.85, I^2=27.4%) (SOE: moderate).
- There was no clear effect of acupuncture on pain (0-10 scale) versus sham acupuncture in the short term (3 trials, pooled mean difference -0.13, 95% CI -1.06 to 0.79, I^2=72%) or intermediate term (3 trials, pooled mean difference – 0.53, 95% CI -1.15 to 0.09, I2=45.5%) (SOE: low)

Multidisciplinary Rehabilitation

- Multidisciplinary treatment was associated with a slight improvement in function (based on a 0-100 FIQ total score) versus usual care or waitlist in the short term (3 trials, pooled mean difference -6.52, 95% CI -12.84 to -0.21, I^2=67.3%) and versus usual care at intermediate term (3 trials, pooled mean difference -7.84, 95% CI -11.43 to -4.25, I^2=18.2%) and long term (2 trials, pooled mean difference -8.42, 95% CI -13.76 to -3.08, I^2 =24.9%). More multidisciplinary treatment participants experienced a clinically meaningful improvement in FIQ total score compared with usual care at short (odds ratio [OR] 3.1, 95% CI 1.6 to 6.2), intermediate (OR 3.1, 95% CI 1.5 to 6.4) and long term (OR 8.8, 95% CI 2.5 to 30.9) in one trial (SOE: low for short, intermediate and long term).
- Multidisciplinary treatment was associated with a slight improvement in pain compared with usual care or waitlist at intermediate term (3 trials, pooled mean difference -0.68, 95% CI -1.07 to -0.30, I^2=0%); there were no clear differences compared with usual care or waitlist in the short term (2 trials [excluding an outlier trial], pooled mean difference on a 0-10 scale -0.24, 95% CI -0.63 to 0.15, I^2=0%) or with usual care in the long-term (2 trials, pooled mean difference -0.25, 95% CI -0.68 to 0.17, I^2=0%) (SOE: low for short, intermediate and long term).

Comparative Effectiveness of Interventions for Fibromyalgia

- CBT was associated with a slight benefit compared with pharmacological treatment (pregabalin; duloxetine) for function (mean difference -4.0 on the 0-100 FIQ, 95% CI -7.7 to -0.27), but not for pain (mean difference 0.2 on a 0-100 VAS, 95% CI -4.0 to 4.4) at intermediate term in one trial (SOE: low).
- There was no evidence of an effect for multidisciplinary treatment versus aerobic exercise at long term for function (mean difference -1.10, 95% CI -8.40 to 6.20, 0-100 FIQ total score) or pain (mean difference 0.10, 95% CI -0.67 to 0.87, 0-10 FIQ pain scale) in one trial (SOE: low).

Key Question 5: Chronic Tension Headache

Manual Therapies

- Spinal manipulation therapy was associated with slight to moderate improvements, respectively, compared with usual care in function (difference -5.0, 95% CI -9.02 to -1.16 on the Headache Impact Test, scale 36-78 and difference -10.1, 95% CI -19.5 to -0.64 on the Headache Disability Inventory, scale 0-100) and pain intensity (difference -1.4 on a 0-10 Numerical Rating Scale scale, 95% CI -2.69 to -0.16) over the short term in one trial (SOE: low). Approximately a quarter of the patients had comorbid migraine.

Acupuncture

- Laser acupuncture was associated with slight improvement in pain intensity (median difference -2, IQR 6.3, on a 0-10 VAS scale) and in the number of headache days per month (median difference -8, IQR 21.5) over the short term versus sham in one trial (SOE: low).

Comparative Effectiveness of Interventions for Chronic Tension Headache

- 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 or comorbidities modify the effects of treatment.

Harms

Although data on harms were limited, no evidence suggested serious harms 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. Trials that did report such data found infrequent or rare 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.

Discussion

Key Findings and Strength of Evidence

The key findings of this review, including SOE ratings, are summarized for each chronic pain condition in the Results and evidence summary Tables A–M. Interventions and comparators with insufficient evidence or no evidence (no RCTs meeting inclusion criteria) for either function or pain outcomes are not shown. Domains used to determine the overall SOE are shown in Appendix G of the full report. All outcomes were considered direct.

The strength of evidence 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 post-intervention 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 outcomes.

The majority of trials compared interventions with usual care, and very few trials employed pharmacological treatments or exercise as comparators. In general, effect sizes for most interventions were small, based on mean 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.

No trials directly compared interventions with opioids and few trials reported effects of interventions on opioid use. Our previous reviews found opioids associated with small to moderate effects on pain during treatment (effects would not be expected to persist) with evidence almost exclusively from short-term (≤3 month) trials.[10,11,15]

Harms were poorly reported across interventions. No serious intervention-related adverse events requiring 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).

