Comparative Effectiveness Review
Number 227

Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update

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Key Messages

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.

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00009-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

People using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Disease Control and Prevention requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract Number 290-2015-00009-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Prior to publication of the final evidence report, the EPC sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update

Structured Abstract

Objectives. We updated the evidence from our 2018 report assessing persistent improvement in outcomes following completion of therapy for noninvasive nonpharmacological treatment for selected chronic pain conditions.

Data sources. Electronic databases (Ovid MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews) through November 2017 (for prior report) and from September 2017 through September 2019 (for this update report), reference lists, ClinicalTrials.gov, and our previous report.

Review methods. Using predefined criteria, we selected randomized controlled trials (RCTs) of noninvasive nonpharmacological treatments for five common chronic pain conditions (chronic low back pain; chronic neck pain; osteoarthritis of the knee, hip, or hand; fibromyalgia; and tension headache) that reported results for a at least 1 month postintervention. We analyzed effects and assessed strength of evidence (SOE) at short term (1 to <6 months following treatment completion), intermediate term (≥6 to <12 months), and long term (≥12 months).

Results. We included 233 RCTs (31 new to this update). Many were small (N<70), and evidence beyond 12 months after treatment completion was sparse. The most common comparison was with usual care. Evidence on harms was limited, with no evidence suggesting increased risk for serious treatment-related harms for any intervention. Effect sizes were generally small for function and pain.

Chronic low back pain: Psychological therapies were associated with small improvements compared with usual care or an attention control for both function and pain at short-term, intermediate-term, and long-term followup (SOE: moderate). Function improved over short and/or intermediate term for exercise, low-level laser therapy, spinal manipulation, massage, yoga, acupuncture, and multidisciplinary rehabilitation (SOE moderate at short term for exercise, massage, and yoga; low for all others). Improvements in pain at short term were seen for massage, mindfulness-based stress reduction, acupuncture, and multidisciplinary rehabilitation (SOE: moderate), and exercise, low-level laser therapy, and yoga (SOE: low). At intermediate term, spinal manipulation, yoga, multidisciplinary rehabilitation (SOE: moderate) and exercise and mindfulness-based stress reduction (SOE: low) were associated with improved pain. Compared with exercise, multidisciplinary rehabilitation improved both function and pain at short and intermediate terms (small effects, SOE: moderate.)

Chronic neck pain: In the short term, low-level laser therapy (SOE: moderate) and massage (SOE: low) improved function and pain. Exercise in general improved function long term, and combination exercise improved function and pain both short and long term compared with usual care (SOE: low). Acupuncture improved function short and intermediate term, but there was no pain improvement compared with sham acupuncture (SOE: low). Compared with acetaminophen, Pilates improved both function and pain (SOE: low).

Osteoarthritis pain: Exercise resulted in small improvements in function and pain at short-term (SOE: moderate) and long-term (SOE: low), and moderate improvement at intermediate-term (SOE: low) followup for knee osteoarthritis versus nonactive comparators. Small improvements in function and pain with exercise were seen for hip osteoarthritis short term (SOE: low). Functional improvement persisted into intermediate term, but pain improvement did not (SOE: low).

Fibromyalgia: Functional improvements were seen with exercise, mind-body practices, multidisciplinary rehabilitation (SOE: low) and acupuncture (SOE: moderate) short term compared with usual care, attention control, or sham treatment. At intermediate term, there was functional improvement with exercise and acupuncture (SOE: moderate), cognitive-behavioral therapy (CBT), mindfulness-based stress reduction, myofascial release, and multidisciplinary rehabilitation (SOE: low). Long term, functional improvements persisted for multidisciplinary rehabilitation without improvement in pain (SOE: low). Compared with exercise, tai chi conferred improvement in function short and intermediate term (SOE: low). Pain was improved with exercise (short and intermediate term, SOE moderate), and for CBT (short term), mindfulness practices, and multidisciplinary rehabilitation (intermediate term) (SOE low).

Chronic tension headache: Evidence was sparse and the majority of trials were of poor quality. Spinal manipulation resulted in moderate improvement in pain short term.

Conclusions. Trials identified subsequent to the earlier report largely support previous findings—namely that exercise, multidisciplinary rehabilitation, acupuncture, CBT, mindfulness practices, massage, and mind-body practices most consistently improve function and/or pain beyond the course of therapy for specific chronic pain conditions. Additional research, including comparisons with pharmacological and other active controls, on effects beyond the immediate post-treatment period is needed, particularly for conditions other than low back pain.

Contents

Tables

Figures

Appendixes

Summary of Changes Since the Previous Report

This systematic review is an update to an earlier report published in 2018 and is one of three concurrent systematic reviews on treatment of chronic pain. The other reviews are on opioid and nonopioid pharmacological treatments. The scope and Key Questions for this update were the same as for the original review with the following additions: (1) we sought trials including pregnant or breastfeeding women with a history of one of the five chronic pain conditions; (2) topical agents (lidocaine, diclofenac, capsaicin), medical cannabis, and muscle relaxants were considered for inclusion as active comparators; and (3) we sought to evaluate the degree of nociplasticity/central sensitization as a possible modifier of treatment effect.

Meta-analyses from the 2018 report were updated, and new analyses conducted to summarize data and obtain more precise estimates on the primary outcomes of function and pain. Summary strength of evidence (SOE) tables were updated based on the totality of underlying evidence (i.e., the 2018 review evidence in combination with that from newly identified studies). To the evidence base of 218 publications (202 trials) in the 2018 report, 34 publications (31 trials) were added for this update, with the following results.

- No trials in pregnant or breastfeeding women with pre-existing chronic pain or 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.
- Few new trials compared interventions with active comparators.
- Only two new trials of exercise for knee osteoarthritis provided long-term information.
- No new trials of interventions for chronic tension headache were identified.

In the update report, the Key Points summarize the main findings across the evidence included in the prior report and new trials, and note where new trials were added. Footnotes to the summary SOE tables denote changes in effect size and/or SOE based on new trials. New trials with at least low evidence at timeframes where previously no evidence was identified included randomized controlled trials (RCTs) of massage (neck pain) and mindfulness practices (fibromyalgia). RCTs with at least low evidence of new interventions or comparators included interferential therapy (low back pain), exercise versus acetaminophen (neck pain) or versus analgesics and nonsteroidal anti-inflammatory drugs (NSAIDS) (knee OA), and tai chi versus exercise (fibromyalgia).

In many instances, neither effect size nor SOE changed with the addition of new trials, and evidence was insufficient for some new trials. Changes to SOE or effect size versus the prior report based on new RCTs included the following.

- For low back pain, SOE was upgraded from low to moderate for short-term functional improvement with exercise but downgraded to low for pain improvement (due to increased inconsistency across trials), and effect size for pain improvement increased to moderate. Effect size for yoga was upgraded to moderate for short-term function but downgraded to small for short-term pain.
- For neck pain, new evidence for massage led to an effect size upgrade for function from none to small short term, and added evidence for intermediate-term pain. A new RCT compared exercise with acetaminophen.
- For knee osteoarthritis, there were no changes in SOE, but effect estimates for exercise were upgraded for function (small to moderate) intermediate term and pain at long term

(none to small). Effect size was upgraded for improved short-term pain from none to small with cognitive behavioral therapy. Effect sizes for function and pain for ultrasound were downgraded from small to none, and there was no effect of exercise compared with analgesics and NSAIDS.

- For fibromyalgia, there were no changes in SOE, but effect sizes for pain were upgraded (none to small) intermediate term for exercise; for function with cognitive behavioral therapy effect, sizes were downgraded (small to none) short term but upgraded one level at intermediate term (small to moderate), and one new RCT on mindfulness contributed data for the intermediate term.

Changes to effect size and/or SOE with the addition of new trials are summarized in Table i.

Table i. Changes in effect size or SOE between the 2018 report and the 2019 update report

Condition	Intervention (Comparator)	Outcome, Timing	Prior (2018) Report	2019 Update	Change
LBP	**Exercise** (vs. UC, AC, or placebo)	Function, short term	Small effect Low SOE 6 RCTs (N=553)	Small effect Moderate SOE 9 RCTs (N=1,056)	SOE upgraded one level
		Pain, short term	Small effect Moderate SOE 6 RCTs (N=553)	Moderate effect Low SOE 10 RCTs (N=1,098)	Effect size upgraded one level; SOE downgraded one level[a]
	Physical modalities: Interferential therapy (vs. placebo)	Function and pain, short term	No evidence	No effect Low SOE 1 new RCT (N=150)	New evidence
	Mind-body practices: Yoga (vs. AC or WL)	Function, short term	Small effect Moderate SOE 6 RCTs (N=922)	Moderate effect Moderate SOE 8 RCTs (N=1,149)	Effect size upgraded one level
		Pain, short term	Moderate effect Low SOE 5 RCTs (N=770)	Small effect Low SOE 7 RCTs (N=997)	Effect size downgraded one level
Neck pain	**Exercise** (Pilates) (vs. acetaminophen)	Function, short term	Insufficient evidence 1 RCT (N=40)	Small effect Low SOE 1 new trial (N=64)	SOE upgraded one level, new evidence[b]
		Pain, short term	Insufficient evidence 1 RCT (N=40)	Large effect Low SOE 1 new trial (N=64)	SOE upgraded one level, new evidence[b]
	Manual Therapies: Massage (vs. AC or WL)	Function, short term	No effect Low SOE 1 RCT (N=58)	Small effect Low SOE 2 RCTs (N=150)	Effect size upgraded one level
		Pain, short term	No evidence	Moderate effect Low SOE 1 new RCT (N=92)	New evidence
Knee OA	**Exercise** (vs. UC, NT, sham or AC)	Function, intermediate term	Small effect Low SOE 9 RCTs (N=637)	Moderate effect Low SOE 11 RCTs (N=879)	Effect size upgraded one level
		Pain, long term	No effect Low SOE 2 RCTs (N=914)	Small effect Low SOE 4 RCTs (N=1,199)	Effect size upgraded one level
	Exercise (vs. acetaminophen and NSAIDs)	Function and Pain, intermediate term	No evidence	No effect Low SOE 1 new RCT (N=93)	New evidence

Condition	Intervention (Comparator)	Outcome, Timing	Prior (2018) Report	2019 Update	Change
	Psychological Therapies: CBT/MI/pain coping skills training (vs. UC)	Pain, Short term	No effect Low SOE 2 RCTs (N=222)	Small effect Low SOE 2 new trials (N=210)	Effect size upgraded one level, new evidence[c]
	Physical Modalities: continuous and pulsed US (vs. sham)	Function and pain, Short term	Small effect Low SOE 1 RCT (N=90)	No effect Low SOE 3 RCTs (N=249)	Effect size downgraded one level
FM	**Exercise** (vs. UC, NT, sham or AC)	Pain, intermediate term	No effect Moderate SOE 7 RCTs (N=327)	Small effect Moderate SOE 8 RCTs (N=362)	Effect size upgraded one level
	Psychological Therapies: CBT, biofeedback, guided-imagery (vs. UC, AC, WL)	Function, Short term	Small effect Low SOE (CBT) 2 RCTs Pooled (N=97)	No effect Low SOE (CBT) 3 RCTs Pooled (N=169)	Effect size downgraded one level
		Function, Intermediate term	Small effect Low SOE (CBT) 2 RCTs Pooled (N=176) 1 RCT (N=82)	Moderate effect Low SOE (CBT) 3 RCTs Pooled (N=280) 1 RCT (N=82)	Effect size upgraded one level
	Mindfulness Practices: MBSR, MAT (vs. AC or WL)	Function and pain, Intermediate term	No evidence	Small effect Low SOE 1 RCT (N=148)	New evidence
	Mind-Body Therapies: Yang Style tai chi (vs. exercise)	Function, Short- and intermediate term	No evidence	Small effect Low SOE 1 RCT (N= 181)	New evidence
		Function, Long term	No evidence	No effect Low SOE 1 RCT (N=158)	New evidence

AC = attention control; CBT = cognitive-behavioral therapy; FM = fibromyalgia; LBP = low back pain; MAT = meditation awareness training; MBSR = mindfulness-based stress reduction; MI = Motivational Interviewing (IMPAACT); NSAID = nonsteroidal anti-inflammatory drug; NT = no treatment; OA = osteoarthritis; RCT = randomized controlled trial; SOE = strength of evidence; UC = usual care; WL = waitlist.

[a] SOE downgraded; addition of 4 new trials increased inconsistency/heterogeneity across trials

[b] Differences in study quality and pharmacological therapies precluded pooling of the trial included in the prior report (poor quality; NSAIDs and muscle relaxants) with the new trial (fair quality; acetaminophen); both trials reported effect sizes in the same direction (favoring exercise) though the differences were not statistically significant in the trial included in the previous (2018) report.

[c] The two previously included trials (1 fair, 1 poor) averaged effects across time frames finding no difference between groups. Only the two new fair quality trials could be pooled at this time frame.

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 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 November 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).

- **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 ++

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: 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 +

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

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 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.
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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Introduction

Background

Nature and Burden of Chronic Pain

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] A monumental public health challenge, chronic pain affects millions of adults in the United States, with a conservative annual cost in personal and health system expenditures estimated at $560 billion to $635 billion.[3] 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.[4,5]

Pain is usually regarded as chronic when it lasts or recurs for more than 3 to 6 months, however definitions vary.[6,7] For purposes of this report, chronic pain is defined as pain lasting 3 months or longer, or persisting past the normal time for tissue healing.[3,8] Nervous system changes that occur with chronic pain, combined with its psychological and cognitive impacts, have led to conceptualization of some types of chronic pain as a distinct disease entity.[3] Chronic pain is multifaceted and influenced by multiple factors (e.g., genetic, central nervous system, psychological, and environmental factors) and complex interactions of factors, making pain assessment and management a challenge. A number of characteristics influence the development of and response to chronic pain, including sex, age, presence of comorbidities, and psychosocial factors. For example, women report chronic pain more frequently than do men, are at higher risk for some conditions such as fibromyalgia,[3] and may respond to treatment differently than men. Older adults are more likely to have comorbidities and are more susceptible to polypharmacy, impacting choices and consequences of therapies. Pain is greatly influenced by psychosocial factors, which may predict who will develop chronic disabling pain, as well as who will respond to various treatments.

Management of Chronic Pain

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 Task Force report recommends that pain management be integrated, multimodal, interdisciplinary, evidence-based, and tailored to individual patient needs.[9] In addition to addressing biological factors when known, optimal management of chronic pain must also address psychosocial contributors to pain, while taking into account individual susceptibility and treatment responses. Self-care is also an important part of chronic pain management.

Opioids have been used in the treatment of chronic pain. In the past 20 years, evidence shows only modest short-term benefits of these drugs.[10-12] Lack of evidence on long-term effectiveness[13] and safety concerns[14] have been noted in the literature. The recent evidence-based CDC guidelines on opioid use for chronic pain,[15] which include a recommendation on the preferred use of nonopioid treatment over opioid therapy, has prompted additional primary research on alternative methods of managing chronic pain.

Other pharmacological treatments for chronic pain include nonsteroidal anti-inflammatory drugs, acetaminophen, muscle relaxants, antiseizure medications, antidepressants, and corticosteroids, used alone or in combination with each other or with opioids. Each has potential side effects and contraindications.

Nonpharmacological treatments for chronic pain examined in this review include exercise, mind-body practices, psychological therapies, multidisciplinary rehabilitation, mindfulness practices, manual therapies, physical modalities, and acupuncture.

Rationale for This Review Update

This systematic review updates our 2018 review. Our 2018 review[16] provided some support for clinical strategies and policies that focus on 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.

The review is intended to address some of the needs described in the National Pain Strategy Task Force[9] and Institute of Medicine[3] reports and others for evidence to inform guidelines and healthcare policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments. Both the Institute of Medicine report and the National Pain Strategy Task Force report describe the need for evidence-based strategies for the treatment of chronic pain that address the biopsychosocial nature of this disease, including nonpharmacological treatment. These initiatives, and others, speak to the importance of understanding current evidence on noninvasive nonpharmacological treatment of chronic pain.

Many trials have examined the impact of interventions on outcomes during or immediately after the course of treatment. A number of them are associated with 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. This review also aims to provide additional insights into research gaps related to use of noninvasive nonpharmacological alternatives for treating chronic pain. Musculoskeletal pain, particularly related to joints and the back, is the most common single type of chronic pain.[3,17] This systematic review thus focuses on five of the most common causes of musculoskeletal pain: chronic low back pain, chronic neck pain, osteoarthritis (OA), fibromyalgia, and chronic tension headache.

Scope and Key Questions

This Comparative Effectiveness Review focused on noninvasive nonpharmacological therapy for five common chronic pain conditions: low back pain, neck pain, OA, fibromyalgia, and headache. Individual pain management strategies 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 training), mindfulness practices (meditation, mindfulness-based stress reduction practices), manual therapies (e.g., musculoskeletal manipulation), physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation, low-level laser therapy, interferential therapy, superficial heat or cold, bracing for knee, back or neck, electro-muscular stimulation, and magnets), and acupuncture.

We focused on single active interventions and comparators over the long term. The Key Questions, PICOTS (populations, interventions, comparators, outcomes, timing, settings, and study designs), and analytic framework that guided this review are provided below.

Key Questions

Key Question 1: Adults with chronic low back pain

Key Question 2: Adults with chronic neck pain

Key Question 3: Adults with osteoarthritis-related pain (knee, hip, hand)

Key Question 4: Adults with fibromyalgia

Key Question 5: Adults with chronic tension headache

Key Question 6: Do estimates of benefits and harms differ by age, sex, presence of comorbidities (e.g., emotional or mood disorders), or degree of nociplasticity/central sensitization?

Key Questions 1–5 incorporate the following subquestions:

d. What are the benefits and harms of noninvasive nonpharmacological therapies compared with sham treatment, no treatment, waitlist, attention control, or usual care?
e. What are the benefits and harms of noninvasive nonpharmacological therapies compared with pharmacological therapy (e.g., opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, antiseizure medications, antidepressants, topical agents, medical cannabis, and muscle relaxants)?
f. What are the benefits and harms of noninvasive nonpharmacological therapies compared with exercise or, for headache, biofeedback?

The three-part format for Key Questions 1–5 reflects the following research concepts:

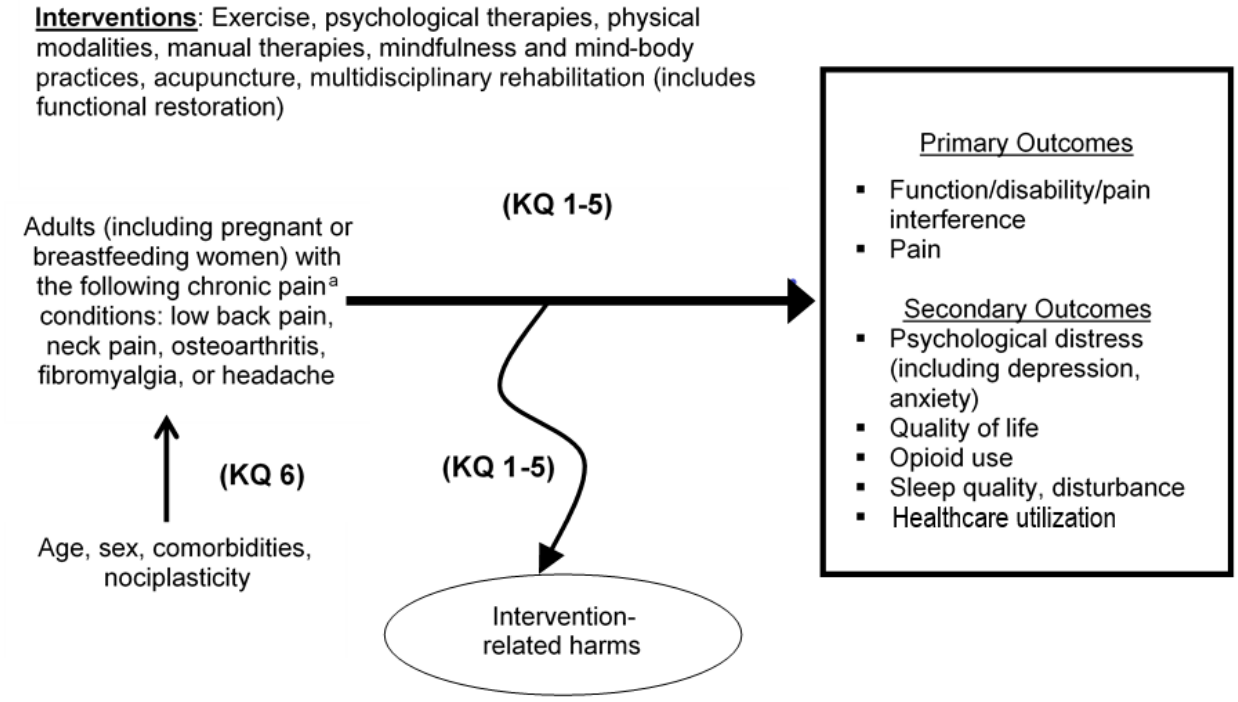
- Part "a" answers the question of whether the various interventions work overall compared with sham, waitlist control, attention control, no treatment, or usual care. For this review, usual care was defined as care that might be provided or recommended by a primary care provider.
- Part "b" answers the question of whether the various interventions work compared with pharmacological alternatives.
- Part "c" answers the question of how outcomes for individual interventions (e.g., acupuncture) compare with a common comparator. Exercise is the most frequent comparison in the literature for many chronic pain conditions, so it provides a common comparator for analysis. It is also recommended in most guidelines for conditions including low back pain, neck pain, fibromyalgia, and osteoarthritis and is widely

available. Exercise served as common comparator for these conditions. For chronic headache, biofeedback provided a common comparator for analysis.

Analytic Framework

The analytic framework (Figure 1) illustrates the population, interventions, outcomes, and adverse effects that guided the literature search and synthesis.

Figure 1. Analytic framework



KQ = Key Question

[a] Chronic pain is defined as pain lasting ≥12 weeks or pain persisting past the normal time for tissue healing

Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*[18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. See the review protocol (https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/protocol) for details.

Topic Refinement and Review Protocol

The Evidence-based Practice Center (EPC) review team reexamined the Key Questions and PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Studies, Settings) in consultation with the AHRQ Task Order Officer (TOO), representatives from the Centers for Disease Control and Prevention, and the Technical Expert Panel (TEP).

The TEP consisted of members with expertise in primary care, rheumatology, pain medicine, behavioral sciences, physical medicine and rehabilitation, and physical therapy. TEP members had expertise in treating patients with one or more of the five conditions included in this report.

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) on March 1, 2019. The protocol was also registered in the PROSPERO 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 November 1, 2017 and for this update, from September 1, 2017 through September 20, 2019. For the prior report, searches were conducted without publication date restrictions with the exception of studies of chronic low back pain, as we relied on a recent AHRQ review[19] to identify primary studies for inclusion through 2016 (see Appendix A for full search strategies). As there are multiple manufacturers/sources for many of the devices examined in this review, 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 against the inclusion/exclusion criteria. No new trials eligible for inclusion were identified from these responses. We also searched for unpublished studies in ClinicalTrials.gov. Reference lists of included articles and the bibliographies of systematic reviews (published since 2010 for the prior report) were reviewed for includable literature. Literature searches will be updated during the public comment and peer review period to capture any new publications. Resulting citations and any suggested during peer review and public comment will be evaluated against the inclusion/exclusion criteria following the same process of dual review as all other studies considered for inclusion in the report.

Inclusion and Exclusion Criteria and Study Selection

Inclusion and exclusion criteria were developed *a priori* based on the Key Questions and PICOTS, in accordance with the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[18] Criteria are detailed below in Table 1. Abstracts were reviewed by at

least two investigators, and full-text articles were retrieved for all citations deemed potentially appropriate for inclusion by at least one of the reviewers. Two investigators then independently reviewed all full-text articles for final inclusion. Discrepancies were resolved by discussion and consensus. A list of the included studies appears in Appendix B; excluded studies and primary reason for exclusion are listed in Appendix C.

The focus of this review is on randomized controlled trials (RCTs) reporting on longer-term outcomes (at least 1 month postintervention) that otherwise meet our PICOTS criteria.

Table 17. Inclusion and exclusion criteria

PICOTS	Inclusion	Exclusion
Population **All KQs**	**General Inclusion Criteria** • Adults with the following chronic pain (defined as pain lasting 12 weeks or longer or pain persisting past the time for normal tissue healing) conditions: low back pain, neck pain, osteoarthritis pain, fibromyalgia, or tension headache. • Pregnant or breastfeeding women who have a history of chronic pain prior to pregnancy	**General Exclusion Criteria** • Acute pain • Children (<18 years), pregnant or breastfeeding women with pregnancy-related back or pelvic pain or who do not have chronic pain prior to pregnancy; • Patients with chronic pain related to "active" cancer, infection, inflammatory arthropathy, • <90% of study sample has the defined condition of interest or <90% received the treatment(s) of interest • Treatment for addiction • Pain at the end of life • Neuropathic pain
Population **KQ1**	**KQ1: Low back pain** • Adults with chronic, nonradicular low back pain	**KQ1: Low back pain** • Patients with radiculopathy • Low back pain associated with severe or progressive neurological deficits • Failed back surgery syndrome
Population **KQ2**	**KQ2: Neck pain** • Adults with chronic neck pain	**KQ2: Neck pain** • Patients with radiculopathy or myelopathy • Traumatic spinal cord injury • Neck pain associated with progressive neurological deficit, loss of strength
Population **KQ3**	**KQ3: Osteoarthritis** • Adults with osteoarthritis-related pain (primary or secondary osteoarthritis) of the hip, knee or hand	**KQ3: Osteoarthritis** • Other types of arthritis (e.g., rheumatoid) • Patients with joint replacement
Population **KQ4**	**KQ4: Fibromyalgia** • Adults with fibromyalgia	**KQ4: Fibromyalgia** • Conditions with generalized pain not consistent with fibromyalgia • Systemic exertion intolerance disease, (myalgic encephalomyelitis/chronic fatigue syndrome) • Somatization disorder (Briquet's syndrome)

PICOTS	Inclusion	Exclusion
Population KQ5	**KQ5: Headache** • Adults with primary chronic tension headache (International Classification of Headache Disorders, 3rd edition definition). o Primary headaches are attributed to the headache condition itself, not headache caused by another disease or medical condition. Tension headaches are the most common. Chronic headache is defined as 15 or more days each month for at least 12 weeks or history of headache more than 180 days a year.	**KQ5: Headache** • Migraine headache • Mixed headache (also known as coexistent tension and migraine headache, chronic daily headache, transformed migraine) • Trigeminal neuralgia • Cluster headache • Secondary headache types as defined in *The International Classification of Headache Disorders*, 3rd edition[20] (i.e., headaches due to an underlying pathology such as cancer, prior medical procedures, temporomandibular joint disorders, neck pathology, cervicogenic headache, and medication over-use headache) • Traumatic brain injury
Interventions	**All KQs:** • Exercise (exercise as part of physical therapy, supervised exercise, home exercise, group exercise, formal exercise program) • Psychological therapies (cognitive and/or behavioral therapy, biofeedback, relaxation training) • Physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation, low-level laser therapy, interferential therapy, electro-muscular stimulation diathermy, superficial heat or cold, bracing for knee, back, neck, hand and magnets) • Manual therapies (musculoskeletal manipulation, massage) • Mindfulness practices (meditation, mindfulness-based stress reduction practices) • Mind-body practices (yoga, tai chi, qigong) • Acupuncture • Multidisciplinary/interdisciplinary rehabilitation[a]	**All KQs:** • Invasive nonsurgical treatments (e.g., injections, nerve block, spinal cord stimulators, parenterally-administered medications) • Surgical interventions (including minimally invasive surgical interventions) • Diet interventions or dietary supplementation • Studies evaluating incremental value of adding a noninvasive nonpharmacological intervention to another noninvasive nonpharmacological intervention • Self-management interventions or programs, self-management education programs • Others not listed for inclusion

PICOTS	Inclusion	Exclusion
Comparators	**<u>All KQs, subquestion a</u>** • Sham treatment • Waitlist • Usual care • No treatment • Attention control intended to control for nonspecific effects (e.g., time, attention, expectations); **<u>All KQs subquestion b</u>** • Commonly used nonopioid pharmacological therapy used to treat chronic pain [NSAIDS, acetaminophen, anti-seizure medications, antidepressants (SNRIs, TCAs), muscle relaxants (including benzodiazepines)] • Topical agents (lidocaine, diclofenac, capsaicin) • Medical cannabis (inhaled, oral, topical); phytocannabinoids (plant derived, THC and CBD); FDA approved synthetic cannabinoids [Dronabionol (THC), Nabilone (similar to THC)] • Opioid analgesics **<u>KQs 1-4, 6 subquestion c</u>** • Exercise[b] **<u>KQ 5, 6 subquestion c</u>** • Biofeedback[c]	**All KQs:** • Supplements (e.g., glucosamine, chondroitin, d-ribose, herbal or homeopathic treatments)Invasive nonsurgical treatments (e.g., injections, nerve block, spinal cord stimulators, parenterally-administered medications) • Antidepressants not typically used for chronic pain including SSRIs and MAOIs • Anti-seizure medications not typically used to treat chronic pain including topiramate, lamotrigine, levetiracetam, phenytoin, valproic acid, zonisamide, tiagabine • Surgical interventions (including minimally invasive surgical interventions) • Studies evaluating incremental value of adding a noninvasive nonpharmacological intervention to another noninvasive nonpharmacological intervention • Comparisons within nonpharmacological intervention types (e.g., comparisons of different types of exercise with each other, different types of massage with each other) • Corticosteroids, biologic drugs • Salicylates (oral and topical) • Topical menthol preparations • Others not listed for inclusion
Outcomes	**All KQs:** Primary efficacy outcomes; we will focus on outcomes from validated measures for • Function/disability/pain interference[d] • Pain[d] Harms and Adverse effects Secondary outcomes • Psychological distress (including measures of depression and anxiety) • Quality of life • Opioid use • Sleep quality, sleep disturbance • Healthcare utilization	**All KQs:** • Intermediate outcomes (e.g., biomarkers for inflammation) • Other nonclinical outcomes
Timing	Duration of followup: short term (1 to <6 months), intermediate term (≥6 to <12 months) and long term (≥12 months); focus on longer term (>12 month) effects. Trials lasting ≥6 months that include a supervised intervention followed by continued home treatment as part of the intervention will be included even though the only followup occurs directly after the intervention.	• Studies with <1 month followup after treatment

PICOTS	Inclusion	Exclusion
Studies	Randomized controlled trials or high quality systematic reviews of randomized controlled trials published in English; cross-over trials with random assignment of initial treatment will be considered.	**All KQs:** • Studies reporting on intermediate outcomes only • Nonrandomized studies • Abstracts, editorials, letters, conference proceedings • Duplicate publications of the same study that do not report on different outcomes • Single site reports from multicenter trials • White papers • Narrative reviews • Articles identified as preliminary reports when results are published in later versions • Indirect comparisons • Studies with fewer than 15 patients per treatment arm • Systematic reviews on treatment of chronic neck pain, fibromyalgia, chronic headache, or osteoarthritis that are of low methodological quality. Those that do not report outcomes or time frames of interest may be excluded. Systematic reviews may be excluded based on currency or relevance (e.g., if there is a substantial new body of evidence reflected in a later review).
Settings	Any nonhospital setting or in self-directed care	• Hospital care, hospice care, emergency department care

CBD = cannabidiol; FDA = Food and Drug Administration; KQ = Key Question; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; PICOTS = populations, interventions, comparators, outcomes, timing, settings, study designs; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; THC = tetrahydrocannabinol.

[a] Multidisciplinary rehabilitation (MDR) (also known as interdisciplinary rehabilitation), is defined as a coordinated program with biopsychosocial treatment components (e.g., exercise therapy and cognitive-behavioral therapy) provided by professionals from at least two different specialties. Functional restoration training is included as part of MDR.

[b] Different forms of exercise will not be compared to each other. Exercise will be compared with nonexercise interventions for low back pain, neck pain, fibromyalgia and osteoarthritis

[c] Different forms of biofeedback will not be compared to each other. Biofeedback will be compared with the noninvasive interventions for chronic headache

[d] The magnitude of effects for pain and function will be classified using the same system as in the AHRQ-funded noninvasive treatment for low back pain review recognizing that small effects using this system may not meet standard thresholds for clinically meaningful effects. A small effect was defined for pain as a mean between-group difference following treatment of 5 to 10 points on a 0- to 100-point visual analog scale (VAS), 0.5 to 1.0 points on a 0- to 10-point numeric rating scale, or equivalent; for function as a mean difference of 5- to 10-point difference on the 0- to 100-point Oswestry Disability Index (ODI) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent; and for any outcome as a standardized mean difference (SMD) of 0.2 to 0.5. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS, for function as a mean difference of 10 to 20 points on the ODI or 2 to 5 points on the RDQ, and for any outcome as an SMD of 0.5 to 0.8. Large/substantial effects were defined as greater than moderate. We will apply similar methodology to outcomes measures for the other condition. The clinical relevance of effects classified as small might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors

Data Abstraction and Data Management

Using templates, data from included trials were abstracted into categories that included but were not limited to: study design, year, setting, country, sample size, eligibility criteria, attrition, population and clinical characteristics (including age, sex, comorbidities, diagnostic classifications/information), intervention characteristics (including the type, number, intensity, duration of, and adherence to treatments), comparator characteristics, and results (including harms). We also recorded the funding source and role of the sponsor. All abstracted study data

were verified for accuracy and completeness by a second team member (Appendix D). Details are further outlined in the protocol.

Quality (Risk of Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality of included trials. We focused on trials with the least potential for bias and the fewest limitations. RCTs were assessed based on criteria and methods established in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8.5 Risk of Bias Tool),[21] and precepts for appraisal developed by the Cochrane Back and Neck Group.[22] These criteria and methods were used in conjunction with the approach recommended in the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Research*.[18] Two team members independently appraised each included study, with disagreements resolved by consensus. Studies were rated as "good," "fair," or "poor" as described in Table 2. Assessments of included studies are in Appendix E.

Table 18. Criteria for grading the quality of individual studies

Rating	Description and Criteria
Good	• Least risk of bias, results generally considered valid • Employ valid methods for selection, inclusion, and allocation of patients to treatment; report similar baseline characteristics in different treatment groups; clearly describe attrition and have low attrition; use appropriate means for preventing bias (e.g., blinding of patients, care providers, and outcomes assessors); and use appropriate analytic methods (e.g., intention-to-treat analysis)
Fair	• Susceptible to some bias but not enough to necessarily invalidate results • May not meet all criteria for good quality, but no flaw is likely to cause major bias; the study may be missing information making it difficult to assess limitations and potential problems • Category is broad; studies with this rating will vary in strengths and weaknesses; some fair-quality studies are likely to be valid, while others may be only possibly valid
Poor	• Significant flaws that imply biases of various kinds that may invalidate results; "fatal flaws" in design, analysis or reporting; large amounts of missing information; discrepancies in reporting; or serious problems with intervention delivery • Studies are at least as likely to reflect flaws in the study design or execution as the true difference between the compared interventions • Considered to be less reliable than higher quality studies when synthesizing the evidence, particularly if discrepancies between studies are present

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 (e.g., ranges and descriptive analysis) and quantitatively using meta-analysis where appropriate. Results are organized by Key Question (i.e., by condition) and intervention and then by comparators for each subquestion (e.g., intervention vs. waitlist or sham for subquestion a). To the extent that the interventions were distinct, we explored separating them out for analysis and reporting. For example, we categorized various forms of exercise based on their primary mechanisms of action (Appendix F). Interventions with similar characteristics were combined (e.g., cognitive-behavioral therapy [CBT] and acceptance and commitment therapy [ACT], which is a type of CBT).[23] Duration of followup postintervention was reported and categorized as short term (1 to <6 months), intermediate term (≥6 to <12 months), and long term (≥12 months).

Prioritized outcomes of function and pain, based on validated measures, are presented first. Based on input from stakeholders, improvement in function was prioritized as the most important outcome. There is overlap between functional outcome measures and quality of life measures.

Short-Form 36 (SF-36) and EuroQoL-5 Dimensions (EQ-5D) are two such outcome measures and they were categorized as quality of life measures for this report. For some conditions, such as osteoarthritis, results were organized by affected region (e.g., knee, hip, hand). Based on input from stakeholders, improvement in function was prioritized as the most important outcome.

Results for continuous outcomes as well as dichotomous outcomes were synthesized. Binary outcomes were based on the proportion of patients achieving specific thresholds of success for improved function, or other measure of success as defined in the trials (e.g., ≥30% improvement in pain score), and a risk ratio and 95% confidence interval were calculated to evaluate the presence of an association and estimate relative effect size using the Rothman Episheet.[24] For continuous outcomes, mean differences between treatments and 95% confidence intervals were calculated using GraphPad or Stata®/IC 12.1 (StataCorp, College Station, TX) to provide effect sizes and determine presence of a statistical association.

We conducted meta-analysis to quantitatively synthesize evidence. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Two continuous primary outcomes (pain and function) and one secondary outcome (quality of life) provided adequate data for meta-analysis. Mean difference (MD) was used as the effect measure if the studies reported outcomes using the same scale, or if the outcomes could be converted to the same scale (e.g., 0-100 pain ratings were converted to 0-10 scale); otherwise, standardized mean difference (SMD) was used when the reported outcomes used different scales but measured the same underlying construct (e.g., function). In the primary analysis, MD and SMD were calculated using the followup score, and sensitivity analyses were conducted using the change score from the baseline. When standard deviation (SD) was not reported, or could not be calculated from the reported data, it was imputed using the average SD or assuming the same coefficient of variation from the studies of the same meta-analysis, or using the SD value from the baseline if the baseline SD was reported and the followup SD was not.

We assumed random effects across studies and used both the Dersimonian-Laird method[25] and the profile-likelihood model[26] to combine studies. Statistical heterogeneity among the studies was assessed using the standard Cochran's chi-square test and the I^2 statistic.[27] The p-values for the chi-square test were reported in the forest plots. Primary analyses were stratified by disease type, intervention, control group (usual care, exercise, or pharmacological treatment) and length of followup (short, intermediate, and long term). Controls included usual care, waitlist, no treatment, placebo, sham treatment, attention control, or other groups that involved at most minimal active treatment. 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 (as described above) and by excluding outlying studies and studies rated as poor as data permitted. Meta-regression was conducted to test the interaction between the intervention effects and intervention characteristics if warranted by data.

To facilitate interpretation of results across trials and interventions, we categorized the magnitude of effects for function and pain outcomes as in our previous reviews.[19,28] In general 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/substantial (>2 points) (see additional information in Assessing Applicability). Where data were available, proportions of patients meeting clinically important improvement were reported. 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.

Grading the Strength of Evidence for Major Comparisons and Outcomes

The strength of evidence for each Key Question and primary outcome (function, pain, harms) was initially assessed by one researcher with experience in determining strength of evidence for each primary clinical outcome in accordance with AHRQ guidance[29,30] and as described in the protocol. The initial assessment was independently reviewed by at least one other experienced senior investigator. The overall strength of evidence (SOE) was determined based on assessment of study limitations (graded low, moderate, high); consistency of results across trials (graded consistent, inconsistent, or for single studies, unknown); the directness of the evidence linking the interventions with health outcomes (graded direct or indirect); effect estimate precision (graded precise or imprecise); and reporting bias (suspected or undetected). Bodies of evidence consisting of RCTs were initially considered high strength. All outcomes were considered direct.

The final strength of evidence grade was assigned by evaluating and weighing the combined results of the above domains and considering the highest quality evidence available. While studies rated as poor quality were not excluded, such studies were considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies across studies were noted. The strength of evidence was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale (Table 3). When all of the studies for a primary outcome were rated poor quality, we rated the strength of evidence as insufficient. SOE tables for primary outcomes are presented in Appendix G. Summary strength of evidence tables were updated based on the totality of underlying evidence (i.e., the 2018 systematic review[16] evidence in combination with that newly identified studies) and the impact of new trials on SOE is the summary tables.

Table 19. Description of the strength of evidence grades

Strength of Evidence	Description
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Assessing Applicability

Applicability was assessed using the PICOTS framework by examining the abstracted characteristics of the patient populations for each condition (e.g., demographic characteristics, condition-specific diagnostic criteria, symptoms, presence of medical and psychiatric

comorbidities, and other psychosocial factors); the interventions (e.g., availability in the United States; dose, frequency, or intensity of treatment, and methods for administration); and clinical settings (e.g., primary care, specialty setting, or developing country vs. developed country) in which the included studies are performed.

The magnitude of effects for pain and function (Appendix H) were classified with the system used in our previous AHRQ review on noninvasive treatment for low back pain,[28] recognizing that small effects using this system may not meet standard thresholds for clinically meaningful effects. We applied the following definitions:

- Small effect
  - For pain: as a mean between-group difference following treatment of 5 to 10 points on a 0-to 100-point visual analog scale (VAS), 0.5 to 1.0 point on a 0- to 10-point numeric rating scale (NRS), or equivalent
  - For function: as a mean difference of 5 to 10 points on the 0- to 100-point Oswestry Disability Index (ODI) or Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) or 1 to 2 points on the 0- to 24-point Roland-Morris Disability Questionnaire (RDQ) or Lequesne Index (LI), or equivalent
  - For any outcome: as a SMD of 0.2 to 0.5

- Moderate effect
  - For pain: as a mean difference of 10 to 20 points on a 0- to 100-point VAS
  - For function: as a mean difference of 10-20 points (on a 0-100 scale) on the ODI or WOMAC or 2 to 5 points on RDQ or LI, or equivalent
  - For any outcome: as a SMD of >0.5 to 0.8

- Large effect
  - For pain: as a mean difference of ≥20 points on a 0- to 100-point VAS
  - For function: as a mean difference of ≥20 (on a 0-100 scale) on the ODI or WOMAC or 5 points on RDQ or LI, or equivalent
  - For any outcome: as a SMD of >0.8

Information regarding effect size definitions for other outcome measures is available in Appendix H. There is variability across individual patients regarding what may constitute a clinically import effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs.

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 TOO and an EPC Associate Editor also provided comments and editorial review. Subsequently, the peer-reviewed draft report was posted on the AHRQ website for 4 weeks for public comment. A disposition of comments report with authors' responses to the peer and public review comments will be posted after publication of the final Comparative Effectiveness Review on the AHRQ website.

Results

Introduction

Results are organized by Key Question (i.e., by condition) and intervention and then organized by comparators for each subquestion. We categorized postintervention followup as short term (1 to <6 months), intermediate term (≥6 to <12 months) and long term (≥12 months). We prioritized function and pain outcomes based on validated measures. For some conditions (e.g., osteoarthritis [OA]), results are organized by affected region.

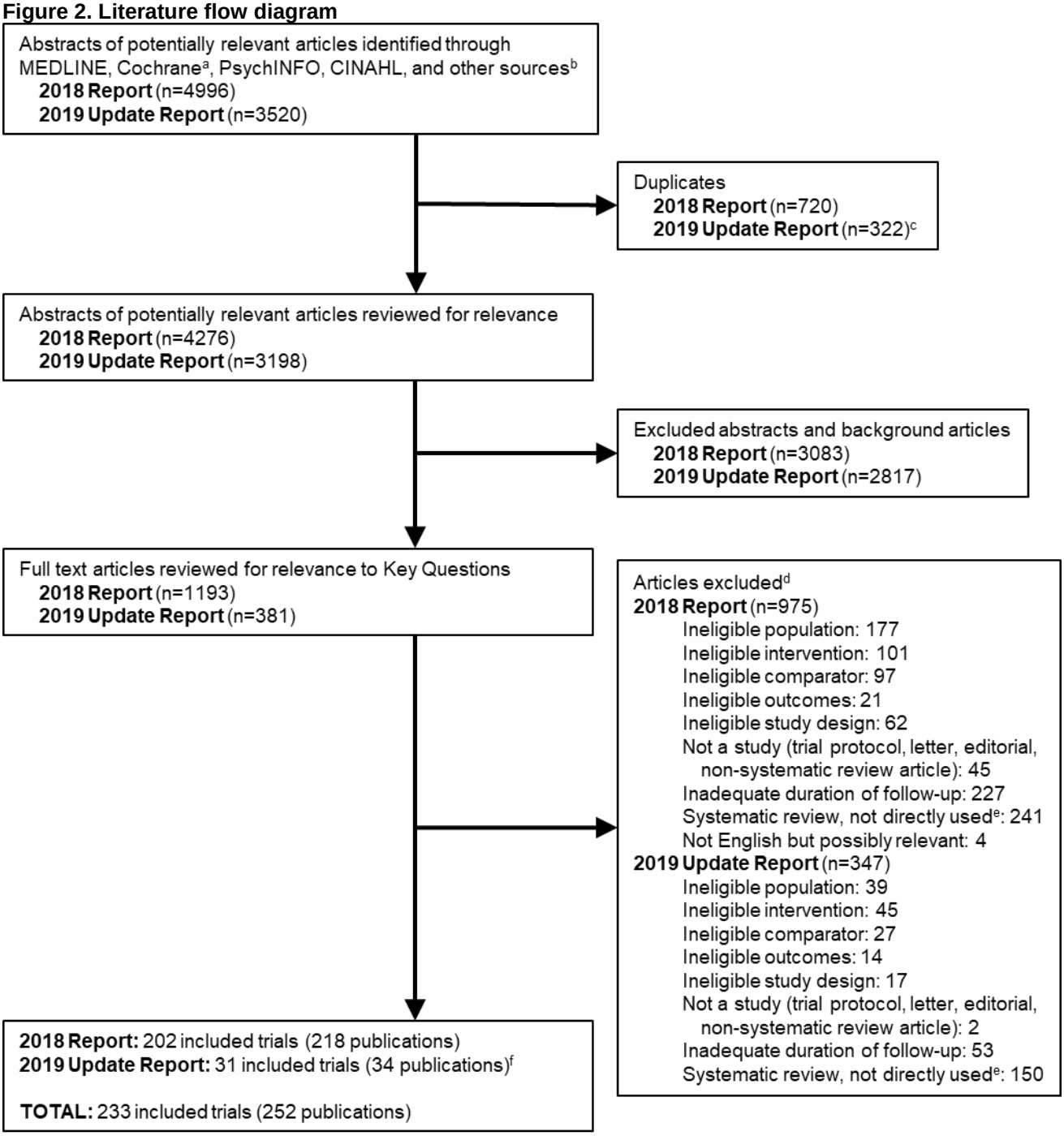
We synthesized data qualitatively and quantitatively, using meta-analysis where appropriate. Two continuous primary outcomes (pain, function) provided adequate data for meta-analysis. For meta-analyses providing pooled estimates, we report results from heterogeneity testing. I-squared and corresponding p-values describe the degree and statistical significance of heterogeneity across studies; pooled (subtotal) estimates are statistically significant if the confidence interval does not include the value of 0 for mean differences (MDs) or the value of 1 for risk ratios (RR). (See the Methods section of this report and the protocol for additional details on data analysis and synthesis.) In general, 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.

A list of acronyms and abbreviations appears at the end of the report.

Results of Literature Searches

The search and selection of articles are summarized in the literature flow diagram (Figure 2). 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 publications (34 added for this update) were determined to meet inclusion criteria and were included in this review. Nearly one-fourth of the trials excluded at full text did not meet our criteria for followup duration (i.e., a minimum of 1 month of followup after termination of the intervention, or postintervention if the intervention duration was at least 6 months). Other common reasons for exclusion of primary trials included ineligible population and ineligible intervention or comparator (i.e., combination of treatments or if treatments were additive in nature). Data abstraction and quality assessment tables for all included studies are available in Appendixes D and E.

Figure 2. Literature flow diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews

[b] Other sources include prior reports, reference lists of relevant articles, systematic reviews, etc.

[c] Includes 10 trials that were identified in the 2018 report search.

[d] Publications may be included or excluded for multiple interventions

[e] Studies checked for inclusion

[f] One of the publications identified for update report was a followup study to a trial included in the previous report, therefore this study is not counted in the number of included trials but is counted under total publications.

Description of Included Studies

A total of 233 trials (in 252 publications) were included. For each intervention category, the comparisons evaluated and their respective studies are listed in Table 4. The number of studies and related publications included for each condition (and the number of new studies and publications in this update review) are:

- Chronic low back pain: 77 studies in 83 publications (9 new trials)
- Chronic neck pain: 27 studies in 28 publications (2 new trials, 1 new publication)
- Osteoarthritis: 62 studies in 66 publications (9 new trials in 10 publications
- Fibromyalgia: 58 studies in 66 publications (11 new trials in 12 publications)
- Chronic tension headache: 9 studies

Table 20. Overview of included studies

Intervention	Comparator	Chronic Low Back Pain	Chronic Neck Pain	Osteoarthritis	Fibromyalgia	Chronic Tension Headache
Exercise	Sham, usual care, waitlist, no treatment, attention	10[31-40] [4 new trials]	6[41-46]	Knee OA: 22 (25)[47-71] [4 new trials] Hip OA: 4[47,72-74] Hand OA: 1[75]	22 (24)[76-99]	0
	Pharmacological therapy	0	2[100,101] [1 new trial]	1 (2)[102,103] [1 new trial in 2 publications]	1[93]	0
Psychological Therapies	Sham, usual care, waitlist, no treatment, attention	5[104-108]	1[45]	Knee OA: 4[109-112] [2 new trials] Hip, Hand OA: 0	16 (18)[78,97,98,113-127] [6 new trials in 7 publications]	2[128,129]
	Pharmacological therapy	0	0	0	4 (5)[113,122,123,130,131] [1 new trial in 2 publications]	2[129,132]
	Exercise (or biofeedback for CTTH)	1[133]	1[45]	Knee OA: 1[134] Hip, Hand OA: 0	5[78,97,98,135,136]	0
Physical Modalities	Sham, usual care, waitlist, no treatment, attention	8[137-144] [1 new trial]	5[145-149]	Knee OA: 15[150-164] [2 new trials] Hip OA: 0 Hand OA: 2[165,166]	2[167,168]	1[169]
	Pharmacological therapy	0	0	0	0	0
	Exercise (or biofeedback for CTTH)	1[170]	0	0	0	0
Manual Therapies	Sham, usual care, waitlist, no treatment, attention	12[108,143,171-180] [2 new trials]	3[181-183] [1 new trial]	Knee OA: 2[47,184] Hip OA: 1[47] Hand OA: 0	2[185,186]	1[187]

Intervention	Comparator	Chronic Low Back Pain	Chronic Neck Pain	Osteoarthritis	Fibromyalgia	Chronic Tension Headache
	Pharmacological therapy	0	0	0	0	1[188]
	Exercise (or biofeedback for CTTH)	5[174,189-192]	1[181]	Knee OA: 1[47] Hip OA: 2[47,193] Hand OA: 0	0	0
Mindfulness Practices	Sham, usual care, waitlist, no treatment, attention	5 (7)[104,194-199]	0	0	3 (4)[200-203] [1 new trial]	0
	Pharmacological therapy	0	0	0	0	0
	Exercise (or biofeedback for CTTH)	0	0	0	0	0
Mind-body Practices	Sham, usual care, waitlist, no treatment, attention	11[37,40,204-212] [4 new trials]	1 (2)[213,214] [1 new publication]	Knee OA: 2[215,216] Hip, Hand OA: 0	2[217,218]	0
	Pharmacological therapy	0	0	0	0	0
	Exercise (or biofeedback for CTTH)	7[37,40,205-207,219,220] [2 new trials]	2[221,222]	0	1[223] [1 new trial]	0
Acupuncture	Sham, usual care, waitlist, no treatment, attention	8[176,224-230]	8 (9)[213,214,231-237] [1 new publication]	Knee OA: 9[67,238-245] Hip, Hand OA: 0	5[246-250] [2 new trials]	3[251-253]
	Pharmacological therapy	0	2[231,254]	0	0	0
	Exercise (or biofeedback for CTTH)	0	0	Knee OA: 1[67] Hip, Hand OA: 0	0	0
Function Restoration Training	Sham, usual care, waitlist, no treatment, attention	0	0	0	0	0
	Pharmacological therapy	0	0	0	0	0
	Exercise (or biofeedback for CTTH)	0	0	0	0	0
Multi-disciplinary Rehabilitation	Sham, usual care, waitlist, no treatment, attention	7[255-260]	0	Knee, Hip OA: 0 Hand OA: 1[261]	6 (8)[96,262-268]	0
	Pharmacological therapy	1[269]	0	0	0	0
	Exercise (or biofeedback for CTTH)	9 (13)[133,270-281]	0	0	1[96]	0

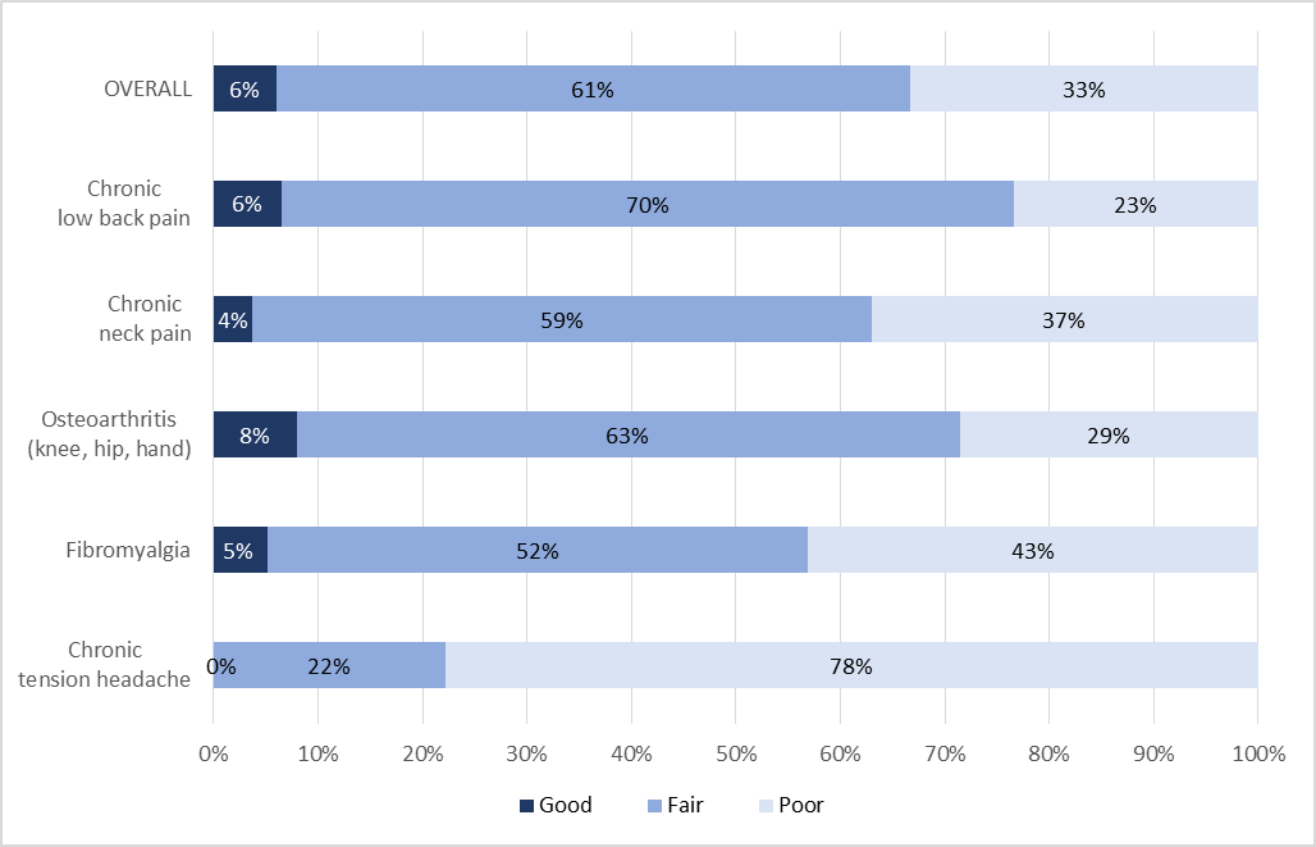
CTTH = chronic tension-type headache; OA = osteoarthritis

Thirty-six percent of the included trials were small (<70 participants). Across trials, most patients were female (>57%), with a mean ages ranging from 31 to 78 years; patients with OA tended to be older in general than those in the other conditions (range, 52 to 76 years). Mean pain duration for patients with chronic low back pain, chronic neck pain, and OA were similar and varied widely from 6 months to 15 years. Mean symptom duration in trials of fibromyalgia and

chronic tension headache tended to be at least 4 years (up to 22 years). Exercise interventions were the most commonly studied for OA and fibromyalgia. Psychological therapies were most commonly studied for fibromyalgia, and manual therapies were most commonly studied for chronic low back pain. We identified trials of acupuncture for all included conditions. Multidisciplinary rehabilitation was studied primarily for chronic low back pain and fibromyalgia. Most trials of multidisciplinary rehabilitation used a functional restoration approach either explicitly or implicitly. Limited evidence was available for hip or hand OA or chronic tension headache. The majority of trials compared nonpharmacological interventions with usual care, waitlist, no treatment, attention control, or placebo/sham, with very few trials employing pharmacological treatments or exercise as comparators. Little long-term evidence was available across conditions and interventions.

The majority of trials (61%) were rated fair quality with only 6 percent considered good quality (Figure 3). For chronic tension headache, no study was considered good quality. In the majority of trials (72%), attrition was under 20 percent and therefore rated as acceptable. Across trials where attrition was not acceptable, the range was 20 to 63 percent. A primary methodological limitation in many trials was the inability to effectively blind participants and in many cases providers. Poor reporting of randomization and allocation concealment methods were common shortcomings. Acceptable adherence, defined as completion of a minimum of 80 percent of planned treatment, was reported in 44 percent of trials. It was either unclear (40%) or unacceptable (16%) in the majority of trials.

Figure 3. Overview and distribution of quality analysis ratings



Key Question 1: Chronic Low Back Pain

For chronic low back pain, 68 randomized controlled trials (RCTs) (in 74 publications) were included in the prior Agency for Healthcar Research and Quality (AHRQ) report (N=13,163). Two studies were rated good-quality, 49 studies fair quality, and 17 studies poor quality. The prior AHRQ report found massage, yoga, psychological therapies, exercise, acupuncture, low-level laser therapy, spinal manipulation, and multidisciplinary rehabilitation associated with greater effects than usual care, attention control, sham, or placebo on improved pain or function. The strength of evidence was low or moderate, generally stronger for pain than for function, and observed at short- or intermediate-term followup, with the exception of psychological therapies, which were associated with small effects at long-term followup.

For this update, we identified nine new RCTs (N=1,026). Three of the new studies were rated good quality; four were rated fair quality, and two were rated poor quality. The new trials evaluated exercise (5 trials) massage (2 trials), yoga (2 trials), and interferential therapy (1 trial); one trial evaluated both exercise and yoga interventions. The Key Points summarize the main findings based on the evidence included in the prior report and new trials; the Key Points note where new trials contributed to findings.

Exercise for Chronic Low Back Pain

Key Points

- 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], pooled standardized mean difference [SMD] −0.31, 95% confidence interval [CI] −0.50 to −0.13, I^2=32%) after excluding an outlier trial; there were no effects on intermediate-term function (5 trials [2 new], pooled SMD −0.17, 95% CI −0.39 to 0.02, I^2=0%) 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) (strength of evidence [SOE]: moderate for short term, low for intermediate and long term).
- Exercise was associated with moderate effects on pain versus usual care, an attention control, or a placebo intervention at short-term (11 trials [5 new], pooled difference −1.21 on a 0 to 10 scale, 95% CI −1.77 to −0.65, I^2=64%) and long-term (1 trial, difference –1.55, 95% CI −2.76 to −0.34), and a small effect at intermediate-term (5 trials [2 new], pooled MD −0.85, 95% CI −1.67 to −0.07, I^2=50%) followup (SOE: low for all timepoints).
- No trial evaluated exercise versus pharmacological therapy.
- Comparisons involving exercise versus other nonpharmacological therapies are addressed in the sections for the other therapies.
- Harms were not reported in most trials; one trial did not find an association between exercise and increased pain versus placebo and one trial reported no adverse events (SOE: low).

Detailed Synthesis

Eleven trials of exercise therapy for low back pain met inclusion criteria (Table 5 and Appendix D).[31-40,212] Six trials[31-36] were included in the prior AHRQ report and five[37-40,212] were added for this update. Three trials (1 new) evaluated neuromuscular re-education exercise (motor

control exercises),[31,32,38] four trials 2 new) muscle performance exercises (Pilates or modified Pilates),[35,36,40,212] three trials (1 new) combined exercise techniques,[33,34,39] and one trial evaluated strength training.[37] Sample sizes ranged from 42 to 295 (total sample=1,204). Five trials compared exercise versus an attention control,[32,33,35,37,38] four trials compared exercise versus usual care,[34,36,40,212] and two trials compared exercise versus a placebo intervention (detuned diathermy and ultrasound).[31,39] Five trials (1 new)[31-34,37] were conducted in the United States, Europe, or Australia, four trials (2 new)[35,36,39,212] in Brazil, one new trial[38] in Asia, and one new trial[40] in Iran. The duration of exercise therapy ranged from 6 to 12 weeks and the number of exercise sessions ranged from 6 to 24. Three trials reported outcomes through long-term followup,[32,39,212] four trials reported outcomes through intermediate-term followup[31,33,39,212] and the remainder only evaluated short-term outcomes.

Two trials (both new)[39,212] were rated good quality, seven trials (2 new)[31-33,35-38] were rated fair quality, and two trials (1 new)[34,40] were rated poor quality (Appendix E). In two fair-quality trials,[31,36] the main methodological limitation was the inability to blind interventions. Limitations in the other trials included unclear randomization and allocation concealment methods, high loss to followup, and baseline differences between intervention groups.

Table 21. Chronic low back pain: exercise

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Areeudomwong, 2017[38] 3 months Duration of pain: Mean 9.0 to 10 months Fair	A. Proprioceptive Neuromuscular Facilitation (neuromuscular re-education) (n=21): 30 minute sessions 5 times/week for 4 weeks (20 total sessions) B. Attention control (education) (n=21)	A vs. B Age: 35 vs. 36 years Female: 71% vs. 76% Baseline RDQ (0-24): 4.5 vs. 4.9 Baseline NPS (0-10): 4.1 vs. 4.2	A vs. B <u>3 months</u> RDQ: 1.7 vs. 4.8, difference -3.1 (95% CI -3.9 to -2.3), p<0.001 NPS: 1.5 vs. 3.85, difference -2.31 (95% CI -3.4 to -1.2), p<0.001	A vs. B <u>3 months</u> SF-36 PCS: 53.7 vs. 44.2, difference 9.6 (95% CI 5.4 to 13.3), p<0.001 SF-36 MCS: 49.5 vs. 48.36, difference 1.2 (95% CI -3.1 to 5.4), p>0.05 GPE: 1.4 vs. 0.7, difference 0.7 (95% CI 0.2 to 1.2), p<0.01
Bramberg, 2017[37] 4.2 months Duration of pain: NR Fair	A. Strength training (n=52): Five 60-minute supervised strength-training sessions over 6 weeks. B. Attention control (education) (n=55)	A vs. B Age: 47 vs. 46 vs. 44 years Female: 72% vs. 62% vs. 80% Baseline CPGS-BD (0-100): 37.6 vs. 38.6 Baseline CPGS-BP (0-100): 57.7 vs. 55.6	A vs. B <u>6 months</u> CPGS-BD: 24.8 vs. 32.8, adjusted difference −9.5 (95% CI −19.3 to 0.4), p>0.05 CPGS-BP: 41.7 vs. 50.2, adjusted difference −9.4 (95% CI −18.1 to -0.8), p<0.05	<u>Work absence</u> (mean days over time period)[b] A vs. B -1 to 4 months: 5.0 vs. 8.9, difference −3.9 (95% CI −11.4 to 3.6) -5 to 8 months: 6.4 vs. 12.5, difference −6.1 (95% CI −15.7 to 3.5) -9 to 12 months: 9.5 vs. 9.2, difference 0.3 (95% CI −10.3 to 10.9); Proportion absent ≥1 time: 51% vs. 44%; RR 0.95 (95% CI 0.73 to 1.22)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Costa, 2009[31] 4 and 10 months Duration of pain: Mean 328 to 335 weeks Fair	A: Neuromuscular re-education (motor control exercise) (n=77), 12 sessions over 8 weeks B: Placebo (n=77) (detuned shortwave diathermy and detuned ultrasound) 12 sessions, two sessions/week for 4 weeks, then 1 session/week for 4 weeks	A vs. B Age: 55 vs. 53 years Female: 58% vs. 62% Baseline RDQ (0-24): 13.1 vs. 13.4 Baseline pain (0-10 VAS): 6.8 vs. 6.6	A vs. B <u>4 months</u> RDQ: 5.3 vs. 4.3, adjusted difference 1.0 (95% CI 0.3 to 1.8) Pain (0-10 VAS): 5.0 vs. 5.6, adjusted difference 1.4 (95% CI 0.3 to 2.4) <u>10 months</u> RDQ: 11.4 vs. 12.3, adjusted difference −1.0 (95% CI −2.8 to 0.8) Pain: 5.0 vs. 6.3, adjusted difference −1.0 (95% CI −1.9 to −0.1)	A vs. B <u>4 months</u> Global impression of recovery (−5 to +5): 1.5 vs. 0.3, adjusted difference 1.4 (95% CI 0.3 to 1.8) <u>10 months</u> Global impression of recovery: 1.2 vs. −0.3, adjusted difference 1.6 (95% CI 0.6 to 2.6)
Garcia, 2018[39] 1.75, 4.75, and 11.75 months Duration of mean pain: Mean 36 to 48 months Good	A. McKenzie Method of Mechanical Diagnosis and Therapy (directional preference) (n=74): In addition to the supervised treatment sessions, patients were instructed to do 10–15 repetitions of exercise, three to five times per day at home. B. Placebo (n=73) (ultrasound)	A vs. B Age: 58 vs. 56 years Female: 78.4% vs. 74% Baseline PSFS (0-10): 4.0 vs. 3.9 Baseline RDQ (0-24): 13.3 vs. 14.3 Baseline NRS (0-10): 7.2 vs. 7.0	A vs. B <u>4.75 months</u> PSFS: 6.2 vs. 5.9, adjusted difference −0.1 (95% CI −0.9 to 0.7), p=0.82 RDQ: 8.3 vs. 9.9, adjusted difference −0.5 (95% CI −2.3 to 1.3), p=0.61 NRS: 4.5 vs. 5.0, adjusted difference −0.8 (95% CI −1.8 to 0.3), p=0.15 <u>11.75 months</u> PSFS: 5.5 vs. 6.0, adjusted difference 0.66 (95% CI −0.13 to 1.45), p=0.10 RDQ: 7.7 vs. 8.5, adjusted difference 0.5 (95% CI −1.3 to 2.3), p=0.56 NRS: 5.1 vs. 4.9, adjusted difference −0.1 (95% CI −1.0 to 1.1), p=0.88	A vs. B <u>4.75 months</u> GPE: 2.10 vs. 1.63, adjusted difference 0.65 (95% CI −0.43 to 1.74), p=0.23 <u>11.75 months</u> GPE: 1.6 vs. 1.3, adjusted difference 0.0 (95% CI −1.0 to 1.1), p=0.95

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Goldby, 2006[32] 3, 6, 12 and 24 months Duration of pain: Mean 11 to 12 years Fair	A: Neuromuscular re-education (motor control exercise) (n=84), 10 sessions over 10 weeks B: Attention control (education) (n=40)	A vs. B Age: 43 vs. 41 years Female: 68% vs. 68% Race: 80% vs. 62% Baseline ODI (0-100): 40.5 vs. 33.5 Baseline LBO (0-75): 43.9 vs. 44.0 vs. 47.6 Baseline back pain (0-100 NRS): 45.8 vs. 37.6	<u>3 months</u> ODI (0-100): 31.00 vs. 28.1, difference 2.9 (95% CI −3.89 to 9.69) LBO (0-75): 50.92 vs. 54.4, difference −3.48 (95% CI −9.67 to 2.71) Back pain (0-100 NRS): 28.81 vs. 34.4, difference −5.59 (95% CI −17.86 to 6.68) <u>6 months</u> ODI: 25.81 vs. 23.9, difference 1.91 (95% CI −6.28 to 10.10) LBO: 55.42 vs. 57.85, difference −2.43 (95% CI −9.14 to 4.28) Back pain: 23.16 vs. 30.25, difference −7.09 (95% CI −20.22 to 6.04) <u>12 months</u> ODI: 24.76 vs. 26.9 difference −2.14 (95% CI −10.14 to 5.86) LBO: 53.86 vs. 50.95, difference 2.91 (95% CI −4.29 to 10.11) Back pain: 29.23 vs. 30, difference −0.77 (95% CI −14.13 to 12.59) <u>24 months</u> ODI: 27 vs. 27; difference 0.00 (95% CI −11.44 to 11.44) LBO: 54.7 vs. 55.2, difference −0.5 (95% CI −9.20 to 8.20) Back pain: 35.4 vs. 50.9, difference −15.50 (95% CI −33.06 to 2.06)	<u>3 months</u> Nottingham Health Profile: 94.97 vs. 94.32, difference 0.65 (95% CI −36.97 to 38.27) <u>6 months</u> Nottingham Health Profile: 76.3 vs. 77.50, difference −1.20 (95% CI −37.76 to 35.36) <u>12 months</u> Nottingham Health Profile: 70.06 vs. 87.47 difference −17.41 (95% CI −56.12 to 21.30) <u>24 months</u> Nottingham Health Profile: 82 vs. 83, difference −1.00 (95% CI −60.85 to 58.85)
Kankaanpaa, 1999[33] 3 and 9 months Duration of pain: Mean 7 to 9 years Fair	A. Combined exercise (exercises, stretching, relaxation, muscle function and ergonomic advice) (n=30), 24 sessions over 12 weeks B. Attention Control (n=24) (thermal therapy and minimal massage)	A vs. B Age: 40 vs. 39 years Female: 36.6% vs. 33.3% Baseline Pain and Disability Index (0-70 PDI): 13.2 vs. 9.5 Baseline back pain (0-100 mm VAS): 55.2 vs. 47.0	<u>3 months</u> Pain and Disability Index (0-70): 5.7 vs. 12.6, difference −6.9 (95% CI −11.69 to - 2.11) Back pain (0-100 VAS): 26.6 vs. 43.4; difference −16.80 (95% CI −31.12 to −2.47) <u>9 months</u> Pain and Disability Index: 5.7 vs. 11.4, difference −5.7 (95% CI −11.31 to −0.09) Back pain intensity: 23.9 vs. 45.1, difference −21.20 (95% CI −32.69 to −9.71)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Mazloum, 2017[40] 1 month Duration of pain: Mean 30.8 to 32.4 months Poor	A. Pilates (n=20): 3 days per week for 6 weeks B. Exercise (n=20): 3 days per week for 6 weeks C. Usual care (n=20) (no treatment)	A vs. B vs. C Age: 37 vs. 43 vs. 39 years Baseline ODI (0-100): 30.8 vs. 27.2 vs. 26.2 Baseline VAS (0-10): 6.8 vs. 7.2 vs. 6.5	<u>1 month</u> A vs. C ODI: 22.9 vs. 26.6, difference −3.7 (95% CI −6.8 to −0.6) VAS: 3.0 vs. 6.9, difference −3.9 (95% CI −4.8 to −3.0) B vs. C ODI: 23.1 vs. 26.6, difference −3.5 (95% CI −8.1 to 1.2) VAS: 4.8 vs. 6.9, difference -−2.1 (95% CI −3.1 to -−1.1) A vs. B ODI: 22.9 vs. 23.1. difference −0.2 (95% CI −4.5 to 4.1) VAS: 3.0 vs. 4.8, difference −1.8 (95% CI −2.5 to −1.1)	NR
Miyamoto, 2013[35] 4.5 months Duration of pain: Mean 5 to 6 years Fair	A. Muscle performance (Pilates) (n=43),12 sessions over 6 weeks B. Attention control (n=43) (education)	A vs. B Age: 41 vs. 38 years Female: 84% vs. 79% Baseline RDQ: 9.7 vs. 10.5 Baseline pain (0-10 VAS): 6.6 vs. 6.5	<u>4.5 months</u> RDQ (0-24): 4.5 vs. 6.7, adjusted difference −1.4 (95% CI −3.1 to 0.03) Patient-Specific Functional Scale (0-10): 6.9 vs. 6.1, adjusted difference 0.2 (95% CI −0.6 to 1.1) Pain (0-10 VAS): 4.5 vs. 5.3, adjusted difference −0.9 (95% CI −1.9 to 0.1)	<u>4.5 months</u> Global impression of recovery (−5 to +5): 2.4 vs. 1.7, adjusted difference 0.7 (95% CI −0.4 to 1.8)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Miyamoto, 2018[212] 4.5 and 11.5 months Duration of pain: Mean 36 to 57 months Good	A. Pilates (n=74): 1 session/week for 6 weeks (6 total sessions). Patients attended 81% of sessions. B. Pilates (n=74): 2 sessions/week for 6 weeks (12 total sessions). Patients attended 85% of sessions. C. Pilates (n=74): 3 sessions/weeks for 6 weeks (18 total sessions). Patients attended 82% of sessions. D. Usual care (n=73) (no treatment)	A vs. B. vs. C vs. D Age: 47 vs. 47 vs. 49 vs. 49 years Female: 78% vs. 70% vs. 78% vs. 76% Baseline RDQ (0-24): 11.0 vs. 12.8 vs. 10.6 vs. 12.3 Baseline PSFS (0-10): 3.7 vs. 3.8 vs. 3.9 vs. 3.6 Baseline NRS (0-10): 6.1 vs. 6.4 vs. 6.0 vs. 6.3	A vs. D <u>4.5 months</u> RDQ: 8.8 vs. 10.2, adjusted difference 0.0 (−1.7 to 1.8), p>0.05 PSFS: 5.5 vs. 6.0, adjusted difference −0.5 (−1.3 to 0.3), p>0.05 NRS: 5.0 vs. 5.4, adjusted difference −0.3 (−1.3 to 0.6), p>0.05 <u>11.5 months</u> RDQ: 7.3 vs. 8.9, adjusted difference 0.2 (−1.6 to 2.0), p>0.05 PSFS: 6.1 vs. 6.2, adjusted difference −0.2 (−1.0 to 0.6), p>0.05 NRS: 4.8 vs. 4.9, adjusted difference 0.1 (−0.9 to 1.0), p>0.05 B vs. D <u>4.5 months</u> RDQ: 7.9 vs. 10.2, adjusted difference −2.4 (−4.1 to −0.6), p≤0.01 PSFS: 6.5 vs. 6.0, adjusted difference 0.4 (−0.4 to 1.2), p>0.05 NRS: 4.4 vs. 5.4, adjusted difference −1.0 (−2.0 to −0.1), p≤0.05 <u>11.5 months</u> RDQ: 7.2 vs. 8.9, adjusted difference −1.7 (−3.5 to 0.0), p>0.05 PSFS: 6.9 vs. 6.2, adjusted difference 0.5 (−0.4 to 1.3), p>0.05 NRS: 4.1 vs. 4.9, adjusted difference −0.8 (−1.8 to 0.2), p>0.05 C vs. D <u>4.5 months</u> RDQ: 6.4 vs. 10.2, adjusted difference −1.7 (−3.5 to 0.1), p>0.05 PSFS: 6.7 vs. 6.0, adjusted difference 0.3 (−0.5 to 1.2), p>0.05 NRS: 4.3 vs. 5.4, adjusted difference −0.7 (−1.7 to 0.2), p>0.05 <u>11.5 months</u> RDQ: 5.9 vs. 8.9, adjusted difference −0.7 (−2.5 to 1.1), p>0.05 PSFS: 6.6 vs. 6.2, adjusted difference 0.0 (−0.8 to 0.8), p>0.05 NRS: 4.1 vs. 4.9, adjusted difference −0.4 (−1.4 to 0.6), p>0.05	A vs. D <u>4.5 months</u> GPE: 1.5 vs. 1.2, adjusted difference 0.5 (−0.5 to 1.6), p>0.05 SF-6D: 0.80 vs. 0.80, adjusted difference 0.01 (−0.02 to 0.03), p>0.05 <u>11.5 months</u> GPE: 1.6 vs. 1.9, adjusted difference −0.1 (−1.2 to 1.0), p>0.05 SF-6D: 0.81 vs. 0.80, adjusted difference 0.01 (−0.01 to 0.04), p>0.05 Mean total societal costs (SEM): 574 vs. 649, p>0.05 B vs. D <u>4.5 months</u> GPE: 2.1 vs. 1.2, adjusted difference 1.5 (0.4 to 2.6), p≤0.01 SF-6D: 0.82 vs. 0.80, adjusted difference 0.02 (−0.00 to 0.05), p>0.05 <u>11.5 months</u> GPE: 2.1 vs. 1.9, adjusted difference 0.9 (−0.2 to 1.9), p>0.05 SF-6D: 0.83 vs. 0.80, adjusted difference 0.04 (0.01 to 0.06), p≤0.01 Mean total societal costs (SEM): 824 vs. 649 C vs. D <u>4.5 months</u> GPE: 2.6 vs. 1.2, adjusted difference 1.7 (0.6 to 2.8), p≤0.01 SF-6D: 0.84 vs. 0.80, adjusted difference 0.03 (0.00 to 0.06), p≤0.05 <u>11.5 months</u> GPE: 2.6 vs. 1.9, adjusted difference 1.0 (−0.1 to 2.1), p>0.05 SF-6D: 0.84 vs. 0.80, adjusted difference 0.03 (0.02 to 0.07), p≤0.05 Mean total societal costs (SEM): 880 vs. 649

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Nassif, 2011[34] 4 months Duration of pain: NR Poor	A. Combined exercise (n=37) (stretching, stability, coordination, and muscle strengthening exercises), 24 sessions over 8 weeks B. Usual care (n=38)	A vs. B Age: 45 vs. 45 Female: 11% vs. 21% Baseline RDQ: 13.9 vs. 12.3 Baseline pain (0-10 VAS): 4.5 vs. 4.9	4 months RDQ (0-24): 10.0 vs. 10.6, difference −0.6 (95% CI −3.5 to 2.3) Quebec Back Pain Disability Questionnaire: 27.2 vs. 30.2, difference −3.0 (95% CI −11.7 to 5.7) Pain (0-10 NRS): 3.2 (2.3) vs. 3.5 (2.5), difference −0.3 (95% CI −1.6 to 1.0)	4 months Dallas Pain Questionnaire anxiety and depression: 31.2 vs. 28.9, difference 2.3 (95% CI −8.2 to 12.8)
Natour, 2014[36] 3 months Duration of pain: >1 year Fair	A. Exercise (Pilates) (n=30), 24 sessions over 12 weeks B. Usual care (n=30) (no treatment)	A vs. B Age: 48 vs. 48 Female: 80% vs. 77% Baseline RDQ: 1.1 vs. 10.6 Baseline pain (0-10 VAS): 5.5 vs. 5.8	3 months RDQ (0-24): 7.0 vs. 10.7, difference −3.6, p<0.001 Pain (0-10 VAS): 4.2 vs. 5.8, difference −1.6, p<0.001	3 months SF-36 physical function (0-100): 65.4 vs. 59.6, difference 5.8, p=0.026 SF-36 role physical: 56.4 vs. 40.0, difference 16.4, p=0.086 SF-36 bodily pain: 52.2 vs. 43.9, difference 8.3, p=0.030 SF-36 general health: 65.2 vs. 62.1, difference 3.1, p=0.772 SF-36 mental health: 67.9 vs. 65.3, difference 2.6, p=0.243 SF-36 social functioning: 86.0 vs. 80.4, difference 5.6, p=0.09 No differences on other SF-36 subscales

CI = confidence interval; CPGS=Von Korff Chronic Pain Grade Score; GPE = Global Perceived Effect Scale; LBO = Low Back Outcome Score; MCS = Mental Component Score; NPS= numeric pain scale; NR = not reported; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; PCS = Physical Component Score; PSFS = Patient Specific Functional Scale; RDQ = Roland-Morris Disability Questionnaire; RR = relative risk; SEM = standard error of the mean; SF-36 = Short-Form 36 questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

[b] For missed work days: time period 1 (months 1-4), time period 2 (months 5-8) and time period 3 (months 9-12).

Exercise Compared With Usual Care, an Attention Control, or a Placebo Intervention

Exercise was associated with small effects on short-term function versus controls (11 trials, pooled SMD −0.51, 95% CI −0.98 to −0.08, I^2=88%) (Figure 4).[31-40,212] Excluding one trial[38] that reported a much higher SMD (−3.1) and smaller standard deviation (~1.0) compared to the other trials (SMD range −0.81 to 0.17 and standard deviation range 5 to 17) also resulted in a pooled estimate that favored exercise, though the difference was attenuated (10 trials, pooled SMD −0.31, 95% CI −0.50 to −0.13, I^2=32%). Seven trials that evaluated function using the Roland-Morris Disability Questionnaire (RDQ) (0 to 24 scale) reported a pooled difference of −2.86 points (95% CI −3.36 to −1.05).[31,34-36,38,39,212] and two trials that used the ODI (0 to 100 scale) reported differences that ranged from 3.7 points favoring exercise[40] to 2.9 points favoring an attention control.[32] There were no clear differences in estimates when analyses were stratified according to the type of exercise (pooled SMD estimates ranged from −0.08 to −0.54) or the type

of control, or when poor-quality trials were excluded. There were no differences between exercise versus controls in intermediate-term function (5 trials, pooled SMD −0.17, 95% CI −0.39 to 0.02, I^2=0%)[31-33,39,212] or long-term function (1 trial, difference 0.00, 95% CI −11.4 to 11.4 on the ODI).[32]

Exercise was associated with moderate effects on short-term pain versus usual care, an attention control, or a placebo intervention (11 trials, pooled difference −1.21 on a 0 to 10 scale, 95% CI −1.77 to −0.65, I^2=64%) (Figure 5).[31-36,38-40,212] There were no clear differences in estimates when analyses were stratified according to the type of exercise (pooled differences ranged from −0.59 to −0.98 points on a 0 to 10 scale), the type of control (usual care, attention control, or placebo intervention), and when poor-quality trials were excluded. Exercise was associated with small effects on intermediate-term pain versus controls (5 trials, pooled difference −0.85, 95% CI −1.67 to −0.07, I^2=50%).[31-33,39,212] For long-term pain, effects of exercise on pain were moderate compared with attention control, but findings were based on one trial (difference −1.55, 95% CI −2.76 to −0.34).[32]

Evidence on effects of exercise on quality of life was limited. One trial[32] found no differences between exercise versus an attention control on the Nottingham Health Profile at short-term, intermediate-term, or long-term followup, and one trial[36] found exercise associated with higher scores on the Short-Form 36 (SF-36) physical functioning (difference 5.8 points on 0 to 100 scale, p=0.026), bodily pain (difference 8.3 points, p=0.03), and vitality subscales (difference 5.3 points, p=0.029) at short-term followup; there were no differences on other SF-36 subscales **(**Table 5). Another trial found exercise associated with greater improvement in the SF-36 Physical Component Summary versus an attention control (difference 8.26 on a 0 to 100 scale, 95% CI 5.27 to 11.25) but no difference on the SF-36 Mental Component Summary (difference 1.27, 95% CI −3.38 to 5.92).[38]

No trial evaluated effects of exercise on use of opioid therapies or healthcare utilization. There was insufficient evidence to determine effects of duration of exercise therapy or number of sessions on outcomes.

Exercise Compared With Pharmacological Therapy

No trial of exercise versus pharmacological therapy met inclusion criteria.

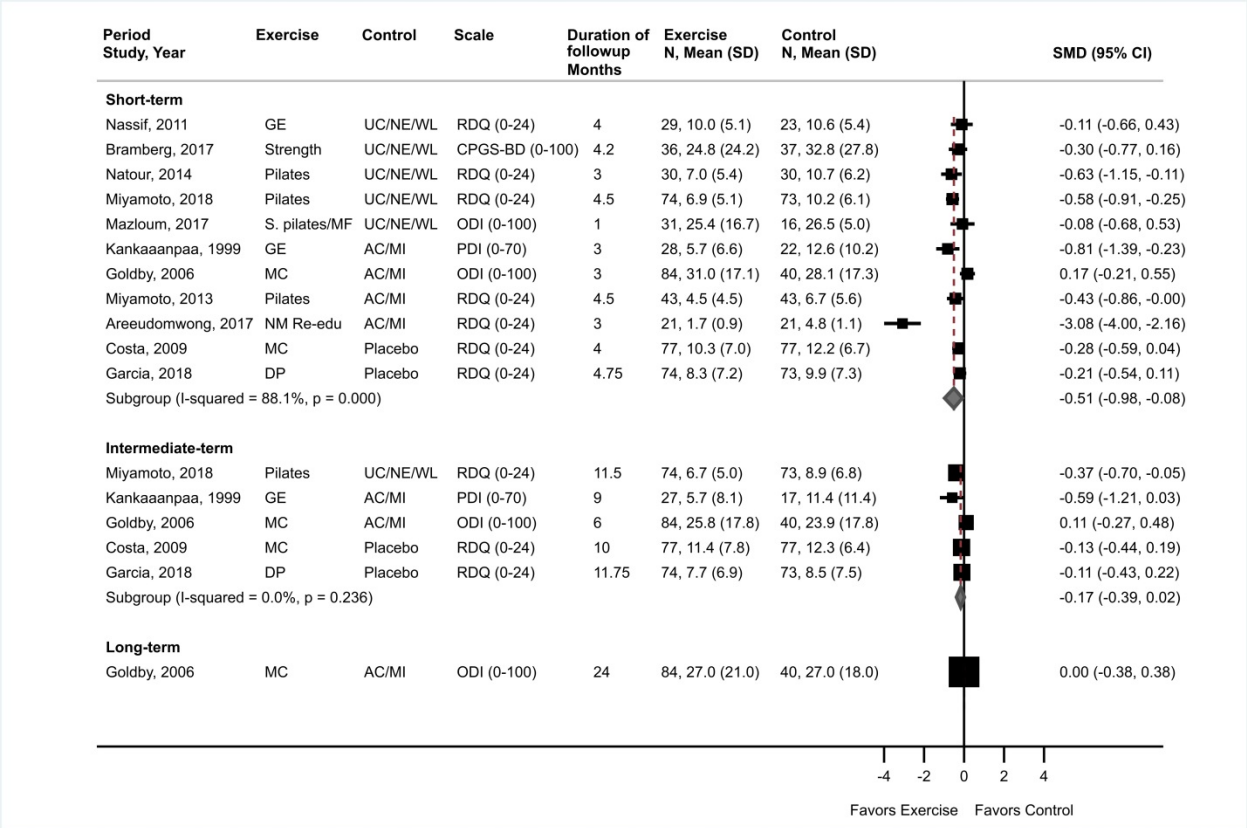
Exercise Compared With Other Nonpharmacological Therapies

Findings for exercise versus other nonpharmacological therapies are addressed in the sections on other nonpharmacological therapies.

Harms

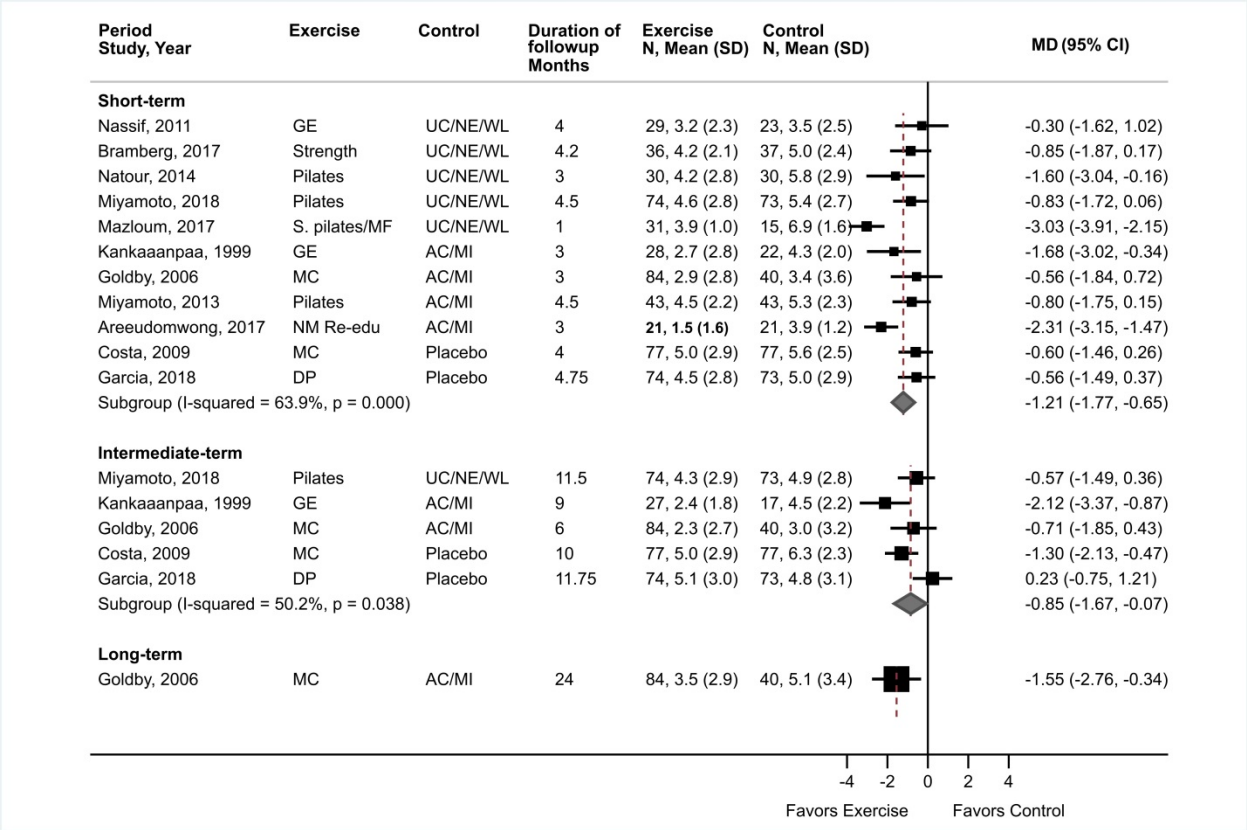
Harms were not reported in most trials. One trial[31] found no difference between exercise and a placebo intervention (detuned diathermy) in likelihood of increased pain, and another trial[35] reported no adverse events (Appendix D).

Figure 4. Exercise versus usual care, an attention control, or a placebo intervention for chronic low back pain: effects on function



AC = attention control; CI = confidence interval; CPGS –BD =Von Korff Chronic Pain Grade Score Back Disability; DP = directional preference; GE= general exercise; MC = motor control; MF = mobility/flexibility; MI = minimal intervention; N = number; NE = no exercise; NM = neuromuscular re-education; ODI = Oswestry Disability Index; PDI = Pain Disability Index; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; S. pilates = selective Pilates; Strng=Strength training; UC = usual care; WL = waitlist

Figure 5. Exercise versus usual care, an attention control, or a placebo intervention for chronic low back pain: effects on pain



AC = attention control; CI = confidence interval; CPGS –BD =Von Korff Chronic Pain Grade Score Back Disability; DP = directional preference; ; GE= general exercise; MC = motor control; MD = mean difference; MF = mobility/flexibility; MI = minimal intervention; N = number; NE = no exercise; NM = neuromuscular re-education; ODI = Oswestry Disability Index; PDI = Pain Disability Index; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; S. pilates = selective Pilates; Strng=Strength training; UC = usual care; WL = waitlist

Psychological Therapies for Chronic Low Back Pain

Key Points

- Psychological therapy was associated with small improvements in function compared with usual care or an attention control at short-term (3 trials, pooled SMD −0.24, 95% CI −0.38 to −0.04, I^2=0%), intermediate-term (3 trials, pooled SMD −0.24, 95% CI −0.38 to −0.10, I^2=0%), and long-term followup (3 trials, pooled SMD −0.28, 95% CI −0.43 to −0.13, I^2=0%) (SOE: moderate).
- Psychological therapy was associated with small improvements in pain compared with usual care or an attention control at short-term (3 trials, pooled difference −0.75 on a 0 to 10 scale, 95% CI −1.01 to −0.41, I^2=0%), intermediate-term (3 trials, pooled difference −0.71, 95% CI −0.97 to −0.46, I^2=0%), and long-term followup (3 trials, pooled difference −0.55, 95% CI −0.92 to −0.23, I^2=0%) (SOE: moderate).
- Evidence from one poor-quality trial was too unreliable to determine effects of psychological therapy versus exercise (SOE: insufficient).

- One trial of cognitive behavioral therapy versus an attention control reported no serious adverse events and one withdrawal due to adverse events in 468 patients (SOE: low).

Detailed Synthesis

Five trials (reported in 6 publications) of psychological therapies for low back pain met inclusion criteria (Table 6 and Appendix D).[104-108,133,195] All of the trials were included in the prior AHRQ report. Three trials evaluated group cognitive-behavioral therapy (CBT),[104-107] one trial evaluated respondent therapy (progressive muscle relaxation),[108] and one trial evaluated operant therapy.[133] Sample sizes ranged from 49 to 701 (total sample=1,308). The number of psychological therapy sessions ranged from six to eight, and the duration of therapy ranged from 6 to 8 weeks. In one trial[106,107] the duration of therapy was unclear. Three trials compared psychological therapies versus usual care,[104,105,108] one trial compared psychological therapy versus an attention control (advice),[106,107] and one trial compared psychological therapy versus exercise therapy.[133] All trials were conducted in the United States or the United Kingdom. Four trials reported outcomes through long-term (12 to 34 months) followup,[105-107,133,195] one trial evaluated outcomes through intermediate-term followup,[104] and one trial only evaluated short-term outcomes.[108]

Three trials[104-107] were rated fair quality and two trials poor quality (Appendix E).[108,133] The major methodological limitation in the fair-quality trials was the inability to effectively blind patients and caregivers to the psychological intervention. Other methodological shortcomings in the poor-quality trials included unclear randomization and allocation concealment methods and high attrition.