Table A. Chronic low back pain: 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	slight +	none +	none +	slight ++	moderate +	moderate +
Psychological Therapies: CBT primarily	slight ++	slight ++	slight ++	slight ++	slight ++	slight ++
Physical Modalities: Ultrasound	insufficient evidence	no evidence	no evidence	none +	no evidence	no evidence
Physical Modalities: Low-Level Laser Therapy	slight +	none +	no evidence	moderate +	none +	no evidence
Manual Therapies: Spinal Manipulation	slight +	slight +	no evidence	none +	slight ++	no evidence
Manual Therapies: Massage	slight ++	none +	no evidence	slight ++	none +	no evidence
Manual Therapies: Traction	none +	no evidence	no evidence	none +	no evidence	no evidence
Mindfulness Practices: MBSR	none +	none +	none +	slight ++	slight +	none +
Mind-Body Practices: Yoga	slight ++	slight +	no evidence	moderate +	moderate ++	no evidence
Acupuncture	slight +	none +	none +	slight ++	none +	slight +
Multidisciplinary Rehabilitation	slight +	slight +	none +	slight ++	slight ++	none +

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

Effect Size: none, slight/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.

Table B. Chronic low back pain: 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	slight +	no evidence
Manual Therapies: Spinal Manipulation	none +	none +	no evidence	none +	slight +	no evidence
Manual Therapies: Massage	no evidence	none +	no evidence	no evidence	none +	no evidence
Mind-Body Practices: Yoga	none +	none +	no evidence	slight +	none +	no evidence
Mind-Body Practices: Qigong	none +	slight favoring exercise +	no evidence	slight favoring exercise +	none +	no evidence
Multidisciplinary Rehabilitation	slight ++	slight ++	none +	slight ++	slight ++	none +

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, slight/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: 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	none +	no evidence	no evidence	none +	no evidence	no evidence
Psychological Therapies: PT-lead 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	none +	none +	no evidence	no evidence	no evidence	no evidence

Table C. Chronic neck pain: effects of nonpharmacological interventions compared with usual care, placebo, sham, attention control, or waitlist (continued)

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 Practices: Alexander Technique	slight +	slight +	no evidence	no evidence	no evidence	no evidence
Acupuncture	slight +	slight +	none +	none +	none +	none +

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
Effect Size: none, slight/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 D. Chronic neck pain: 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-lead 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, slight/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 E. Osteoarthritis of the knee: 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	slight ++	slight +	slight +	slight ++	moderate +	none +
Psychological Therapies: Pain coping, CBT	none +	none +	none +	none +	none +	none +
Physical Modalities: Ultrasound	slight +	none +	no evidence	slight +	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, slight/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

Table F. Osteoarthritis of the knee: 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, slight/small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
none = no effect/no statistically significant effect; SOE = strength of evidence

Table G. Osteoarthritis of the hip: 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	slight +	slight +	insufficient evidence	slight +	none +	insufficient evidence

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

Table H. Osteoarthritis of the hip: 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	slight +	slight +	no evidence	slight +	insufficient evidence	no evidence

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

Table I. Osteoarthritis of the hand: 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, slight/small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
none = no effect/no statistically significant effect; SOE = strength of evidence

Table J. Fibromyalgia: 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	slight +	slight ++	none +	slight ++	none ++	none ++
Psychological Therapies: CBT	slight +	slight +	insufficient evidence	slight +	none +	insufficient evidence
Physical Modalities: Magnetic Pads	insufficient evidence	none +	no evidence	insufficient evidence	none +	no evidence
Manual Therapies: Massage (Myofascial Release)	no evidence	slight +	none +	insufficient evidence	insufficient evidence	slight +
Mindfulness Practices: MBSR	none ++	no evidence	no evidence	none ++	no evidence	no evidence
Mind-Body Practices: Qigong, Tai Chi	slight +	no evidence	no evidence	moderate +	no evidence	no evidence
Acupuncture	slight ++	slight ++	no evidence	none +	none +	no evidence
Multidisciplinary Rehabilitation	slight +	slight +	slight +	none +	slight +	none +

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

Effect Size: none, slight/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

Table K. Fibromyalgia: 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
CBT vs. pregabalin; duloxetine	no evidence	slight +	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, slight/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

Table L. Fibromyalgia: 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
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, slight/small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
none = no effect/no statistically significant effect; SOE = strength of evidence

Table M. Chronic tension headache: 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	slight +	no evidence	no evidence	moderate +	no evidence	no evidence
Acupuncture	no evidence	no evidence	no evidence	slight + (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, slight/small, moderate, or large improvement
Strength of Evidence: + = low, ++ = moderate, +++ = high
SOE = strength of evidence

Findings in Relationship to What Is Already Known

Many 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 post-intervention.

This review updates our previous review on low back pain[10] by incorporating new evidence on nonpharmacological treatments for chronic low back pain. Consistent with the prior review, we 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 in and 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. For example, subanalyses of specific interventions within a given category of intervention (e.g., aerobic exercise within the general category of exercise suggested that despite the inherent heterogeneity within some of the categories, effect estimates for specific interventions may be similar). 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.