Table 22. Chronic low back pain: psychological therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cherkin, 2016[104] Herman, 2017[196] Cherkin, 2017[195] (2 year data from Cherkin, 2016) 22 months Duration of pain: >3 months (>1 year in 80% of patients) Fair	A. CBT (n=112), 8 sessions over 8 weeks B. Usual care (n=113)	A vs. B 49 vs. 49 years Female: 59% vs. 77% Baseline modified RDQ (0-23): 11.5 vs. 10.9 Baseline pain bothersome-ness (0-10): 6.0 vs. 6.0	A vs. B <u>4.5 months</u> Modified RDQ (0-23): −4.38 (95% CI −5.3 to −3.47) vs. −2.96 (95% CI −3.79 to −2.14) Pain (0-10): −1.56 (95% CI −2.02 to −1.11) vs. −0.84 (95% CI −1.21 to −0.46) <u>10 months</u> Modified RDQ (0-23): −4.78 (95% CI −5.67 to −3.89) vs. −3.43 (95% CI −4.33 to −2.52) Pain (0-10): −1.76 (95% CI −2.14, −1.39) vs. −1.10 (95% CI −1.48, −0.71) ≥30% improvement in pain: 39.6% (95% CI 31.7 to 49.5) vs. 31.0% (95% CI 23.8 to 40.3) ≥30% improvement in modified RDQ: 58.8% (95% CI 50.6 to 68.4) vs. 48.6% (95% CI 40.3 to 58.6) <u>22 months</u> Modified RDQ (0-23): −4.59 (95% CI−5.60 to −3.57) vs. −2.74 (95% CI−3.81 to −1.68) ≥30% improvement in modified RDQ: 62.0% (95% CI 53.5 to 71.7) vs. 42.0% (95% CI 33.8 to 52.2) Pain: −1.79 (95% CI −2.21 to −1.37) vs. −1.25 (95% CI −1.69 to −0.81) ≥30% improvement in pain: 39.6% (95% CI 31.4 to 49.8) vs. 31.1% (95% CI 23.9 to 40.5)	A vs. B <u>4.5 months</u> PHQ-8 (0–24): −1.80 (95% CI −2.35 to −1.26) vs. −0.64 (95% CI −1.23 to −0.06) SF-12 Physical component (0-100): 3.78 (95% CI 2.56to 5.00) vs. 3.27 (95% CI 2.09 to 4.44) SF-12 Mental component (0-100): 2.13 (95% CI 0.86 to 3.40) vs. −1.11 (95% CI −2.39 to 0.17) <u>10 months</u> PHQ-8 (0–24): 1.72 (95% CI −2.28 to −1.16) vs. −0.88 (95% CI −1.50 to −0.27) SF-12 Physical component: 3.79 (95% CI 2.55 to 5.03) vs. 2.93 (95% CI 1.70 to 4.16) SF-12 Mental component: 1.81 (95% CI 0.59 to 3.03) vs. 0.75 (95% CI −0.58 to 2.08) Total costs: $6,428 (95% CI $4676 to $10,262) vs. $6,304 (95% CI $4,193, $9,805)
Johnson, 2007[105] 12 months Duration of pain: 6 months Fair	A. CBT (n=116), 8 sessions over 6 weeks B. Usual care (n=118)	A vs. B Age: 47 vs. 49 Female: 61% vs. 58% Baseline RDQ (0-24): 10.6 vs. 10.9 Baseline pain (0-100 VAS): 44.9 vs. 51.6	A vs. B <u>6 months</u> RDQ (0-24): 6.5 vs. 8.0, adjusted difference −1.09 (95% CI −2.28 to 0.09) Pain (0-100 VAS): 26.1 vs. 35.0, adjusted difference −4.60 (95% CI −11.07 to 1.88) <u>12 months</u> RDQ (0-24): 6.7 vs. 8.0, adjusted difference −0.93 (95% CI −2.30 to 0.45) Pain (0-100 VAS): 27.9 vs. 36.4, adjusted difference −5.49 (95% CI −12.43 to 1.44)	A vs. B <u>6 months</u> Quality of life (0-1 EQ-5D): 0.75 vs. 0.71, adjusted difference 0.03 (95% CI −0.05 to 0.10) <u>12 months</u> Quality of life (0-1 EQ-5D): 0.75 vs. 0.71, adjusted difference 0.03 (95% CI −0.04 to 0.09)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lamb 2010[106] and 2012[107] 34 months Duration of pain: 13 years Fair	A. CBT (n=468), 8 sessions over unclear number of weeks B. Attention control (n=233)	A vs. B Age: 53 vs. 54 years Female: 59% vs. 61% Korff disability (0-100): 49 vs. 46 Baseline RDQ (0-24): 9 vs. 9 Baseline pain (0-100 Modified Von Korff): 59 vs. 59 Modified Von	A vs. B <u>3 months</u> Modified Von Korff disability (0-100): −13.2 (−15.74 to −10.59) vs. −8.9 (−12.27 to −5.56), adjusted difference −4.2 (−8.10 to −0.40) RDQ (0-24): −2.0 (−2.43 to −1.58) vs. −1.1 (−1.54 to −0.35) adjusted difference −1.1 (−1.71 to −0.38) Modified Von Korff pain (0-100): −12.2 (−14.56 to −9.83) vs. −5.4 (−8.40 to −2.49), adjusted difference −6.8 (−10.20 to −3.31) <u>4.5 months</u> Modified Von Korff disability: −13.9 (CI −16.25 to −11.55) vs. −5.7 (−9.22 to −2.28), adjusted difference −8.2 (−12.01 to −4.31) RDQ: −2.5 (−3.03 to −1.96) vs. −1.0 (CI −1.67 to −0.40), adjusted difference −1.5 (−2.22 to −0.70) Modified Von Korff pain: −13.7 (−16.20 to −11.29) vs. −5.7 (−8.99 to −2.41), adjusted difference −8.0 (−11.80 to −4.28) <u>10.5 months</u> Modified Von Korff disability: −13.8 (−16.28 to −11.39) vs. −5.4 (−8.90 to −1.99), adjusted difference −8.4 (−12.32 to −4.47) RDQ: −2.4 (−2.84 to −1.89) vs. −1.1 (−1.72 to −0.39), adjusted difference −1.3 (−2.06 to −0.56) Modified Von Korff pain: −13.4 (−15.96 to −10.77) vs. −6.4 (−9.66 to −3.14), adjusted difference −7.0 (−10.81 to −3.12) <u>34 months</u> Modified Von Korff disability: −16.7 (−19.43 to −13.93) vs. −11.2 (−15.59 vs. −6.86), adjusted difference −5.5 (−10.64 to −0.27) RDQ: −2.9 (−3.42 to −2.38) vs. −1.6 (−2.48 to −0.80), adjusted difference −1.3 (−2.26 to −0.27 Modified Von Korff pain: −17.4 (−20.35 to −14.44) vs. −12.8 (−17.52 to −7.99), adjusted difference −4.6 (−10.28 to 1.00)	A vs. B <u>3 months</u> SF-12 PCS (0-100): 3.7 (2.82 to 4.59) vs. 1.5 (0.26 to 2.83), adjusted difference 2.2 (0.74 to 3.57) SF-12 MCS (0-100): 1.3 (0.19 to 2.42) vs. 0 (−1.45 to 1.46), adjusted difference 1.3 (−0.36 to 2.96) <u>4.5 months</u> SF-12 PCS: 3.6 (2.72 to 4.52) vs. 1.8 (0.54 to 3.08), adjusted difference 1.8 (0.37 to 3.25) SF-12 MCS: 2.5 (1.44 to 3.48) vs. −0.09 (−1.61 to 1.43), adjusted difference 2.6 (0.85 to 4.25) <u>10.5 months</u> SF-12 PCS: 4.9 (4.00 to 5.84) vs. 0.8 (−0.52 to 2.11), adjusted difference 4.1 (2.63 to 5.62) SF-12 MSC: 0.9 (−0.10 to 1.90) vs. 0.7 (−0.75 to 2.20), adjusted difference 0.2 (−1.48 to 1.84) <u>34 months</u> EQ-5D: 0.07 (0.04 to 0.10) vs. 0.04 (−0.01 to 0.09), adjusted difference 0.03 (−0.03 to 0.08)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Poole, 2007[108] 4.5 months Duration of pain: 10.6 vs. 9.5 years Poor	A. Respondent therapy (progressive muscle relaxation) (n=54), 6 sessions over 6-8 weeks B. Usual care (n=45)	A vs. B Age: 46 vs. 47 Female: 65% vs. 51% Baseline Oswestry Disability Index (0-100% ODI): 33.2 vs. 36.6 Baseline pain (0-100 VAS): 40.7 vs. 40.6	A vs. B 4.5 month ODI (0-100): 31.3 vs. 32.9 Pain (0-100 VAS): 41.3 vs. 42.7	A vs. B 4.5 month Beck Depression Inventory (0-63): 12.6 vs. 12.8 SF-36 physical functioning (0-100): 57.3 vs. 52.2 SF-36 social functioning (0-100): 66.7 vs. 61.5 SF-36 emotional role limitations (0-100): 63.0 vs. 62.0 SF-36 pain (0-100): 48.8 vs. 44.4 SF-36 mental health (0-100): 64.4 vs. 67.7 SF-36 general health perception (0-100): 52.4 vs. 55.0
Turner, 1990[133] 12 months Duration of pain: 12.9 years Poor	A. Operant therapy (n=25), 8 sessions over 8 weeks B. Exercise (n=24)	Overall Age: 44 Female: 48% A vs. B Baseline function (0-100 SIP): 7.9 vs. 8.4 Baseline pain (0-78 McGill Pain Rating): 21.0 vs. 19.4	A vs. B 6 months Sickness Impact Profile (0-100): 7.6 vs. 6.3 McGill Pain Questionnaire Pain Rating Index (0-78): 19.5 vs. 15.7 12 months Sickness Impact Profile (0-100): 5.3 vs. 4.7 McGill Pain Questionnaire Pain Rating Index: 16.4 vs. 14.9	A vs. B 6 months CES-D Scale (0-60): 11.4 vs. 9.3 12 months CES-D Scale: 8.3 vs. 9.3

CBT = cognitive-behavioral therapy; CES-D = Center for Epidemiologic Studies-Depression; CI = confidence interval; MCS = Mental Component Score; ODI = Oswestry Disability Index; PCS = Physical Component Score; PHQ-8 = Patient Health Questionnaire 8-item depression scale; RDQ = Roland-Morris Disability Questionnaire; SF-12 = Short-Form 12 Questionaire; SF-36, Short-Form 36 Questionnaire; SIP = Sickness Impact Profile; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Psychological Therapy Compared With Usual Care or an Attention Control

Psychological therapy was associated with small improvements in function compared with usual care or an attention control at short-term (3 trials, pooled SMD −0.24, 95% CI −0.38 to −0.04, I^2=0%),[104,106,108] intermediate-term (3 trials, pooled SMD −0.24, 95% CI −0.38 to −0.10, I^2=0%)[104-106] and long-term followup (3 trials, pooled SMD −0.28, 95% CI −0.43 to −0.13, I^2=0%) (Figure 6).[105,106,195] Pooled differences on the RDQ or modified RDQ were −1.2 to −1.5 points at all time points. For short-term function, two fair-quality trials[104,106,107] evaluated CBT and one poor-quality trial[108] evaluated respondent therapy (progressive relaxation). Excluding the poor-quality trial of progressive relaxation,[108] which found no effect on short-term function (SMD −0.08, 95% CI −0.48 to 0.31), had no effect on the pooled estimate (2 trials, pooled SMD −0.26, 95% CI −0.44 to −0.05).

Psychological therapy was associated with small improvements in pain compared with usual care or an attention control at short-term (3 trials, pooled difference −0.75 on a 0 to 10 scale, 95% CI −1.01 to −0.41, I^2=0%),[104,106,108] intermediate-term (3 trials, pooled difference −0.71, 95% CI −0.97 to −0.46, I^2=0%),[104-106] or long-term followup (3 trials, pooled difference −0.55, 95% CI −0.92 to −0.23, I^2=0%) (Figure 7).[105,107,195] Excluding a poor-quality trial of progressive relaxation, which found no effect on short-term pain (difference −0.14, 95% CI −1.27 to 0.99), did not change the pooled estimate (2 trials, pooled difference −0.78, 95% CI −1.08 to −0.47). For intermediate-term and long-term pain, all trials were fair quality and evaluated CBT.

Effects of psychological therapy on short-term or intermediate-term SF-36 Physical Component (PCS) or Mental Component (MCS) scores were small (differences 0 to 2 points on a 0 to 100 scale) and not statistically significant, except for short-term MCS (2 trials, pooled difference 2.18, 95% CI 0.37 to 4.05).[104,106] One trial found no effect of psychological therapy on work status or healthcare visits[107] and one trial found no effect of psychological therapy on markers of healthcare utilization.[196]

Psychological Therapy Compared With Pharmacological Therapy

No trial of psychological versus pharmacological therapy met inclusion criteria.

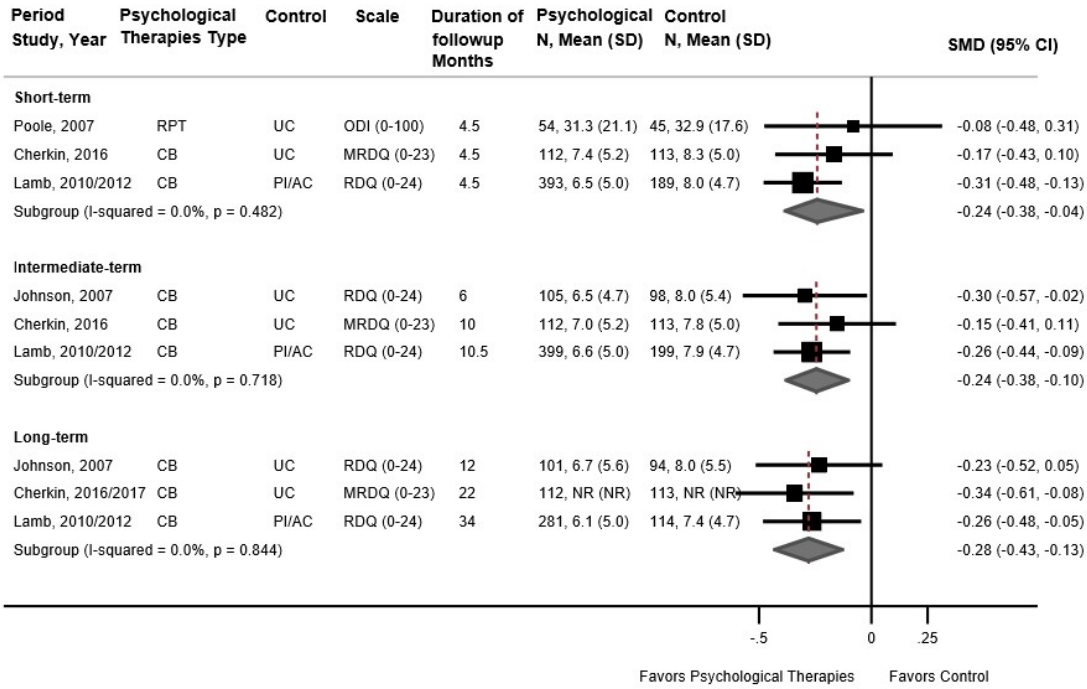
Psychological Therapy Compared With Exercise

One poor-quality trial found no differences between psychological versus exercise therapy in intermediate-term or long-term function.[133] Differences on the McGill Pain Questionnaire were less than 0.5 points on a 0 to 78 scale, and differences on the Sickness Impact Profile were 0.60 to 1.30 points on a 0 to 100 scale.

Harms

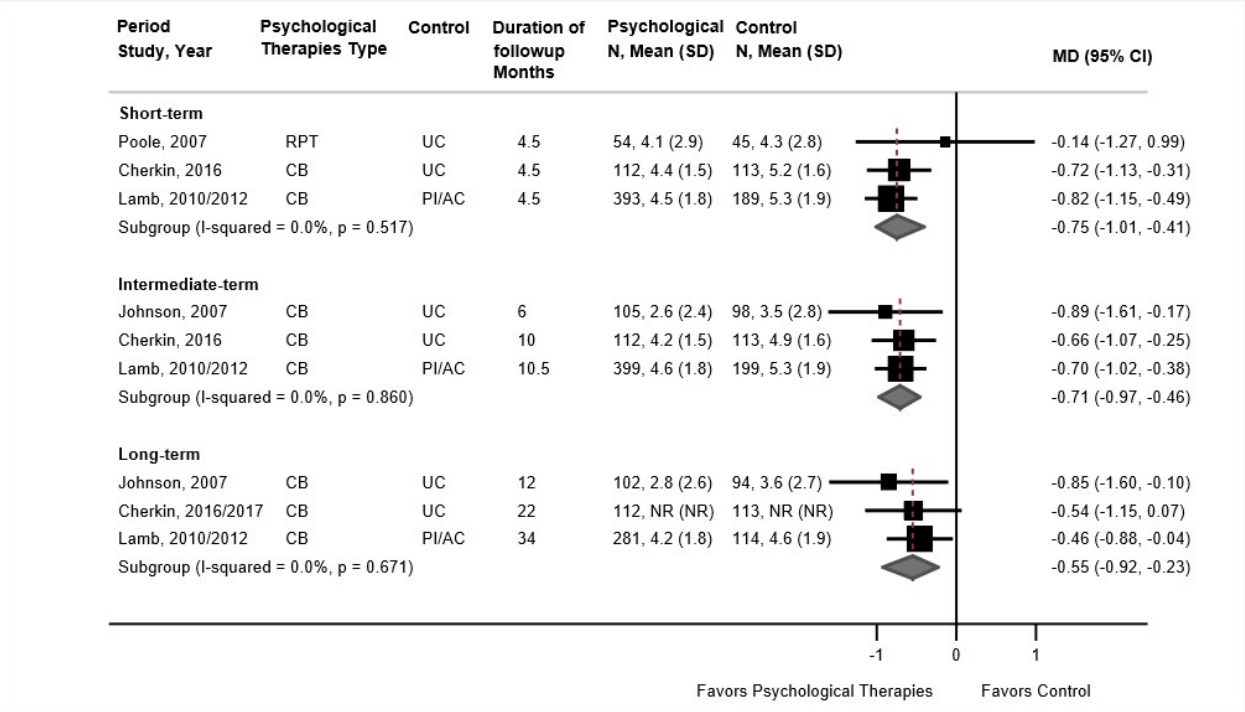
Data on harms were sparse. One trial of cognitive-behavioral therapy versus an attention control reported no serious adverse events and one withdrawal due to adverse events among 468 patients randomized to CBT.[106,107]

Figure 6. Psychological therapy versus usual care or an attention control for chronic low back pain: effects on function



AC = attention control; CB = cognitive-behavioral therapy; CI = confidence interval; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; ODI = Oswestry Disability Index; PI = placebo intervention; RDQ = Roland-Morris Disability Questionnaire; RPT = respondent therapy (progressive relaxation); SD = standard deviation; SMD = standardized mean difference; UC = usual care

Figure 7. Psychological therapy versus usual care or an attention control for chronic low back pain: effects on pain



AC = attention control; CB = cognitive-behavioral therapy; CI = confidence interval; N = number; PI = placebo intervention; RPT = respondent therapy (progressive relaxation); SD = standard deviation; UC = usual care.

Physical Modalities for Chronic Low Back Pain

Key Points

Ultrasound

- 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 trial found no differences between ultrasound versus sham ultrasound in risk of any adverse events or risk of serious adverse events (SOE: low).

Interferential Therapy

- 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).

Low-Level Laser Therapy

- One trial found low-level laser therapy associated with a small improvement compared with sham laser for short-term function (difference −8.2 on the 0 to 100 ODI, 95% CI −13.6 to −2.8) and a moderate improvement for short-term pain (difference −16.0 on a 0 to 100 scale, 95% CI −28.3 to −3.7) (SOE: low).

- One trial found no differences between low-level laser therapy versus exercise therapy in intermediate-term function or pain (SOE: low).
- One trial of low-level laser therapy reported no adverse events (SOE: low).

Traction

- Two trials found no differences between traction versus sham traction in short-term function or pain (SOE: low).
- Harms were not reported in either trial.

Short-Wave Diathermy

- Data from a small, poor-quality trial were insufficient to determine effects of short-wave diathermy versus sham (detuned) diathermy (SOE: insufficient).

Detailed Synthesis

Ultrasound

Two trials (n=50 and n=455) of ultrasound versus sham ultrasound for low back pain met inclusion criteria (Table 7 and Appendix D).[139,140] Both of the trials were included in the prior AHRQ report. The duration of ultrasound therapy was 4 and 8 weeks and the number of sessions was 6 and 10. Both trials evaluated outcomes at short-term (1 month) followup. One good-quality trial[140] was conducted in the United States and one fair-quality trial[139] in Iran (Appendix E). Methodological limitations in the fair-quality trial included failure to blind care providers and unclear blinding of outcome assessors.

Table 23. Chronic low back pain: physical modalities (ultrasound)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Ebadi, 2012[139] 1 month Duration of pain: Mean 6 to 8 years Fair	A. Ultrasound (n=25), 1.5 W/cm^2 at 1 MHz, 10 sessions over 4 weeks B. Sham ultrasound (n=25)	A vs. B Age: 31 vs. 37 years Female: 25% vs. 50% Functional Rating Index (mean, 0-100): 41 vs. 44 Pain intensity (mean, 0-100 VAS): 47 vs. 49	A vs. B <u>1 month</u> Functional Rating Index (0-40): 22.8 vs. 30.5; p=0.004 Pain (0-100 VAS): 27.7 vs. 25.5; p=0.48	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Licciardone, 2013[140] 3 months Proportion with LBP duration >1 year: 50% Good	A. Ultrasound (n=233), 1.2 W/cm^2 at 1 MHz, 6 sessions over 8 weeks B. Sham ultrasound (n=222)	A vs. B Age: 38 vs. 43 years Female: 58% vs. 68% RDQ (0-24): 5 vs. 5 Pain intensity (0-100 VAS): 44 vs. 44	A vs. B <u>1 month, median (IQR)</u> RDQ (0-24): 3 (1-7) vs. 3 (1-7); p=0.93 Pain improved ≥30%: RR 1.03 (95% CI 0.87 to 1.23) Pain improved ≥50%: RR 1.09 (95% CI 0.88 to 1.35) Pain improved ≥20 mm on 0 to 100 VAS): RR 1.01 (95% CI 0.80 to 1.26) <u>2 months</u> RDQ (0-24): 3 vs. 4; p=0.76 ≥50% improvement in pain: RR 1.09 (95% CI 0.88 to 1.35) <u>3 months</u> RDQ (0-24): 3 vs. 3; p=0.93	A vs. B <u>1 month</u> SF-36 general health (0-100): 72 (52-87) vs. 74 (54-87); p=0.6 Lost 1 or more days work in past 4 weeks because of low back pain: 13% vs. 6%, p=0.11 Prescription drug use for LBP: 16% vs. 18%, p=0.54 SF-36 general health (0-100): 72 (52-87) vs. 74 (54-87), p=0.73 <u>2 months</u> SF-36 general health (0-100): 72 vs.72 (57-85); p=0.53 ≥50% improvement in pain: RR 1.09 (95% CI 0.88 to 1.35) <u>3 months</u> SF-36 general health (0-100): 72 vs. 74, p=0.66

CI = confidence interval; IQR = inter-quartile range; LBP = low back pain; MHz = megahertz; NR = not reported; RDQ = Roland-Morris Disability Questionnaire; RR = relative risk; SF-36 = Short-Form 36 Questionnaire; VAS = visual analog scale; W/cm^2 = Watt per square centimeter

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Ultrasound Compared With Sham Ultrasound

Limited evidence indicated no clear differences between ultrasound versus sham ultrasound at short-term followup. One good-quality trial (n=455) found no difference between ultrasound versus sham ultrasound in the RDQ (median 3 vs. 3, p=0.93), likelihood for ≥50 percent improvement in pain (RR 1.09, 95% CI 0.88 to 1.35), SF-36 general health (median 72 vs. 74), likelihood of prescription drug use for low back pain (16% vs. 18%, p=0.54), or risk of serious adverse events (1.3% vs. 2.7%, RR 0.48, 95% CI 0.12 to 1.88) or any adverse event (6.0% vs. 5.9%, RR 1.03, 95% CI 0.49 to 2.13).[140] In the smaller (n=50) fair-quality trial, there was no difference between ultrasound versus sham ultrasound in pain (mean 27.7 vs. 25.5 on a 0 to 100 scale, p=0.48), although ultrasound was associated with better function (mean 22.8 vs. 30.5 on the 0 to 40 Functional Rating Index, p=0.004).[139] No trial evaluated longer-term outcomes.

Ultrasound Compared With Pharmacological Therapy or With Exercise

No trial of ultrasound versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

One trial found no differences between ultrasound versus sham ultrasound in risk of any adverse event (RR 1.03, 95% CI 0.49 to 2.13) or serious adverse event (RR 0.48, 95% CI 0.12 to 1.88).[140]

Interferential Therapy

One new trial (n=150)[144] of interferential therapy met inclusion criteria (Table 8 and Appendix D). It found small differences between 1 kHz or 4 kHz interferential therapy versus placebo therapy in the RDQ (differences 0.2 or 0.3 points) and pain (differences 0.2 or 0.4 points) at short-term followup; the statistical significance of findings was unclear due to errors in reporting of the confidence intervals (confidence intervals did not incorporate the point estimates). The trial was rated fair-quality due to the data discrepancies.

Interferential Therapy Compared With Pharmacological Therapy or With Exercise

No trial of interferential therapy versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

One trial found no differences between 1 kHz or 4 kHz interferential therapy versus placebo interferential current in withdrawals due to adverse event (4% vs. 4% vs. 4%, RR 1.0, 95% CI 0.14 to 6.8).[144]

Table 24. Chronic low back pain: physical modalities (interferential therapy)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Correa, 2016[144] 3 months Duration of pain: Mean 95.3 to 99.4 months Fair	All groups received: 3 sessions/week for 4 weeks (12 total sessions) A. 1 kHz Interferential current (n=50) B. 4 kHz Interferential current (n=50) C. Placebo interferential current (n=50)	A vs. B vs. C Age: 51 vs. 54 vs. 49 years Female: 70% vs. 80% vs. 80% Baseline RDQ (0-24): 13.3 vs. 14.2 vs. 15.1 Baseline NRS pain score in last 7 days (0-10): 7.5 vs. 7.5 vs. 7.4	A vs. C <u>3 months</u> RDQ: 9.0 vs. 10.3, adjusted difference 0.3 (CI unclear) [b] NRS at rest: 4.6 vs. 4.7, adjusted difference 0.4 (CI unclear) B vs. C <u>3 months</u> RDQ: 9.3 vs. 10.3, adjusted difference 0.2 (CI unclear) [b] NRS at rest: 4.4 vs. 4.7, adjusted difference 0.2 (CI unclear)	A vs. C <u>3 months</u> GPE: 1.7 (3.1) vs. 1.6 (3.1), adjusted difference 0.6 (CI unclear) Mean number of times that patients needed to take pain medication between treatment sessions: 12.5 (6.0) vs. 30.7 (15.2), p=0.01; difference –18.2 (95% CI –22.79 to –13.61) B vs. C <u>3 months</u> GPE: 1.8 (3.0) vs. 1.6 (3.1), adjusted difference 0.5 (CI unclear) Mean number of times that patients needed to take pain medication between treatment sessions: 13.1 (6.9) vs. 30.7 (15.2), p=0.014; difference -17.6 (95% CI -22.28 to -12.92)

CI = confidence interval; GPE= global perceived effect; kHz = kilohertz; NRS= Numerical Rating Scale, RDQ = Roland-Morris Disability Questionnaire

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] There appeared to be errors in reporting of the confidence intervals for this study since the confidence intervals did not include the point estimates.

Low-Level Laser Therapy

Three trials of low-level laser therapy (n=34, 56, and 71) met inclusion criteria (Table 9 and Appendix D).[141,142,170] All of the trials were included in the prior AHRQ report. One trial[142] evaluated neodymium:yttrium-aluminum-garnet (Nd:YAG) laser and two trials[141,170] evaluated gallium-arsenide (GaAs) laser. Two trials compared low-level laser therapy versus sham laser therapy[141,142] and one trial low-level laser therapy versus exercise plus sham laser.[170] One trial was conducted in the United States,[142] one in Iran,[170] and one in Argentina.[141] The duration of laser therapy ranged from 2 to 6 weeks and the number of sessions ranged from 10 to 12. One trial[141] reported intermediate-term outcomes and the other two trials reported short-term outcomes.

Two trials[142,170] were rated fair quality and one trial[141] poor quality (Appendix E). The major methodological limitation in the fair-quality trials was unclear allocation concealment methods.[142,170] The poor-quality trial also did not report randomization methods, did not conduct intention-to-treat analysis at intermediate-term followup, and reported high attrition; it was also unclear if timing of followup was the same in all patients.[141]

Table 25. Chronic low back pain: physical modalities (low-level laser therapy)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Basford, 1999[142] 2 months Duration of pain: 4.5 vs. 6.5 months Fair	A. Nd:YAG laser (542 mW/cm^2, 90 seconds, two sites, applied to eight points along L2 to S3 paraspinal tissues) (n=27) 12 sessions over 4 weeks B. Sham laser (n=29)	A vs. B Age: 48 vs.48 years Female: 40% vs. 55% Baseline ODI: 21 vs. 25 Baseline maximal pain, last 24 hours (0-100 VAS): 35.2 vs. 37.4	A vs. B <u>2 months</u> ODI (0-100): 14.7 vs. 22.9, difference -8.2 (95% CI −13.6 to −2.8); p=0.004 Maximal pain in last 24 hours (0-100 VAS): 19.1 vs. 35.1, difference −16.0 (95% CI −28.3 to −3.7); p=0.012	A vs. B <u>2 months</u> Patient perception of benefit (VAS, lower = less pain): 28.3 vs. 37.8 (95% CI −20.9 to 1.9); p=0.101
Djavid, 2007[170] 1.5 months Duration of pain: 29 months vs. 29 months vs. 25 months Fair	A. GaAs laser (wavelength 810 nm, 50 mW wave, and 0.2211 cm^2 spot area laser applied to 8 points along L2 to S2-S3 paraspinal tissues, dose 27 J/cm^2) (n=16) 12 sessions over 6 weeks B. Low-level laser therapy plus exercise (n=19) C. Exercise plus sham laser (strengthening, stretching, mobilizing, coordination) (n=18)	A vs. B vs. C Age: 40 vs. 38 vs. 36 years Female: 5% vs. 7% vs. 2% Baseline ODI (0-100): 33.0 vs. 31.8 Baseline pain (0-10 VAS): 7.3 vs. 6.3	A vs. C <u>1.5 months</u> ODI (0-100): 20.8 vs. 24.1, difference in change from baseline −4.4 (95% CI −11.4 to 2.5) Pain (0-10 VAS): 4.4 vs. 4.3, difference in change from baseline −0.9 (95% CI −2.5 to 0.7) A vs. B <u>1.5 months</u> ODI (0-100): 20.8 vs. 16.8 difference in change from baseline −4.4 (95% CI −11.4 to 2.5) Pain (0-10 VAS): 4.4 vs. 2.4, difference in change from baseline −0.9 (95% CI −2.5 to 0.7)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Soriano, 1998[141] 6 months Duration of pain: greater than 3 months Poor	A GaAs laser (wavelength 904 nm, pulse frequency 10,000 Hz, pulse width 200 nsec, peak power 20W, average power 40mW, administered at dose of 4 J/cm^2 per point to pain areas) (n=38) 10 sessions over 5 weeks B. Sham laser (n=33)	A vs. B Age: 63 vs. 64 years Female: 58% vs. 52% Baseline function: NR Baseline pain (1 to 10): 7.9 vs. 8.1	6 months No pain: 44.7% vs. 15%; p<0.01	Pain recurrence in subgroup of patients with a good or excellent response at end of treatment: 35 % vs. 70%; p=NR

CI =confidence interval; Hz = hertz; J/cm^2 = Joules per square centimeter; mW = megawatt; Nd:YAG = neodymium-doped yttrium aluminum garnet; NR = not reported; ODI = Oswestry Disability Index; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Low-Level Laser Therapy Compared With Sham Laser

One fair-quality trial found Nd:YAG laser therapy associated with moderate improvement in pain (difference −16.0 on a 0 to 100 scale, 95% CI −28.3 to −3.7) and a small improvement in function (difference −8.2 points on the 0 to 100 ODI, 95% CI −13.6 to −2.8) at short-term followup.[142] A poor-quality trial found GaAs laser therapy associated with increased likelihood of having no pain at intermediate-term followup (44.7% vs. 15%, p<0.01), but the analysis was restricted to patients who reported that laser therapy was effective at the end of a 2-week course of treatment.[141]

Low-Level Laser Therapy Compared With Pharmacological Therapy

No trial of low-level laser therapy compared with pharmacological therapy met inclusion criteria.

Low-Level Laser Therapy Compared With Exercise Therapy

One fair-quality trial found no clear differences between GaAs laser therapy versus exercise plus sham laser in function (difference in change from baseline −4.4 on the 0 to 100 ODI, 95% CI −11.4 to 2.5) or pain (difference in change from baseline −0.9 on a 0 to 10 scale, 95% CI −2.5 to 0.7) at intermediate-term followup.[170] For pain, the difference at followup was similar to the baseline difference (mean 7.3 vs. 6.3), and final scores were very similar (4.4 vs. 4.3).

Harms

No adverse events were reported in any of the three trials of low-level laser therapy.[141,142,170]

Traction

Two trials of traction (n=151 and 60) met inclusion criteria (Table 10 and Appendix D).[137,138] Both of the trials were included in the prior AHRQ report. One trial[137] evaluated continuous traction (12 sessions in 5 weeks) and the other[138] evaluated intermittent traction (20 sessions in 6 weeks). The comparator in both trials was sham traction (traction at <10% or 20% of body weight, compared with 35% to 50% for active traction). Both trials were conducted in the Netherlands and reported only short-term outcomes. The trials were rated fair quality due to failure to blind care providers (Appendix E).

Table 26. Chronic low back pain: physical modalities (traction)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Beurskens, 1997[137] 1.75 and 5 months Duration of pain: 1.5 months Fair	A. Continuous traction (n=77) B. Sham traction (20% body weight) (n=74) 12 sessions, 5 weeks	A vs. B Age: 39 vs. 42 years Female: 44% vs. 43% Baseline RDQ (0-24): 2 vs. 12 Baseline pain (0-100 VAS): 61 vs. 55	A vs. B <u>1.75 months</u> RDQ: 4.4 vs. 4.3, difference 0.1 (95% CI −1.8 to 1.9) Pain at the moment (0-100 VAS): 28.5 vs. 22.8, difference 5.7 (95% CI −4.6 to 15.9) <u>5 months</u> RDQ: 4.7 vs. 4.0, difference 0.7 (95% CI −1.1 to 2.6) Pain at the moment (0-100 VAS): 23.8 vs. 20.1, difference 3.7 (95% CI −8.4 to 15.8)	A vs. B <u>1.75 months</u> ADL disability (0 to 100 VAS): 27.1 vs. 29.4, difference −2.4 (95% CI −13.6 to 8.9) Work absence (days): 23.5 vs. 27.8, difference −4.3 (95% CI −14.7 to 6.1) Medical consumption: 34% vs. 25%, difference 9% (95% CI −6 to 24) <u>5 months</u> ADL disability: 25.7 vs. 25.8, difference 0.1 (95% CI −11.5.0 to 11.2) Work absence (days): 35.7 vs. 43.7, difference −8.0 (95% CI −27 to 11) Medical consumption: 45% vs. 42%, difference 3% (95% CI −13% to 19%)
Schimmel, 2009[138] 2 months Duration of pain: 1 year Fair	A. Intermittent traction (n=31) B. Sham traction (<10% body weight) (n=29) 20 sessions, 6 weeks	A vs. B Age (mean): 42 vs. 46 years Female: 39% vs. 52% Baseline ODI: 36 vs. 33 Baseline back pain (0-100 VAS): 61 vs. 53	A vs. B <u>2 months</u> ODI (0-100): 25 vs. 23 (SD, P not reported) Pain (0-100 VAS): 32 vs. 36; p=0.70	A vs. B <u>2 months</u> SF-36, total (0-100): 66 vs. 65 (SD, p-value not reported)

ADL = activities of daily living; CI = confidence interval; ODI = Oswestry Disability Index; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SF-36 =Short-Form 36 Questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Traction Compared With Sham Traction

There were no differences between traction versus sham traction at short-term followup in function (25 vs. 23 on the 0 to 100 ODI in one trial and 4.7 vs. 4.0 on the 0 to 24 RDQ, difference 0.7, 95% CI −1.1 to 2.6) or pain (32 vs. 36 on a 0 to 100 scale, p=0.70 and 24 vs. 20, difference 3.7, 95% CI −8.4 to 15.8).[137,138] One trial[138] also found no difference between intermittent traction versus sham on the total SF-36 (66 vs. 65 on a 0 to 100 scale) and one trial[137] found no difference between continuous traction versus sham in global perceived effect, work absence, or medical consumption.

Traction Compared With Pharmacological Therapy or With Exercise

No trial of low-level laser therapy compared with pharmacological therapy or with exercise met inclusion criteria.

Harms

Neither trial reported harms.

Short-Wave Diathermy

Data were insufficient from one poor-quality trial (n=68) to evaluate effects of short-wave diathermy (3 times weekly for 4 weeks) versus sham (detuned) diathermy for low back pain (Table11 and Appendix D).[143] The trial was included in the prior AHRQ report. Methodological limitations included unclear randomization and allocation concealment methods, differential attrition, and baseline differences between groups (Appendix E). Although diathermy was associated with worse pain than sham treatment at short-term (8 weeks after completion of therapy) followup (25 vs. 13), statistical significance was not reported. There were no statistically significant differences in likelihood of using analgesics (7% vs. 22%, RR 0.34, 95% CI 0.08 to 1.50) or being unable to work or having limited activities (7% vs. 19%, RR 0.40, 95% CI 0.09 to 1.80), but estimates were imprecise.

Harms

Adverse events were not evaluated in the trial.

Table 27. Chronic low back pain: physical modalities (short-wave diathermy)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Gibson, 1985[143] 2 months Duration of pain: 2 to 12 months Poor	A. Short wave diathermy (active SWD) (n=34), 12 sessions, 3 session/per week for 4 weeks B. Placebo (detuned SWD) (n=34)	A vs. B Age: 35 vs. 40 years Female: 47% vs. 32% Pain (0-100 VAS): 45 vs. 48	A vs. B <u>2 months</u> Pain (0-100 VAS, median): 25 vs. 13 (IQR not reported) Unable to work or with limited activities: 7% vs. 19% RR 0.40, 95% CI 0.09 to 1.80	A vs. B <u>2 months</u> Using analgesics: 7% vs. 22%, RR 0.34, 95% CI 0.08 to 1.50

CI = confidence interval; IQR = interquartile range; RR = relative risk; SWD = short wave diathermy; VAS = visual analog scale
[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Manual Therapies for Chronic Low Back Pain

Key Points

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 function (3 trials, pooled SMD −0.34, 95% CI −0.75 to −0.02, I^2=45%) and intermediate-term function (3 trials, pooled SMD −0.40, 95% CI −0.85 to −0.05, I^2=65%) (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, pooled difference −0.36 on a 0 to 10 scale, 95% CI −0.62 to 0.25, I^2=0%), but manipulation was

associated with a small improvement compared with controls on intermediate-term pain (3 trials, pooled difference −0.64, 95% CI −0.93 to −0.35, I^2=0%) (SOE: low for short term, moderate for intermediate term).

- There were no differences between spinal manipulation versus exercise in short-term function (3 trials, pooled SMD 0.02, 95% CI −0.28 to 0.30; I^2=37%) or intermediate-term function (4 trials, pooled SMD 0.01, 95% CI −0.15 to 0.21; I^2=19%) (SOE: low).
- There were no differences between spinal manipulation versus exercise in short-term pain (3 trials, pooled difference 0.31 on a 0 to 10 scale, 95% CI −0.42 to 1.06; I^2=34%) or intermediate-term pain (4 trials, pooled difference 0.23, 95% CI −0.14 to 0.59, I^2=0%) (SOE: low).
- No serious adverse events or withdrawals due to adverse events were reported in seven trials; nonserious adverse events with manipulation (primarily increased pain) were reported in three trials (SOE: low).

Massage

- Massage was associated with small improvements in short-term function compared with sham massage or usual care (6 trials [2 new], SMD −0.38, 95% CI −0.63 to −0.20, I^2=0%). There were no differences between massage versus controls in intermediate-term function (3 trials, SMD −0.09, 95% CI −0.26 to 0.12, I^2=0%) (SOE: moderate for short term, low for intermediate term).
- Massage was associated with a small improvement in short-term pain compared with sham massage or usual care (5 trials [1 new], pooled difference −0.55 on a 0 to 10 scale, 95% CI −0.88 to −0.23, I^2=0%). There was no difference between massage versus controls in intermediate-term pain (3 trials, pooled difference −0.02, 95% CI −0.56 to 0.44, I^2=0%) (SOE: moderate for short term, low for intermediate term).
- One trial found no differences between massage versus exercise in intermediate-term function or pain (SOE: low).
- Four trials of massage reported no serious adverse events; in four trials, the proportion of massage patients who reported increased pain ranged from <1 to 26 percent (SOE: low).

Detailed Synthesis

Spinal Manipulation

Eight trials of spinal manipulation for low back pain met inclusion criteria (Table 12 and Appendix D).[143,171-174,190-192] All of the trials were included in the prior AHRQ report. All of the trials evaluated standard (high-velocity low-amplitude) manipulation techniques; one trial[192] evaluated flexion-distraction manipulation and one trial[172] evaluated both high-velocity low-amplitude and flexion-distraction manipulation. Sample sizes ranged from 75 to 1,001 (total sample=2,580). The number of manipulation therapy sessions ranged from 4 to 24 and the duration of therapy ranged from 4 to 12 weeks. In one trial, patients were randomized to 12 manipulation sessions over 1 month or to 12 sessions over 1 month plus biweekly maintenance sessions for an additional 10 months.[173] Two trials compared spinal manipulation versus usual care,[172,174] one trial spinal manipulation versus an attention control (minimal massage),[171] one trial spinal manipulation versus sham manipulation,[173] one trial spinal manipulation versus a placebo treatment (sham short-wave diathermy),[143] and four trials spinal manipulation versus exercise.[174,190-192] One trial was conducted in Egypt[173] and the rest in the United States, United

Kingdom, or Australia. Six trials reported outcomes through intermediate-term followup[171,173,174,190-192] and two trials only evaluated short-term outcomes.[143,172]

Two trials[143,173] were rated poor quality and the remainder fair quality (Appendix E). The major methodological limitation in the fair-quality trials was use of an unblinded design. Methodological shortcomings in the poor-quality trials included unclear randomization and allocation concealment methods, failure to report intention-to-treat analysis, and high attrition.

Table 28. Chronic low back pain: manual therapies (spinal manipulation)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bronfort, 2011[190] 9 months Duration of pain: 5 years Fair	A. Standard manipulation (n=100), 12-24 sessions over 12 weeks B. Exercise (supervised) (n=100) C. Exercise (home) (n=101)	A vs. B Age: 45.2 vs. 44.5 vs. 45.6 years Female sex: 67% vs. 57% vs. 58% Baseline Modified RDQ (0-23): 8.7 vs. 8.4 vs. 8.7 Baseline pain (0-10 NRS): 5.4 vs. 5.1 vs. 5.2	A vs. B <u>4 months</u> Modified RDQ (0-23): 4.9 vs. 4.0 vs. 4.2, adjusted difference 0.5 (95% CI −1.0 to 2.1) for A vs. B and 0.7 (95% CI −0.9 to 2.3) for A vs. C Pain (0-10 NRS): 3.3 vs. 2.9 vs. 3.1, adjusted difference 0.3 (95% CI −0.5 to 1.0) for A vs. B and 0.1 (95% CI −0.6 to 0.9) for A vs. C <u>9 months</u> Modified RDQ (0-23): 5.1 vs. 3.8 vs. 4.1, adjusted difference 0.4 (95% CI −1.2 to 2.0) for A vs. B and −0.1 (95% CI −0.7 to 0.5) for A vs. C Pain (0-10 NRS): 3.3 vs. 2.8 vs. 2.8, adjusted difference 0.3 (95% CI −0.5 to 1.1) for A vs. B and 0.3 (95% CI −0.6 to 1.1) for A vs. C	A vs. B <u>4 months</u> SF-36 PCS (norm-based mean=50): 48.6 vs. 50.6 vs. 49.1, adjusted difference −1.8 (95% CI −4.4 to 0.9) for A vs. B and −0.3 (95% CI −3.0 to 2.4) for A vs. C SF-36 MCS (norm-based mean=50): 55.9 vs. 54.8 vs. 55.1, adjusted difference 0.4 (95% CI −2.0 to 2.9) for A vs. B and −0.5 (95% CI −3.0 to 2.1) for A vs. C OTC pain medication use, past week (days): 1.6 vs. 1.4 vs. 1.5, adjusted difference 0.4 (95% CI −0.4 to 1.1) for A vs. B and 0.4 (95% CI −0.3 to 1.2) for A vs. C <u>9 months</u> SF-36 PCS (norm-based mean=50): 48.4 vs. 50.4 vs. 49.6, adjusted difference −1.7 (95% CI −4.2 to 0.8) for A vs. B and −1.0 (95% CI −3.5 to 1.5) for A vs. C SF-36 MCS (norm-based mean=50): 55.2 vs. 53.9 (8.6) vs. 56.0, adjusted difference 2.4 (95% CI −0.2 to 5.0) for A vs. B and −2.2 (95% CI −4.9 to 0.5) for A vs. C OTC pain medication use, past week (days): 1.8 vs. 1.8 vs. 1.6, adjusted difference 0.1 (95% CI −0.8 to 0.9) for A vs. B and 0.4 (95% CI −0.4 to 1.3) for A vs. C

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Ferreira, 2007[191] 10 months Duration of pain: Not reported Fair	A. Standard manipulation and mobilization (n=80), 12 sessions over 8 weeks B. Exercise (motor control) (n=80) C: Exercise (general exercise) (n=80)	A vs. B vs. C Age: 54 vs. 52 vs. 55 years Female: 70 % vs. 66% vs. 70% Baseline RDQ (0-24): 12.4 vs. 14.0 vs. 14.1 Baseline pain (0-10 VAS): 6.2 vs. 6.3 vs. 6.5	A vs. B vs. C <u>4 months</u> RDQ (0-24): 7.7 vs. 8.4 vs. 10.1, difference 0.2 (95% CI −1.5 to 1.9) for A vs. B and −0.9 (95% CI −2.7 to 0.9) for A vs. C Pain (0-10 VAS): 4.3 vs. 4.3 vs. 4.8, difference 0.0 (95% CI −0.9 to 0.8) for A vs. B and −0.5 (95% CI −1.4 to 0.3) for A vs. C <u>10 months</u> RDQ (0-24): 9.2 vs. 8.8 vs. 9.6, difference 1.8 (95% CI 0.0 to 3.6) for A vs. B and 1.2 (95% CI −0.6 to 3.0) for A vs. C Pain (0-10 VAS): 4.9 vs. 4.9 vs. 5.2, difference 0.1 (95% CI −0.8 to 1.0) for A vs. B and −0.2 (95% CI −1.1 to 0.6) for A vs. C	A vs. B vs. C <u>4 months</u> Patient Specific Functional Scale (3-30): 17.3 vs. 16.4 vs. 15.0, difference 0.7 (95% CI −1.3 to 2.7) for A vs. B and 1.7 (95% CI −0.4 to 3.,8) for A vs. C <u>10 months</u> Patient Specific Functional Scale (3-30): 15.2 vs. 15.7 (6.8) vs. 13.9, difference −0.8 (95% CI −2.9 to 1.2) for A vs. B and 0.3 (95% CI −1.7 to 2.3) for A vs. C
Gibson, 1985[143] 2 months Duration of pain: 2 to 12 months Poor	A. Manipulation (technique unclear) and mobilization (n=41), 4 sessions over 4 weeks B. Placebo (detuned short-wave diathermy) (n=34)	A vs. B 34 vs. 40 years Female: 61% vs. 32% Baseline pain (0-100 VAS): 35 vs. 48	A vs. B <u>1 month</u> Pain (median [range], 0-100 VAS): 28 (0−96) vs. 27(0-80) <u>3 months</u> Pain (median [range], 0-100 VAS): 25 (4-90) vs. 6 (10-96) p<0.01	A vs. B <u>1 month</u> Using analgesics: 25% vs. 50% <u>3 months</u> Using analgesics: 18% vs. 22%
Gudavalli, 2006[192] 11 months Duration of pain: >3 months Fair	A. Flexion–distraction manipulation (n=123), 8-16 sessions over 4 weeks B. Exercise (n=112)	A vs. B Age: 42 vs. 41 years Female: 34% vs. 41% Baseline RDQ (0-24): 6.64 vs. 6.84 Baseline pain VAS (0-100: 38.00 vs. 35.70	A vs. B <u>2 months</u> RDQ (0-24): 3.50 vs. 3.75 Pain (0-100 VAS): 16.52 vs.12.04 <u>5 months</u> RDQ (0-24): 3.89 vs. 3.42 Pain (0-100 VAS): 18.26 vs. 8.92 <u>11 months</u> RDQ (0-24): 3.90 vs. 3.77 Pain (0-100 VAS): 17.10 vs. 12.36	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Haas, 2014[171] 10.5 months Duration of pain: 11 to 12 years Fair	A. Standard spinal manipulation (n=100), 6 sessions over 6 weeks B. Standard manipulation (n=100), 12 sessions over 6 weeks C. Standard manipulation (n=100), 18 sessions over 6 weeks D: Attention control (minimal massage) (n=100)	A vs. B vs. C vs. D Age: 41 vs. 42 vs. 41 vs. 41 Female: 49% vs. 49% vs. 52% vs. 49% Baseline Modified Von Korff functional disability (0–100): 44.8 vs.46.1 vs.45.2 vs. 45.2 Baseline Pain (0–100 VAS): 51.0 vs. 51.6 vs. 51. vs. 52.2 Baseline Von Korff pain intensity (0–100): 51.0 vs. 51.6 vs. 51.5 vs. 52.2	A vs. B <u>4 months</u> Von Korff functional disability (0-100): 25.6 vs. 24.0 vs. 24.1 vs. 27.1, adjusted difference −1.4 (95% CI −7.2 to 4.5) for A vs. D, −3.4 (95% CI −9.3 to 2.4) for B vs. D, and −2.9 (95% CI −8.8 to 2.9) for C vs. D Von Korff functional disability improved ≥50%: 51.5% vs. 59.8% vs. 54.0% vs. 49.5%, adjusted difference 2.5% (95% CI −11.5 to 16.5%) for A vs. D, 10.4% (95% CI −3.4 to 24.3%) for B vs. D, and 4.8% (95% CI −9.1 to 18.6%) for C vs. D Von Korff pain intensity (0-100): 32.5 vs. 33.7 vs. 32.1 vs. 34.9, adjusted difference −1.7 (95% CI −6.9 to 3.4) for A vs. D, −0.8 (95% CI −6.0 to 4.4) for B vs. D, and −2.4 (95% CI −7.6 to 2.9) for C vs. D <u>10.5 months</u> Von Korff functional disability (0-100): 22.6 vs. 22.4 vs. 19.1 vs. 28.0, adjusted difference −5.2 (95% CI −10.9 to 0.5) for A vs. D, −5.9 (95% CI −11.8 to −0.1) for B vs. D, and −8.8 (95% CI −14.4 to −3.3) for C vs. D Von Korff functional disability improved ≥50%: 57.6% vs. 57.7% vs. 62.0% vs. 58.9%, adjusted difference −1.1% (95% CI −14.8 to 12.6%) for A vs. D, −1.4% (95% CI −15.4 to 12.6%) for B vs. D, and 2.7% (95% CI −11.0 to 16.5%) for C vs. D Von Korff pain intensity (0-100): 30.7 vs. 31.9 (vs. 28.7 vs. 36.5, adjusted difference −5.4 (95% CI −11.1 to 0.4) for A vs. D, −4.6 (95% CI −10.3 to 1.2) for B vs. D, and −7.6 (95% CI −13.2 to −2.0) for C vs. D	A vs. B <u>4 months</u> SF-12 PCS (norm-based mean=50): 50.5 vs. 51.4 vs. 50.9 vs. 50.0, adjusted difference 0.0 (95% CI −2.4 to 2.3) for A vs. D, −0.8 (95% CI −3.2 to 1.6) for B vs. C, and −1.3 (95% CI −3.6 to 1.1) for C vs. D SF-12 MCS (norm-based mean=50): 52.8 vs. 50.8 vs. 51.3 vs. 51.8, adjusted difference −2.1 (95% CI −4.2 to 0.0) for A vs. D, −0.7 (95% CI −2.8 to 1.3) for B vs. D, and −0.1 (95% CI −2.2 to 2.1) for C vs. D EuroQoL (0-100): 77.8 vs. 77.0 vs. 74.5 vs. 73.9, difference −2.9 (95% CI −6.9 to 1.0) for A vs. D, −1.4 (95% CI −5.5 to 2.6) for B vs. D, and −1.5 (95% CI −5.8 to 2.7) for C vs. D <u>10.5 months</u> SF-12 PCS (norm-based mean=50): 50.8 vs. 52.6 vs. 52.5 vs. 50.7, adjusted difference −0.3 (95% CI −2.1 to 2.7) for A vs. D, −1.4 (95% CI −4.0 to 1.2) for B vs. D, and −2.2 (95% CI −4.5 to 0.2) for C vs. D SF-12 MCS (norm-based mean=50): 50.4 vs. 50.6 vs. 50.4 vs. 51.3, adjusted difference −0.2 (95% CI −2.7 to 2.3) for A vs. D, −1.1 (95% CI −3.7 to 1.6) for B vs. D, and 0.3 (95% CI −2.3 to 2.9) for C vs. D EuroQoL (0-100): 77.1 vs. 77.3 vs. 77.2 vs. 74.8, adjusted difference −1.3 (95% CI −5.4 to 2.7) for A vs. D, −0.9 (95% CI −4.9 to 3.1) for B vs. D, and −3.3 (95% CI −7.2 to 0.5) for C vs. D

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Hondras, 2009[172] 4.5 months Duration of pain: Mean 9 to 13 years Fair	A. Standard manipulation (n=96), 12 sessions over 6 weeks B. Flexion distraction manipulation (n=95), 12 sessions over 6 weeks C: Usual care (n=49)	A vs. B vs. C Age: 64 vs. 62 vs. 63 years Female: 45% vs. 44% vs. 41% Baseline RDQ (0-24), mean: 6.5 vs. 6.6 vs. 5.7 Baseline pain (0-100 VAS): 42.1 (23.6) vs. 42.5 (25.2) vs. 42.4 (24.5)	<u>1.5 months</u> RDQ (0-24): adjusted difference −1.5 (95% CI −3.1 to 0.1) for A vs. C and −2.2 (95% CI −3.7 to −0.6) for B vs. C Global improvement from baseline (1-10): adjusted difference 1.3 (95% CI 0.2 to 2.3) for A vs. C and 1.6 (95% CI 0.5 to 2.7) for B vs. C <u>4.5 months</u> RDQ (0-24): adjusted difference −1.3 (95% CI −2.9 to 0.6) for A vs. C and −1.9 (95% CI −3.6 to −0.2) for B vs. C Global improvement from baseline (1-10): adjusted difference 1.7 (95% CI 0.5 to 2.8) for A vs. C and 1.8 (95% CI 0.6 to 3.0) for B vs. C	NR
Senna, 2011[173] 9 months Duration of pain: 18-19 months Poor	A. Standard manipulation (n=25), 12 sessions over 4 weeks B. Standard manipulation maintained (n=26) , 12 sessions over 4 weeks, plus every 2 weeks for 9 months C. Sham manipulation (n=37)	A vs. B Age: 40 vs. 42 vs. 42 years Female: 27% vs. 24% vs. 24% Baseline function (0-100 ODI): 39 vs. 40 vs. 38 Baseline pain (0-100 VAS): 42 vs. 43 vs. 41	A vs. B <u>3 months</u> ODI (0-100): 29.8 vs. 23.1 vs. 33.5; p>0.05 Pain (0-100 VAS): 35.2 vs. 25.9 vs. 35.2; p>0.05 <u>6 months</u> ODI (0-100): 32.2 vs. 22.4 vs. 35.3; p>0.05 Pain (0-100 VAS): 35.5 vs. 25.4 vs. 36.8; p>0.05 <u>9 months</u> ODI (0-100): 34.9 vs. 20.6 vs. 37.4 Pain (0-100 VAS): 38.5 vs. 23.5 vs. 38.3	A vs. B <u>3 months</u> SF-36, total (0-100): 29.2 vs. 32.8 vs. 26.4; p>0.05 <u>6 months</u> SF-36, total (0-100): 27.8 vs. 33.1 vs. 26.1; p>0.05 <u>9 months</u> SF-36, total (0-100): 27.6 vs. 33.70 vs. 25.9; p>0.05

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
UK BEAM Trial Team, 2004[174] 9 months Duration of pain: >3 months in 59% Fair	A: Standard manipulation (n=353), 8 sessions over 12 weeks B: Usual care (n=338) C: Exercise (n=310)	A vs. B vs. C Age: 42 vs. 42 vs. 44 Female: 63% vs. 53% vs. 55% Baseline RDQ (0-24): 8.9 and 8.9 vs. 9.0 vs. 9.2 Baseline Von Korff Pain (0-100): 61.4 and 61.6 vs. 60.5 vs. 60.8	A vs. B 9 months RDQ (0-24): 5.15 vs. 6.16, adjusted difference −1.01 (95% CI −1.81 to −0.22) Von Korff Disability (0-100): 29.85 vs. 35.50, adjusted difference −5.65 (95% CI −9.72 to −1.57) Von Korff Pain (0-100): 41.68 vs. 47.56, adjusted difference −5.87 (95% CI −10.17 to −1.58) A vs. C 9 months RDQ (0-24): 5.15 (0.29) vs. 5.74 (0.31) Von Korff Disability (0-100): 29.85 (1.50) vs. 29.73 (1.68) Von Korff Pain (0-100): 41.68 (1.58) vs. 41.54 (1.84)	A vs. B 9 months SF-36 PCS (0-100): 44.18 vs. 42.50, adjusted difference 1.68 (95% CI 0.18 to 3.19) SF-36 MCS (0-100): 48.09 vs. 46.41, adjusted difference 1.68 (95% CI −0.21 to 3.57) A vs. C 9 months SF-36 PCS (0-100): 44.18 (0.55) vs. 44.39 (0.63) SF-36 MCS (0-100): 48.09 (0.69) vs. 46.77 (0.81)

CI = confidence interval; MCS = Mental Component Summary; NR = not reported; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; OTC = over-the-counter; PCS = Physical Component Score; RDQ = Roland-Morris Disability Questionnaire; SF-12 = Short-Form 12 Questionnaire; SF-36 = Short-Form 36 Questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Spinal Manipulation Compared With Sham Manipulation, Usual Care, an Attention Control, or a Placebo Intervention

Spinal manipulation was associated with small improvements in function compared with controls at short-term followup (3 trials, SMD −0.34, 95% CI −0.75 to −0.02, I^2=45%)[171-173] and intermediate-term followup (3 trials, SMD −0.40, 95% CI −0.85 to −0.05, I^2=65%)[171,173,174] (Figure 8). Based on the original 0 to 100 scales (ODI and Von Korff functional disability [VF]) used in two trials, the pooled difference was −5.12 (95% CI −10.53 to 0.77) for short-term function and −9.27 (95% CI −13.42 to −5.12) for intermediate-term function. Estimates were similar when a poor-quality trial[173] was excluded. For short-term function, one trial reported similar effects for standard manipulation (difference −1.3 on the RDQ, 95% CI −2.9 to 0.6) and flexion-distraction manipulation (difference −1.9, 95% CI −3.6 to −0.2); therefore, results for both arms were combined for the pooled analysis.[172]

There was no clear difference between spinal manipulation versus sham manipulation, an attention control, or a placebo intervention in short-term pain (3 trials, pooled difference −0.36 on a 0 to 10 scale, 95% CI −0.62 to 0.25, I^2=0%) (Figure 9).[143,171,173] Two of the trials were rated poor quality; the results of the fair-quality trial[171] were consistent with the overall estimate (difference −0.21, 95% CI −0.69 to 0.26). Manipulation was associated with a small improvement in intermediate-term pain compared with sham manipulation, usual care, or an attention control (3 trials, pooled difference −0.64 on a 0 to 10 scale, 95% CI −0.93 to −0.35, I^2=0%).[171,173,174] The estimate was similar when a poor-quality trial[173] was excluded (2 trials, difference −0.60, 95% CI −0.98 to −0.21).[171,174]

Two trials found no differences between spinal manipulation versus controls on the SF-36 MCS and PCS.[171,174] One trial[171] found no differences in short-term PCS (mean difference 0.94

on a 0 to 100 scale, 95% CI −1.55 to 3.42) or MCS scores (mean difference −0.17 on a 0 to 100 scale, 95% CI −2.70 to 2.36) at short-term followup. At intermediate-term followup, pooled differences were also very small and not statistically significant for the PCS (2 trials, mean difference 1.54, 95% CI −0.03 to 3.10, I^2=0%) or the MCS (2 trials, mean difference 0.52, 95% CI −1.94 to 2.97, I^2=44%).[171,174]

Spinal Manipulation Compared With Pharmacological Therapy

No trial of spinal manipulation versus pharmacological therapy met inclusion criteria.

Spinal Manipulation Compared With Exercise

There were no differences between spinal manipulation versus exercise in function at short-term (3 trials, SMD 0.02, 95% CI −0.28 to 0.30, I^2=37%)[190-192] or intermediate-term followup (4 trials, SMD 0.01, 95% CI −0.15 to 0.21, I^2=19%)[174,190-192] (Figure 10). Excluding one trial[192] of flexion-distraction manipulation resulted in similar findings.

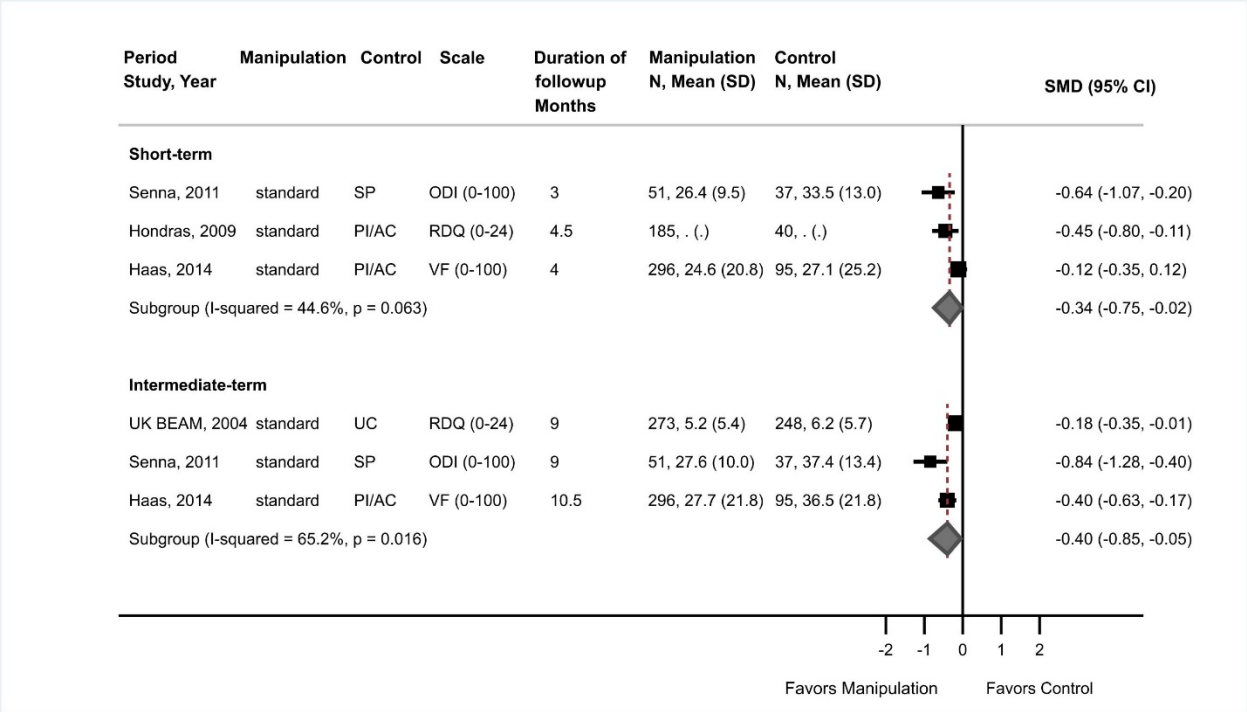
There were no differences between spinal manipulation versus exercise in short-term pain (3 trials, pooled difference 0.31, 95% CI −0.42 to 1.06, I^2=34%)[190-192] or intermediate-term pain (4 trials, pooled difference 0.23, 95% CI −0.14 to 0.59, I^2=0%) (Figure 11).[174,190-192] Excluding one trial[192] of flexion-distraction manipulation resulted in similar findings.

Two trials found no differences between spinal manipulation versus controls on the SF-36 MCS and PCS.[174,190] One trial found no differences in short-term PCS (mean difference −1.25 on a 0 to 100 scale, 95% CI −3.32 to 0.83) or MCS scores (mean difference 0.95, 95% CI −0.96 to 2.86).[190] At intermediate-term followup, pooled differences were also very small (<1 point) and not statistically significant for the PCS (2 trials, mean difference −0.89, 95% CI −2.33 to 0.55, I^2=0%) or the MCS (2 trials, mean difference 0.64, 95% CI −0.96 to 2.24).[174,190]

Harms

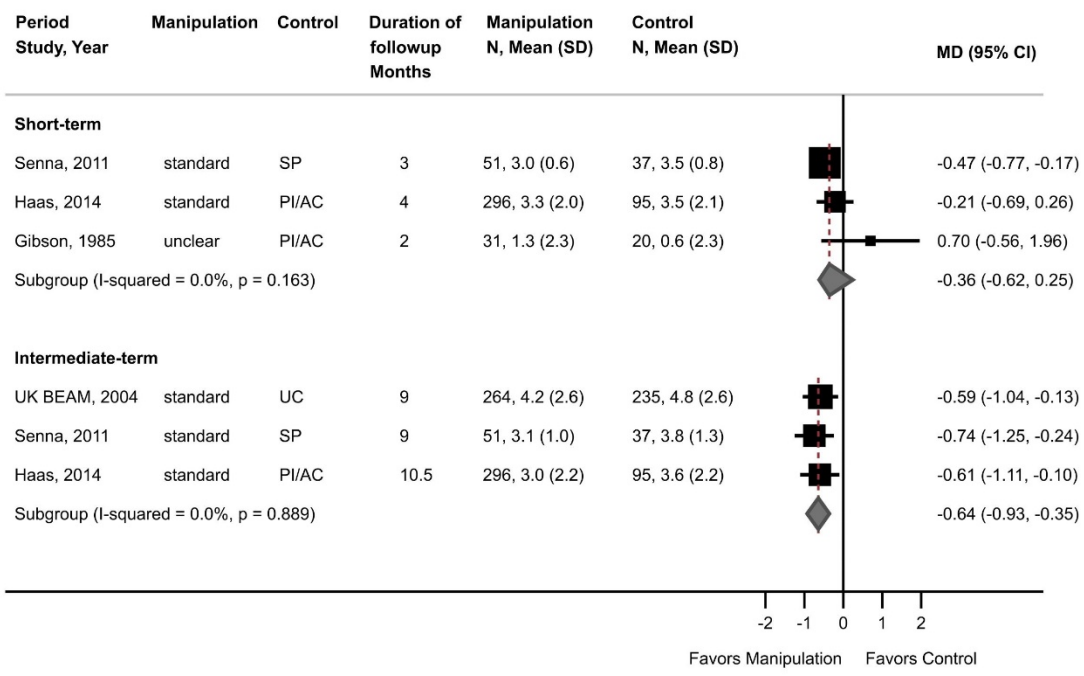
Seven trials of spinal manipulation reported no serious adverse events or withdrawals due to adverse events.[171-174,190-192] Nonserious adverse events (primarily increased pain) were reported in three trials.[171,173,190]

Figure 8. Spinal manipulation versus sham manipulation, usual care, an attention control, or a placebo intervention for chronic low back pain: effects on function



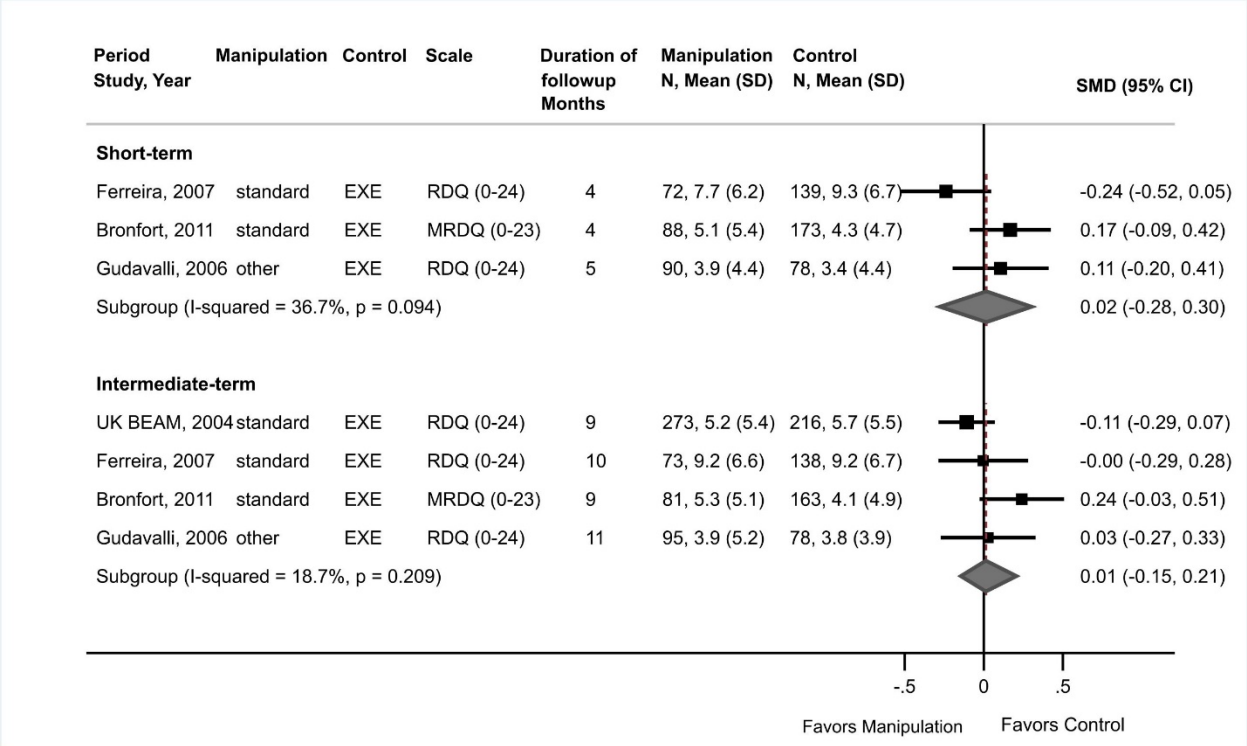
AC = attention control; CI = confidence interval; N = number; ODI = Oswestry Disability Index; PI = placebo intervention; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; SP= sham manipulation; UC = usual care; UK BEAM = UK Back pain exercise and manipulation trial; VF = Von Korff functional disability

Figure 9. Spinal manipulation versus sham manipulation, usual care, an attention control, or a placebo intervention for chronic low back pain: effects on pain



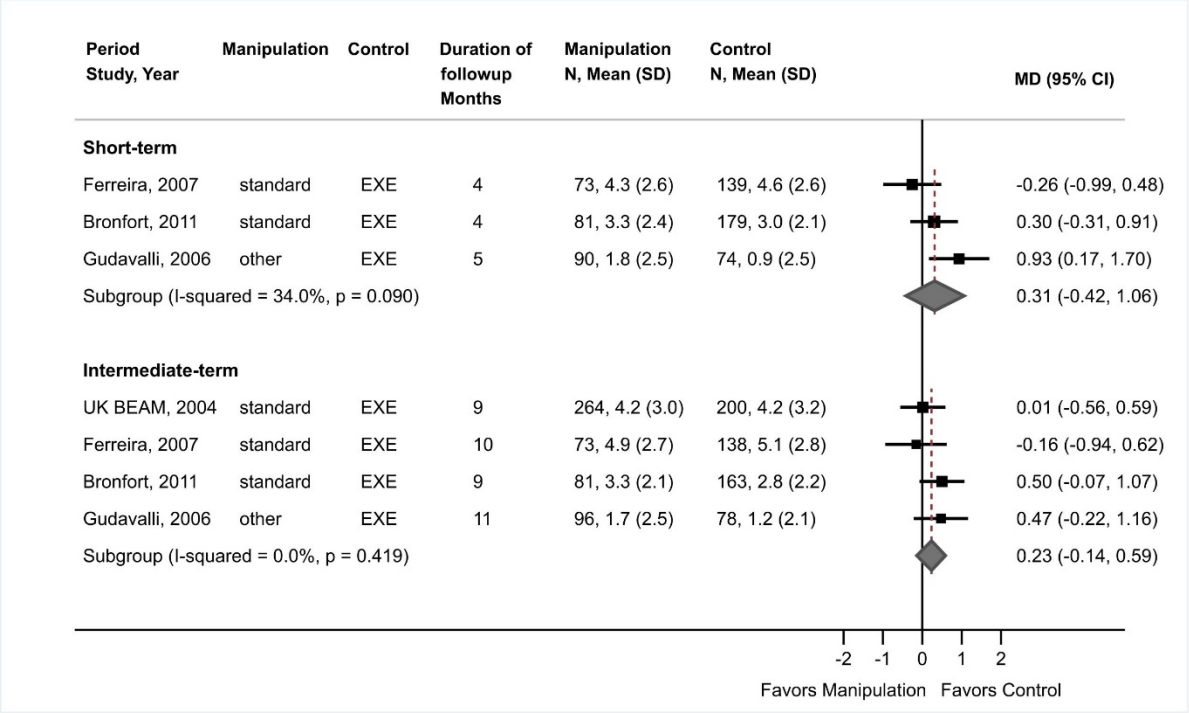
AC = attention control; CI = confidence interval; N = number; PI = placebo intervention; SD = standard deviation; SP = sham manipulation; UC = usual care; UK BEAM = UK Back pain exercise and manipulation trial

Figure 10. Spinal manipulation versus exercise for chronic low back pain: effects on function



CI = confidence interval; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; UK BEAM = UK Back pain exercise and manipulation trial

Figure 11. Spinal manipulation versus exercise for chronic low back pain: effects on pain



CI = confidence interval; EXE = exercise; N = number; SD = standard deviation; UK BEAM = UK Back pain exercise and manipulation trial

Massage

Eight trials of massage for low back pain met inclusion criteria (Table 13 and Appendix D).[108,175-180,189] Six trials[108,175-178,189] were included in the prior AHRQ report and two new trials[179,180] were identified for this update. Massage techniques varied across trials. Two trials evaluated reflexology,[108,178] two trials (one new) myofascial release,[175,179] one trial relaxation or structural massage,[177] one trial (new) acupressure[180] and two trials mixed massage techniques that included Swedish massage.[176,189] Sample sizes ranged from 15 to 401 (total sample=1,133). Two trials compared massage versus sham massage,[175,178] three trials massage versus usual care,[108,177,189] and one trial compared massage versus an attention control (self-care education).[176] Two new trials compared the intervention to sham, one new trial compared acupressure to sham acupressure,[180] and one new trial compared myofascial release to sham myofascial release.[179] One trial was conducted in India,[175] one trial in Iran,[180] and the rest in the United States or Europe. The duration of massage therapy ranged from 2 to 10 weeks and the number of massage sessions ranged from 4 to 24. Three trials reported outcomes through intermediate-term followup,[176,177,189] and five only reported short-term outcomes.[108,175,178-180] No trial reported long-term outcomes.

Seven of the massage trials were rated fair-quality[108,175-179,189] and one trial was rated poor-quality[180] (Appendix E). Methodological limitations included unclear allocation concealment methods and unblinded design. One trial reported high loss to followup[108]; the poor quality trial[180] also was unclear regarding blinding of outcome assessors and did not provide information on treatment compliance.

Table 29. Chronic low back pain: manual therapies (massage)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Ajimsha, 2014[175] 1 month Duration of pain: 2.3 vs. 2.25 years Fair	A. Myofascial release (n=38) 24 sessions, 3 session/week for 8 weeks B. Sham myofascial release (n=36)	A vs. B Age: 36 vs. 34 years Female: 76% vs. 78% Baseline Quebec Back Disability Scale (0-100): 37.1 vs. 35.3 Baseline pain (0-78 McGill Pain): 23.2 vs. 23.0	A vs. B <u>1 month</u> Quebec Back Disability Scale (0-100): 28.7 vs. 32.5, difference −2.02, p<0.005 McGill Pain Questionnaire (0-78): 13.1 vs. 18.3, difference −3.25, p<0.005	NR
Arguisuelas, 2017[179] 3 months Duration of pain: 7.1 to 7.9 years Fair	A. Myofascial release (n=27): Two 40-minute sessions per week for 2 weeks. B. Sham myofascial release (n=27)	A vs. B Age: 47 vs. 46 years Female: 59% vs. 63% Baseline RDQ (0-24, MCID= 3 points): 11.1 vs. 11.1 Baseline VAS (0-100, MCID= ≥20mm): 60.5 vs. 63.3 Baseline SF-MPQ (0-45, MCID= 5 points): 22.3 vs. 23	A vs. B <u>3 months</u> RDQ: 8.1 (95% CI 5.4 to 10.9) 11.8 (95% CI 9.1 to 14.5), difference −3.7 (95% CI −7.6 to −0.2), p≤0.05 VAS: 43.0 (95% CI 31.1 to 54.9) 52.0 (95% CI 40.1 to 63.9), difference −9.0 (95% CI −-25.8 to 7.9), p≤0.05 SF-MPQ: 15.28 (95% CI 11.1 to 20.6) vs. 23.7 (95% CI 18.9 to 28.4), difference −7.8 (95% CI −14.5 to −1.1), p≤0.05 RDQ improved ≥3 points: 81.8% vs. 25% Pain (VAS) improved ≥20 points: 50.0% vs. 37.5% SF-MPQ improved ≥5 points: 59.1% vs. 29.1%	A vs. B <u>3 months</u> FABQ: 48.1 (95% CI 38.1 to 58.1) vs. 61.6 (95% CI 51.7 to 71.6), difference -13.5 (95% CI −27.6 to 0.5), p≤0.05
Cherkin, 2001[176] 10.5 months Duration of pain >1 year: 64% vs. 62% Fair	A. Mixed massage (including Swedish) (n=78) Up to 10 sessions over 10 weeks B. Attention control (self-care education) (n=90)	A vs. B Age: 46 vs. 44 years Female: 69% vs. 56% Baseline modified RDQ (0-23): 11.8 vs. 12.0 Baseline symptom bothersomeness (0-10): 6.2 vs. 6.1	A vs. B <u>10.5 months</u> Modified RDQ (0-23): 6.8 vs. 6.4, p=0.03 Symptom bothersomeness (0-10): 3.2 vs. 3.8, p=0.003	A vs. B <u>10.5 months</u> Low back pain medication: 2.5 vs. 4.0, p=0.69 SF-12 Mental Component Score: no differences, data not shown

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cherkin, 2011[177] 9.5 months Duration of pain ≥1 year: 77% vs. 72% vs. 78% Fair	A. Structural massage (n=132): (myofascial, neuromuscular, and other soft-tissue techniques) 10 sessions for 10 weeks B. Relaxation massage (n=136): 10 sessions for 10 weeks C. Usual care (n=133)	A vs. B vs. C Age: 46 vs. 47 vs. 48 years Female: 66% vs. 65% vs. 62% Symptom bothersomeness (0-10): 5.6 vs. 5.6 vs. 5.8 Modified RDQ (0-23): 10.1 vs. 11.6 vs.10.5	A vs. B vs. C 9.5 months Symptom bothersomeness (0-10): 4.6 (95% CI 4.2 to 5.0) vs. 3.9 (95% CI 3.5 to 4.3) vs. 4.2 (95% CI 3.8 to 4.6) Modified RDQ (0-23): 7.2 (95% CI 6.4, 7.9) vs. 6.0 (95% CI 5.2 to 6.9) vs. 7.4 (95% CI 6.6 to 8.3), adjusted difference −0.3 (95% CI −1.4 to 0.9) for A vs. C and −1.4 (95% CI −2.6 to −0.2) for B vs. C	A vs. B vs. C 9.5 months SF-12 Mental (0-100): 52.4 (95% CI 50.9 to 53.8) vs. 53.5 (95% CI 52.2 to 54.8) vs. 51.9 (95% CI 50.2 to 53.6) SF-12 Physical (0-100): 37.7 (95% CI 36.8 to 38.7) vs. 37.9 (95% CI 37.0 to 38.7) vs. 37.7 (95% CI 36.8 to 38.6) Opioid use in last week for LBP: 4.8% (95% CI 3.1 to 7.3) vs. 4.9% (95% CI 3.1 to 7.9) vs. 4.9% (95% CI 2.7 to 8.7) Global rating of improvement "much better" or "gone": 26.1% (95% 19.8 to 34.6) vs. 36.2% (95% CI 29.1 to 45.0) vs. 20.5 (95% CI 14.5 to 29.0), RR 1.3 (95% CI 0.8, 2.0) for A vs. C and RR 1.8 (95% CI 1.2, 2.6) for B vs. C Healthcare costs (median): $38 (range $0 to $1443) vs. $78 (range $0 to $3,764) vs. $25 (range $0 to $8,082)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Little, 2008[189] 11.5 months Duration of pain: NR Fair	A. Mixed massage (including Swedish) (n=75), 6 sessions over 6 weeks/ B: Usual care (n=72) C: Exercise (regular exercise) (n=72) 5 times per week	Age: 45-46 years Female: 64-78% Baseline RDQ (0-24): 10.8-11.3 Baseline Deyo troublesome-ness (1-5): 3.3−3.4	A vs. B <u>10.5 months</u> RDQ (0-24): NR vs. 9.23 (5.3), difference −0.45 (95% CI −2.3 to 1.39) Von Korff disability (0-10): NR vs. 3.32 (2.25), difference 0.46 (95% CI −0.43 to 1.35) Von Korff pain (0-10): NR vs. 4.74 (2.20), difference 0.29 (95% CI −0.58 to 1.16) A vs. C <u>10.5 months</u> RDQ: −0.45 (−2.3 to 1.39) vs. −1.65 (−3.62 to 0.31) Von Korff disability: 0.46 (−0.43 to 1.35) vs. 0.05 (−0.92 to 1.02) Von Korff pain: 0.29 (−0.58 to 1.16) vs. −0.31 (−1.26 to 0.63)	A vs. B <u>10.5 months</u> Von Korff overall (0-10): NR vs. 4.19, difference 0.31 (95% CI −0.52 to 1.14) SF-36 PCS (0-100): NR vs. 56.1 (18.6), difference −1.45 (95% CI −9.04 to 6.15) SF-36 MCS (0-100): NR vs. 64.8 (17.5), difference −2.11 (95% CI −9.37 to 5.16) Deyo troublesomeness scale (1-5): NR vs. 3.05 (0.80), difference 0.04 (−0.25 to 0.33) A vs. C <u>10.5 months</u> Von Korff overall: 0.31 (−0.52 to 1.14) vs. −0.19 (−1.09 to 0.72) SF-36 Physical Component Score: −1.45 (−9.04 to 6.15) vs. −2.08 (−10.6 to 6.40) SF-36 Mental Component Score: −2.11 (−9.37 to 5.16) vs. 0.72 (−7.38 to 8.81) Deyo troublesomeness scale: 0.04 (−0.25 to 0.33) vs. −0.21 (−0.52 to 0.09)
Movahedi, 2017[180] 1 month Duration of pain: NR Poor	A. Acupressure (n=25): Three 14-minute sessions per week for 3 weeks (9 total sessions). B. Sham acupressure (n=25)	A vs. B Age: 37 vs. 37 years Female: 100% vs. 100% Baseline FSS (9-63): 34.9 (12.3) vs. 34.8 (13.4)	A vs. B <u>1 month</u> FSS: 24.3 vs. 36.6, p<0.001; difference −12.2 (95% CI −18.57 to −5.83)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Poole, 2007[108] 4.5 months Duration of pain: 10 vs. 11 vs. 9.5 years Fair	A. Reflexology (n=77) 6 sessions over 6−8 weeks B. Usual care (n=75)	A vs. B Age: 47 vs. 47 years Female: 62% vs. 51% Baseline ODI: 33.0 vs. 36.6 Baseline pain (0-100 VAS): 44.5 vs. 40.6	A vs. B <u>4.5 months</u> ODI (0-100): 29.0 (20.2) vs. 32.9 (17.6) Pain (0-100 VAS): 39.8 (29.2) vs. 42.7 (28.4)	A vs. B <u>4.5 months</u> Beck Depression Inventory (0-63): 11.6 (10.9) vs. 12.8 (9.2) SF-36 Physical Functioning: 57.1 (31.8) vs. 52.2 (29.5) SF-36 Social Functioning: 68.1 (31.8) vs. 61.5 (30.8) SF-36 Physical Limitations: 48.2 (46.4) vs. 37.8 (42.5) SF-36 Emotional Limitations: 55.0 (46.5) vs. 62.0 (44.0)
Quinn, 2008[178] 1.5 and 3 months Duration of pain: At least 3 months Fair	A. Reflexology (pressure massage stimulation) (n=7) 6 sessions over 6 weeks B. Sham reflexology (n=8)	A vs. B Age (median): 42 vs. 45 Female: 86% vs. 50% Baseline RDQ: 5 vs. 7.5 Baseline pain (0-10 VAS): 4.7 vs. 3.4	A vs. B <u>1.5 months, median (IQR)</u> RDQ: 4 (3 to 4.5) vs. 4.5 (1 to 7) Pain (0-10 VAS): 2.1 (1.5 to 4.9) vs. 4.1 (2.7 to 5.1) McGill Pain Questionnaire (0-77): 11 (6 to 17) vs. 6.5 (5 to 13) <u>3 months, median (IQR)</u> RDQ: 4 (2 to 5) vs. 3.5 (1.8 to 4.8) VAS: 2.2 (1.6 to 3.2) vs. 3.2 (2.6 to 4.6) McGill Pain Questionnaire (0-77): 6 (4 to 13) vs. 7.5 (3.8 to 9.8)	A vs. B <u>1.5 months, median (IQR)</u> SF-36 General health: 52.9 (49 to 54) vs. 42.2 (40 to 51) SF-36 Physical functioning: 48.6 (47 to 50) vs. 43.4 (40 to 50) SF-36 Mental health: 47.2 (43 to 56) vs. 47.2 (42 to 53) <u>3 months, median (IQR)</u> SF-36 General health: 48.2 (46 to 52) vs. 47.0 (38 to 53) SF-36 Physical functioning: 50.7 (44 to 51) vs. 45.5 (44 to 50) SF-36 Mental health: 52.8 (39 to 53) vs. 48.6 (44 to 51)

Abbreviations: CI = confidence interval; FABQ = Fear-Avoidance Beliefs Questionnaire; FSS = Fatigue Severity Scale; IQR = interquartile range; LBP = low back pain; NR = not reported; MCS = Mental Component Summary; MCID = minimal clinically important difference; MPQ = McGill Pain Questionnaire; NR = not reported; PCS = Physical Component Summary; ODI = Oswestry Disability Index; RDQ =Roland-Morris disability questionnaire; RR = relative risk; SF-12 = Short-Form 12 questionaire; SF-36 = Short-Form 36 questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Massage Compared With Sham Massage, Usual Care, or an Attention Control

Massage was associated with small effects on short-term function versus sham massage or usual care (6 trials, SMD −0.38, 95% CI −0.63 to −0.20, I^2=0%) (Figure 12).[108,175,177-180] The massage technique was myofascial release in two trials (pooled SMD −0.45, 95% CI −0.88 to −0.04,[175,179] structural or relaxation massage in one trial (difference −1.72 on the 0 to 23 modified RDQ, 95% CI −2.78 to −0.67),[177] foot reflexology in two trials (pooled SMD −0.15,

95% CI −0.60 to 0.50),[108,178] and acupressure in one trial (mean difference −12.2, 95% CI −18.6 to -5.8 on the 9 to 63 Fatigue Severity Scale).[180] Estimates were similar when trials were stratified according to whether the comparator was sham massage or usual care. There was no effect on intermediate-term function (3 trials, SMD −0.09, 95% CI −0.26 to 0.12, I^2=0%) (Figure 12).[176,177,189]

Massage was associated with small effects on short-term pain versus sham massage or usual care (5 trials, pooled difference −0.55 on a 0 to 10 scale, 95% CI −0.88 to −0.23, I^2=0%) (Figure 13).[108,175,177-179] On a 0 to 10 scale, effects were −0.60 points (95% CI −1.72 to 0.46) in two trials of foot reflexology,[108,178] −0.68 points (95% CI −1.35 to −0.10) in two trials of myofascial release,[175,179] and −0.35 points (95% CI −0.82 to 0.12) in a trial of relaxation or structural massage.[177] Estimates were similar when trials were stratified according to whether the comparator was sham massage or usual care. There was no difference between massage (structural or relaxation massage or mixed massage techniques, including Swedish massage) versus an attention control or usual care in intermediate-term pain (3 trials, pooled difference −0.02, 95% CI −0.56 to 0.44, I^2=0%).[176,177,189]

One trial found no difference between massage versus usual care in use of opioids at intermediate-term followup or healthcare costs.[177] There was insufficient evidence to determine effects of duration of massage or number of massage sessions on findings. Two trials[177,189] found no differences between massage versus usual care on the SF-36 MCS (mean difference 0.87 on a 0 to 100 scale, 95% CI -1.01 to 2.75, I^2=0%) or PCS scores (mean difference 3.91 on a 0 to 100 scale, 95% CI -4.50 to 12.31, I^2=77%) at intermediate-term followup, and one trial[108] found no effects on various SF-36 subscales or the Beck Depression Inventory at short-term followup. One trial found massage associated with greater likelihood of experiencing ≥3 point improvement in the RDQ or ≥20 point improvement on a 0 to 100 VAS pain scale, but did not report statistical significance, which could not be calculated because the denominators were unclear.[179]

Massage Compared With Pharmacological Therapies

No trial of massage versus pharmacological therapy met inclusion criteria.

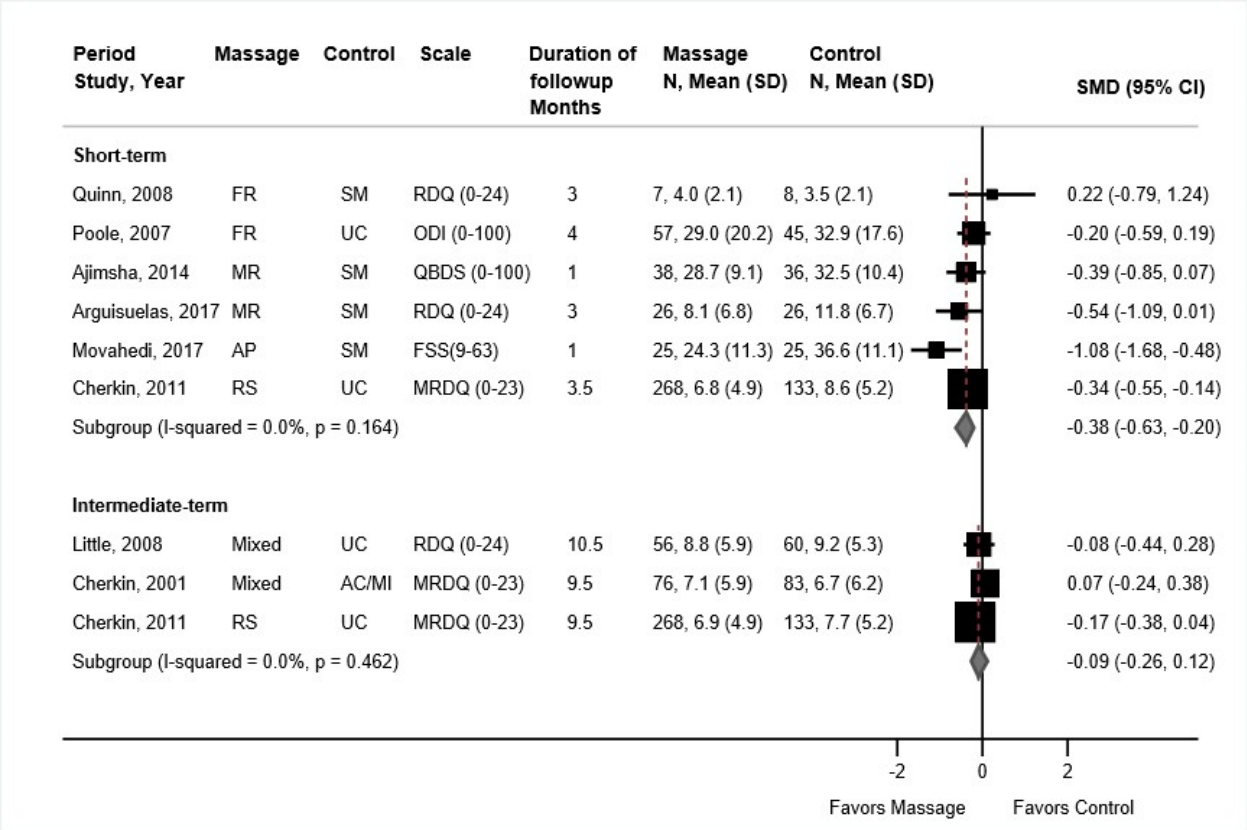
Massage Compared With Exercise

One trial found no differences between massage versus exercise in intermediate-term function (difference 1.2 on the 0 to 24 RDQ, 95% CI −1.47 to 3.87), pain (difference 0.60 on the 0 to 10 Von Korff pain scale, 95% CI −0.67 to 1.87), or the SF-36 MCS or PCS scores (differences 0 to 3 points on 0 to 100 scales, p>0.05).[189]

Harms

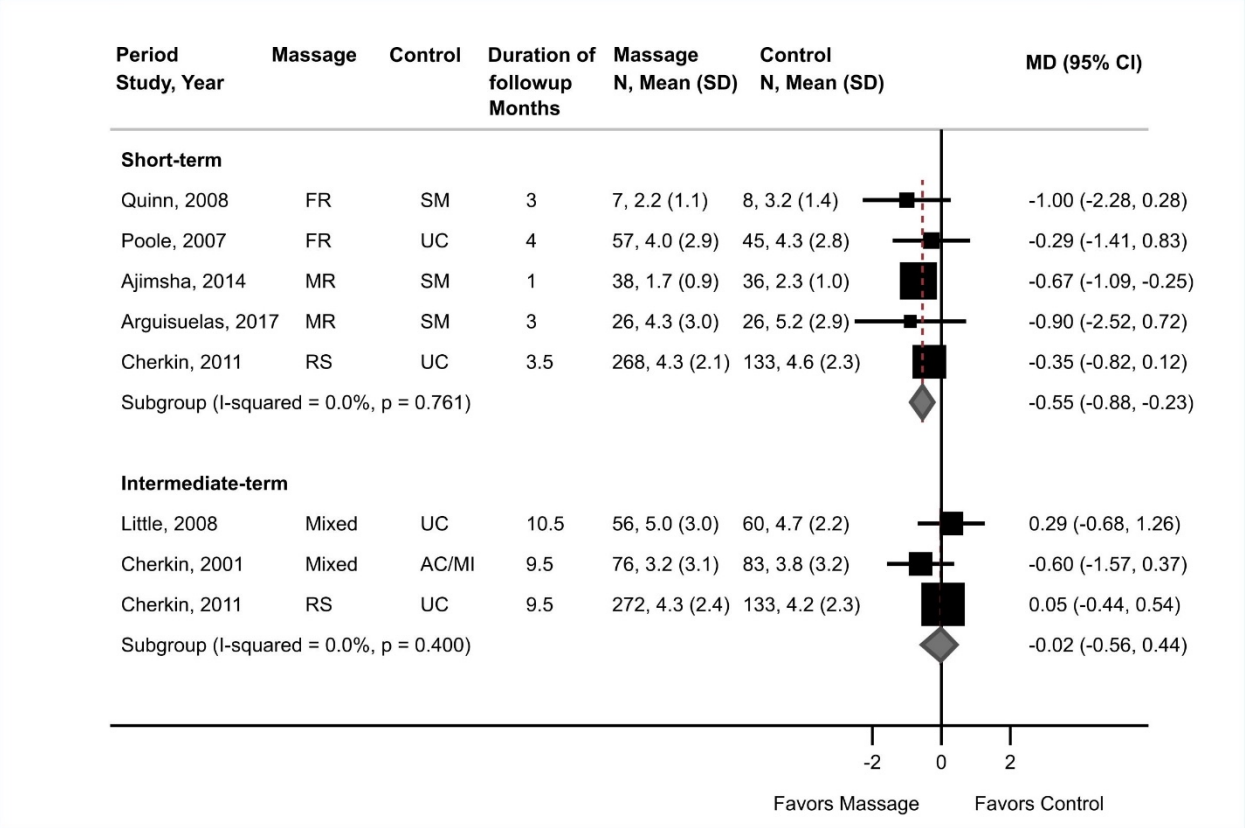
Four trials[175,176,179,180] of massage reported no serious adverse events, and one trial[178] reported no adverse events. In four trials, the proportion of massage patients who reported increased pain ranged from <1 to 26 percent.[175-177,189]

Figure 12. Massage versus sham massage, usual care, or attention control intervention for chronic low back pain: effects on function



AC = attention control; AP = acupressure; CI = confidence interval; FR = foot reflexology; MD = mean difference; MI = minimal intervention; MRDQ = Modified Roland-Morris Disability Questionnaire; MR = myofascial release; N = number; QBDS = Quebec Back Pain Disability Scale; RDQ = Roland-Morris Disability Questionnaire; RS = relaxation/structural; SD = standard deviation; SM = sham massage, SMD = standardized mean difference; UC = usual care

Figure 13. Massage versus sham massage, usual care, or attention control for chronic low back pain: effects on pain



AC = attention control; CI = confidence interval; FR = foot reflexology; MI = minimal intervention; MR = myofascial release; N = number; RS = relaxation/structural; SD = standard deviation; SM = sham massage, UC = usual care

Mindfulness-Based Stress Reduction for Chronic Low Back Pain

Key Points

- There were no differences between mindfulness-based stress reduction (MBSR) versus usual care or attention control in short-term function (4 trials, pooled SMD −0.14, 95% CI −0.51 to 0.02, I^2=0%), intermediate-term function (1 trial, SMD −0.20, 95% CI −0.46 to 0.06), or long-term function (1 trial, SMD −0.09, 95% CI −0.35 to 0.16) (SOE: low).
- MBSR was associated with a small improvement compared with usual care or an attention control in short-term pain (3 trials, pooled difference −0.68 on a 0 to 10 scale, 95% CI −1.29 to −0.28, I^2=45%) after excluding two poor-quality trials; MBSR was also associated with a small improvement in intermediate-term pain (1 trial, difference −0.75, 95% CI −1.16 to −0.34), with no statistically significant effects on long-term pain (1 trial, difference −0.22, 95% CI −0.63 to 0.19) (SOE: moderate for short term, low for intermediate and long term).
- One trial reported temporarily increased pain in 29 percent of patients undergoing MBSR, and three trials reported no harms (SOE: low).