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 (ICER) review on chronic low back pain and neck pain,[16] an AHRQ report on knee osteoarthritis treatment[17] and with recent reviews that included a variety of chronic pain conditions which examined exercise,[18] acupuncture,[19] and complementary health approaches[20] for chronic pain management, as well as a review of chronic pain treatment guidelines on the use of manual and physical therapies.[21]

Applicability

The applicability of our findings may be impacted by a number of factors. Included trials provided limited information on, symptom duration, clinical characteristics, comorbid conditions and concomitant treatments, thus it is not clear to what extent this reflects the populations seen in clinical practice or may how these factors impact our results. In addition, with the exception of fibromyalgia, information regarding diagnostic criteria for the pain condition of interest was limited. Information on presence of overlapping chronic pain conditions or psychosocial factors was generally not provided in included trials. The extent to which these characteristics were present in trial populations and their impact on our results is not clear. Across conditions, a majority of trial participants were female. The age of included populations generally reflected the ages impacted by the conditions. Evidence to evaluate how effectiveness varies by ages was limited. There was also heterogeneity in populations enrolled in the trials with regard to 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). Our findings are generally most applicable to persons without such 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.

Variability in interventions, comparators and co-interventions may impact applicability. For interventions, there was variability in the numbers of sessions, length of sessions, duration of treatment, methods of delivering the intervention and the experience and training of those providing the intervention. 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. In general, there were no clear differences in effects based on intervention factors or comparators; however analyses were 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 It is unclear to what extent our findings represents conditions under which the various interventions are currently delivered. Evidence to identify optimal techniques and delivery of interventions is needed.

Implications for Clinical and Policy Decisionmaking

Our review provides some evidence that an array of nonpharmacological treatments provide small to moderate benefits in function and pain that are durable for more than 1 month for five chronic pain conditions addressed in this review. Musculoskeletal pain, particularly of back and joint pain, is the most common single type of chronic pain. Age-adjusted rates of adults reporting pain in the last three months were highest for low back pain

(28%), neck pain (15%), knee pain (19.5%), and severe headache or migraine (16%).[1,5] The evidence synthesized in this review may help inform guidelines and health care 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[4] in the United States and the Canadian Guidelines for Opioid Use in Chronic Non-Cancer Pain[21] recommend nonopioid treatment as preferred treatment for chronic pain. Further, American College of Physicians guidelines recommend nonpharmacological therapies over medications for chronic back pain.[12] Our findings support the feasibility of these guidelines by showing that there are nonpharmacological treatments for chronic pain that have evidence of sustained effectiveness after the completion of therapy. Importantly, some 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 also were associated with some sustained effects on function, although evidence beyond 12 months is 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. Consistent with a biopsychosocial understanding of chronic pain,[1,2] 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 therapies (particularly cognitive-behavioral therapy), 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, policymakers 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). Although the Affordable Care Act has improved access to complementary and integrative medicine therapies, variability in reimbursement and authorization procedures remain a potential barrier. 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.[22] 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 was sparse for most interventions. Data on long-term outcomes was particularly limited. There were also limited data on outcomes other than pain and function and on harms. 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 (59%).

There were limitations in the systematic review process. We did not include trials of patients with chronic pain conditions other than those specified in the methods 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. 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.

Research Recommendations

The gaps in the available evidence are many across the common conditions we included (Table N). 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 (IMMPACT)[23] and the Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks (ACTTION)[24] and the research priorities outlined in the recent Federal Pain Research Strategy.[25]

Table N. Summary of evidence gaps and research recommendations

Research Component	Evidence Gap	Future Research Recommendation
Study Design Methods and Reporting	Sparse evidence on the sustainability of effects; 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. Documentation of adherence. Consider recommendations from IMMPACT, ACTTION and Federal Pain Research Strategy
Patient populations	Information on overlapping chronic pain conditions or psychosocial factors was generally not provided in included trials	Documentation of coexisting conditions and factors in trials with sufficient sample-size to evaluate the differential impact of conditions and factors.
Interventions and comparators	Lack of information on optimal techniques, duration and frequency of treatment; Lack of evidence comparing interventions to pharmacological agents	Research leading to standardization of techniques and their delivery to be used in future trials and understanding best combinations of interventions. Pragmatic trials may provide valuable information. Trails comparing interventions with pharmacological treatments.
Outcomes measures	Lack of consistency in types outcomes measures used for function and pain across trials 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 know harms are not routinely collected	Standardized protocols for types of outcomes to be assessed (including harms). Use measures that incorporate understanding of pathophysiological mechanisms and address multiple domains of pain. Report the proportions of patients achieving a clinically meaningful improvement for measures of pain and function as well as outcomes related to change in use of opioids, health care utilization and quality of life. Consider recommendations from IMMPACT, ACTTION and Federal Pain Research Strategy

ACTTION = Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks; IMMPACT = Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials; NRS = Numerical Rating Scale; VAS = Visual Analog Scale

Conclusions

Exercise, multidisciplinary rehabilitation, acupuncture, cognitive behavioral therapy, and mind-body practices were most consistently associated with durable slight to moderate improvements in function and pain for specific chronic pain conditions. Our findings provide 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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