Detailed Synthesis

Five trials (7 publications) of MBSR for low back pain met inclusion criteria (Table 14 and Appendix D).[104,194-199] All of the trials were included in the prior AHRQ report. In three trials,[104,195-198] the MBSR intervention was closely modeled on the program developed by Kabat-Zinn;[282] in the other two trials, the MBSR intervention appeared to have undergone some adaptations from the original Kabat-Zinn program.[194,199] In all trials, the main intervention consisting of 1.5 to 2 hour weekly group sessions for 8 weeks. Sample sizes ranged from 35 to 282 (total sample=629). Three trials compared MBSR versus usual care[104,194-196,199] and two trials compared MBSR versus an attention control (education).[197,198] Four trials[104,195-199] were conducted in the United States and one trial[194] in Iran. One trial focused on patients on opioid therapy for low back pain.[199] One trial reported outcomes through long-term (22 months after 8-week MBSR course) followup,[104,195,196] and the others only evaluated short-term outcomes.

Three trials[104,195-198] were rated fair quality and two trials poor quality (Appendix E).[194,199] The major methodological limitation in the fair-quality trials was the inability to effectively blind patients and caregivers to the MBSR intervention. One poor-quality trial reported unclear randomization and allocation concealment methods and had high attrition,[194] and another poor-quality trial reported a large baseline difference in baseline pain scores (Brief Pain Inventory score 6.3 on a 0 to 10 scale with MBSR versus 4.9 with usual care).[199]

Table 30. Chronic low back pain: mindfulness-based stress reduction

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Banth, 2015[194] 1 month Duration of pain: ≥6 months Poor	A. Mindfulness-based stress reduction (n=24) 8 1.5-hour sessions over 8 weeks B. Usual care (n=24) 48 of 88 patients were analyzed, n for each group NR	A vs. B (NR) Age: 40 years Female: 100% Baseline function: NR McGill Pain questionnaire total score (0-45): 26.08 vs. 26.71	A vs. B <u>1 month</u> McGill Pain questionnaire total score (0-45): 13.58 vs. 23.60	A vs. B <u>1 month</u> SF-12 Mental component (0-100): 31.54 (4.3) vs. 24.29 (5.2) SF-12 Physical component (0-100): 28.08 (4.2) vs. 21.08 (3.3)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cherkin, 2016[104] Herman, 2017[196] Cherkin, 2017[195] (2 year data from Cherkin, 2016) 22 months Duration of pain: >3 months (>1 year in 80% of patients) Fair	A. Mindfulness-based stress reduction (n=116), 8 2-hour sessions over 8 weeks (optional 6 hour retreat) B. Usual care (n=113)	A vs. B 50 vs. 49 years Female: 61% vs. 77% Baseline modified RDQ (0-23): 11.8 vs. 10.9 Baseline pain bothersomeness (0-10): 6.1 vs. 6.0	A vs. B <u>4.5 months</u> Modified RDQ (0-23), mean change from baseline: −4.33 (95% CI −5.16 to −3.51) vs. −2.96 (95% CI −3.79 to −2.14) Pain bothersomeness (0-10), mean change from baseline: −1.48 (95% CI −1.86 to −1.11) vs. −0.84 (95% CI −1.21 to −0.46) ≥30% improvement in RDQ: 60.5% (95% CI 52.0 to 70.3) vs. 44.1% (95% CI 35.9to 54.2) ≥30% improvement in pain bothersomeness: 43.6% (95% CI 35.6 to 53.3) vs. 26.6% (95% CI 19.8 to 35.9) <u>10 months</u> Modified RDQ, mean change from baseline:−5.3 (95% CI −6.16to −4.43) vs. −4.78 (95% CI −5.67to −3.89) vs. −3.43 (95% CI −4.33 to −2.52) Pain bothersomeness, mean change from baseline: −1.95 (95% CI −2.32 to −1.59) vs. −1.10 (95% CI −1.48 to −0.71) ≥30% improvement in RDQ: 68.6% (95% CI 60.3 to 78.1) vs. 48.6% (95% CI 40.3t o 58.6) ≥30% improvement in pain bothersomeness: 48.5% (95% CI 40.3 to 58.3) vs. 31.0% (95% CI 23.8 to 40.3) <u>22 months</u> Modified RDQ (0-23): −4.09 (95% CI−5.08 to −3.10) vs. −2.74 (95% CI−3.81to −1.68) ≥30% improvement in modified RDQ: 55.4% (95% CI 46.9 to 65.5) vs. 42.05% (95% CI 33.8 to 52.2) Pain bothersomeness: −1.57 (95% CI −1.97 to −1.17) vs. −1.25 (95% CI −1.69 to −0.81 ≥30% improvement in pain bothersomeness: 41.2% (95% CI 33.2 to 51.0) vs. 31.1% (95% CI 23.9 to 40.5)	A vs. B <u>4.5 months</u> SF-12 MCS, mean change from baseline (0-100): 0.45 (95% CI −0.85 to 1.76) vs. 2.13 (95% CI 0.86 to 3.40) vs. −1.11 (95% CI −2.39 to 0.17) SF-12 PCS, mean change from baseline (0-100): 3.58 (95% CI 2.15 to 5.01) vs. 3.27 (95% CI 2.09 to 4.44) Used medications for LBP: 43.4% (95% CI 35.9to 52.6) vs. 54.2 (95% CI 46.2 to 63.6) <u>10 months</u> SF-12 MCS, mean change from baseline: 2.01 (95% CI 0.74 to 3.28) vs. 0.75 (95% CI −0.58 to 2.08) SF-12 PCS, mean change from baseline: 3.87 (95% CI 2.55 to 5.19) vs. 2.93 (95% CI 1.70 to 4.16) Used medications for LBP: 46.8% (95% CI 39.2 to 55.9) vs. 52.9% (95% CI 45.1 to 62.0) Total costs: $5,580 (95% CI $3,465, $8,343) vs. $6,304 (95% CI $4,193, $9,805)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Morone, 2009[198] 4 months Duration of pain: Mean 9.4 to 11 years Fair	A. Mindfulness-based stress reduction (n=16), 8 1.5-hour sessions over 8 weeks B. Attention control (education) (n=19)	A vs. B Age 78 vs. 73 years Female: 69% vs. 58% Baseline RDQ: 8.8 vs. 11.3 Baseline McGill Pain Questionnaire Current Pain (0-10): 2.9 vs. 4.4	A vs. B 4 months RDQ: 7.6 (95% CI 6.2 to 8.7) vs. 10.0 (95% CI 8.7 to 11.2) McGill Pain Questionnaire Total Score (0-45): 12.4 (95% CI 10.4 to 14.6) vs. 12.0 (95% CI 10.2 to 13.7) McGill Pain Questionnaire Current Pain (0-10): 2.3 (95% CI 1.6 to 2.8) vs. 3.7 (95% CI 3.1 to 4.3)	A vs. B 4 months SF-36 Pain Score (10-62): 41.4 (95% CI 39.8 to 43.1) vs. 40.5 (95% CI 38.7 to 42.2)
Morone, 2016[197] 4.5 months Duration of pain: Mean 11 years Fair	A. Mindfulness-based stress reduction (n=140), 8 1.5-hour sessions over 8 weeks, with 6 monthly booster sessions B. Control, (health education) (n=142)	A vs. B Age: 75 vs. 74 years Female: 66% vs. 66% Baseline RDQ (0-24): 15.6 vs. 15.4 Baseline Pain (0-20 NRS): 11.0 vs. 10.5	A vs. B 4.5 months RDQ: 12.2 vs. 12.6, adjusted difference −0.4 (95% CI −1.5 to 0.7) RDQ improved ≥2.5 points: 49.2% (58/117) vs. 48.9% (66/135), p=0.97 Pain (0-20 NRS): 9.5 vs. 10.6, adjusted difference −1.1 (95% CI −2.2 to −0.01) Pain improved ≥30%: 36.7% (43/117) vs. 26.7% (36/135), p=0.09	A vs. B 4.5 months SF-36 Global Health Composite (9-67): 42.4 vs. 41.2, adjusted difference 0.2 (95% CI −1.9 to 2.4) SF-36 Physical Health Composite (20 to 65): 41.2 vs. 41.2, adjusted difference −0.1 (95% CI −1.9 to 1.8)
Zgierska, 2016[199] 4.5 months Duration of pain: Mean 14 years Poor	A. Mindfulness-based stress reduction (n=21): 8 weekly 2 hour group sessions plus 30 minutes/day, 6 days/week of at home practice B. Usual care (n=14)	Overall Age: 51.8 years Female: 80% Baseline ODI (0-100): 68.1 vs. 64.5 Baseline Brief Pain Inventory pain intensity (0-10): 6.3 vs. 4.9 Baseline Opioid dose 166.9 vs. 120.3	A vs. B 4.5 months ODI (0-100): −5.0 (95% CI 9.7 to 0.2) vs. 1.6 (95% CI −4.3 to 7.4) Brief Pain Inventory pain intensity: −0.5 (95% CI −1.1 to 0.02) vs. 0.5 (95% CI 0.2 to 1.2)	A vs. B 4.5 months Opioid dose (mg morphine equivalents): −10.1 (95% CI −35.5 to 15.2) vs. −0.2 (95% CI −31.4 to 30.9)

CI = confidence interval; MCS = Mental Component Summary; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PCS = Physical Component Summary; RDQ = Roland-Morris Disability Questionnaire; SF-12 = Short-Form 12 Questionaire SF-36 = Short-Form 36 Questionnaire

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

MBSR Compared With Usual Care or an Attention Control

MBSR was associated with no statistically significant differences in short-term function compared with usual care or an attention control (4 trials, pooled SMD −0.14, 95% CI −0.51 to 0.02, I^2=0%) (Figure 14).[104,197,198] Three trials[104,197,198] evaluated function using the RDQ (pooled difference −0.89 points on a 0 to 24 scale, 95% CI −2.37 to 0.30), and one trial[199] used the ODI (difference −3.00 points on a 0 to 100 scale, 95% CI −11.39 to 5.39). One trial found no difference between MBSR versus usual care in intermediate-term (SMD −0.20, 95% CI −0.46 to 0.06) or long-term function (SMD −0.09, 95% CI −0.35 to 0.16).[104,195] There was no clear

difference between MBSR versus controls in likelihood of a clinically meaningful effect on function (≥30% improvement in RDQ or RDQ improved by ≥2.5 points) at short term (2 trials, 1.17, 95% CI 0.88 to 1.57).[104,197] Data were restricted to one trial for intermediate-term (RR 1.41, 95% CI 1.13 to 1.77)[104] and long-term followup (RR 1.32, 95% CI 1.00 to 1.74).[195]

MBSR was associated with no statistically significant effects on short-term pain compared with usual care or an attention control, when all trials were included in the analysis (5 trials, pooled difference −0.88 on a 0 to 10 scale, 95% CI −1.82 to 0.08, I^2=89%) (Figure 15).[104,194,197-199] However, the estimate favored MBSR and statistical heterogeneity was substantial. Excluding two poor-quality trials,[194,199] one of which reported the largest effect in favor of MBSR (−2.23 points) as well as one of which was the only trial with results that favored usual care (mean difference 0.40 points), resulted in a small, statistically significant effect on short-term pain (3 trials, pooled difference −0.68, 95% CI −1.29 to −0.28, I^2=45%) and reduced statistical heterogeneity.[104,197,198] Estimates were similar when analyses were stratified according to whether the trial evaluated usual care or an attention control comparator. One trial found MBSR associated with a small improvement compared with an attention control on intermediate-term pain (difference −0.75 on a 0 to 10 scale, 95% CI −1.16 to −0.34); there was no statistically significant effect on long-term pain (difference −0.22, 95% CI −0.63 to 0.19).[195] MBSR was associated with greater likelihood of a clinically meaningful effect on pain (defined as ≥30% improvement) at short-term (2 trials, RR 1.49, 95% CI 1.14 to 1.95, I^2=0%)[104,197] and intermediate-term followup (1 trial, RR 1.56, 95% CI 1.14 to 2.14),[104] but not at long-term followup (41% vs. 31%, RR 1.32, 95% CI 0.95 to 1.85).[195]

Three trials found no clear differences between MBSR versus usual care or an attention control on quality of life measured by the 12-Item Short Form Health Survey (SF-12) or 36-Item Short Form Health Survery (SF-36).[104,194,197] Two trials reported conflicting effects on short-term PCS (mean difference 2.89, 95% CI −5.13 to 10.92, I^2=97%) and MCS scores (mean difference 4.27, 95% CI −0.07 to 9.51, I^2=88%), though statistical heterogeneity was high.[104,194] One trial found no difference in intermediate-term PCS (mean difference −0.56, 95% CI −2.52 to 1.40) or MCS scores (mean difference 2.06, 95% CI 0.05 to 4.07) scores.[104] One trial found MBSR associated with less medication use for low back pain at short term (43% vs. 54%) but not at intermediate term (47% vs. 53%); MBSR was associated with a small decrease in severity of depression (difference 0.63 points on the Patient Health Questionnaire (PHQ-8) at intermediate-term), with no clear differences in measures of healthcare utilization.[104,196]

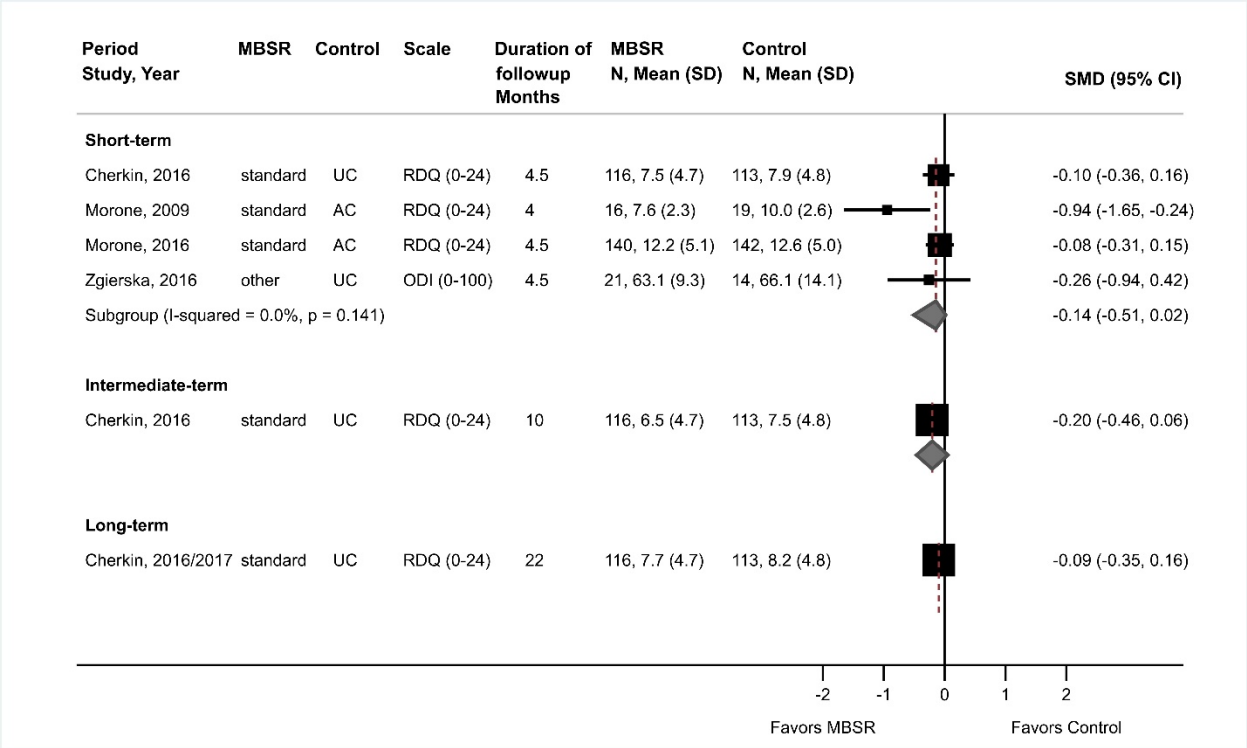
MBSR Compared With Pharmacological Therapy or With Exercise

No trial of MBSR versus pharmacological or versus exercise therapy met inclusion criteria.

Harms

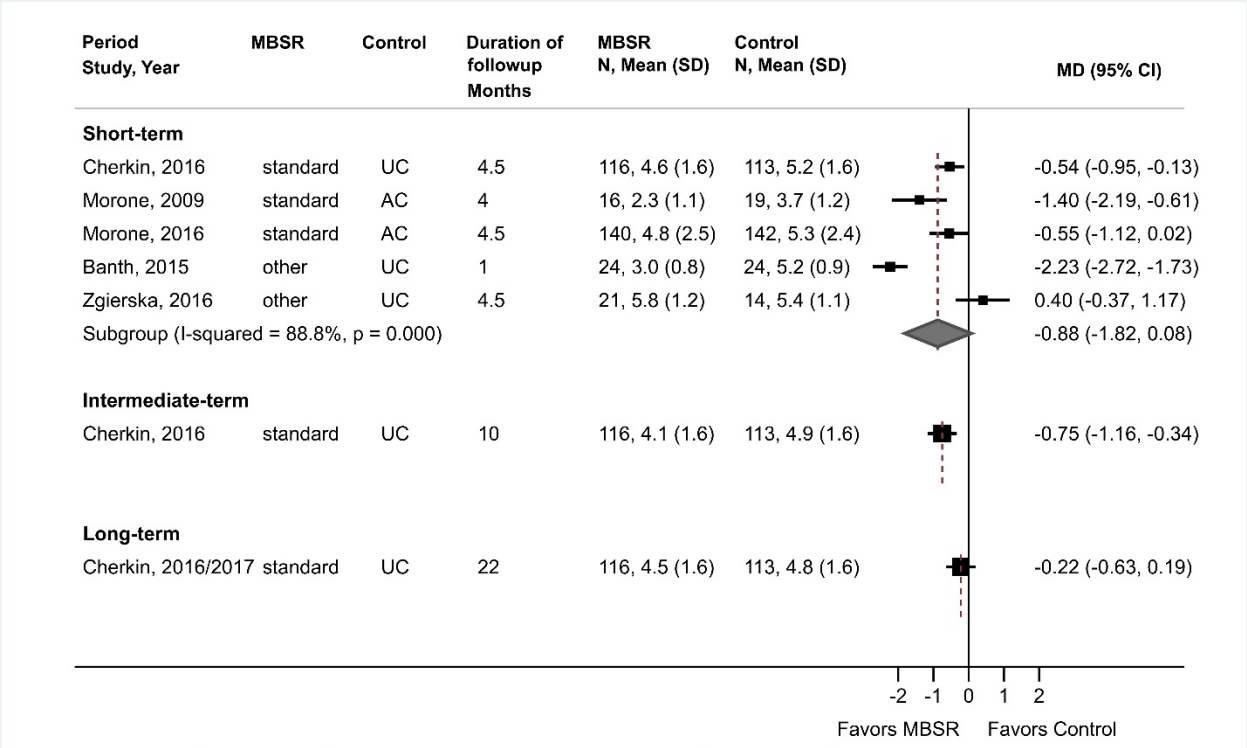
In one trial, 29 percent of MBSR patients reported temporarily increased pain.[104] Three trials[197-199] reported no adverse events and one trial[194] did not report adverse events.

Figure 14. Mindfulness-based stress reduction versus usual care or an attention control for chronic low back pain: effects on function



AC = attention control; CI = confidence interval; MBSR = mindfulness-based stress reduction; N = number; ODI = Oswestry Disability Index; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; UC = usual care

Figure 15. Mindfulness-based stress reduction versus usual care or an attention control for chronic low back pain: effects on pain



AC = attention control; CI = confidence interval; MBSR = mindfulness-based stress reduction; N=number; SD = standard deviation; UC = usual care

Mind-Body Practices for Chronic Low Back Pain

Key Points

Yoga

- Yoga was associated with moderate effects on function versus an attention or waitlist control at short-term (8 trials [2 new], pooled SMD −0.45, 95% CI −0.69 to −0.28, I^2=31%) and small effects at intermediate-term (3 trials, pooled SMD −0.29, 95% CI −0.47 to −0.11, I^2=0%) (SOE: moderate for short term, low for intermediate term).
- Yoga was associated with small effects on pain versus an attention or waitlist control at short-term (7 trials [2 new], pooled difference −0.87 on a 0 to 10 scale, 95% CI −1.49 to −0.24, I^2=64%) and moderate effects at intermediate-term (2 trials, pooled difference −1.16, 95% CI −2.16 to −0.27, I^2=0%) (SOE: low for short term, moderate for intermediate term).
- Yoga was associated with no statistically significant differences versus exercise in short-term or intermediate-term pain or function (SOE: low).
- Yoga was not associated with increased risk of harms versus controls (SOE: low).

Qigong

- One trial found no differences between qigong versus exercise in short-term function (difference 0.9 on the RDQ, 95% CI −0.1 to 2.0), although intermediate-term results showed a small improvement favoring exercise (difference 1.2, 95% CI 0.1 to 2.3) (SOE: low).
- One trial found qigong associated with a small improvement in 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).
- One trial found no difference between qigong versus exercise in risk of adverse events (SOE: low).

Detailed Synthesis

Yoga

Ten trials of yoga for low back pain met inclusion criteria (Table 15, Appendix D).[37,204-211,220] Eight trials[204-210,220] were included in the prior AHRQ report and two trials[37,211] were added for this update. In the prior AHRQ report, four trials evaluated Iyengar yoga,[208-210,220] two trials Viniyoga,[206,207] –and two trials Hatha yoga[204,205]; one new trial evaluated Kundalini yoga[37] and the other new trial evaluated (Restorative Exercise and Strength Training for Operational Resilience and Excellence) RESTORE yoga.[211] Across all trials, sample sizes ranged from 60 to 320 (total sample=1,520). Six trials compared yoga versus an attention control (education),[37,205-208,210] two trials yoga versus wait list control,[204,209] one trial yoga versus usual care,[211] and five trials yoga versus exercise.[37,205-207,220] One trial was conducted in India[220] and the rest in the United States or Europe. The duration of yoga therapy ranged from 4 to 24 weeks and the number of sessions ranged from 4 to 48. In one trial, patients who received 12 weeks of yoga therapy were randomized to ongoing once-weekly maintenance sessions or to no maintenance.[205] Three trials reported outcomes through intermediate-term followup,[205,208,209] and seven only reported short-term outcomes.[37,204,206,207,210,211,220]

All of the trials were rated fair quality (Appendix E). Trials could not effectively blind patients; other methodological limitations included unclear allocation or randomization methods and high attrition.

Table 31. Chronic low back pain: mind-body practices (yoga)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bramberg, 2017[37] 4.2 months Duration of pain: NR Fair	A. Kundalini yoga (n=52): Two 60-minute yoga classes per week for 6 weeks (12 total yoga classes). B. Strength training (n=52): Five 60-minute supervised strength-training sessions over 6 weeks. C. Attention control (self-care advice) (n=55):	A vs. B vs. C Age: 47 vs. 46 vs. 44 years Female: 72% vs. 62% vs. 80% Baseline CPGS-BD (0-100): 37.2 vs. 37.6 vs. 38.6 Baseline CPGS-BP (0-100): 57.1 vs. 57.7 vs. 55.6	A vs. C <u>6 months</u> CPGS-BD: 29.4 vs. 32.8, adjusted difference -6.0 (95% CI -15.6 to 3.6), p>0.05 CPGS-BP: 47.0 vs. 50.2, adjusted difference -6.5 (95% CI -14.9 to 1.8), p>0.05 B vs. C <u>6 months</u> CPGS-BD: 24.8 vs. 32.8, adjusted difference -9.5 (95% CI -19.3 to 0.4), p>0.05 CPGS-BP: 41.7 vs. 50.2, adjusted difference -9.4 (95% CI -18.1 to -0.8), p<0.05 A vs. B <u>6 months</u> CPGS-BD: 29.4 vs. 24.8, adjusted difference -3.5 (95% CI -12.2 vs. 5.3), p>0.05 CPGS-BP: 47.0 vs. 41.7, adjusted difference - 2.9 (95% CI -10.9 to 5.1), p>0.05	<u>Work absence</u> (mean days over time period)[b] A vs. C -1 to 4 months: 4.1 vs. 8.9 , difference -4.8 (95% CI -11.4 to 1.8) -5 to 8 months: 4.0 vs. 12.0, difference -8.0 (95% CI -15.8 to -0.2) -9 to 12 months: 3.6 vs. 9.2, difference -5.6 (95% CI -12.7 to 1.5); Proportion absent ≥1 time (%): RR 0.82 (95% CI 0.6 to 1.1) B vs. C -1 to 4 months: 5.0 vs. 8.9, difference -3.9 (95% CI -11.4 to 3.6) -5 to 8 months: 6.4 vs. 12.5, difference -6.1 (95% CI -15.7 to 3.5) -9 to 12 months: 9.5 vs. 9.2, difference 0.3 (95% CI -10.3 to 10.9); Proportion absent ≥1 time (%): RR 0.95 (95% CI 0.73 to 1.22) A vs. B -1 to 4 months: 4.1 vs. 5.0, difference -0.9 (95% CI -4.7 to 2.8) -5 to 8 months: 4.0 vs. 6.4, difference -2.4 (95% CI -7.5 to 2.7) -9 to 12 months: 3.6 vs. 9.5, difference -5.9 (95% CI -12.7 to 0.9); ≥1 day: 50% vs. 51%; Proportion absent ≥1 time (%): RR 0.86 (95% CI 0.65 to 1.14)
Groessl, 2017[204] 3.5 months Duration of pain: >6 months Fair	A. Hatha yoga (n=75): Two sessions per week for 12 weeks, 15–20 minutes of home practice on days without sessions B. Wait list (n=75): Usual care, with yoga started after 6 months	A vs. B Age: 53 vs. 54 years Female: 27% vs. 25% Baseline RDQ (0-24): 9.40 vs. 10.3 Baseline pain (0-10 Brief Pain Inventory): 4.64 vs. 4.68	A vs. B <u>3.5 months</u> RDQ (0-24): −3.37 (95% CI −4.51 to −2.23) vs. −0.89 (95% CI−2.02 to 0.23); between group difference −2.48 (95% CI - 4.08 to −0.87) Pain intensity, Brief Pain Inventory (0-10): −0.44 (95% CI- 0.78 to - 0.11) vs. 0.15 (95% CI −0.18 to 0.47); between-group difference −0.59 (95% CI −1.05 to −0.13)	A vs. B <u>3.5 months</u> Opioid medication use: 9% vs. 7%, p=0.40 Other medical treatments for pain: 39% vs. 37, p=0.42

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Highland, 2017[211] 3 and 6 months Duration of pain: >3 months Fair	A. Restorative Exercise and Strength Training for Operational Resilience and Excellence (RESTORE) Yoga Program (n=34): Participants completed 2 individual yoga sessions per week in weeks 1 to 4 and then once-weekly sessions in weeks 5 to 8. B. Usual care (n=34)	A + B Age: 44 years Female: 63% A vs. B Baseline PROMIS-PF (0-100; MCID = 3 point change): 40.67 vs. 42.03 Baseline RDQ (0-24; MCID = 30% reduction): 9.21 vs. 8.68 Baseline DVPRS (0-10; MCID = 2 point change or 30% reduction): 4.68 vs. 4.32	A vs. B <u>3 months</u> PROMIS-PF: 47.34 vs. 43.38, difference 3.96 (95% CI 0.93 to 6.99) RDQ: 4.43 vs. 7.04, difference −2.61 (95% CI −4.83 to −0.34) DVPRS: 2.75 vs. 3.35, difference −0.6 (95% CI −1.63 to 0.43) PROMIS-SB: 49.04 vs. 52.04, difference −3.0 (95% CI −5.82 to −0.18) <u>6 months</u> PROMIS-PF: 47.05 vs. 44.06, difference 2.99 (95% CI −0.57 to 6.55) RDQ: 3.25 vs. 6.52, difference −3.27 (95% CI −5.39 to −1.15) DVPRS: 2.79 vs. 2.86, difference −0.07 (95% CI −1.13 to 0.99) PROMIS-SB: 48.11 vs. 51.80, difference −3.69 (95% CI −7.27 to −0.11) Proportion of patients achieving a MCID (at 6 months)[c] PROMIS-PF: 35% (8/23) vs. 20% (4/20); adjusted p=1.0 RDQ: 79% (19/24) vs. 52% (11/21), adjusted p=0.66 DVPRS: 63% (15/24) vs. 48% (10/21), adjusted p=1.0	A vs. B <u>3 months</u> PROMIS-SB: 49.04 vs. 52.04, difference −3.0 (95% CI −5.82 to −0.18) <u>6 months</u> PROMIS-SB: 48.11 vs. 51.80, difference −3.69 (95% CI −7.27 to −0.11) Proportion of patients achieving an MCID (at 6 months)[c] PROMIS-SB (MCID = 5 point change): 83% (19/23) vs. 40% (8/20), adjusted p=0.03
Nambi, 2014[220] 5.5 months Duration of pain: >3 months Fair	A. Iyengar yoga (29 poses) (n=30) 5 sessions a week for 4 weeks B. Exercise (stretching exercises for soft tissue flexibility and range of motion) (n=30)	A vs. B Age: 44 vs. 43 years Female: 63% vs. 43% Baseline function, Physically unhealthy days: 18.0 vs. 17.8 Baseline pain (0-10 VAS): 6.7 vs. 6.7	A vs. B <u>5 months</u> Physically unhealthy days: 2.6 vs. 6.9, p=0.001 Pain (0-10 VAS): 1.8 vs. 3.8, p=0.001	A vs. B <u>5 months</u> Mentally unhealthy days: 2.1 vs. 5.0, p=0.001 Activity limitation (days): 2.0 vs. 5.0, p=0.001

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Saper, 2017[205] 10 months Duration of pain: >3 months Fair	A. Hatha yoga (n=127) 12 sessions over 12 weeks, with or without ongoing weekly maintenance sessions B. Exercise (n=129) C. Attention control (education) (n=64)	A vs. B vs. C Age: 46 vs. 46 vs. 44 Female: 57% vs. 70% vs. 66% Baseline modified RDQ: 13.9 vs. 15.6 vs. 15.0 Baseline pain (0-10 NRS): 7.1 vs. 7.2 vs. 7.0	A1 (no maintenance) vs. A2 (maintenance) vs. C, mean <u>3.5 months</u> Modified RDQ (0-23): 10.1 vs. 9.5 vs. 11.6 Pain (0-10 NRS): 4.3 vs. 4.6 vs. 5.5 <u>9 months</u> Modified RDQ (0-23): 9.2 vs. 8.9 vs. 11.1 Pain (0-10 NRS): 4.3 vs. 4.4 vs. 5.2 A1 vs. A2 vs. B1 vs. B2 <u>3.5 months</u> Modified RDQ (0-23): 10.1 vs. 9.5 vs. 10.4 vs. 10.1 Pain (0-10 NRS): 4.3 vs. 4.6 vs. 4.7 vs. 4.8 <u>9 months</u> Modified RDQ (0-23): 9.2 vs. 8.9 vs. 8.9 vs. 9.4 Pain (0-10 NRS): 4.3 vs. 4.4 vs. 4.0 vs. 4.1	NR
Sherman, 2005[206] 3.5 months Duration of pain: 3 to 15 months Fair	A. Viniyoga (n=36) 12 sessions 1 session/week for 12 weeks B. Exercise (n=35) C. Attention control (self-care advice) (n=30)	A vs. B vs. C Age: 44 vs. 42 vs. 45 Female: 69% vs. 63% vs. 67% Baseline RDQ: 8.1 vs. 9.0 vs. 8.0 Baseline symptom bothersomeness (0-10): 5.4 vs. 5.7 vs. 5.4	A vs. B <u>3.5 months</u> Modified RDQ (0-23): 3 vs. 5 (estimated from graph), adjusted difference −1.5 (−3.2 to 0.2)[d] Reduction in RDQ score ≥50%:69% vs. 50%, RR 1.4 (95% CI 0.91 to 2.1) Bothersomeness: 1.8 vs. 3.3 (estimated from graph), adjusted difference −1.4 (95% CI −2.5 to −0.2)[d] Medication use: 21% vs. 50%, RR 0.41 (95% CI 0.20 to 0.87) A vs. C <u>3.5 months</u> Symptom bothersomeness (0-10): 1.8 vs. 4.1, adjusted difference −2.2 (95% CI −3.2 to −1.2) Modified RDQ (0-23): 3 vs. 7, adjusted difference −3.6 (95% CI −5.4 to −1.8) Reduction in RDQ ≥50%: 69% vs. 30%, RR 2.3 (95% CI 1.3 to 4.2)	A vs. B <u>3.5 months</u> Medication use: 21% vs. 59%, RR 0.35 (95% CI 0.15 to 0.73) SF-36: No significant differences (data not provided)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sherman, 2011[207] 3.5 months Duration of pain: 3 to 6 months Fair	A. Viniyoga (n=92) 12 sessions 1 session/week for 12 weeks B. Exercise (n=91) C. Attention control (self-care advice) (n=30)	A vs. B Age: 47 vs. 49 vs. 50 Female: 67% vs. 63% vs. 60% Baseline RDQ: 9.8 vs. 8.6 vs. 9.0 Baseline symptom bothersomeness (0-10): 4.9 vs. 4.5 vs. 4.7	A vs. B <u>3.5 months</u> Modified RDQ (0-23): 4.49 (95% CI 3.51 to 5.48) vs. 4.26 (95% CI 3.30 to 5.22), adjusted difference −0.35 (95% CI −1.52 to 0.83)[d] Reduction in RDQ score ≥50%: 60% vs. 51%, RR 1.17 (95% CI 0.88 to 1.54) Symptom bothersomeness (0-10): 3.59 (95 % CI 3.12 to 4.06) vs. 3.34 (95% CI 2.86 to 3.81) A vs. C <u>3.5 months</u> Modified RDQ (0-23): 4.49 vs. 5.73, adjusted difference −1.81 (95% CI −3.12 to −0.50)[d] Reduction in RDQ score ≥50%: 60% vs. 31%, RR 1.90 (95% CI 1.21 to 2.99) Symptom bothersomeness (0-10): 3.59 (95% CI 3.12 to 4.06) vs. 3.80 (95% CI 3.14 to 4.46)	A vs. B <u>3.5 months</u> LBP better, much better, or completely gone: 51% vs. 51%, RR 1.00 (95% CI 0.75 to 1.34) A vs. C LBP better, much better, or completely gone: 51% vs. 20%, RR 2.57, 95% CI 1.39 to 4.78)
Tilbrook, 2011[208] 3 and 6 months Duration of pain: 96 vs. 72 months Fair	A. Iyengar yoga (n=152) 12 sessions 1 session/week for 12 weeks B. Attention control (self-care advice) (n=147)	A vs. B Age: 46 vs. 46 Female: 68% vs. 73% Baseline RDQ (0-24): 7.84 vs. 7.75 Baseline Aberdeen Back Pain Scale (0-100): 25.36 vs. 26.69	A vs. B Difference in change from baseline (95% CI) <u>3 months</u> RDQ (0-24): −1.48 (−2.62 to −0.33) Aberdeen Back Pain Scale (0 to 100): −1.74 (−4.32 to 0.84) <u>6 months</u> RDQ(0-24): −1.57 (−2.71 to −0.42) Aberdeen Back Pain Scale: −0.73 (−3.30 to 1.84)	A vs. B Difference in change from baseline (95% CI) <u>3 months</u> SF-12 PCS (0-100): 1.24 (−0.83 to 3.33) SF-12 MCS (0-100): 2.02 (−0.34 to 4.37) <u>6 months</u> SF-12 PCS: 0.80 (−1.28 to 2.87) SF-12 MCS: 0.42 (−1.92 to 2.77)
Williams, 2005[210] 3 months Duration of pain: 11.3 vs. 11.0 years Fair	A. Iyengar yoga (n=30), 16 sessions 1 session/week for 16 weeks B. Attention control (education) (n=30)	A vs. B Age: 49 vs. 48 Female: 65% vs. 70% Pain Disability Index (7-70): 14.3 vs. 21.2 Pain intensity, McGill Pain Questionnaire (0-10 VAS): 2.3 vs. 3.2	A vs. B <u>3 months</u> Pain Disability Index (7-70): 3.9 vs. 12.7, p=0.009 Pain, McGill Pain Questionnaire (0-10 VAS): 0.6 vs. 2.0, p=0.039 Present Pain Index (0-5): 0.5 vs. 1.1, p=0.013	A vs. B <u>3 months</u> Stopped or decreased medication use: 50% vs. 33%, p=0.007

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Williams, 2009[209] 6 months Duration of pain: 47 vs. 78 months Fair	A. Iyengar yoga (n=43) 48 sessions for 24 weeks B. Waitlist (standard medical care) (n=47)	A vs. B Age: 48 vs. 48 years Female: 74% vs. 79% Oswestry Disability Index (0-100): 25.2 vs. 23.1 Pain (0-100 VAS): 41.9 vs. 41.2	A vs. B <u>6 months</u> Oswestry Disability Index (0-100): 19.3 vs. 23.5, p=0.001 Pain (0-100 VAS): 22.2 vs. 38.3, p=0.0009	A vs. B <u>6 months</u> Beck Depression Inventory (0-63): 4.6 vs. 7.8, p=0.0004

CI = confidence interval; CPGS=Von Korff Chronic Pain Grade Score; DVPRS = Defense and Veterans Pain Rating Scale; LBP = low back pain; MCID = minimally clinically important difference; NR = not reported; NRS = numeric rating scale; ODI = Oswestry Disability Index; PROMIS-PF = Patient-Reported Outcomes Measurement Information System Physical Functioning; PROMIS-SB =Patient-Reported Outcomes Measurement Information System Symptom Burden; RDQ = Roland-Morris Disability Questionnaire; RR = relative risk; SF-36 = Short-Form 36 Questionaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

[b] For missed work days: time period 1 (months 1-4), time period 2 (months 5-8) and time period 3 (months 9-12).

[c] n/N not reported; calculated fromTable 3 of article.

[d] Adjusted for baseline scores.

Yoga Compared With an Attention Control or Waitlist

Yoga was associated with small effects on short-term function versus an attention control or waitlist (8 trials, pooled SMD −0.45, 95% CI −0.69 to −0.28, I^2=31%) (Figure 16).[37,204-208,210,211] Results were similar for Viniyoga (2 trials, pooled SMD −0.54, 95% CI −1.36 to 0.18),[206,207] Hatha yoga (2 trials, SMD −0.45, 95% CI −0.82 to −0.09),[204,205] Iyengar yoga (2 trials, SMD −0.38, 95% CI −1.38 to 0.14),[208,210] Kundalini yoga (1 trial, SMD −0.13, 95% CI −0.57 to 0.31),[37] or RESTORE yoga (1 trial, SMD −0.74, 95% CI −1.23 to −0.25).[211] Six trials evaluated function using the RDQ or modified RDQ, with a difference on a 0 to 24 or 0 to 23 scale of −2.32 (95% CI −3.48 to −1.40, I^2=46%).[204-208,211] Yoga was also associated with small effects on intermediate-term function versus controls (3 trials, pooled SMD −0.29, 95% CI −0.47 to −0.11, I^2=0%).[205,208,209] In two trials that evaluated intermediate-term function with the RDQ or modified RDQ, the difference was −1.65 points (95% CI −3.17 to −0.32, I^2=0%).[205,208] No trials were rated poor quality.

Yoga was associated with small effects on short-term pain versus controls (7 trials, pooled difference −0.87, 95% CI −1.49 to −0.24 on a 0 to 10 scale, I^2=64%) (Figure 17).[37,204-207,210,211] Estimates were similar from two trials of Viniyoga (pooled difference −1.25, 95% CI −3.78 to 1.27),[206,207] two trials of Hatha yoga (difference −0.80, 95% CI −1.46 to −0.20),[204,205] and one trial of Iyengar yoga (difference −1.40, 95% CI −2.43 to −0.37);[210] one trial of Kundalini yoga[37] and one trial of RESTORE yoga[211] showed no clear effects on pain, but estimates were imprecise. Yoga was also associated with moderate effects on intermediate-term pain versus controls, based on two trials (pooled difference −1.16, 95% CI −2.16 to −0.27, I^2=0%).[205,209]

Data on effects of yoga on quality of life were limited. One trial found no difference between yoga versus an attention control on the SF-36 Physical and Mental Component Summaries at short-term or intermediate-term followup (differences 0.42 to 2.02 points on a 0 to 100 scale).[208] One other trial found no differences between yoga versus an attention control on the SF-36, but did not provide data.[206]

One trial found yoga associated with lower (better) scores on the Beck Depression Inventory than waitlist at intermediate-term followup (mean 4.6 vs. 7.8 on a 0 to 63 scale, p=0.004)[209] and one trial found no difference between yoga versus waitlist in opioid use (9% vs. 7%, p=0.40) or other medical treatments for pain (39% vs. 37%, p=0.42) at short-term followup.[204] One trial found yoga associated with fewer work absence days compared with an attention control at 5 to 8 months followup (mean difference −8.0 days, 95% CI −15.8 to −0.2), but differences were not statistically significant at 1 to 4 months for at 9 to 12 months.[37]

Yoga Compared With Pharmacological Therapy

No trial of yoga versus pharmacological therapy met inclusion criteria.

Yoga Compared With Exercise

There were no differences between yoga versus exercise in short-term function (4 trials, pooled SMD −0.04, 95% CI −0.27 to 0.16, I^2=0%)[37,205-207] or intermediate-term function (1 trial, SMD −0.01, 95% CI −0.26 to 0.24)[205] (Figure 18). One trial found no difference between yoga versus exercise on the SF-36 at short-term followup (data not provided).[206] No trials were rated poor quality.

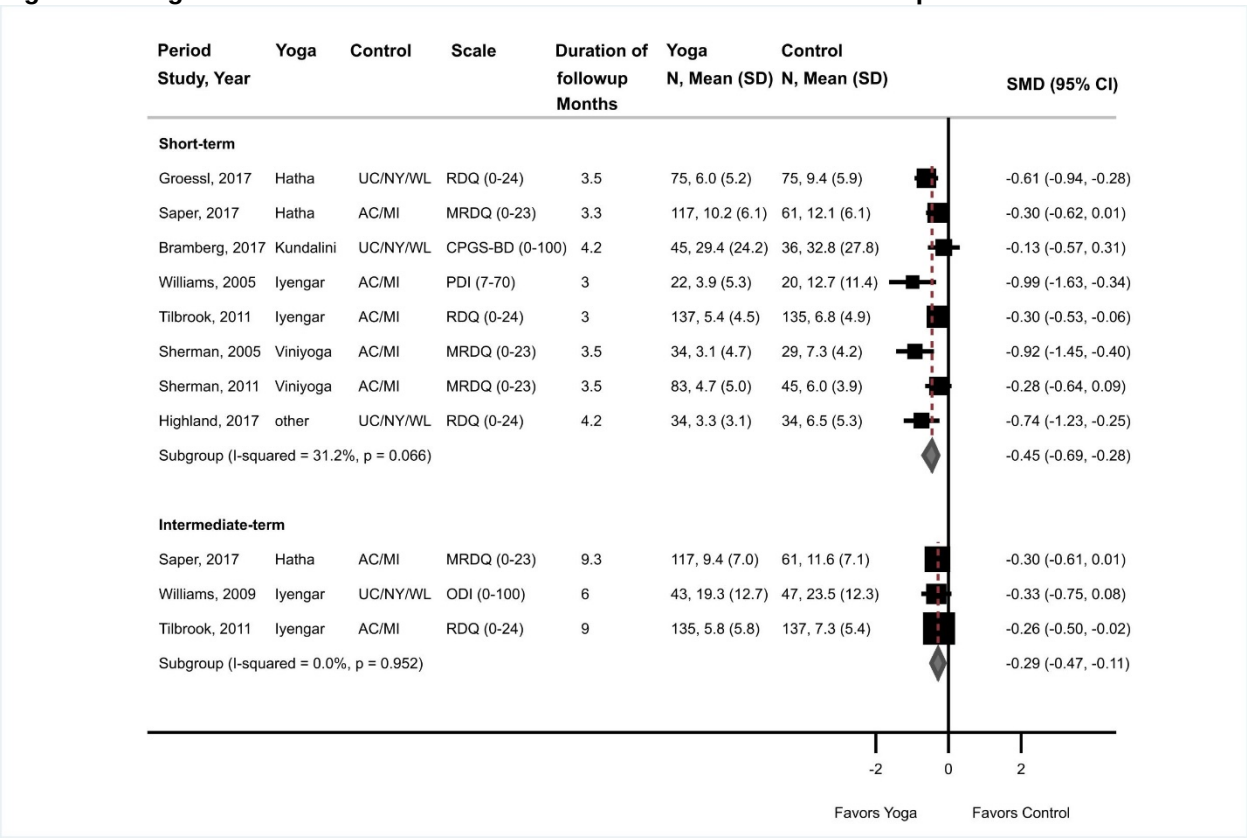
Effects of yoga versus exercise on short-term pain were not statistically significant and there was marked heterogeneity (5 trials, pooled difference −0.63 on a 0 to 10 scale, 95% CI −1.68 to 0.45, I^2=88%) (Figure 19).[37,205-207,220] Effects favored yoga in one trial of Iyengar yoga (difference −2.00, 95% CI −2.50 to −1.50) and in one trial of Viniyoga (difference −1.50, 95%

CI −2.36 to −0.64). The other three trials (one trial each of Viniyoga, Kundalini yoga, and Hatha yoga) each found no differences between yoga versus exercise. One trial found no difference between yoga versus exercise in intermediate-term pain (difference 0.30, 95% CI −0.39 to 0.99).[205]

Harms

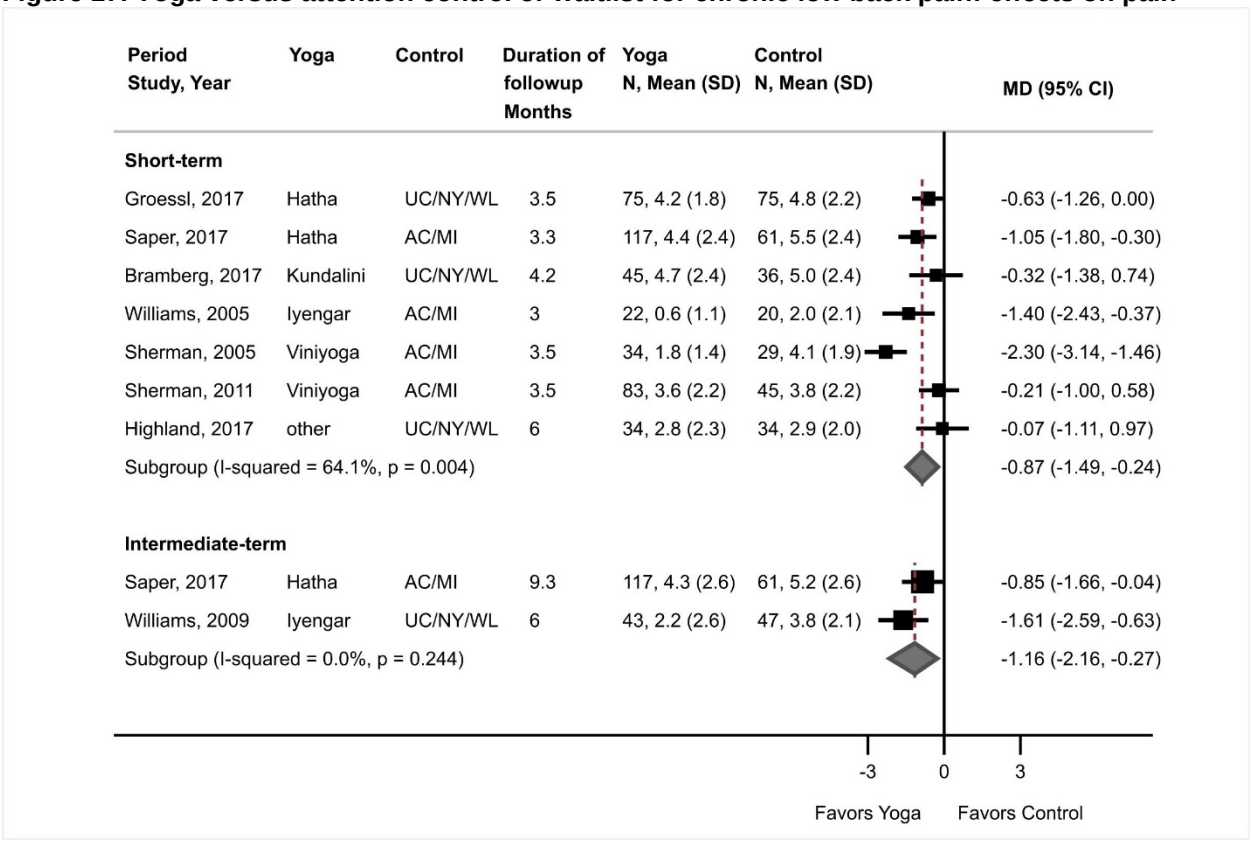
Data on harms were limited, but trials reported no clear difference between yoga versus control interventions in risk of any adverse event (primarily mild, self-limiting back or joint pain).[205,207,208] Three serious adverse events were reported across three trials (≤1% of patients), all in patients randomized to yoga: worsening back pain due to yoga,[205,207,208] herniated disc[205,207,208] and cellulitis[205] (whether the latter two complications were related to yoga is unclear).

Figure 16. Yoga versus attention control or waitlist for chronic low back pain: effects on function



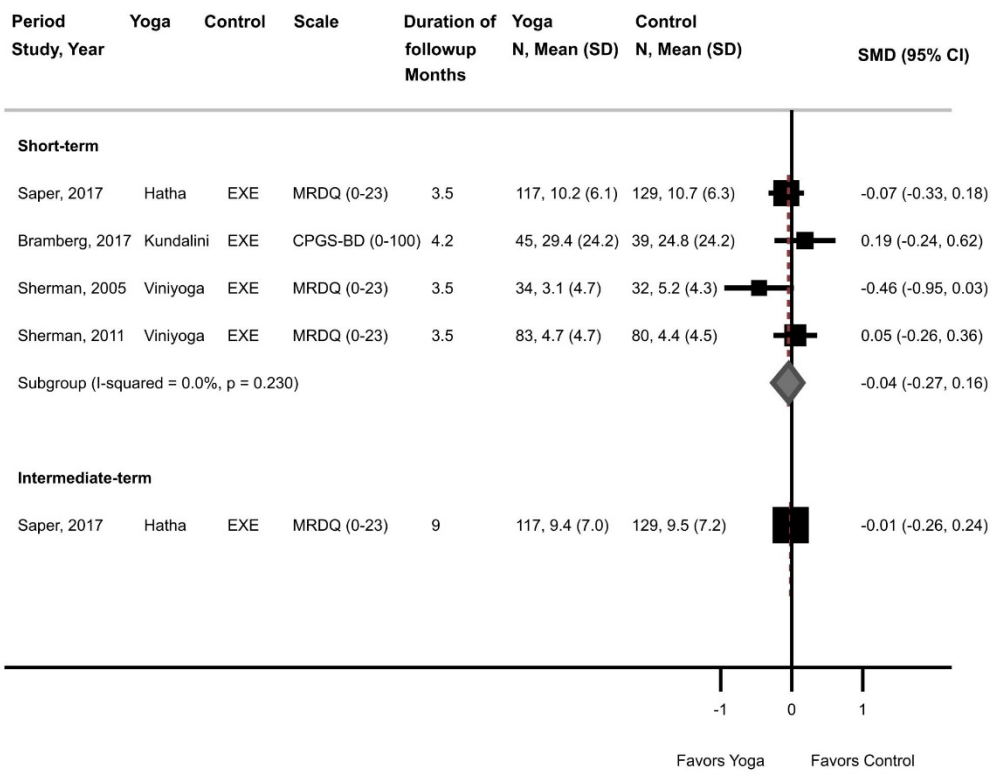
AC = attention control; CI = confidence interval; CPGS=Von Korff Chronic Pain Grade Score; MI = minimal intervention; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; NY = no yoga; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference; UC = usual care; WL = waitlist

Figure 17. Yoga versus attention control or waitlist for chronic low back pain: effects on pain



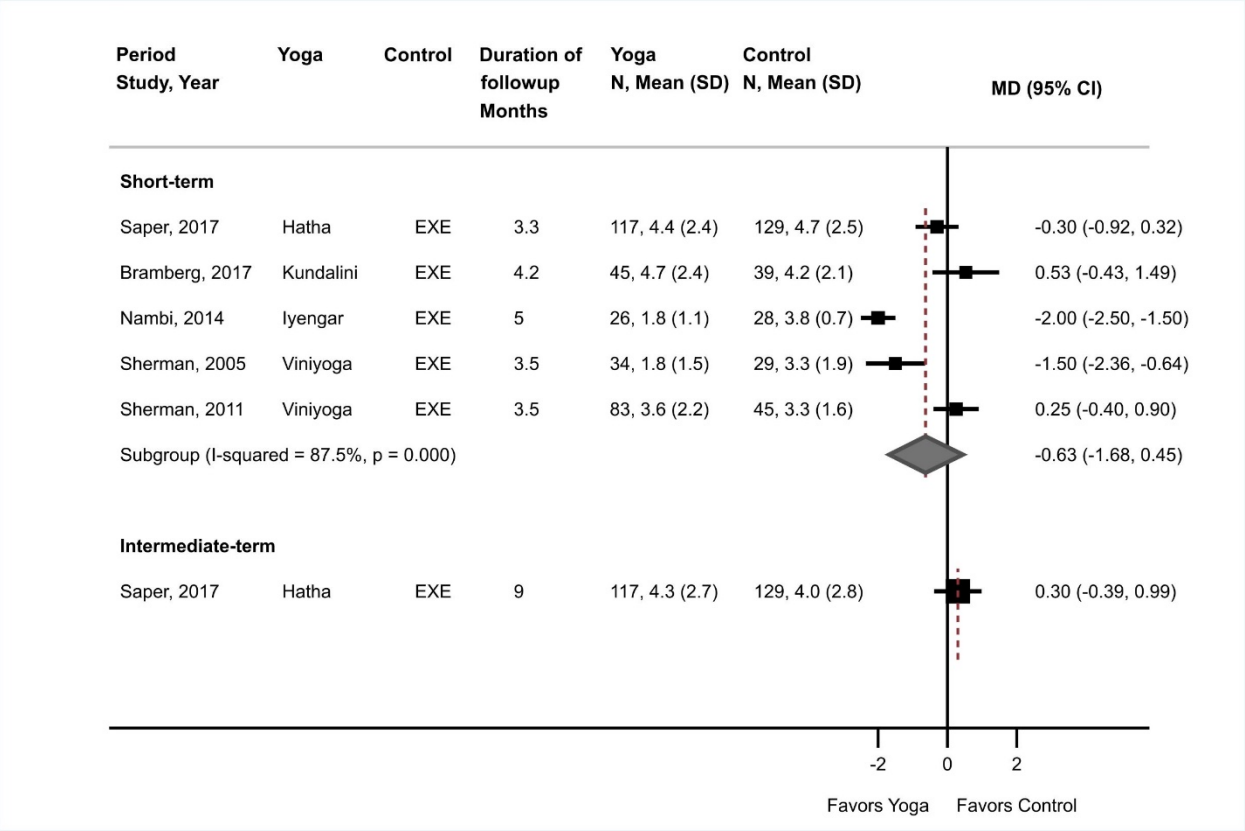
AC = attention control; CI = confidence interval; MI = minimal intervention; N=number; NY = no yoga; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; UC = usual care; WL = waitlist

Figure 18. Yoga versus exercise for chronic low back pain: effects on function



CI = confidence interval; CPGS=Von Korff Chronic Pain Grade Score; EXE = exercise; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; SD = standard deviation; SMD = standardized mean difference

Figure 19. Yoga versus exercise for chronic low back pain: effects on pain



CI = confidence interval; EXE = exercise; N = number; SD = standard deviation

Qigong

One German trial (n=125) compared qigong (weekly sessions for 3 months) versus exercise therapy (including stretching and strengthening) (Table 16 and Appendix D).[219] The trial was included in the prior AHRQ report. It was rated fair quality due to baseline differences between groups, unblinded design, and suboptimal compliance (Appendix E). There was no difference between qigong versus exercise in short-term function (difference 0.9 on the 0 to 24 RDQ, 95% CI −0.1 to 2.0), although intermediate-term results slightly favored exercise (difference 1.2, 95% CI 0.1 to 2.3). Qigong was associated with slightly worse 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). There were no differences in sleep, measures of the SF-36 PCS or MCS scores, or in risk of adverse events.

Table 32. Chronic low back pain: mind-body practices (qigong)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Blodt, 2015[219] 3 and 9 months Duration of pain: Mean 3 years Fair	A. Qigong (movement exercises and exercise to change "qi") (n=64) 12 sessions over 12 weeks B. Exercise (strengthening, stretching and relaxation exercises) (n=63)	A vs. B Age (mean): 46 vs. 48 years Female: 91% vs. 70% Baseline RDQ: 6.2 vs. 5.7 Baseline pain (0-100 VAS): 55.6 vs. 52.1	A vs. B <u>3 months</u> RDQ (0-24): 4.1 vs. 3.1, difference 0.9 (95% CI –0.1 to 2.0) Average low back pain (0-100 VAS): 35.1 vs. 27.4, difference 7.7 (95% CI 0.7 to 14.7) <u>9 months</u> RDQ: 4.3 vs. 3.1, difference 1.2 (95% CI 0.1 to 2.3) Average low back pain (0-100 VAS): 35.9 vs. 28.8, difference 7.1 (95% CI –1.0 to 15.2)	A vs. B <u>3 months</u> SF-36 Bodily pain (0-100): 43.0 vs. 44.6, difference 1.5 (95% CI −1.2 to 4.2) SF-36 Physical component score: 45.8 vs. 46.6, difference −0.8 (95% CI –3.4 to 1.9) SF-36 Mental component score: 45.4 vs. 46.6, difference 11.2 (95% CI –4.9 to 2.4) Quality of sleep (0-10): 4.6 vs. 4.5, difference 0.0 (95% CI–0.9 to 1.0) Sleep satisfaction (0-10): 5.0 vs. 4.8, difference 0.3 (95% CI –0.6 to 1.1) <u>9 months</u> SF-36 Bodily pain: 41.4 vs. 43.4, difference −2.0 (95% CI −5.4 to 1.4) SF-36 Physical component score: 44.8 vs. 46.5, difference −1.8 (95% CI −4.9 to 1.3) SF-36 Mental component score: 45.0 vs. 45.5, difference −0.5 (95% CI −4.6 to 3.6) Quality of sleep: 4.5 vs. 4.7, difference −0.2 (95% CI −1.0 to 0.7) Sleep satisfaction: 5.1 vs. 5.1, difference −0.1 (95% CI –0.9 to 0.8)

CI = confidence interval; RDQ = Roland-Morris Disability Questionnaire; SF-36 = Short-Form 36 Questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Acupuncture for Chronic Low Back Pain

Key Points

- Acupuncture was associated with a small improvement in short-term function compared with sham acupuncture or usual care (4 trials, pooled SMD −0.23, 95% CI −0.35 to −0.04, I^2=25%). There were no differences between acupuncture versus controls in intermediate-term function (3 trials, pooled SMD −0.08, 95% CI −0.42 to 0.28, I^2=64%) 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 small improvements in short-term pain compared with sham acupuncture, usual care, an attention control, or a placebo intervention (5 trials, pooled difference −0.54 on a 0 to 10 scale, 95% CI −0.91 to −0.16, I^2=25%). There was no difference in intermediate-term pain (5 trials, pooled difference −0.22, 95% CI −0.67 to 0.21, I^2=0%); one trial found acupuncture associated with greater effects on long-term pain (difference −0.83, 95% CI −1.53 to −0.13) (SOE: moderate for short term, low for intermediate term and long term).
- There was no clear difference between acupuncture versus control interventions in risk of study discontinuation due to adverse events. Serious adverse events were rare with acupuncture and control interventions (SOE: low).

Detailed Synthesis

Eight trials of acupuncture for low back pain met inclusion criteria (Table 17 and Appendix D).[176,224-230] All of the trials were included in the prior AHRQ report. All trials evaluated needle acupuncture to body acupoints; one trial also evaluated electroacupuncture.[225] Sample sizes ranged from 46 to 1,162 (total sample=2,645). Four trials compared acupuncture versus sham acupuncture,[224,226-228] three trials acupuncture versus usual care,[226,228,230] two trials acupuncture versus a placebo intervention (sham transcutaneous electrical nerve stimulation [TENS]),[225,229] and one trial acupuncture versus an attention control (self-care education).[176] One trial was conducted in Asia[227] and the rest in the United States or Europe. The duration of acupuncture therapy ranged from 6 to 12 weeks and the number of acupuncture sessions ranged from 6 to 15. One trial reported outcomes through long-term followup,[230] four trials through intermediate-term followup,[176,224-226] and the remainder only evaluated short-term outcomes.

One trial was rated good quality,[224] five trials fair quality,[176,226-228,230] and two trials[225,229] poor quality (Appendix E). Limitations in the fair-quality and poor-quality trials included unblinded design, unclear randomization or allocation concealment methods, and high attrition.

Table 33. Chronic low back pain: acupuncture

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Brinkhaus, 2006a[224] 4 and 10 months Duration of pain: 14.7 vs. 13.6 years Good	A: Needle acupuncture to body acupoints (n=140) 12 sessions over 8 weeks B: Sham acupuncture (n=70)	A vs. B Age: 59 vs. 58 years Female: 64% vs. 75% Baseline Functional (FFbH-R) score: 57.1 vs. 57.2 Baseline pain (0-100 VAS): 63 vs. 66 Baseline Pain Disability Index (0-70): 28.9 vs. 31.5	A vs. B <u>4 months</u> Functional (0-10, FFbH-R 0, higher scores indicate better function): 66.0 vs. 64.1, difference 1.9 (95% CI −4.2 to 8.0) Number of days with limited function in past 6 months: 40.9 vs. 59.5, difference −18.6 (95% CI −33.3 to −3.9) Pain (0-100 VAS): 38.4 vs. 42.1, difference −3.8 (95% CI −12.4 to 4.9) Pain Disability Index (0-70): 19.3 vs. 21.4, difference −2.1 (95% CI −6.3 to 2.1) <u>10 months</u> Functional (0-100 FFbH-R): 66.0 vs. 63.1, difference 2.9 (95% CI −3.2 to 9.0) Number of days with limited function in past 6 months: 42.4 vs. 52.9, difference −10.5 (95% CI −27.0 to 6.1) Pain (0-100 VAS): 39.2 vs. 44.9, difference −5.7 (95% CI −14.4 to 3.0) Pain Disability Index: 19.0 vs. 23.0, difference −4.0 (95% CI −8.1 to 0.1)	A vs. B <u>4 months</u> SF-36 bodily pain subscale (0-100): 53.6 vs. 49.6, difference 3.9 (95% CI −2.7 to 10.7) SF-36 PCS (0-100): 39.3 vs. 37.6, difference 1.7 (95% CI −1.3 to 4.7) SF-36 MCS (0-100): 49.9 vs. 46.8, difference 3.1 (95% CI −0.5 to 6.6) Allgemaine Depressionssskala (ADS, t standard): 49.7 vs. 50.3, difference −0.6 (95% CI −2.5 to 3.7) <u>10 months</u> SF-36 bodily pain subscale: 52.4 vs. 44.0, difference 8.5 (95% CI 1.7 to 15.2) SF-36 PCS: 38.9 vs. 36.1, difference 2.8 (95% CI −0.2 to 5.7) SF-36 MCS: 50.5 vs. 47.2, difference 3.3 (95% CI 0.1 to 6.5) ADS: 48.2 vs. 50.7, difference −2.5 (95% CI −5.3 to 0.4)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Carlsson, 2001[225] 1, 3, 6 months Duration of pain: 6 months or longer Poor	A. Needle acupuncture or electroacupuncture (n=34), 8 sessions over 8 weeks, with followup session at 3 and 6 months B. Placebo (sham transcutaneous electrical nerve stimulation) (n=16)	A vs. B (NR) Age: 50 years Female: 66% Baseline function: NR Baseline Pain (0-100 VAS): 57 vs. 46	A vs. B <u>1 month</u> Pain (0-100 VAS): 50 vs. 60, P not reported Global assessment "pain improved": 47% vs. 13%, RR 3.76 (95% CI 0.98 to 14.4) <u>3 months</u> Pain (0-100 VAS): 42 vs. 56, P not reported Global assessment "pain improved": 44% vs. 13%, RR 6.87 (95% CI 1.87 to 25.1) <u>≥6 months outcomes</u> Pain (0-100 VAS): 41 vs. 50, P not reported Global assessment "pain improved": 41% vs. 13%, RR 3.29 (95% CI 0.85 to 12.8)	A vs. B <u>≥6 months</u> Analgesic intake (tablets per week): 21.4 vs. 21.5 Work full time: 32% vs. 31%
Cherkin, 2001[176] 9.5 months Duration of pain: 3 to 12 months, mean not reported Fair	A. Needle acupuncture (n=94),10 sessions over 10 weeks B. Attention control (education) (n=90)	A vs. B Age: 54 vs. 44 years Female: 52% vs. 44% Baseline symptom bothersomeness (0-10): 6.2 vs. 6.1 Baseline modified RDQ (0-23): 12. vs. 12.0	A vs. B <u>9.5 months</u> Symptom bothersomeness (0-10): 4.5 vs. 3.8, adjusted p=0.002 Modified RDQ (0-23): 8.0 vs. 6.4, adjusted p=0.05	A vs. B <u>9.5 months</u> ≥1 work-loss day due to LBP in past month: No difference (data not reported) Medication use: 51% vs. 62%, p<0.05 Provider visits:1.9 vs. 1.5 LBP medication fills: 4.4 vs. 4.0 Imaging studies: 0.2 vs. 0.1 Cost of services (1998 $): 252 vs. 200

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cherkin, 2009[226] 4.5 and 10.5 months Duration of pain: 3 to 12 months, mean not reported Fair	A. Needle acupuncture (individualized) (n=157), 10 sessions over 7 weeks B. Needle acupuncture (standardized) (n=158), 10 sessions over 7 weeks C. Sham acupuncture (n=162) D. Usual care (n=161)	A vs. B vs. C vs. D Age: 47 vs. 49 vs. 47 vs. 46 years Female: 68% vs. 56% vs. 60% vs. 64% Symptom bothersomeness (0-10): 5.0 vs. 5.0 vs. 4.9 vs. 5.4 Baseline pain (0-10 VAS): 5.0 vs. 5.0 vs. 4.9 vs. 5.3 Baseline modified RDQ (0-23): 10.8 vs. 10.8 vs. 9.8 vs. 11.0	A vs. B <u>4.5 months</u> Symptom bothersomeness (0-10): 3.8 (2.5) vs. 3.7 (2.6) vs. 3.5 (2.7) vs. 4.4 (2.6) ≥2 point decrease in symptom bothersomeness: 49% vs. 44% vs. 48% vs. 41% Modified RDQ (0-23): 6.8 (5.5) vs. 6.7 (5.8) vs. 6.4 (6.0) vs. 8.4 (6.0) <u>10.5 months</u> Symptom bothersomeness (0-10): 3.7 (2.6) vs. 3.5 (2.7) vs. 3.4 (2.7) vs. 4.1 (2.6) ≥2 point decrease in symptom bothersomeness: 52% vs. 49% vs. 50% vs. 47% Modified RDQ (0-23): 6.0 (5.4) vs. 6.0 (5.8) vs. 6.2 (5.8) vs. 7.9 (6.5) ≥3 point decrease on RDQ: 65% vs. 65% vs. 59% vs. 50% >7 days with cutting down on activities due to LBP in the past month: A, B and C 5-7% vs. D 18%, p=0.0005	A vs. B <u>10.5 months</u> SF-36 PCS: No differences, data not provided SF-36 MCS: No differences, data not provided Missed work/school for >1 day in past month: A, B and C 5-10% vs. D 16%, p=0.01 Mean total costs of back-related health services: $160-221 across groups, p=0.65
Cho, 2013[227] 1.5 and 4 months Duration of pain: 3 months Fair	A. Needle acupuncture (n=57), 12 sessions over 6 weeks B. Sham acupuncture (n=59)	A vs. B Age: 42 vs. 42 years Female: 83% vs. 86% Baseline ODI (0-100): 28.2 vs. 24.2 Baseline pain (0-10 VAS): 6.5 vs. 6.4	A vs. B <u>1.5 months</u> ODI (0-100): 15.5 vs. 15.5 bothersomeness (0-10 VAS): 2.83 vs. 3.99 Pain (0-10 VAS): 2.78 vs. 4.06 <u>4 months</u> ODI: 15.3 vs. 15.3 Symptom bothersomeness: 2.85 vs. 3.63 Pain (0-10 VAS): 2.79 vs. 3.52	A vs. B <u>1.5 months</u> Beck Depression Inventory (0-63): 6 vs. 7.5 <u>4 months</u> Beck Depression Inventory: 6 vs. 7

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Haake, 2007[228] 1.5 and 4.5 months Duration of pain: Mean 8 years Fair	A. Needle acupuncture (n=387), 10-15 sessions over 5 weeks B. Sham acupuncture (n=387) C. Usual care (n=388)	A vs. B vs. C Age: 50 vs. 49 vs. 51 years Female: 57% vs. 64% vs. 58% Baseline Hannover Functional Ability Questionnaire (0-100): 46.3 vs. 46.3 vs. 46.7 Baseline Von Korff Chronic Pain Grade Scale (0-100): 67.7 vs. 67.8 vs. 67.8	A vs. B <u>1.5 months</u> Hannover Functional Ability (0-100): 65.4 vs. 61.3 vs. 56.0 Von Korff Chronic Pain Grade Scale (0-100): 45.4 vs. 48.5 vs. 54.8 <u>4.5 months</u> Hannover Functional Ability (0-100): 66.8 vs. 62.2 vs. 55.7 Von Korff Chronic Pain Grade Scale: 40.2 vs. 43.3 vs. 52.3	A vs. B <u>1.5 months</u> SF-12 PCS (0-100): 40.3 vs. 39.2 vs. 36.1 SF-12 MCS (0-100): 50.5 vs. 50.2 vs. 48.6 Treatment response (≥33% improvement in pain or ≥12% improvement in function): 55.0% (213/387) vs. 51.9% (201/387) vs. 41.9% (162/387), RR 1.05 (95% CI 0.93 to 1.21) for A vs. B and RR 1.31 (95% CI 1.13 to 1.52) for A vs. C <u>4.5 months</u> SF-12 PCS (0-100): 41.6 vs. 39. vs. 35.8 SF-12 MCS (0-100): 50.7 vs. 50.9 vs. 49.2 Treatment response: 47.6% (184/387) vs. 44.2% (171/387) vs. 27.4% (106/387), RR 1.08 (95% CI 0.92 to 1.25) for A vs. B and RR 1.74 (95% CI 1.43 to 2.11) for A vs. C
Kerr, 2003[229] 4.5 months Duration of pain: Mean 86 vs. 73 months Poor	A. Needle acupuncture (n=26), 6 sessions over 6 weeks B. Placebo (sham TENS) (n=20)	A vs. B Age: 43 vs. 43 years Female: 50% vs. 35% Baseline function: NR Baseline pain (0-100 VAS): 79.7 vs. 76	A vs. B <u>4.5 months</u> Pain relief "yes": 91% vs. 75%, RR 1.19 (95% CI 0.89 to 1.60)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Thomas, 2006[230] 9 and 21 months Duration of pain: Mean 17 weeks Fair	A. Needle acupuncture (n=159), 10 sessions over 12 weeks B. Usual care (n=80)	A vs. B Age: 42 vs. 44 Female: 62% vs. 58% Baseline ODI (0-100): 33.7 vs. 31.4 Baseline McGill Present Pain Index (0-5): 2.64 vs. 2.70	A vs. B <u>9 months</u> ODI (0-100): 20.6 vs. 19.6, adjusted difference −0.5 (−5.1 to 4.2) McGill Present Pain Index (0-5): 1.43 vs. 1.53, adjusted difference −0.1 (−0.4 to 0.3) <u>21 months</u> ODI: 18.3 vs. 21.0, adjusted difference −3.4 (−7.8 to 1.0) McGill Present Pain Index: 1.42 (1.1) vs. 1.71, adjusted difference −0.2 (−0.6 to 0.1)	A vs. B <u>9 months</u> SF-36 bodily pain (0-100): 64.0 vs. 58.3, adjusted difference 5.6 (95% CI −0.2 to 11.4) <u>21 months</u> Used medication for LBP in the past 4 weeks: 40% vs. 59%, difference −19% (−35 to −3), p=0.03 <u>21 months</u> SF-36 bodily pain: 67.8 vs. 59.5, adjusted difference 8.0 (2.8 to 13.2)

CI = confidence interval; FFbH-R = Funktionsfragebogen Hannover-Rücken (Hannover Functional Ability Questionnaire-back); LBP = low back pain; MCS = Mental Component Summary; NR = not reported; ODI = Oswestry Disability Index; PCS = Physical Component Summary; RDQ = Roland-Morris Disability Questionnaire; RR = Relative risk; SF-36 = Short-Form 36 Questionnaire; TENS = transcutaneous electrical nerve stimulation; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Acupuncture Compared With Sham Acupuncture, Usual Care, an Attention Control, or a Placebo Intervention

Acupuncture was associated with small improvements in short-term function compared with sham acupuncture or usual care (4 trials, pooled SMD −0.23, 95% CI −0.35 to −0.04, I^2=25%) (Figure 20).[224,226-228] Each trial measured function using a different scale; across trials the SMD ranged from −0.34 to 0.00. Differences were slightly greater in trials that compared acupuncture against usual care (2 trials, SMD −0.43, 95% CI −0.60 to −0.22)[226,228] than against sham acupuncture (4 trials, SMD −0.13, 95% CI −0.24 to 0.01).[224,226-228] None of the trials were rated poor quality. There were no differences between acupuncture versus controls in intermediate-term function (3 trials, pooled SMD −0.08, 95% CI −0.42 to 0.28, I^2=64%)[176,224,226] or long-term function (1 trial, adjusted difference −3.4 on the 0 to 100 ODI, 95% CI −7.8 to 1.0).[230]

Acupuncture was associated with small improvements in short-term pain compared with sham acupuncture, usual care, an attention control, or a placebo intervention (5 trials, pooled difference −0.54 on a 0 to 10 scale, 95% CI −0.91 to −0.16, I^2=25%) (Figure 21).[224-228] The pooled estimate was similar when poor-quality trials were excluded. When stratified according to the type of control intervention, acupuncture was associated with greater effects when compared with usual care (2 trials, pooled difference −1.01, 95% CI −1.60 to −0.28)[226,228] than when compared with sham acupuncture (4 trials, pooled difference −0.21, 95% CI −0.66 to 0.18).[224,226-228] There was no difference between acupuncture versus controls in intermediate-term pain (5 trials, pooled difference −0.22, 95% CI −0.67 to 0.21, I^2=0%).[176,224-226,230] One trial found acupuncture associated with greater effects on long-term pain than usual care (difference −0.83, 95% CI −1.53 to −0.13).[230]

Data on effects of acupuncture on quality of life were limited. In two trials, differences between acupuncture versus sham acupuncture or usual care on short-term or intermediate-term SF-36 PCS and MCS scores were small (range 0.64 to 3.92 points on a 0 to 100 scale), and most differences were not statistically significant.[224,228] Two trials found no clear effects of acupuncture and controls on measures of depression.[224,227]

Two trials found no clear differences between acupuncture versus an attention control in measures of healthcare utilization (provider visits, medication fills, imaging studies, costs of services),[176,226] and one trial found no clear differences at intermediate-term followup between acupuncture versus placebo TENS in likelihood of working full time.[225]

One trial found acupuncture associated with a higher likelihood of short-term (4.5 months) treatment response (defined as ≥33% pain improvement and ≥12% functional improvement) versus usual care (48% vs. 27%, RR 1.74, 95% CI 1.43 to 2.11), but there was no difference versus sham acupuncture (RR 1.08, 95% CI 0.92 to 1.25).[228]

No trial evaluated effects of acupuncture on use of opioid therapies or healthcare utilization. There was insufficient evidence to determine effects of duration of acupuncture or number of acupuncture sessions on findings.

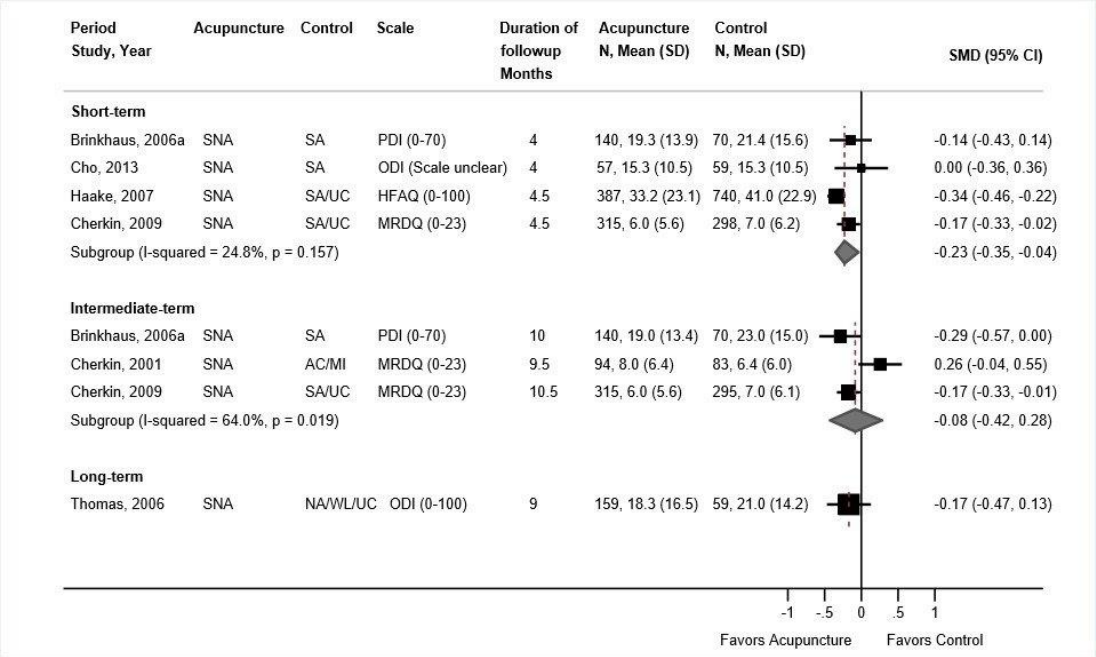
Acupuncture Compared With Pharmacological Therapy or With Exercise

No trial of acupuncture versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

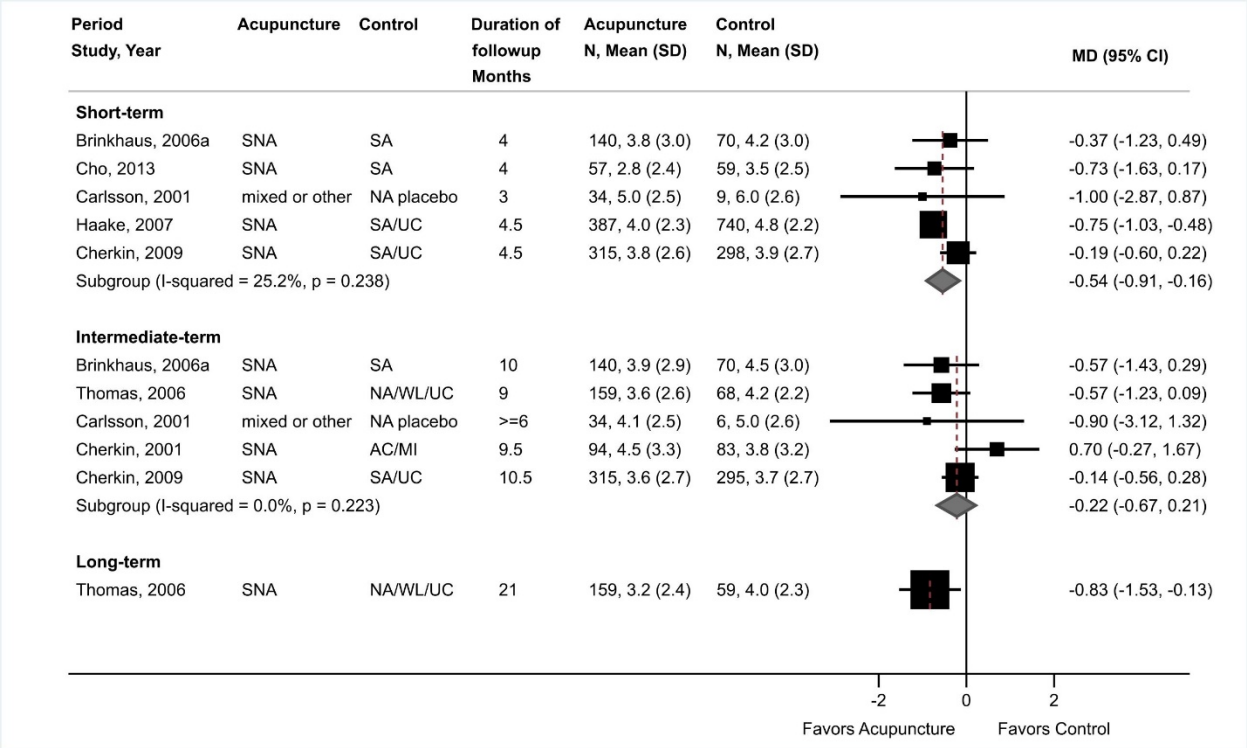
Data on harms were limited but indicated no clear difference between acupuncture versus control interventions in risk of withdrawal due to adverse events.[226,230] Serious adverse events were rare with acupuncture and control interventions.[176,224,226-228]

Figure 20. Acupuncture versus sham acupuncture, usual care, attention control, or a placebo intervention for chronic low back pain: effects on function



AC = attention control; CI = confidence interval; HFAQ = Hannover Functional Ability Questionnaire; MI = minimal intervention; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; NE = no exercise; ODI = Oswestry Disability Index; PDI = Pain Disability Index; SA=sham acupuncture; SD = standard deviation; SMD = standardized mean difference; SNA =standard needle acupuncture; UC = usual care; WL = waitlist

Figure 21. Acupuncture versus sham acupuncture, usual care, an attention control, or a placebo intervention for chronic low back pain: effects on pain



AC = attention control; CI = confidence interval; MI = minimal intervention; N = number; NA = needle acupuncture; SA=sham acupuncture; SD = standard deviation; SNA = standard needle acupuncture; UC = usual care; WL = waitlist

Multidisciplinary Rehabilitation for Chronic Low Back Pain

Key Points

- Multidisciplinary rehabilitation was associated with small improvements in function compared with usual care at short-term (4 trials, pooled SMD −0.30, 95% CI −0.63 to 0.00, I^2=58%) and intermediate-term followup (4 trials, pooled SMD −0.37, 95% CI −0.69 to −0.08, I^2=34%); there was no difference in long-term function (2 trials, pooled SMD −0.04, 95% CI −0.36 to 0.35, I^2=0%) (SOE: low).
- Multidisciplinary rehabilitation was associated with small improvements in pain compared with usual care at short-term followup (4 trials, pooled difference −0.53 on a 0 to 10 scale, 95% CI −0.86 to −0.11, I^2=0%) and intermediate-term followup (4 trials, pooled difference −0.62, 95% CI −1.06 to −0.18, I^2=0%); the long-term difference was smaller and not statistically significant (2 trials, pooled difference −0.35, 95% CI −1.10 to 0.34, I^2=0%) (SOE: moderate for short term and intermediate term, low for long term).
- Multidisciplinary rehabilitation was associated with a small improvement compared with exercise in short-term function (6 trials, pooled SMD −0.20, 95% CI −0.54 to 0.00, I^2=0%) and intermediate-term function (5 trials [excluding outlier trial], pooled SMD −0.20, 95% CI −0.40 to −0.00, I^2=0%); there was no effect on long-term function (2 trials [excluding outlier trial], pooled SMD −0.07, 95% CI −0.50 to 0.39, I^2=0%) (SOE: moderate for short term and intermediate term, low for long term).

- Multidisciplinary rehabilitation was associated with a small improvement compared with exercise in short-term pain (6 trials, pooled difference −0.69 on a 0 to 10 scale, 95% CI −1.16 to −0.22, I^2=0%) and intermediate-term pain (5 trials [excluding outlier trial], pooled difference −0.55, 95% CI −1.00 to −0.11, I^2=0%); there was no effect on long-term pain (2 trials [excluding outlier trial], pooled difference 0.00, 95% CI −1.31 to 1.17) (SOE: moderate for short term and intermediate term, low for long term).
- Data on harms were sparse; no serious harms were reported (SOE: insufficient).

Detailed Synthesis

Sixteen trials (reported in 21 publications) of multidisciplinary rehabilitation for low back pain met inclusion criteria (Table 18 and Appendix D).[35,133,140,189,255-260,269-281] All of the trials were included in the prior AHRQ report. In accordance with our definition for multidisciplinary rehabilitation, the intervention in all trials included a psychological therapy and an exercise therapy component, with therapy developed by clinicians from at least two disciplines. Most multidisciplinary rehabilitation interventions incorporated techniques and approaches consistent with principles of functional restoration.[283] The intensity of multidisciplinary rehabilitation varied substantially, with treatment ranging from 4 to 150 hours. Five trials evaluated a multidisciplinary rehabilitation intervention that met our criteria for high intensity (≥20 hours/week or >80 hours total).[255,260,270,271,278] The duration of therapy ranged from 4 days to up to 13 weeks. Sample sizes ranged from 20 to 459 (total sample=1,964). Six trials compared multidisciplinary rehabilitation versus usual care,[255-260] nine trials compared multidisciplinary rehabilitation versus exercise therapy,[133,257,270,271,273-278] and one trial compared multidisciplinary rehabilitation versus oral medications.[269] One trial[269] was conducted in Iran and the remainder were conducted in the United States, the United Kingdom, or Australia. Five trials reported outcomes through long-term (12 to 60 months) followup,[133,255,269,270,276] eight trials evaluated outcomes through intermediate-term followup,[133,258-260,271,273,275,278,279] and three trials only evaluated short-term outcomes.[256,274,277]

Ten trials[255,257,258,270,271,274-278] were rated fair quality and six trials poor quality (Appendix E).[133,256,259,260,269,273] The major methodological limitation in the fair-quality trials was the inability to effectively blind patients and caregivers to the multidisciplinary rehabilitation. Other methodological shortcomings included unclear randomization and allocation concealment methods and high attrition.

Table 34. Chronic low back pain: multidisciplinary rehabilitation

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Abbassi, 2012[259] 10.25 months Duration of pain: ~6 years Poor	A. Multidisciplinary rehabilitation (n=12), 7 sessions over 7 weeks B. Multidisciplinary pain management (spouse-assisted) (n=10). 7 sessions over 7 weeks C: Usual care (n=11)	A + B + C Overall Age (mean): 45 years Female: 88% A vs. B vs. C Baseline RDQ (0–24): 12.1 vs. 11.2 vs. 8.4 Baseline pain (0-10 VAS): 4.6 vs. 5 vs. 3.6	A vs. B vs. C <u>10.25 months</u> RDQ (0–24): 8.8 vs. 8.2 vs. 10.4, p=0.44 Pain (0–10 VAS): 3.7 vs. 2.8 vs. 4.3, p=0.44	NR
Bendix, 1995,[270] 1997,[280] 1998[281] 60 months Duration of pain: >6 months Fair	A. Multidisciplinary rehabilitation (n=40), 18 sessions over 6 weeks (total ~135 hours) B. Multidisciplinary rehabilitation (n=35), 12 sessions over 6 weeks (total 24 hours) C. Exercise (n=31)	A vs. B vs. C Age: 40 vs. 44 vs. 42 Female: 75% vs. 77% vs. 74% Baseline pain (0-10 NRS): 5.3 vs. 5.9 vs. 5.4 Baseline Low Back Pain Rating Scale (0-30): 15.5 vs. 15.3 vs. 14.4	A vs. B vs. C <u>3.25 months</u> Back pain (0-10 NRS): 2.7 vs. 5.6 vs. 4.4, p<0.001 Low Back Pain Rating Scale (0-30): 8.5 vs. 16.1 vs. 13.5, p=0.002 <u>12 months</u> Back pain (0-10 NRS): 3.3 vs. 6.5 vs. 5.3, p=0.005 Low Back Pain Rating Scale (0-30): 8.9 vs. 16.4 vs. 13.7, p<0.001 <u>24 months</u> Back pain (0-10 NRS): 3 vs. 6 vs. 5, p=0.08 Low Back Pain Rating Scale (0-30): 10 vs. 17 vs. 14, p=0.003 <u>60 months</u> Back pain (0-10 NRS): 4 vs. 6 vs. 5, p=0.3 Low Back Pain Rating Scale (0-30): 8 vs. 16 vs. 14, p=0.02	A vs. B vs. C <u>3.25 months</u> Days of sick leave: 25 vs.122 vs. 13, p=0.005 Healthcare system contacts: 0.5 vs. 2.8 vs. 1.3, p=0.05 <u>12 months</u> Days of sick leave: 52 vs. 295 vs. 100, p=0.002 Healthcare system contacts: 4.5 vs. 12.0 vs. 11.8, p=0.002 Days of sick leave: 2.5 vs. 37 vs. 11, p=0.06 <u>24 months</u> Healthcare system contacts: 5 vs. 21 vs. 14, p=0.03 Overall assessment (1-5): 2 vs. 3 vs. 3, p=0.005 <u>60 months</u> Overall assessment (1-5): 2 vs. 3 vs. 3, p=0.004 Increase in proportion able to work: 30% vs. 23% vs. 0%, p=0.001 Days of sick leave: 13 vs. 11 vs. 88, p=0.2 Healthcare system contacts: 15 vs. 10 vs. 24, p=0.2 Back surgery: 5% vs. 10% vs. 10%, p=0.7

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bendix,1996,[255] 1998[281] 60 months Duration of pain: >6 months Fair	A. Multidisciplinary rehabilitation (n=55), 18 sessions over 6 weeks (total ~135 hours) B. Usual care (n=51)	A vs. B Age 41 vs.40 years Female: 71% vs. 69% Baseline pain (0-10 NRS): 6.1 vs. 6.1 Baseline Low Back Pain Rating Scale (0-30): 16.9 vs. 15.9	A vs. B <u>3.25 months</u> Back pain (0-10 NRS): 5.7 vs. 6.9, p=0.05 Low Back Pain Rating Scale (0-30): 12.1 vs. 16.8, p<0.001 <u>24 months</u> Back pain (0-10 NRS): 6 vs. 6.5, p=0.5 Low Back Pain Rating Scale (0-30): 16 vs. 15, p=0.9 <u>60 months</u> Back pain (0-10 NRS): 5 vs. 5, p=1.0 Low Back Pain Rating Scale (0-30): 12 vs. 16, p=0.2	A vs. B <u>3.25 months</u> Days of sick leave: 10 vs. 122, p=0.02 Contacts to health-care system: 1.6 vs. 5.3, p<0.001 <u>24 months</u> Days of sick leave: 15 vs. 123, p<0.001 Healthcare system contacts: 12 vs. 26, p<0.001 <u>60 months</u> Days of sick leave: 10 vs. 50, p=0.4 Healthcare system contacts: 16 vs. 48, p=0.1 Back surgery: 7% vs. 12%, p=0.4
Bendix, 2000[271] 10 months Duration of pain: Not reported Fair	A. Multidisciplinary rehabilitation (n=59), 18 sessions over 8 weeks (total ~139 hours) B. Exercise (n=68)	A vs. B Age: 40 vs. 43 years Female: 66% vs. 65% Baseline function: NR Baseline pain: NR	A vs. B <u>10 months</u> Back pain (0–10): 5.1 vs. 5.7, p=0.33 Low Back Pain Rating Scale (0–30 ADL): 12 vs. 13, p=0.41	A vs. B <u>10 months</u> Overall assessment (1–5): 1.7 vs. 2.7, p=0.03 Work capable: 75% vs. 69%, p=0.64 Healthcare contacts (number): 2.5 vs. 4, p=0.28
Harkapaa, 1989[256] 1 month Duration of pain: >2 years Poor	A. Multidisciplinary rehabilitation (inpatient) (n=156), 3 weeks (number of sessions and total hours unclear) B. Multidisciplinary rehabilitation (outpatient) (n=150), 15 sessions over 8 weeks (total hours unclear) C. Usual care (n=153)	A vs. B vs. C Age: 45 vs. 45 vs. 45 years Female: 37% vs. 39% vs. 35% Baseline function, LBP Disability Index (0-45): 16.7 vs. 17.6 vs. 16.7 Baseline Pain Index (0-400): 184.9 vs. 178.6 vs. 175.8	A vs. B vs. C <u>1 month</u> LBP Disability Index (0-45): 13.8 vs. 14.7 vs. 17.3, p<0.004 for A vs. C and p<0.01 for B vs. C Pain Index (0-400): 127 vs. 145 vs. 160, p<0.001 for A vs. C and p<0.04 for B vs. C	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Jousset, 2004[272] 5 months Duration of pain: >4 months Poor	A. Multidisciplinary rehabilitation (n=44), 25 sessions over 5 weeks (total 150 hours) B. Exercise (n=42)	A vs. B Age: 41 vs. 40 years Female: 30% vs. 37% Baseline function Quebec Disability Scale (0-100): 34.6 vs. 31.6 Baseline pain (0-10 NRS): 5.0 vs. 4.6	A vs. B <u>5 months</u> Quebec Disability Scale (0-100): 22.0 vs. 22.9, p=0.80 Pain (0-10 NRS): 3.1 vs. 4.0, p=0.01 Dallas Pain Questionnaire ADL (0-100): 36.7 vs. 41.5, p=0.36	A vs. B <u>5 months</u> Hospital Anxiety Depression Scale (0-21): 12.7 vs. 13.4 (6.4), p=0.62 Dallas Pain Questionnaire Social interest (0-100): 19.6 vs. 24.3, p=0.37
Lambeek 2010[258] 9 months Duration of pain: >4 months Fair	A. Multidisciplinary rehabilitation (n=66), 26+ sessions over up to 13 weeks (total hours unclear) B. Usual care (n=68)	A vs. B Age: 46 vs. 47 years Female: 44% vs. 40% Baseline modified RDQ (0-23): 14.7 vs. 15.0 Baseline pain (0-10 VAS): 5.7 vs. 6.3	A vs. B <u>3 months</u> Modified RDQ (0-23): 4.8 vs. 5.0 (0.9), adjusted difference 0.06, 95% CI −2.3 to 2.5 Pain (0-10 VAS): 1.3 vs. 2.3, adjusted difference 0.5, 95% CI −0.6 to 1.6 <u>9 months</u> Modified RDQ (0-23): 7.2 vs. 4.4, adjusted difference −2.9, 95% CI −4.9 to −0.9 Pain (0-10 VAS): 1.6 vs. 1.9, adjusted difference 0.21, 95% CI −0.8 to 1.2	A vs. B <u>9 months</u> General practitioner visits (# of patients): 13 vs. 29 Medical specialist visits (# of patients): 13 vs. 29 Total costs (pounds): 13,165 (SD 13,600) vs. 18,475 (SD 13,616), difference −5,310 (95% CI −10,042 to −391)
Monticone 2013[276] 23 months Duration of pain: 25 vs. 26 months Fair	A. Multidisciplinary rehabilitation (n=45), 26 sessions over 5 weeks (total 26 hours) B. Exercise (n=45)	A vs. B Age: 49 vs. 50 years Female: 60% vs. 56% Baseline RDQ (0-24): 15.3 vs. 15.0 Baseline pain (0-10 VAS): 7.0 vs. 7.0	A vs. B <u>11 months</u> RDQ (0-24): 1.3 (1.6) vs. 11.0 (2.0) Pain (0-10 VAS): 1.4 (1.1) vs. 5.3 (1.2) <u>23 months</u> RDQ (0-24): 1.4 vs. 11.1, difference −9.7, 95% CI −10.4 to −9.0 Pain (0-10 VAS): 1.5 vs. 6.2, difference −4.7, 95% CI −5.1 to −4.3	A vs. B <u>11 months</u> SF-36 physical pain (0-100): 79.0 (14.6) vs. 52.0 (16.2) SF-36 physical functioning (0-100): 85.7 (19.6) vs. 62.1 (19.4) SF-36 general health (0-100): 85.0 (13.8) vs. 56.4 (15.9) SF-36 mental health (0-100): 89.8 (13.0) vs. 54.1 (11.9) <u>23 months</u> SF-36 physical pain: 80.4 vs. 61.8, difference 18.6, 95% CI 12.8 to 24.3 SF-36 physical functioning (0-100): 87.6 vs. 65.0, difference 22.6, 95% CI 15.0 to 30.1 SF-36 general health: 86.3 vs. 63.1, difference 23.2, 95% CI 17.3 to 29.1 SF-36 mental health: 91.0 vs. 58.8, difference 32.2, 95% CI 27.4 to 37.0)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Monticone 2014[277] 3 months Duration of pain: 15 vs. 14 months Fair	A. Multidisciplinary rehabilitation (n=10), 16 sessions over 8 weeks (total 16 hours) B. Exercise (n=10)	A vs. B Age: 59 vs. 57 years Female: 7% vs. 4% Baseline function (0-100 ODI): 26 vs. 24 Baseline pain (0-10 NRS): 5 vs. 4	A vs. B <u>3 months</u> ODI (0-100): 8 vs. 15, p=0.027 Pain (0-10 NRS): 2 vs. 3, p=1.0	A vs. B <u>3 months</u> SF-36 bodily pain (0-100): 65 vs. 55, p=0.261 SF-36 general health (0-100): 71 vs. 55, p=0.018 SF-36 social function (0-100): 81 vs. 61, p=0.001 SF-36 emotional role (0-100): 77 vs. 57, p=0.007 SF-36 mental health (0-100): 88 vs. 67, p=0.001
Nicholas, 1991[273] 11 months Duration of pain: 7 years Poor	A. Multidisciplinary rehabilitation (cognitive treatment) (n=10) B. Multidisciplinary rehabilitation (behavioral treatment) (n=10) C. Multidisciplinary rehabilitation (cognitive treatment and relaxation treatment) (n=8) D. Multidisciplinary rehabilitation (behavioral treatment and relaxation training) (n=9) E. Exercise + attention control (psychologist-led group discussions) (n=10) F. Exercise (n=11) For all multidisciplinary rehabilitation interventions, 19 sessions over 5 weeks (total 21.5 hours)	Overall Age: 41 years Female: 51% A vs. B vs. C vs. D vs. E vs. F Baseline function, (0-100 Sickness Impact Profile): 37.13 vs. 34.24 vs. 33.41 vs. 20.53 vs. 27.12 vs. 28.06 Baseline pain (0-5 categorical scale): 2.78 vs. 2.96 vs. 3.80 vs. 2.27 vs. 2.84 vs. 2.77	A vs. B vs. C vs. D vs. E vs. F <u>5 months</u> Sickness Impact Profile (0-100): 24.42 (11.78) vs. 15.44 (14.12) vs. 25.69 (8.50) vs. 14.86 (9.08) vs. 19.40 (6.89) vs. 29.78 (8.76) Pain (0-5 categorical scale): 2.18 (0.55) vs. 1.87 (0.73) vs. 3.20 (0.93) vs. 2.22 (0.48) vs. 2.64 (0.90) vs. 3.18 (0.72) <u>11 months</u> Sickness Impact Profile (0-100): 23.85 (12.50) vs. 12.80 (8.62) vs. 20.77 (8.29) vs. 12.87 (6.68) vs. 18.94 (12.79) vs. 25.18 (8.08) Pain (0-5 categorical scale): 2.56 (0.97) vs. 2.66 (1.06) vs. 3.30 (0.83) vs. 1.88 (0.65) vs. 2.70 (0.84) vs. 3.22 (0.69)	A vs. B vs. C vs. D vs. E vs. F <u>5 months</u> Spielberger State Anxiety Inventory (20-80): 57.17 (10.30) vs. 37.57 (12.92) vs. 55.71 (10.47) vs. 36.40 (6.28) vs. 41.13 (11.70) vs. 54.00 (12.03) Beck Depression Inventory (0-63): 18.67 (9.01) vs. 8.14 (5.77) vs. 16.14 (3.80) vs. 9.00 (6.07) vs. 9.88 (5.46) vs. 19.17 (8.78) Medication use (0-5): 1.50 (1.26) vs. 0.57 (0.73) vs. 1.86 (0.64) vs. 1.60 (1.02) vs. 1.50 (0.71) vs. 1.83 (1.07) <u>11 months</u> Spielberger State Anxiety Inventory (20-80): 42.83 (9.42) vs. 37.43 (12.26) vs. 47.17 (17.01) vs. 40.67 (11.81) vs. 46.56 (11.51) vs. 53.40 (18.78) Beck Depression Inventory (0-63): 18.67 (10.04) vs. 8.00 (5.93) vs. 12.83 (6.69) vs. 13.17 (8.51) vs. 10.56 (5.21) vs. 17.60 (6.09) Medication use (0-5): 1.17 (1.37) vs. 0.71 (0.88) vs. 1.67 (1.37) vs. 1.33 (0.75) vs. 1.44 (0.96) vs. 1.60 (1.49)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Nicholas, 1992[274] 5 months Duration of pain: 5.5 years Fair	A. Multidisciplinary rehabilitation (n=10), 18 sessions over 5 weeks, (total 31.5 hours) B. Exercise + attention control (psychologist-led group discussions) (n=10)	Overall Age: 44 years Female: 45% A vs. B Baseline function (0-100 Sickness Impact Profile): 30.87 vs. 32.10 Baseline pain (0-5 categorical scale): 3.13 vs. 2.84	A vs. B <u>5 months</u> Pain intensity (0-5 categorical scale): 2.89 (0.64) vs. 2.75 (1.11)	A vs. B <u>5 months</u> Beck Depression Inventory (0-63): 14.44 (5.98) vs. 18.50 (9.26) Using medication: 44% vs. 88%
Roche, 2007,[278] 2011[279] 10.75 months Duration of pain: >4 months Fair	A. Multidisciplinary rehabilitation (n=68), 25 sessions over 5 weeks (total 150 hours) B. Exercise therapy (n=64)	A vs. B Age: 41 vs. 39 years Female: 32% vs. 38% Baseline function (0-100 Dallas Pain Questionnaire daily activities (0-100): 51.8 vs. 51 Baseline Pain (0-10 VAS): 4.7 vs. 4.5	A vs. B <u>10.75 months</u> Dallas Pain Questionnaire daily activities (0-100): 31.4 vs. 39.1, difference −7.7 (95% CI −16.15 to 0.75) Pain (0-10 VAS): 2.9 vs. 3.5, difference −0.6 (95% CI −1.49 to 0.29)	A vs. B <u>10.75 months</u> Dallas Pain Questionnaire anxiety/depression (0-100): 21.9 vs. 25.5, difference −3.6 (95% CI −12.56 to 5.36)
Strand, 2001[260] 11 months Duration of pain: 10 vs. 9 years Fair	A. Multidisciplinary rehabilitation (n=81), 20 sessions over 4 weeks (total 120 hours) B. Usual Care (n=36)	A vs. B Age: 45 vs. 42 years Female: 59% vs. 64% Baseline function (0-100 Disability Rating Index): 55.6 vs. 58.3 Baseline pain (0-100 VAS): 48.3 vs. 53.0	A vs. B <u>11 months</u> Disability Rating Index (0-100): −27.3 (95% CI −34 to −21) vs. −3.3 (95 % CI −10 to 14) vs. −16.4 (95% CI −26 to −7.3) vs. 0.2 (95% CI −14 to 14), difference −3.8 (95% CI −13.9 to 6.3) Pain (0-100 VAS): −21.1 (95% CI −31 to −11) vs. −2.3 (95% CI −9.4 to 4.8) vs. −23.1 (95% CI −37 to 9.2) vs. 7.1 (95% CI −7.7 to 22), difference −1.0 (95% CI −11.7 to 9.6)	A vs. B <u>11 months</u> Working: 47% vs. 58% difference −11% (95% CI −8 to 30)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Tavafian, 2008[269] 12 months Duration of pain: 9 months Poor	A. Multidisciplinary program (n=37), 5 sessions over 0.5 weeks (total hours unclear) B. Medications (acetaminophen, NSAID and chlordiazepoxide) (n=37)	A vs. B Age: 43 vs. 45 years Female, %: 100 vs. 100 Baseline SF-36 Physical (0-100): 41.2 vs. 42.3 Baseline SF-36 Mental (0-100): 47.5 vs. 47.7	NR	A vs. B <u>3 months</u> SF-36 Physical (0-100): 76.7 vs. 51.2, difference 25.5 (95% CI 14.69 to 36.31) SF-36 MCS (0-100): 80.4 vs. 57.4, difference 23.0 (95% CI 10.78 to 35.22) <u>6 months</u> SF-36 PCS (0-100): 66.6 vs. 51.2, difference 15.4 (95% CI 2.35 to 28.45) SF-36 MCS (0-100): 66.9 vs. 57.9, difference 9.0 (95% CI −3.88 to 21.88) <u>6 months</u> SF-36 PCS (0-100): 64.7 vs. 51.1, difference 13.6 (95% CI −1.48 to 28.68) SF-36 MCS (0-100): 65.1 vs. 60.2, difference 4.9 (95% CI −7.57 to 17.37)
Turner, 1990[133] 12 months Duration of pain: 12.9 years Poor	A. Multidisciplinary rehabilitation (n=24), 16 sessions over 2 weeks (total 32 hours) B. Exercise (n=24)	Overall Age: 44 years Female: 48% A vs. B Baseline function (Sickness Impact Profile): 8.5 vs. 8.4 Baseline pain (0-78 MPQ): 25.5 vs. 19.4	A vs. B <u>6 months</u> Sickness Impact Profile (0-100): 4.5 vs. 6.3 McGill Pain Questionnaire Pain Rating Index (0-78): 13.3 vs. 15.7 <u>12 months</u> Sickness Impact Profile (0-100): 4.8 vs. 4.7 McGill Pain Questionnaire Pain Rating Index (0-78): 18.2 vs. 14.9	A vs. B <u>6 months</u> Center for Epidemiologic Studies-Depression Scale (0-60): 8.3 vs. 9.3 <u>12 months</u> Center for Epidemiologic Studies-Depression Scale (0-60): 10.0 vs. 9.3
van der Roer, 2008[275] 10 months Duration of pain: ~50 weeks Fair	A. Multidisciplinary rehabilitation (n=60), 30 sessions over 10 weeks (total hours unclear) B. Exercise (n=54)	A vs. B Age: 42 vs. 42 years Female: 55% vs. 48% Baseline function RDQ (0-24): 11.6 vs. 12.1 Baseline pain (0-10 NRS): 6.2 vs. 5.9	A vs. B <u>4 months</u> RDQ (0-24): 7.4 vs. 7.7, adjusted difference 0.13 (95% CI −2.24 to 2.50) Pain (0-10 NRS): 4.1 vs. 4.8 , adjusted difference −0.97 (95% CI −1.88 to −0.06) <u>10 months</u> RDQ (0-24): 6.7 vs. 7.1, adjusted difference 0.06 (−2.22 to 2.34) Pain (0-10 VAS): 3.9 vs. 4.6, adjusted difference −1.02 (−2.14 to 0.09)	A vs. B <u>4 months</u> Global Perceived Effect positive (%): 38.2% vs. 39.8%, OR 0.93 (95% CI 0.36 to 2.43) <u>10 months</u> Global Perceived Effect positive (%): 45.0% vs. 32.3%, OR 1.71 (95% CI 0.67 to 4.38)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Von Korff, 2005[257] 22.5 months Duration of pain: >3 months Fair	A. Multidisciplinary rehabilitation (n=119), 4 sessions over 5 weeks (total 4 hours) B. Usual care (n=121)	A vs. B Age: 50 vs. 50 years Female: 65% vs. 60% Modified RDQ (0-23): 12.3 vs. 11.4 Baseline pain (0-10 NRS): 5.7 vs. 5.8	A vs. B <u>4.5 months</u> Function Modified RDQ (0-23): 9.2 (6.6) vs. 10.1 (6.4), p=0.0003 >1/3 reduction in RDQ: 42.2% vs. 23.7%, adjusted OR 3.5, p=0.0007 Pain (0-10 NRS): 4.2 (2.0) vs. 4.7 (2.2), p=0.007 <u>10.5 months</u> Modified RDQ (0-23): 8.4 vs. 9.1, p=0.0063 >1/3 reduction in RDQ: 44.6% vs. 22.7%, adjusted OR 2.1, p=0.03 Pain (0-10 NRS): 4.0 vs. 4.7, p=0.004 <u>22.5 months</u> Modified RDQ (0-23): 8.1 vs. 9.1, p=0.0078 >1/3 reduction in RDQ: 49.4% vs. 37.0%, adjusted OR 1.8, p=0.08 Pain (0-10 NRS): 4.3 vs. 4.6, p=0.115	A vs. B <u>4.5 months</u> SF-36 Social Functioning (0-100): 74.4 vs. 73.6, p=0.26 SF-36 Mental Health (0-100): 70.3 vs. 69.5, p=0.23 <u>10.5 months</u> SF-36 Social Functioning (0-100): 74.4 vs. 73.6, p=0.26 SF-36 Mental Health (0-100): 70.3 vs. 69.5, p=0.23 <u>22.5 months</u> SF-36 Social Functioning (0-100): 76.7 vs. 76.3, p=0.28 SF-36 Mental Health (0-100): 71.0 vs. 72.4, p=0.98

ADL = activity of daily living; CI = confidence interval; LBO = Low Back Outcome Score; LBP = low back pain; MCS = Mental Component Summary; MPQ = McGill Pain Questionnaire; NR = not reported; NRS = Numerical Rating Scale; NSAID = nonsteroidal anti-inflammatory drug; ODI = Oswestry Disability Index; PCS = Physical Component Summary; RDQ = Roland-Morris Disability Questionnaire; SF-36 = Short-Form 36Q; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Multidisciplinary Rehabilitation Compared With Usual Care

Multidisciplinary rehabilitation was associated with small improvements in function compared with controls at short-term (4 trials, pooled SMD −0.30, 95% CI −0.63 to 0.00, I^2=58%),[255-258] and intermediate-term followup (4 trials, pooled SMD −0.37, 95% CI −0.69 to −0.08, I^2=34%) (Figure 22).[257-260] There was no difference in long-term function (2 trials, pooled SMD −0.04, 95% CI −0.36 to 0.35, I^2=0%).[255,257] In trials that measured function using the RDQ, the difference was −0.67 points (95% CI -21.5 to 0.81, 2 trials) at short term and −1.9 points (95% CI -3.70 to -0.18, 2 trials) at intermediate term. Restriction to high-intensity multidisciplinary rehabilitation interventions or exclusion of poor-quality trials had little effect on estimates. At short-term followup, effects on function were somewhat larger with high intensity multidisciplinary rehabilitation interventions (2 trials, pooled SMD −0.50, 95% CI −0.94 to −0.22)[255,256] than with nonhigh intensity interventions (3 trials, pooled difference −0.20, 95% CI −0.38 to 0.04),[256-258] but the interaction was not statistically significant (p=0.19). At intermediate term, there were no clear differences between high intensity (1 trial, SMD −0.59, 95% CI −0.99 to −0.19)[260] and nonhigh intensity (3 trials, pooled difference −0.30, 95% CI −0.69 to 0.06)[257-259] interventions (p=0.48 for interaction).

Multidisciplinary rehabilitation was associated with small improvements compared with usual care in pain at short-term (4 trials, pooled difference −0.53 on a 0 to 10 scale, 95% CI

−0.86 to −0.11, I^2=0%)[255-258] and intermediate-term followup (4 trials, pooled difference −0.62, 95% CI −1.06 to −0.18, I^2=0%)[257-260] (Figure 23). The long-term difference was smaller and not statistically significant (2 trials, pooled difference −0.35, 95% CI −1.10 to 0.34, I^2=0%).[255,257] Excluding poor-quality trials[256,259,260] had little effect on estimates. At short-term followup, effects on pain were somewhat larger with high intensity multidisciplinary rehabilitation interventions (2 trials, pooled difference −0.86, 95% CI −1.57 to −0.31)[255,256] than with nonhigh intensity interventions (3 trials, pooled difference −0.35, 95% CI −0.71 to 0.15),[256-258] but the interaction between intensity and effects of multidisciplinary rehabilitation was not statistically significant (p=0.48). At intermediate term, estimates were similar for high intensity (1 trial, difference −0.53, 95% CI −1.35 to 0.29)[260] and nonhigh intensity (3 trials, pooled difference −0.66, 95% CI −1.22 to −0.09) interventions (p=0.82 for interaction).[257-259]

Data on other outcomes was limited. One trial found no differences between multidisciplinary rehabilitation versus usual care on the SF-36 Social Functioning or Mental Functioning subscales.[257] Three trials reported inconsistent effects on work or disability/sick leave status.[255,257,260] Two trials found multidisciplinary rehabilitation associated with fewer health system contacts versus usual care.[255,258]

Multidisciplinary Rehabilitation Compared With Pharmacological Therapy

One poor-quality trial (n=74) found multidisciplinary rehabilitation (intensity unclear) associated with greater effects on short-term quality of life than oral medications (acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], and chlordiazepoxide).[269] The difference on the SF-36 PCS was 25.5 points (95% CI 14.7 to 36.3) and on the SF-36 MCS was 23.0 points (95% CI 10.8 to 35.2). Effects were smaller at intermediate term and statistically significant for the SF-36 PCS (difference 15.4, 95% CI 2.35 to 28.45) but not for the SF-36 MCS (difference 9.0, 95% CI −3.88 to 21.9). Effects were not statistically significant at long-term (12-month) followup (differences 13.6 and 4.9 points, respectively).

Multidisciplinary Rehabilitation Compared With Exercise

Multidisciplinary rehabilitation was associated with a small improvement in short-term function compared with exercise (6 trials, pooled SMD −0.20, 95% CI −0.54 to 0.001, I^2=32%) (Figure 24).[270,272-275,277] Estimates were similar when a poor-quality trial[273] was excluded and when analyses were restricted to trials of high-intensity multidisciplinary rehabilitation (2 trials, pooled difference −0.14, 95% CI −0.50 to 0.22).[270,272] Multidisciplinary rehabilitation was associated with substantially greater effects than exercise on intermediate-term function (6 trials, pooled SMD −1.04, 95% CI −2.82 to 0.71, I^2=96%), but statistical heterogeneity was very large.[133,271,273,275,276,278,279] Excluding an outlier trial (SMD −5.31, 95% CI −6.20 to −4.42)[276] eliminated statistical heterogeneity and resulted in a markedly attenuated (small) effect (5 trials, pooled SMD −0.20, 95% CI −0.40 to −0.00, I^2=0%). There was no difference between multidisciplinary rehabilitation versus exercise in long-term function (3 trials, pooled SMD −1.82, 95% CI −5.90 to 2.24, I^2=98%).[133,270,276] Excluding the outlier trial[276] described above resulted in a pooled SMD close to 0 (−0.07, 95% CI −0.50 to 0.39, I^2=0%).

Multidisciplinary rehabilitation was associated with small improvements in short-term pain versus exercise (6 trials, pooled difference −0.69 on a 0 to 10 scale, 95% CI −1.16 to −0.22, I^2=0%) (Figure 25). Estimates were similar when one poor-quality trial[273] was excluded (5 trials, pooled difference −0.53, 95% CI −1.12 to 0.11), and estimates were similar when analyses were stratified according to intensity of multidisciplinary rehabilitation. In two trials that evaluated

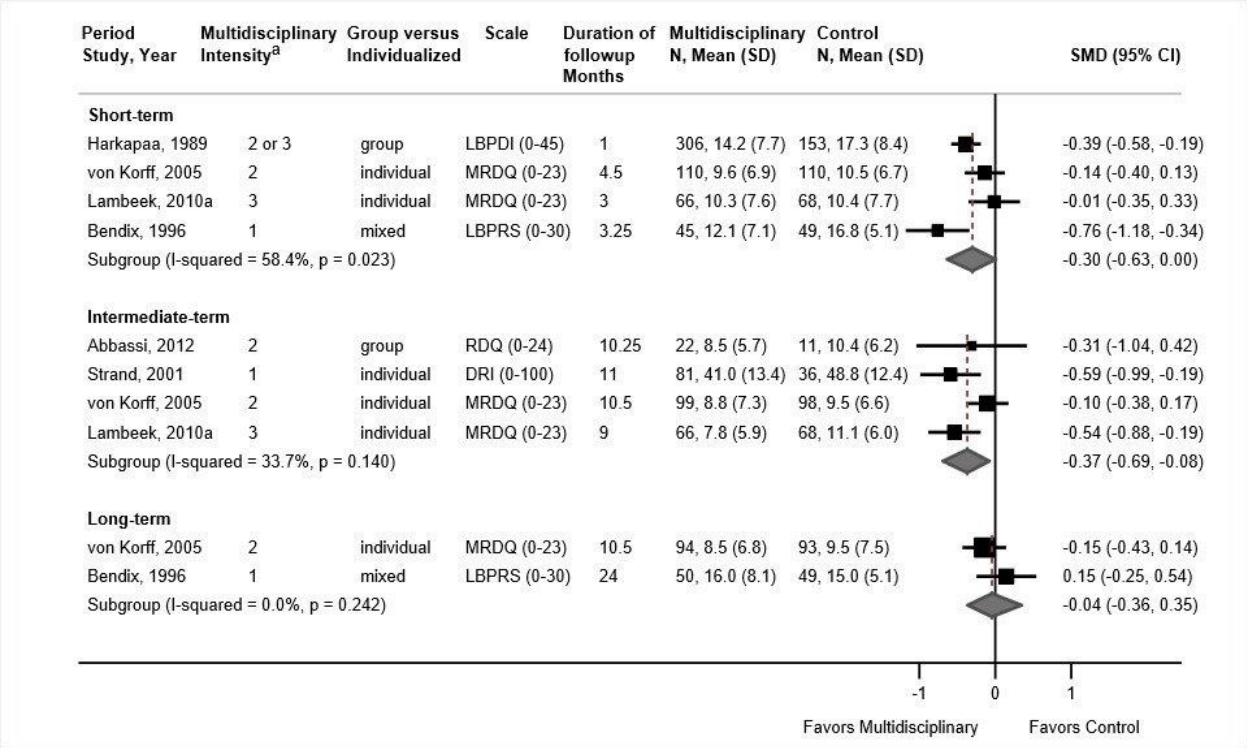
high intensity multidisciplinary rehabilitation, the pooled difference was −0.62 (95% CI −1.61 to 0.37).[270,272] Estimates at intermediate term (6 trials, pooled difference −1.20 points, 95% CI −2.43 to 0.09, I^2=95%)[271,273,275,277-279] and long term (3 trials, pooled difference −1.68, 95% CI −5.25 to 1.97, I^2=98%)[133,270,276] favored multidisciplinary rehabilitation, but differences were not statistically significant. Substantial statistical heterogeneity was present in analyses of intermediate-term and long-term pain, with an outlier trial[276] that reported substantially larger effects than the other trials. For intermediate term, the outlier trial reported a difference of −3.90 points, versus −0.31 to −0.73 points in the other trials. Excluding the outlier trial eliminated statistical heterogeneity and resulted in a small, statistically significant difference in intermediate-term pain that favored multidisciplinary rehabilitation (5 trials, pooled difference −0.55, 95% CI −1.00 to −0.11, I^2=0%); there was no difference in long-term pain (2 trials, pooled difference 0.00, 95% CI −1.31 to 1.17, I^2=0%). For intermediate-term pain, exclusion of a poor-quality trial[273] (5 trials, pooled difference −1.52, 95% CI −3.35 to 0.39) or restriction of analyses to high intensity multidisciplinary rehabilitation interventions (2 trials, pooled difference −0.60, 95% CI −1.44 to 0.24)[271,278,279] did not reduce heterogeneity and differences remained not statistically significant.

Data on other outcomes was limited. One trial found multidisciplinary rehabilitation associated with better scores versus exercise on SF-36 subscales at short-term followup (differences 10 to 21 points).[277] Four trials found no clear differences between multidisciplinary rehabilitation versus exercise on severity of depression.[133,272-274] Two trials found no clear effects on work status[270,278,279] and one trial found high intensity multidisciplinary rehabilitation associated with fewer days or sick leave than exercise, but nonhigh intensity rehabilitation associated with more days of sick leave.[270] Two trials found inconsistent effects on number of health system contacts.[270,271]

Harms

Data on harms were sparse and reported in only two trials. One study reported no clear difference between multidisciplinary rehabilitation versus exercise in risk of transient worsening of pain,[277] and one trial reported no harms with either multidisciplinary rehabilitation or medications alone.[269]

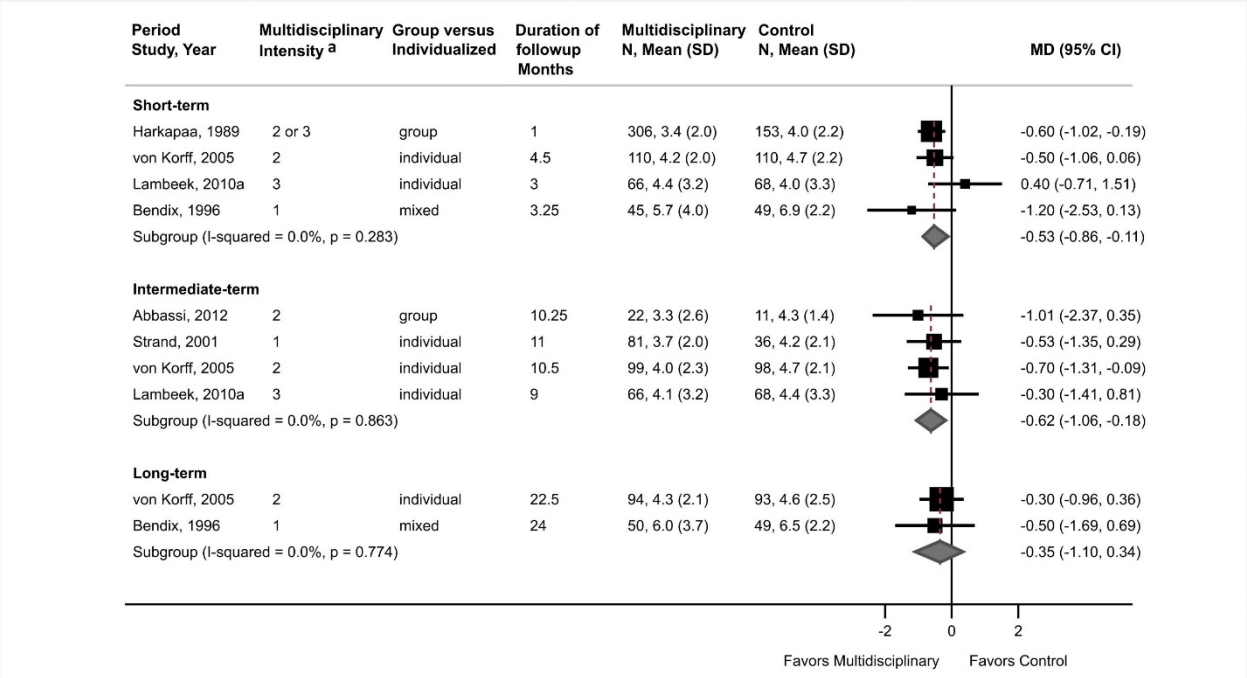
Figure 22. Multidisciplinary rehabilitation versus usual care for chronic low back pain: effects on function



CI = confidence interval; DRI= Disability Rating Index; indvl = individual; LBPDI = low back pain disability index; LBPRS = low back pain rating scale; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SMD = standardized mean difference

[a] Multidisciplinary rehabilitation intensity: 1= high, 2= not high, 3= unclear or not reported

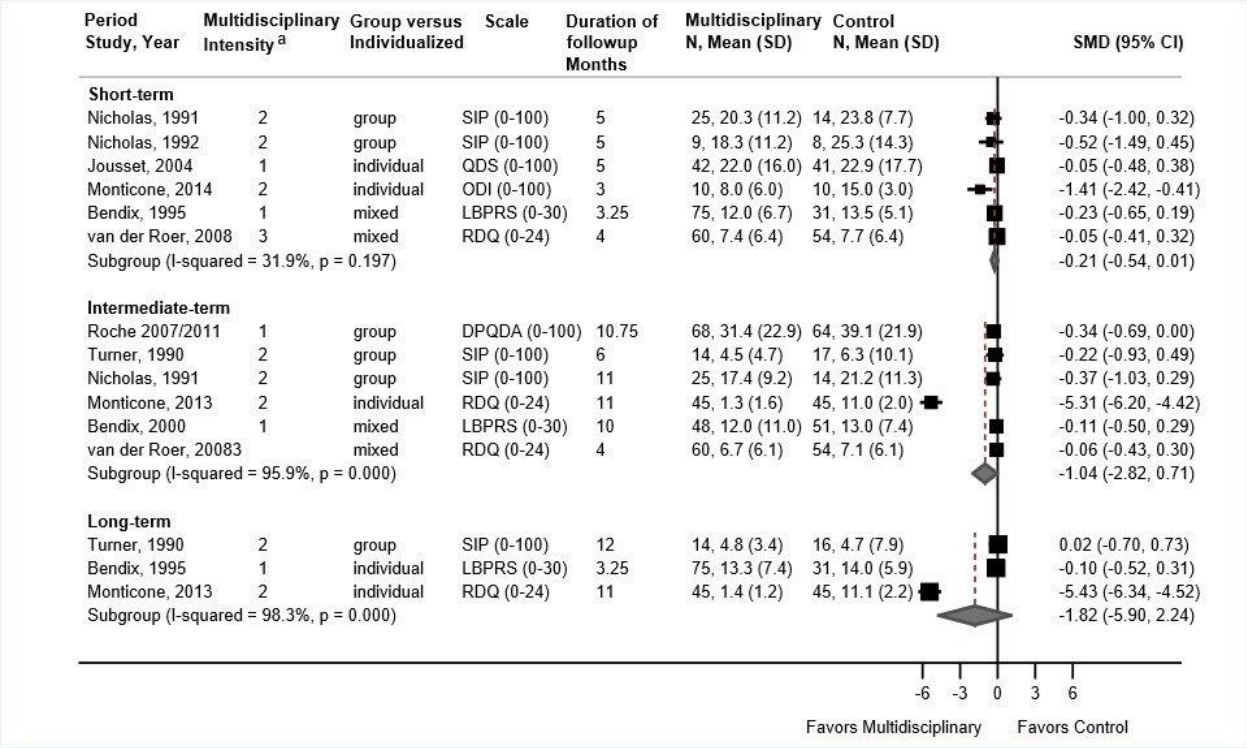
Figure 23. Multidisciplinary rehabilitation versus usual care for chronic low back pain: effects on pain



CI = confidence interval; indvl = individual; N = number; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation

[a] Multidisciplinary rehabilitation intensity: 1 = high, 2 = not high, 3 = unclear or not reported

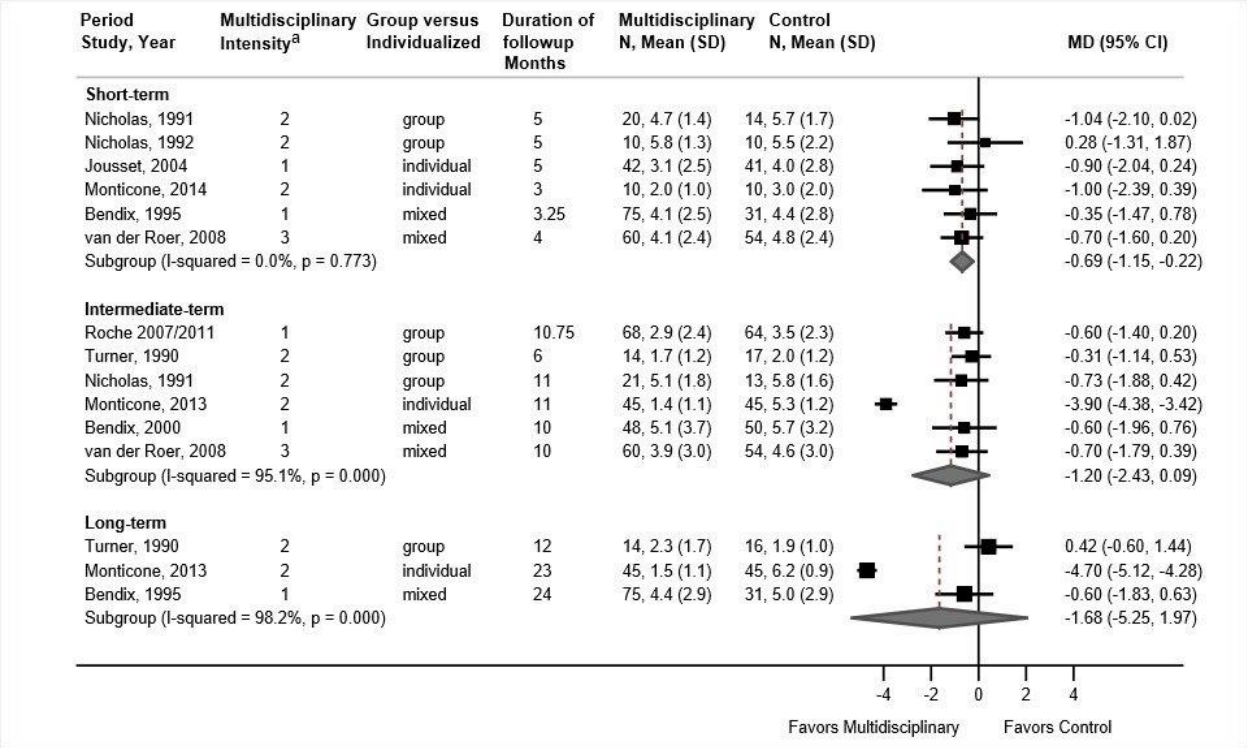
Figure 24. Multidisciplinary rehabilitation versus exercise for chronic low back pain: effects on function



CI = confidence interval; DPQDA = Dallas Pain Questionnaire daily activities; indvl = individual; LBPRS = low back pain rating scale; N = number; ODI = Oswestry Disability Index; QDS = Quebec Disability Scale; RDQ = Roland-Morris Disability Questionnaire; SD = standard deviation; SIP = Sickness Impact Profile; SMD = standardized mean difference

[a] Multidisciplinary rehabilitation intensity: 1= high, 2= not high, 3= unclear or not reported

Figure 25. Multidisciplinary rehabilitation versus exercise for chronic low back pain: effects on pain



CI = confidence interval; indvl = individual; N = number; SD = standard deviation

[a] Multidisciplinary rehabilitation intensity: 1 = high, 2 = not high, 3 = unclear or not reported.

Key Question 2: Chronic Neck Pain

For chronic neck pain, 25 RCTs were included in the prior AHRQ report (N=3294). One study was rated good-quality, sixteen studies fair quality, and eight studies poor quality. The prior AHRQ report found combination exercise, low-level laser therapy, Alexander Technique and acupuncture associated with greater effects than usual care, no treatment, advice alone, or sham on improved function; only combination exercise and low-level laser therapy were also associated with greater improvement in pain. The strength of evidence was low or moderate, and observed at short- intermediate- or long-term followup.

For this update, we identified two new RCTs (N=156) and a new publication (subanalysis) of a previously included trial; all were rated fair quality. One trial evaluated exercise and the other evaluated manual therapy (massage); the subsequent publication provided data for mind-body practices (Alexander Technique) and acupuncture. The Key Points summarize the main findings based on the evidence included in the prior report and new trials; the Key Points note where new trials contributed to findings.

Exercise for Chronic Neck Pain

Key Points

- Across types of exercise, there was no clear improvement in function (3 trials [excluding outlier trial], pooled SMD −0.22, 95% CI −0.66 to 0.17, I^2=73%) or pain (3 trials

[excluding outlier trial], pooled SMD −0.70, 95% CI −1.62 to 0.15, I^2=64%) versus no treatment, waitlist or attention control 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 small benefit for 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).
- There was no clear improvement in function for exercise versus no intervention at intermediate term (1 trial) and a small improvement versus attention control in the long term (1 trial) (SOE: low for both).
- There was no improvement in pain for exercise versus no intervention or attention control at intermediate term (2 trials) and versus attention control at long-term (3 trials) (SOE: low for both).
- The effect of exercise versus NSAIDs and muscle relaxants on function and pain was indeterminate at short or intermediate term due to insufficient evidence from a single poor-quality trial (SOE: insufficient).
- 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 fair quality trial (SOE: low).
- Harms were poorly reported in trials of exercise with only two trials describing adverse events. No serious harms were reported in either trial. Minor complaints included muscle pain with exercise, knee pain and lumbar spine pain (SOE: low).

Detailed Synthesis

Eight trials of exercise therapy for neck pain met inclusion criteria (Table 19 and Appendix D).[41-46,100,101] Seven trials[41-46,100] were included in the prior AHRQ report and one[101] was added for this update. Four trials evaluated participants with chronic neck pain associated with office work,[41,43,45,46] and one trial each included patients with chronic neck pain following whiplash,[44] nonspecific neck pain,[42] cervical arthritis,[100] and mechanical neck pain (new trial).[101] Across trials, participants were predominately female (>80%) with only the new trial predominantly men (78%).[101] Mean ages ranged from 38 to 52 years.

Five trials (1 new) evaluated muscle performance exercises (resistive training),[41,43,45,46,101] three combined exercise techniques,[42,44,100] and one neuromuscular rehabilitation.[46] Sample sizes ranged from 40 to 265 (total sample=973). Four trials compared exercise versus an attention control,[41,43,44,46] one versus no treatment,[45] one versus waitlist,[42] and two (1 new) versus pharmacological care.[100,101] Four trials were conducted in Europe,[41,42,45,46] one in Australia,[44] one in China,[43] one in Turkey,[100] and one in Brazil (new trial).[101] The duration of exercise therapy ranged from 6 weeks to 12 months, and the number of supervised exercise sessions ranged from 3 to 52. Three trials reported outcomes through long-term followup,[41,44,46] two through intermediate-term followup,[45,100] and three (1 new) evaluated only short-term outcomes.[42,43,101]

Four trials, including the new trial, were rated fair quality[43-45,101]and four poor quality[41,42,46,100] (Appendix E). In the four fair-quality trials, the main methodological limitation was the inability to blind interventions. Limitations in the other trials included inability to blind interventions, unclear randomization and allocation concealment methods, unclear or high loss to followup, and baseline differences between intervention groups.

Table 35. Chronic neck pain: exercise therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Andersen, 2008[b,41] 6 and 12 months Duration of pain: NR Poor	A. Dynamic strengthening exercise (muscle performance exercise) (n=61): for the neck/shoulder muscles, performed in in the workplace; 20 minute sessions, 3 times a week (2 of the 3 weekly sessions were supervised by experienced instructors) B. Lifestyle physical exercise and activity increase (combination exercise) (n=59): workplace activities such as steppers placed near the copying machines, punch bags in the hall, group sessions of Nordic walking, and strength and aerobic fitness exercise programs C. Control group (n=62): ergonomics, stress management, organization of work, cafeteria food quality Treatment lasted 1 year. All groups were allowed 1 hour per week during working time for activities	A + B + C Age: 45 years Female: 78% Office workers: 100% A vs. B vs. C Baseline pain (0-10 VAS): 5.0 vs. 5.0 vs. 4.7	A vs. C <u>6 months</u> Pain VAS: 3.4 vs. 4.2, difference −0.8 (95% CI −0.9 to −0.7) <u>12 months</u>[c] Pain VAS: 3.8 vs. 4.6, difference −0.80 (95% CI −0.87 to −0.73) Days of pain in last 3 months (0-90): 25 vs. 30, p>0.05 B vs. C <u>6 months</u> Pain VAS: 3.6 vs. 4.2, difference −0.6 (95% CI −0.7 to −0.5) <u>12 months</u>[c] Pain VAS: 3.6 vs. 4.6, difference −1.0 (95% CI −1.1 to −0.9) Days of pain in last 3 months: 26 vs. 30, p>0.05	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Aslan Telci, 2012[100] 6 months Duration of pain: 12 months Poor	A. Combination exercises (n=20): consisting of posture, active range of motion, stretching, isometric and dynamic strengthening and endurance exercises, relaxation and proprioception exercises. Clinic followup once a week to maintain motivation and check whether exercises performed correctly for a total of 3 weeks and home exercise for at least another month. B. NSAIDs and muscle relaxants for 15 days (n=20): all patients received verbal advice regarding pain control, posture, and ergonomics.	A vs. B Age: 48 vs. 52 years Female: 85% vs. 75% BMI: 25 vs. 27 Employed: 50% vs. 40% Education year: 12 vs. 11 Baseline NDI (0-50): 14.0 vs. 10.7 Baseline pain (0-10 VAS): 6.7 vs. 6.4	A vs. B <u>3 month</u> NDI: 9.4 vs. 11.5, difference −2.2 (95% CI −5.8 to 1.5) Pain VAS: 4.1 vs. 5.1, difference −1.0 (95% CI −2.3 to 0.3) <u>6 month</u> NDI: 11.9 vs. 13.7, difference −1.8 (95% CI −5.7 to 2.1) Pain VAS: 4.5 vs. 5.3, difference −0.8 (95% CI −2.3 to 0.7)	A vs. B <u>3 month</u> NHP (0-100): 89.2 vs. 230.0, difference −140.8 (95% CI −214.0 to −67.5) BDI (0-63): 6.8 vs. 10.7, difference −4.0 (95% CI −8.4 to 0.5) <u>6 month</u> NHP (0-100): 122.3 vs. 257.6, difference −135.3 (95% CI −209.1 to −61.5) BDI (0-63): 8.3 vs. 11.8, difference −3.8 (95% CI −8.5 to 1.0)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
de Araujo Cazotti, 2018[101] 3 months Duration of pain: Range, mean 69 to 86 months Fair [New trial]	A. Pilates (muscle performance exercise) (n=32): 1 hour session, 2 times/week, for 12 weeks. Repetitions/exercise varied from 6 to 12. 91% of participants completed all of the scheduled sessions. B. Pharmacological treatment (n=32): 750 mg acetaminophen every 6 hours if they were experiencing pain. Participants in group A were also instructed to do the same of they were experiencing pain.	A vs. B Age: 49 vs. 49 years Female: 19% vs. 25% Baseline NDI (0-50): 13.3 vs. 12.8 Baseline NPS (0-10): 6.4 vs. 5.8	A vs. B 3 months NDI: 4.2 vs. 9.8, difference −5.6 (95% CI −8.4 to −2.8) NPS: 1.9 vs. 5.0, difference −3.1 (95% CI −4.2 to −2.0)	A vs. B 3 months SF-36 Physical functioning (0-100): 80.3 vs. 73.1, difference 7.2 (95% CI −2.3 to 16.7) SF-36 Role physical (0-100): 75.0 vs. 55.6, difference 19.4 (95% CI −2.6 to 41.4) SF-36 Bodily pain (0-100): 68.6 vs. 50.4, difference 18.2 (95% CI 6.8 to 29.6) SF-36 General health (0-100): 79.5 vs. 74.8, difference 4.7 (95% CI −7.4 to 16.8) SF-36 Vitality (0-100): 66.6 vs. 56.6, difference 10 (95% CI −0.6 to 20.6) SF-36 Social functioning (0-100): 86.7 vs. 76.2, difference 10.5 (95% CI −2.5 to 23.5) SF-36 Role emotional (0-100): 72.9 vs. 72.9, difference 0 (95% CI −19.4 to 19.4) SF-36 Mental health (0-100): 77.4 vs. 65.2, difference 12.2 (95% CI 2.5 to 21.9) Acetaminophen use, Median (IQR): 0 (0 to 39) vs. 3.5 (0 to 159)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lauche, 2016[42] 3 months Duration of pain: NR Poor	A. Combination exercises (n=37): weekly 60-75 minute session for 12 weeks; ergonomic principles, proprioceptive exercises, and isometric and dynamic mobilization, stretching, strengthening neck and core exercises, and relaxation exercises; illustrated written exercises for home use ≥15 minutes/day. B. Wait list (n=39): continuing usual activities/therapies	A vs. B Age: 47 vs. 49 years Female: 86% vs. 82% years Baseline NDI: NR Baseline pain, recently (0-100 VAS): 46.2 vs. 51.5 Baseline pain, considered tolerable (0-100 VAS): 20.5 vs. 20.7	A vs. B <u>3 month</u> NDI: 25.1 vs. 29.4, difference −4.3 (95% CI −10.2 to 1.6) Recent pain VAS: 33.1 vs. 44.6, difference −11.5 (95% CI −20.8 to −2.2) Pain with motion VAS: 34.9 vs. 45.5, difference −10.6 (95% CI −18.5 to −2.7)	A vs. B <u>3 month</u> SF-36 PCS (0-100): difference 2.0 (95% CI −1.6 to 5.6) SF-36 MCS (0-100): difference 0.5 (95% CI −3.9 to 4.9)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Li, 2017[43] 1.5 months Duration of pain: 4 years Fair	A. Progressive resistance training (muscle performance exercise) (n=38): ≥3 sessions per week for 6 weeks. Sessions consisted of four cervical isometric exercises, each repeated 8-12 times. Resistance progressively increased every 2 weeks, starting at 30% of maximal strength and increased to 70%. B. Fixed resistance training (muscle performance exercise) (n=35): ≥3 sessions per week for 6 weeks. Sessions consisted of four cervical isometric exercises, each repeated 8-12 times. Resistance was fixed at 70% of the participant's maximal strength. C. Attention control (n=36): Subjected received information and had weekly discussions about workplace ergonomics, stress management, relaxation, meditation, and diet.	A vs. B vs. C Age: 36 vs. 34 vs. 34 BMI: 21 vs. 22 vs. 22 Years working: 9 vs. 9 vs. 10 Pain duration (years): 3 vs. 4 vs. 4 Work (days/week): 5 vs. 6 vs. 5 Computer use (hours/day): 7 vs. 8 vs. 7 Baseline NDI (0-50): 28.3 vs. 28.9 vs. 27.8 Baseline pain (0-10 VAS): 5.3 vs. 5.4 vs. 5.2	A vs. C <u>1.5 month</u> NDI: 14.9 (4.9) vs. 26.6 (5.4), difference −11.7 (95% CI −14.1 to −9.3) Pain VAS: 1.9 (0.9) vs. 5.1 (1.0), difference −3.2 (95% CI −3.6 to −2.8) B vs. C <u>1.5 month</u> NDI: 15.8 (4.8) vs. 26.6 (5.4), difference −10.8 (95% CI −13.2 to −8.4) Pain VAS: 2.5 (0.9) vs. 5.1 (1.0), difference −2.6 (95% CI −3.1 to −2.1)	None

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Stewart, 2007[44] 1.5 and 12 months Duration of pain: 9 months Fair	A. Combination exercise, plus advice (n=66); aerobic, stretching, functional, speed and endurance, trunk and limb strengthening; 1 hour per session for 12 session over 6 weeks B. Advice alone (n=68): included reassurance of a favorable outcome and encouragement to resume light activity	A vs. B Age: 44 vs. 43 years Female: 73% vs. 62% Baseline NDI (0-50): 18.2 vs. 19.7 Baseline PSFS (0-10): 3.9 vs. 4.1 Baseline pain (0-10 VAS): 5.2 vs. 5.3	A vs. B <u>1.5 months</u> NDI: 12.0 vs. 15.7, difference −2.7 (95% CI −4.5 to −0.9) PSFS: 6.4 vs. 5.6, difference 0.9 (95% CI 0.3 to 1.6) Pain VAS: 3.2 vs. 4.3, difference −1.1 (95% CI −1.8 to −0.3) <u>12 months</u> NDI: 12.1 vs. 15.5, difference −2.3 (95% CI −4.9 to 0.3) PSFS: 6.6 vs. 6.0, difference 0.6 (95% CI −0.1 to 1.4) Pain VAS: 3.5 vs. 3.8, difference −0.2 (95% CI 0.6 to −1.0)	A vs. B <u>1.5 months</u> Bothersomeness (0-10) 3.6 vs. 4.8, p=0.019 SF 36 physical (0-100): 42.1 vs. 38.9, p=0.003 SF 36 mental (0-100): 51.4 vs. 46.4, p=0.005 Global Perceived Effect (−5 to 5) 2.5 vs. 1.5, p=0.006 <u>12 months</u> Bothersomeness 4.1 vs. 4.0, p=0.480 SF 36 physical: 42.3 vs. 38.9, p=0.003 SF 36 mental: 48.4 vs. 46.1, p=0.33 Global Perceived Effect: 2.3 vs. 1.9, p=0.48
Viljanen, 2003[45] 3 and 9 months Duration of pain: 11 years Fair	A. Dynamic strengthening exercises (muscle performance exercises) (n=135): physical-therapist guided; 3 times per week for 12 weeks, 30 minute sessions B. No intervention (n=130)	A vs. B Age: 45 vs. 44 years Female: 100% vs. 100% Office workers: 100% Computer work >6 hours per day: 33% vs. 35% Baseline neck disability scale[e] (0-80): 29 vs. 26 Baseline pain (0-10 VAS): 4.8 vs. 4.1	A vs. B <u>3 months</u> Neck disability scale[e]: 15 vs. 14, adjusted difference −0.1 (95% CI −3.1, 2.9) Pain VAS: 2.9 vs. 2.9, adjusted difference 0.4 (95% CI −0.3, 1.0) <u>9 months</u> Neck disability scale[e]: 19 vs. 17, adjusted difference −0.1 (95% CI −3.0 to 2.9) Pain VAS: 3.1 vs. 3.2, adjusted difference 0.5 (95% CI −0.1 to 1.0)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Waling, 2002[d46] 6 and 36 months Duration of pain: 6.8 years Poor	A. Strength training (muscle performance exercise) (n=29): for neck and shoulder muscles, 3 times per week for 10 weeks, 1 hour/session B. Endurance training (muscle performance exercise) (n=28): using arm-cycling and arm exercises, 30 repetition maximum, 3 times per week for 10 weeks, 1 hour/session C. Coordination training (neuromuscular reeducation exercises) (n=25): focus on balance and postural stability 3 times per week for 10 weeks, 1 hour/session D. Reference group (n=21): stress management 1 time per week for 10 weeks, 2 hour/session	A vs. B vs. C vs. D Age: 38 vs. 39 vs. 38 vs. 39 years Female: 100% all groups Office workers: 100% Baseline pain, at present (0-10 VAS): 2.6 vs. 2.8 vs. 3.3 vs. 3.7	A vs. B vs. C vs. D <u>6 months</u> Proportion of patients with frequent pain (several times per week or more): 76% vs. 91% vs. 78% vs. 73%, p=0.50 <u>36 months</u> Pain VAS at present: 3.1 vs. 2.2 vs. 2.7 vs. 1.6, p=0.073 Pain VAS in general (0-10): 3.2 vs. 2.9 vs. 2.9 vs. 2.0, p=0.249 Pain VAS at worst (0-10): 6.1 vs. 5.8 vs. 5.7 vs. 5.8, p=0.902 Frequent pain: 47% vs. 50% vs. 58% vs. 39%, p=0.66	NR

BDI = Beck Depression Inventory; BMI = body mass index; CI = confidence interval; MCS = Mental Component Summary; NDI = Neck Disability Index; NHP = Nottingham Health Profile; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; PCS = Physical Component Summary; PSFS = Patient Specific Functional Scale; SF-36 = Short-Form 36 questionnaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Cluster RCT where clusters were formed from participants working on the same floor

[c] Intervention lasted 12 months and followup is at the end of the intervention

[d] Cluster RCT where clusters were formed from participants selecting a time that best fit their schedule

[e] Neck disability scale was created by investigators from responses to eight questions related to functional limitations due to pain; this scale is not the same as the more common NDI

Exercise Compared With No Treatment, Waitlist, or an Attention Control

Across types of exercise, there was no clear improvement in function versus no treatment, waitlist or an attention control in the short term (4 trials, pooled SMD −0.73, 95% CI −1.84 to 0.36, I^2=95.1%), but statistical heterogeneity was very large[42-45] (Figure 26). Excluding an outlier trial (SMD −2.22, 95% CI −2.74 to −1.70)[43] reduced the statistical heterogeneity and resulted in an attenuated effect (SMD −0.22, 95% CI −0.66 to 0.17, I^2=72.6%). However, two studies that included combination exercises (3 of the following 4 exercise categories: muscle performance, mobility, muscle re-education, aerobic) found small improvement in function compared with controls short term (2 trials, pooled SMD −0.44, 95% CI −0.76 to −0.09, data not shown in figure).[42,44] A fair-quality study reported a continued small benefit with combination exercise in the long term (SMD −0.39, 95% CI −0.74 to −0.03).[44]

Exercise tended toward moderately greater effects on short-term pain compared with no treatment, waitlist or an attention control (4 trials, pooled difference −1.33, 95% CI −2.68 to 0.07, I^2=89.4%), but statistical heterogeneity was very large,[42-45] (Figure 27). Excluding an outlier trial (difference −2.92, 95% CI −3.38 to −2.46)[43] reduced the statistical heterogeneity and resulted in an attenuated effect (difference −0.70, 95% CI −1.62 to 0.15, I^2=63.7%). The effect of exercise on reducing pain was substantially greater in trials assessing combination exercises (2 trials, pooled difference −1.12, 95% CI −1.82 to −0.43; data not shown in figure).[42,44] There were no differences in pain comparing exercise versus controls in the intermediate term (2 trials, pooled difference −0.25, 95% CI −0.81 to 0.31, I^2=0%)[41,45] or the long term (3 trials, pooled difference 0.07, 95% CI −0.51 to 0.88, I^2=0%).[41,44,46]

Data on effects of exercise on quality of life were limited. One fair-quality trial[44] found significant improvement in SF-36 PCS and MCS in the short term (difference in change score 3.60 on a 0-100 scale, 95% CI 1.23 to 5.97 and 4.00, 95% CI 1.24 to 6.77, respectively) and PCS in the long term (difference in change score 3.80, 95% CI 1.30 to 6.30). A poor-quality trial found no difference in SF-36 PCS or MCS in the short term.[42] No trial evaluated effects of exercise therapies on use of opioid therapies or healthcare utilization.

There was insufficient evidence to determine effects of duration of exercise therapy or number of sessions on outcomes.

Exercise Compared With Pharmacological Therapy

Two trials, (1 new) compared exercise with pharmacological therapy. Differences in the pharmacological therapies and study quality precluded pooling of the trials.

One poor-quality trial (N=40)[100] comparing 1.5 months of home combination exercises (posture, stretching, strengthening and endurance exercises) versus ibuprofen plus thiocolchicoside for 15 days found no between-group difference in function (Neck Disability Index [NDI]) at 3-month (difference −2.2 on 0-50 scale, 95% CI −5.8 to 1.5) or 6-month followup (difference of −1.8, 95% CI −5.7 to 2.1). The study reported similar results for pain intensity (difference −1.0 on a 0-10 scale, 95% CI −2.3 to 0.3 at 3-month and difference −0.8, 95% CI −2.3 to 0.7 at 6-month followup). The exercise group reported a better quality of life compared with the medication group at 3-month and 6-month followup using the Turkish version of the Nottingham Health Profile (difference −141, scale not stated though usual scale 0-100, 95% CI −214 to −68; difference −135, 95% CI −209 to −62, respectively).[100] The groups scored comparably on the Beck Depression Inventory at both followup periods (Table 18).

The new fair-quality trial (N=64)[101] found Pilates exercise to be associated with a small improvement in function according to the NDI (difference −5.6 on 0-50 scale, 95% CI −8.4 to −2.8) and a substantial improvement in pain (difference −3.1 on 0-10 scale, 95% CI −4.2 to −2.1) compared with oral medication (acetaminophen) in the short term. SF-36 scores were reported for individual domains; physical functioning, bodily pain, general health, vitality, and mental health showed a small improvement with exercise compared with acetaminophen.

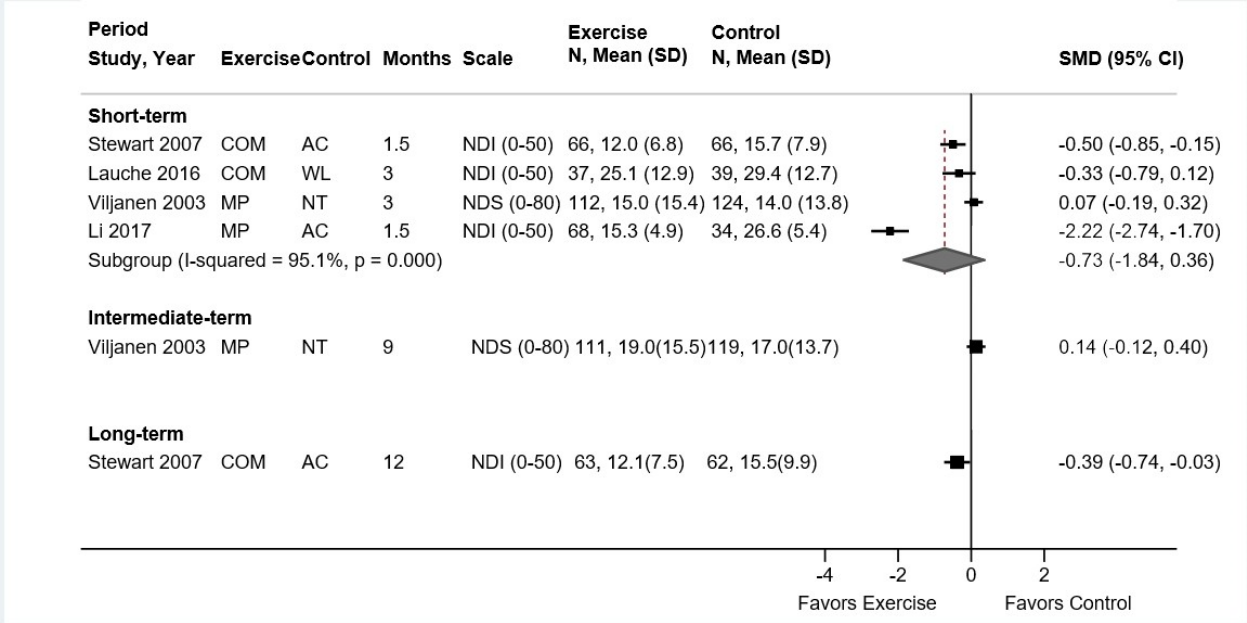
Exercise Compared With Other Nonpharmacological Therapies

Findings for exercise versus other nonpharmacological therapies are addressed in the sections for other nonpharmacological therapies.

Harms

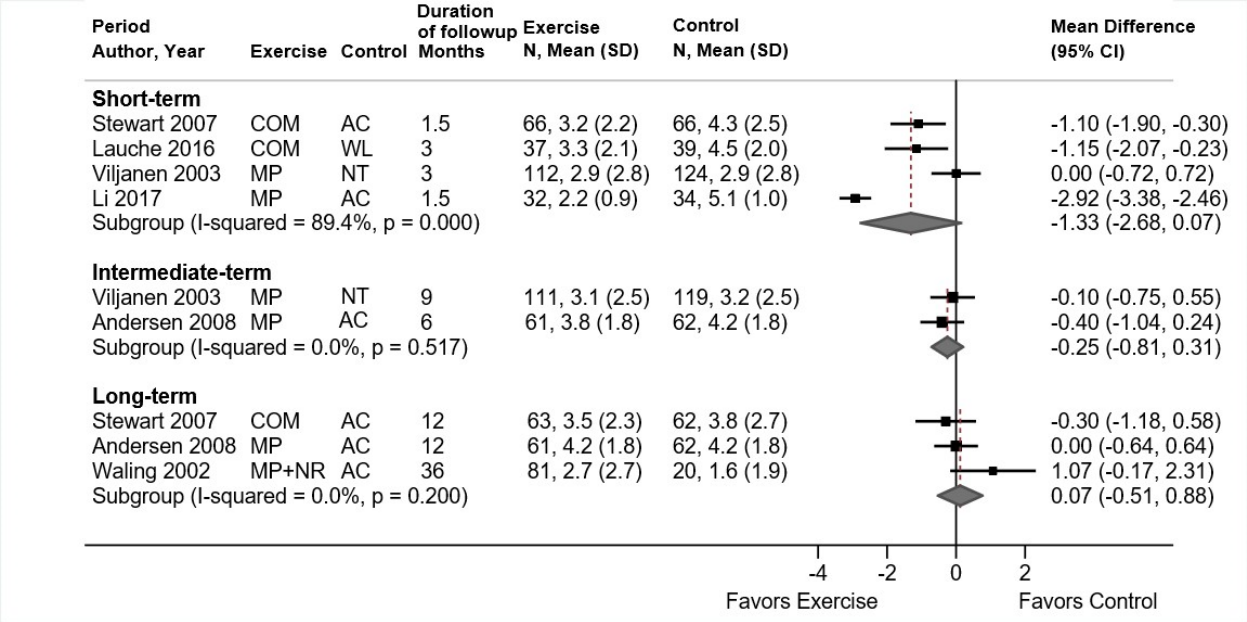
Only two exercise trials reported harms. One reported only mild complaints that included muscle pain with exercise (5%), knee pain (3%), and lumbar spine pain (3%).[44] None required referral to a medical practitioner. In the other, investigators reported no serious harms related to the intervention.[42] One occurrence of minor knee pain was reported in the exercise group.

Figure 26. Exercise versus no treatment, waitlist, or an attention control for chronic neck pain: effects on function



CI = confidence interval; COM = combination exercise therapy; MP = muscle performance exercise; NDI = Neck Disability Index; NDS = neck disability scale; NT = no treatment; SD = standard deviation; SMD = standardized mean difference; WL = waitlist.

Figure 27. Exercise versus no treatment, waitlist, or an attention control for chronic neck pain: effects on pain



AC = attention control; CI = confidence interval; COM = combination exercise therapy; MP = muscle performance exercise; MP+NR = muscle performance plus neuromuscular rehabilitation exercise; NT = no treatment; SD = standard deviation; WL = waitlist

Psychological Therapies for Chronic Neck Pain

Key Points

- No difference was found in function (NDI, 0−80 scale) or pain (visual analog scale [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 fair-quality study comparing relaxation training and no intervention or exercise (SOE: low for all). We found no trials with outcomes assessed in the long term.
- We found no evidence comparing relaxation training with pharmacological therapy.
- The only trial of relaxation training did not report harms.

Detailed Synthesis

We found one trial comparing the effects of relaxation training versus no intervention (N=258) or exercise therapy (N=263) in female office workers with chronic neck pain[45] (Table 20 and Appendix D). This trial was included in the previous AHRQ report. Relaxation training and muscle performance exercise therapy were done in 30-minute sessions three times per week for 12 weeks, with 1 week of reinforcement training 6 months after randomization. Patients in the no-treatment group were instructed not to change their usual activities. Adherence to the relaxation schedule during the intervention period was 42 percent of the scheduled sessions. The nature of the intervention and control precluded blinding of participants and people administering the interventions; therefore, this trial was rated as fair quality.

Table 36. Chronic neck pain: psychological therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Viljanen, 2003[45] 3 and 9 months Pain duration: 11 years *Fair*	A. Physical therapist guided relaxation training (n=128): progressive relaxation, autogenic training, functional relaxation, and systematic desensi-tization (goal was to teach correct activation and relaxation of muscles used in daily activities); 3 times per week for 12 weeks, 30 minute sessions B. Physical therapist guided dynamic strengthening exercises of the shoulder and cervical musculature (muscle performance exercises) (n=135): 3 times per week for 12 weeks, 30 minute sessions C. No intervention (n=130)	A vs. B vs. C Age: 43 vs. 45 vs. 44 years Female: 100% Performing physical activity ≥3x/week: 34% vs. 44% vs. 41% Duration of office work: 20 vs. 23 vs. 21 years Sedentary work >6 hours per day: 75% vs. 76% vs. vs. 73% Computer work >6 hours per day: 39% vs. 33% vs. vs. 35% Absent from work due to neck pain: 12% vs. 12% vs. 12% Pain duration: 11 vs. 11 vs. 10 years Depression index: 16 vs. 16 vs. 16 Baseline neck disability scale[a] (0-80): 29 vs. 29 vs. 26 Baseline pain (0-10 VAS): 4.8 vs. 4.8 vs. 4.1	A vs. C <u>3 months</u> Neck disability scale[b]: 15 vs. 14, adjusted difference 0.1 (95% CI −2.9 to 3.2) Pain VAS: 3.0 vs. 2.9, adjusted difference 0.2 (95% CI −0.4 to 0.8) <u>9 months</u> Neck disability scale[b]: 19 vs. 17, adjusted difference 0.2 (95% CI −2.8 to 3.1) Pain VAS: 3.3 vs. 3.2, adjusted difference 0.2 (95% CI −0.3 to 0.8) A vs. B <u>3 months</u> Neck disability scale[a]: 15 vs. 15, adjusted difference 0.2 (95% CI −2.8 to 3.2) Pain VAS: 3.0 vs. 2.9, adjusted difference −0.2 (95% CI −0.8 to 0.4) <u>9 months</u> Neck disability scale[a]: 19 vs. 19; adjusted difference 0.2 (95% CI −2.7 to 3.2) Pain VAS: 3.3 vs. 3.1, adjusted difference −0.2 (95% CI −0.8 to 0.3)	NR

CI = confidence interval; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Neck disability scale was created by investigators from responses to eight questions related to functional limitations due to pain. This scale is not the same as the more common Neck Disability Index (NDI)

Relaxation Training Compared With No Treatment

The one fair-quality trial found no between-group differences in the short term (3 months) or intermediate term (9 months) as measured by a neck disability scale (difference 0.1 on a 0-80 scale, 95% CI −2.9 to 3.2, and difference 0.2, 95% CI −2.8 to 3.1, respectively)[45] (Table 19). The neck disability scale, a nonvalidated instrument, asked whether the participant had pain or difficulty on eight functional activities, with each activity scored from 0 (no pain or hindrance) to 10 (unbearable pain or maximum hindrance), for a total of 80 points. Likewise, there were no differences in pain intensity between groups at the same time frames, (difference 0.2 on a 10-point scale, 95% CI −0.4 to 0.8, and difference 0.2, 95% CI −0.3 to 0.8, respectively). There were no trials evaluating relaxation in the long term.

Relaxation Training Compared With Pharmacological Therapy

We did not find any trials meeting our criteria that compared a relaxation training with pharmacological therapy.

Relaxation Training Compared With Exercise Therapy

The one fair-quality trial found no differences between relaxation training and exercise therapy in the short term (3 months) or intermediate term (9 months) as measured by a neck disability scale described above (difference 0.2 on a 0-80 scale, 95% CI −2.8 to 3.2, and difference 0.2, 95% CI −2.7 to 3.2, respectively)[45] (Table 19). Similarly, there were no differences in pain intensity between groups at the same time frames (difference −0.2 on a 10-point scale, 95% CI −0.8 to 0.4, and difference −0.2, 95% CI −0.8 to 0.3, respectively). There were no trials comparing relaxation with exercise therapy in the long term.

Harms

The trial on relaxation therapy did not report harms.[45]

Physical Modalities for Chronic Neck Pain

Key Points

- Low-level laser therapy was associated with a moderate improvement in short-term function (2 trials, pooled difference −13.60, 95% CI −26.30 to −6.30, I^2=0%, 0-100 scale) and pain (3 trials, pooled difference −1.89 on a 0-10 scale, 95% CI −3.34 to −0.06, I^2=61%) compared with sham (SOE: moderate for function and pain).
- Data from two small, poor-quality trials, one evaluating cervical traction versus attention control (infrared irradiation) and the other electromagnetic fields versus sham, were insufficient to determine effects on function or pain over the short term (SOE: insufficient).
- No trials assessed outcomes in the intermediate term or long term, or compared a physical modality to pharmacological therapy or exercise.
- Harms were poorly reported in trials of low-level laser. Adverse effects occurred with similar frequency in the laser and sham groups in the one trial reporting such effects. The most frequently reported adverse effects included mild (78%) or moderately (60%) increased neck pain, increased pain elsewhere (78%), mild headache (60%), and tiredness (24%) (SOE: low).
- The trials of cervical traction and electromagnetic fields did not report harms.

Detailed Synthesis

A total of five trials (N range, 53 to 90; total sample=363)[145-149] evaluating physical modalities for the treatment of chronic neck pain met inclusion criteria (Table 21 and Appendixes D and E). All of the trials were included in the prior AHRQ report. Interventions included traction, laser therapy, and electromagnetic field therapy.

One trial (N=79) conducted in Hong Kong compared intermittent cervical traction versus attention control (infrared irradiation).[146] Each treatment was administered for 20 minutes twice weekly for 6 weeks. This trial was considered poor quality due to lack of patient and caregiver blinding, high and unequal attrition (41% in traction group, 58% in control), and dissimilar baseline characteristics between groups.

Three trials (N range, 53 to 90; total sample=203)[145,147,148] compared low-level laser therapy with sham. The mean duration of pain varied from 4 years in two trials[145,148] to 15 years in a third.[147] Treatment consisted of laser application (wavelength range, 830 to 904 nm) over several myofascial tender points; across the trials, duration ranged from 30 seconds to 3 minutes per tender point and frequency varied from daily to twice weekly over periods of 2 or 7 weeks. One trial was rated good quality[147] and two fair quality.[145,148] Common methodological limitations in the two fair-quality trials included inadequate reporting of treatment allocation and no or unclear blinding of the care provider. In addition, baseline characteristics were not similar in one trial, in which the intervention group tended to have more pain and tenderness and longer duration of symptoms.[145]

One trial (N=81) compared the effects of eighteen 30-minute sessions (3-5 times per week) of low frequency pulsed electromagnetic fields versus sham.[149] The treatment consisted of an electromagnetic coil against the back of the neck while the participants were lying on a pillow. The investigators covered the set of light emitting diodes that pulse to signal the coil being energized in order to blind the participants to the treatment or sham. This trial was rated as poor quality due to several factors: failure to describe the number randomized in each group; inadequate reporting of treatment compliance and information to calculate participant attrition and intent to treat analysis; care provider not blinded to treatment; and baseline characteristics dissimilar between groups.

Table 37. Chronic neck pain: physical modalities

Author, Year, Followup[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Altan, 2005[145] 3 months Pain duration: 4.5 years Fair	A. GaAs low-level laser treatment (n=26): over the 3 trigger points bilaterally and 1 point in the taut bands in trapezius muscle bilaterally for 2 min over each point once a day for 2 weeks. Laser wavelength of 904 nm. B. Sham laser treatment (n=27)	A vs. B Age: 43 vs. 43 years Female: 87% vs. 48% Baseline pain (0-10 VAS): 6.9 vs. 6.2 Baseline pain (5-point scale, 0-5): 2.4 vs. 2.2	A vs. B 3 months: Pain (VAS): 3.2 vs. 3.8, difference −0.6 (95% CI −1.0 to −0.3) Pain (5 point scale): 1.1 vs. 1.2, difference −0.1 (95% CI −0.2 to 0.05)	NR
Chiu, 2011[146] 1.5 months Pain duration: NR Poor	A. Cervical Traction (intermittent) (n=39): ranging from 10-20% of patient body weight, holding time 10-25 seconds; resting time 20-50% of holding time; twice/week for 6 weeks; sessions lasting 20 minutes. B. Infrared Irradiation Control (n=40): via infrared lamp positioned so that patients reported minimal warmth over the back of their neck; twice/week for 6 weeks; sessions lasting: 20 minutes.	A vs. B Age: 50.9 vs. 46.8 years Female: 65.2% vs. 76.5% Baseline NPQ (0-100%): 46.1 vs. 38.5 Baseline NPS (0-10): 5.8 vs. 5.2	A vs. B 1.5 months NPQ Disability[b]: 31.4 vs. 29.6; p>0.05, 95% CI 29.7 to 37.5, power=0.15 NPS Pain Severity[b]: 3.5 vs. 2.8; p>0.05, 95% CI 3.3 to 4.5, power=0.17	NR

Author, Year, Followup[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Chow, 2006[147] 1 month Pain duration: 15 years Good	A. Low-level laser therapy (n=45): 2x/week for 7 consecutive weeks, maximum half hour per treatment. Up to 50 tender points in the neck were treated for 30 seconds per point. Laser wavelength of 830 nm. B. Sham laser (n=45)	A vs. B Age: 57 vs. 55 years Female: 64% vs. 67% Baseline NPQ (0-100%): Baseline NPAD (0-100): Baseline pain (0-10 VAS): 5.9 vs. 4.0 MPQ VAS (1-5):	A vs. B <u>1 month</u> NPQ: −3.5 vs. −0.6, difference −3.0 (95% CI −5.0 to −0.9) NPAD: −15.2 vs. −3.1, difference −12.1 (95% CI −19.3 to −4.8) Proportion with improved pain >3 points (%): 40% vs. 7%, RR 6.0 (95% CI 1.9 to 19.0) Pain VAS: −2.7 vs. 0.3, difference 3.0 (95% CI −3.8 to −2.1) MPQ VAS: −2.1 vs. 0.1, difference −2.2 (95% CI −3.5 to −0.9)	A vs. B <u>1 month</u> SF36 PCS (0-100): 3.2 vs. −1.3, difference 4.5 (95% CI 0.7 to 8.2) SF 36 MCS (0-100): 2.4 vs. 5.4, difference −2.9 (95% CI −7.2 to 1.3) MPQ sensory (0-33): −3.4 vs. −1.9, difference −1.5 (95% CI −4.5 to 1.5) MPQ affective (0-12): −1.3 vs. −0.7, difference −0.6 (95% CI −2.3 to 1.1)
Gur, 2004[148] 2.5 months Pain duration: 43 months Fair	A. Active Ga-As low-level laser therapy (n=30): daily for 2 weeks, 3 minutes each myofascial tender point. Laser wavelength of 904 nm. B. Sham laser (n=30)	A vs. B Age: 32 vs. 31 years Female: 82% (total pop only) Employed: 12% vs. 17% Baseline NPAD (0-100): 65.4 vs. 68.5 Baseline pain at rest (0-10 VAS): 7.4 vs. 6.9 Baseline pain at movement (0-10 VAS): 7.4 vs. 7.2	A vs. B <u>2.5 months</u> NPAD: 41.1 vs. 63.3, difference −22.2 (95% CI −36.7 to −7.6) VAS pain at rest: 4.2 vs. 6.3, difference −2.1 (95% CI −3.8 to −0.4) VAS pain at movement: 5.3 vs. 7.3, difference −2.0 (95% CI −3.3 to −0.7)	A vs. B <u>2.5 months</u> BDI (0-63): 14.72 vs. 21.38, difference −6.66 (95% CI −13.24 to −0.08) NHP (0-100): 56.41 vs. 72.48, difference −16.1 (95% CI −30.9 to −1.3),

Author, Year, Followup[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Trock, 1994[149] 1 month Pain duration: 7.5 years Poor	A. Pulsed electromagnetic fields (n=42): extremely low frequency (<2 A, 120 V) applied with stepwise energy characteristics as follows: 5 Hz, 0-15 gauss for 10 minutes; 10 Hz, 15-25 gauss for 10 minutes; and 12 Hz, 15-25 gauss for 10 minutes. Maximum number of pulses/burst was 20. B. Sham (n=39) Treatments were given for 30 minute periods, 3-5 times per week for 18 treatments.	A vs. B Age: 61 vs. 67 years Female: 71% vs. 67% Weight (lb): 161 vs. 162 Duration of symptoms: 7 vs. 8 years Baseline ADL difficulty (0-24) 11.9 vs. 11.5 Baseline pain (0-10 VAS): 7.2 vs. 6.2	A vs. B <u>1 month:</u> ADL difficulty: 3.8 vs. 2.1, difference 1.6 (95% CI −1.5 to 4.8) Pain: 2.6 vs. 1.5, difference 1.1 (95% CI −0.3 to 2.6)	A vs. B <u>1 month:</u> Patients' assessment of improvement (0-100): 41.2 vs. 40.0, difference 1.2 (95% CI −15.2 to 17.6)

ADL = activity of daily living; BDI = Beck Depression Inventory; CI = confidence interval; Ga-As = Gallium Arsenide; MPQ = McGill Pain Questionnaire; NHP = Nottingham Health Profile; NPAD = Neck Pain and Disability Scale; NPQ = Northwick Park Questionnaire; NPS = numeric pain scale; NR = not reported; RR = risk ratio; SF-36 MCS = Short-Form 36 Questionnaire Mental Coomponent Score; SF-36 PCS = Short-Form 36 Questionnaire Physical Component Score; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Results of two-way repeated measures analysis of variance (ANOVA).

Physical Modalities Compared With Attention Control or Sham

Traction. One poor-quality trial found no short-term differences in function comparing intermittent cervical traction versus attention control (infrared irradiation) using the Northwick Park Questionnaire (NPQ) (difference −1.8, 95% CI −10.8 to 7.2, 0-100% scale).[146] Likewise, there was no difference in pain intensity between groups (difference −0.7, 95% CI −2.2 to 0.8, 10 point scale). There were no trials evaluating cervical traction in the intermediate term or long term.

Low-Level Laser Therapy. Laser was associated with moderately greater effects compared with sham on short-term function (2 trials, pooled difference −13.60, 95% CI −26.30 to −6.30, I^2=0%, 0-100 scale) (Figure 28)[147,148] and short-term pain (3 trials, pooled difference −1.89, 95% CI −3.34 to −0.06, I^2=61%, 0-10 scale) (Figure 29).[145,147,148] Pain improvement of greater than −3.0 on a 10-point VAS scale was substantially more common with laser therapy in the good-quality trial (RR 6.0, 95% CI 1.9 to 19.0).[147] Quality of life improvement also favored low-level laser as measured by the SF-36 PCS (difference 4.5, 95% CI 0.7 to 8.2)[147] and the Nottingham Health Profile (difference −16.1 on a 0-100 scale, 95% CI −30.9 to −1.3).[148] Measures demonstrating no difference between groups included the SF36 MCS and the McGill Pain Questionnaire component scores[147] (Table 20). There were no trials evaluating laser therapy in the intermediate term or long term.

Electromagnetic Fields. One poor-quality trial found no between-group differences in short-term difficulty with activities of daily living (ADLs) (difference 1.6 , 95% CI −1.5 to 4.8, scale 0-24, nonvalidated measure).[149] The ADL instrument asked whether the participant had pain or difficulty on eight activities scored from 0 (never) to 3 (always), for a total of 24 points.

Likewise, there was no difference in pain intensity between groups (difference 1.1, 95% CI −0.3 to 2.6, 0-10 scale) or in patients' assessment of improvement (difference 1.2, 95% CI −15.2 to 17.6, 0-100 scale).[149] There were no trials evaluating electromagnetic fields in the intermediate term or long term.

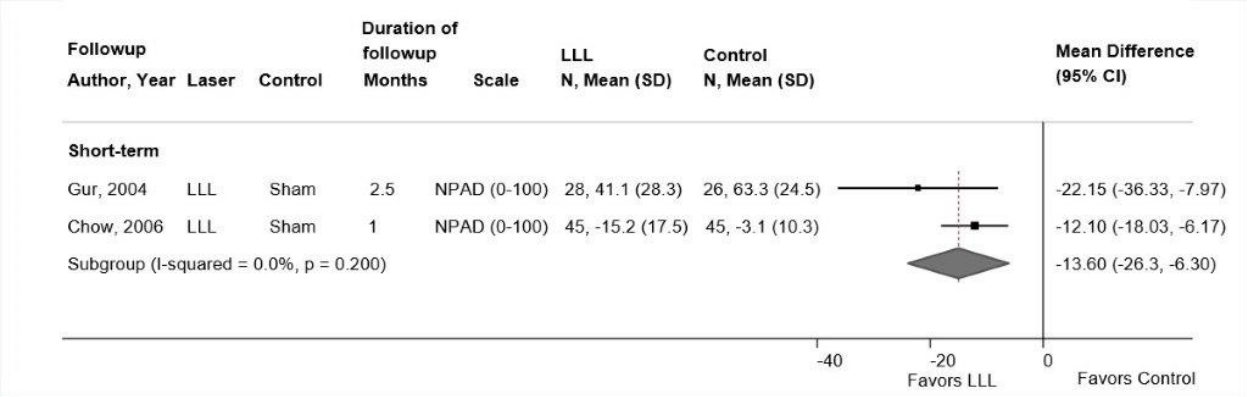
Physical Modalities Compared With Pharmacological Therapy or With Exercise Therapy

We did not find any trials meeting our criteria comparing a physical modality with pharmacological therapy or with exercise.

Harms

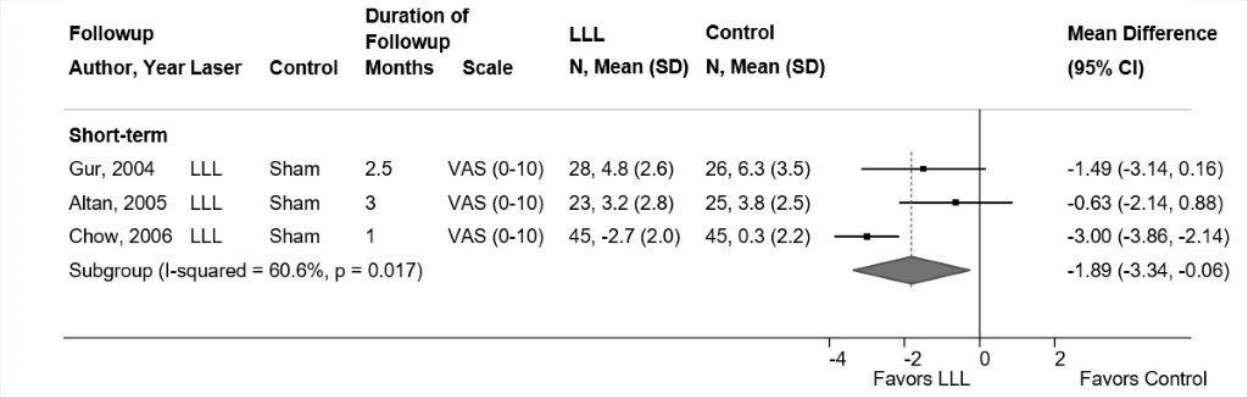
Only one laser trial reported harms.[147] The trial reported a large number of adverse effects with similar frequency in both groups. However, the sham group reported nausea significantly more frequently (42% vs. 20%) while the laser group reported stiffness more frequently (20% vs. 4%). The most frequently reported adverse effects included mild (78%) or moderate (60%) increased neck pain, increased pain elsewhere (78%), mild headache (60%), and tiredness (24%). Harms were not reported by either trial evaluating cervical traction or electromagnetic fields.

Figure 28. Low-level laser therapy versus sham for chronic neck pain: effects on function



CI = confidence interval; LLL = low-level laser therapy; NPAD = Neck Pain and Disability Scale; SD = standard deviation

Figure 29. Low-level laser therapy versus sham for chronic neck pain: effects on pain



CI = confidence interval; LLL = low-level laser therapy; SD = standard deviation

Manual Therapies for Chronic Neck Pain

Key Points

Massage

- The effects of Swedish massage on function (≥5 point improvement on the NDI) versus self-management attention control were small and not statistically significant in one trial in the short term (39% versus 14%, 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).
- Massage was associated with a small improvement in short-term function compared with attention or waitlist control (2 trials [1 new], pooled difference –3.66 on a 0-50 NDI scale, 95% CI –6.58 to –0.56, I^2=10%) (SOE: low).
- Massage was associated with a moderate improvement compared with waitlist control in short-term pain intensity experienced during the previous 7 days (1 new trial, difference –1.8 on a 0-10 scale, 95% CI –2.7 to –0.9) (SOE: low).
- No clear evidence that massage improved pain in the intermediate term versus exercise ($p>0.05$, data not reported) was seen in a third fair-quality trial (SOE: low).
- Three fair-quality trials (1 new) reported no serious adverse effects; transient nonserious pain or soreness was reported during or following massage in two trials (1 new) and during or after exercise, but not massage, in a third trial (SOE: low).

Detailed Synthesis

Massage

Three trials of massage therapy met inclusion criteria (Table 22 and Appendix D).[181-183] Two trials[181,182] were included in the prior AHRQ report and one[183] was added for this update. Sample sizes ranged from 64 to 108 (total sample=264). One trial compared Swedish massage versus attention control (self-care education),[182] the new trial compared Tuina massage versus waitlist[183] and one trial compared classical massage versus two types of exercise (muscle re-education and strength training targeting the neck and shoulder muscles).[181] Swedish and classical massage (nonforceful) were performed on the neck and back, and in some cases the pectoral muscles and rotator cuff or arms. Tuina massage included soft tissue massage, local muscle stretching, mobilization and traction of the cervical spine, and manipulation of local pain (trigger) points; no high-velocity/low-amplitude thrusts were applied. Muscle re-education exercise was performed with a newly developed training device strapped to the head and consisted of a plate with 5 exchangeable surfaces that allow for progression of task difficulty; strength training included both isometric and dynamic exercises targeting the neck and shoulders. One trial was conducted in the United States,[182] one in Sweden[181] and the new trial in Germany.[183] One trial administered 6 massage treatments over 3 weeks,[183] a second trial 10 massage treatments over 10 weeks,[182] and the third trial 22 massage treatments over 11 weeks.[181] The new trial evaluated outcomes in the short term only[183]; trials included in the original report one in reported the intermediate term only,[181] and one reported on the short and intermediate term.[182]

All trials were rated fair quality (Appendix E). Methodological limitations included the inability to blind interventions in all trials, and 21 percent attrition in the trial comparing massage with exercise.[181]

Table 38. Chronic neck pain: manual therapies (massage)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Pach, 2018[183] 1 and 3 months Duration of pain: mean 11.2 to 11.5 years Fair [New trial]	A. Tunia massage (n=46) Two 30-minute sessions/week for 3 weeks (6 sessions total). Authors report high adherence but data is not provided. B. No intervention waitlist (n=46)	A vs. B Age: 46 vs. 45 years Female: 89.1% vs. 84.8% Baseline NDI (0-50): 45.5 vs. 46.5 Baseline NPDS (0-100): 42.7 vs. 42.7 Baseline pain during previous 7 days (0-100 VAS): 55.8 vs. 59.5	A vs. B 3 months NDI: 36.6 (95% CI 33.5 to 39.6) vs. 46.1 (95% CI 42.9 to 49.3), adjusted difference −9.6 (95% CI −14.0 to −5.1) NPDS: 30.2 (95% CI 25.8 to 34.6) vs. 42.3 (95% CI 37.7 to 46.8), adjusted difference −12.1 (95% CI −18.4 to −5.8) Mean VAS score during previous 7 days: 30.1 (95% CI 23.8 to 36.4) vs. 48.1 (95% CI 41.5 to 54.6), adjusted difference −17.9 (95% CI −27.1 to −8.8);	A vs. B 3 months SF-12 Physical health (0-100): 48.1 (95% CI 45.8 to 50.3) vs. 42.4 (95% CI 40.1 to 44.7), adjusted difference 5.6 (95% CI 2.4 to 8.9) SF-12 Mental health (0-100): 48.3 (95% CI 45.4 to 51.1) vs. 45.7 (95% CI 42.8 to 48.5), adjusted difference 2.6 (95% CI −1.4 to 6.6) Proportion of patients using medication for neck pain during the previous 4 weeks: 0.4 (95% CI 0.2 to 0.6) vs. 0.5 (95% CI 0.3 to 0.7), adjusted difference −0.1 (95% CI −0.4 to 0.1)
Rudolfsson, 2014[181] 6 months Duration of pain: median 84 to 123 months Fair	A. Massage, classical (n=36): upper body including the back, neck and shoulders. B. Neck coordination exercise (n=36): performed with a newly developed training device designed to improve the fine movement control of the cervical spine. C. Strength training (n=36): isometric and dynamic exercises targeting the neck and shoulder regions. All 3 interventions consisted of 22 individually supervised single treatment sessions, 30 min each, distributed over 11 weeks	A vs. B vs. C Age: 51 vs. 52 vs. 51 years Female: 100% vs. 100% vs. 100% Baseline pain (0-10 NRS), 5 vs. 6 vs. 6 (median) Baseline NDI: 26 vs. 29 vs. 31 SF-36 PCS (0-100): 43 vs. 39 vs. 39 (median) SF-36 MCS (0-100): 49 vs. 52 vs. 47 (median)	A vs. B: 6 months Pain NRS (0-10): 4.0 vs. 3.8, difference 0.2 (95% CI −0.8 to 1.2) A vs. C: 6 months Pain NRS (0-10): No data given at 6 month, however, authors state no difference among A, B or C.	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sherman, 2009[182] 2.5 and 6.5 months Duration of pain >1 year: 81% Fair	A. Massage (n=32): Swedish and clinical techniques and self-care recommendations; 10 massage treatments over a 10-week period B. Self-care book: (n=32) information on potential causes of neck pain, neck-related headaches, whiplash, recommended strengthening exercises, body mechanics and posture, conventional treatment, complementary therapies for neck pain, and first aid for intermittent flare-ups.	A vs. B Age: 47 vs. 46 years Female: 69% vs. 69% White: 87% vs. 81% Smoker: 9% vs. 6% Pain lasted > 1 year: 81% vs. 81% Baseline NDI (0-50): 14.2 vs. 14.2S	A vs. B <u>2.5 months</u> NDI, % ≥5 points: 39% vs. 14%, RR 2.7 (95% CI 0.99 to 7.5) NDI (0-50): difference −2.3 (95% CI −4.7 to 0.15) <u>6.5 months</u> NDI, % ≥5 points: 57% vs. 31%, RR 1.8 (95% CI 1.0 to 3.5) NDI: difference: −1.9 (95% CI −4.4 to 0.6)	A vs. B <u>2.5 months</u> Bothersome score (0-10): difference −1.2 (95% CI −2.5 to 0.1) Bothersome improvement ≥30%: 55% vs. 25%, RR 2.1 (95% CI 1.04 to 4.2) SF-36 PCS (0-100): 52.8 vs. 53.3, p=0.982 SF-36 MCS (0-100): 45.9 vs. 45.3, p=0.444 <u>6.5 months</u> Bothersome score: difference −0.14 (95% CI −1.5 to 1.2) Bothersome improvement ≥30%: 43% vs. 39%, RR 1.1 (95% CI 0.6 to 2.0) SF-36 PCS and MCS: data not given, no statistical difference Medication use: No change in group A, 14% increase in group B

CI = confidence interval; NDI = Neck Disability Index; NR = not reported; NRS = numeric rating scale; SF-36 MCS = Short-Form 36 Questionnaire Mental Component Scale; SF-36 PCS = Short-Form 36 Questionnaire Physical Component Scale VAS = Visual Analog Scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

Massage Therapy Compared With an Attention Control or Waitlist

One trial of Swedish massage versus attention control found that a greater proportion of participants in the massage group achieved ≥5 point improvement on the NDI in the short-term (39% versus 14%, 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).[153] Massage was associated with a small improvement in short-term function compared with attention or waitlist controls (2 trials [1 new], pooled difference −3.66 on a 0 to 50 NDI scale, 95% CI −6.58 to −0.56, I^2=10.2%) (Figure 30).[182,183] The massage technique in one trial was soft tissue massage and mobilization of upper extremity joints and the cervical spine (i.e., Tuina massage) (difference −4.8, 95% CI −7.0 to −2.6 on the 0 to 50 NDI scale)[183] and structural or relaxation massage (i.e., Swedish massage) in one trial (difference −2.3, 95% CI −4.7 to 0.1 on the 0-50 NDI scale).[182]

One new, small fair quality study reported that Tuina massage was associated with moderate improvement in pain intensity experienced during the previous 7 days compared with waitlist controls (difference −1.8 on a 0-10 scale, 95% CI −2.7 to −0.9).[183]

A greater proportion of participants in the Swedish massage group reported improvement in a symptom bothersomeness scale (≥30%) in the short term (55% versus 25%; RR 2.2, 95% CI 1.04 to 4.2) but not the intermediate term (43% vs. 39%; RR 1.1, 95% CI 0.6 to 2.0) compared with attention controls in one trial.[182] One new trial found no differences between groups in SF-36

PCS and MCS while one reported a better quality of life as measured by the SF-12 PCS (difference 5.6 on a 0-100 scale, 95% CI 2.4 to 8.9), but not on the SF-12 MCS (difference 2.6 on a 0-100 scale, 95% CI −1.4 to 6.6).[183]

Massage Therapy Compared With Pharmacological Therapy

No trial of manual therapy versus pharmacological therapy met inclusion criteria.

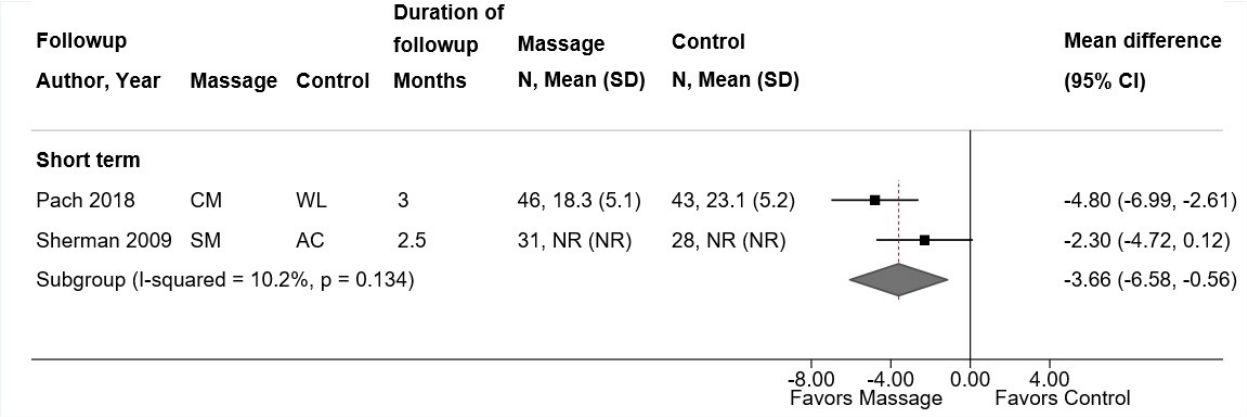
Massage Therapy Compared With Exercise

One fair-quality study reported no difference in intermediate-term pain comparing classical massage with neck coordination exercises (difference 0.2, 95% CI −0.82 to 1.22, 0-10 scale) or muscle performance exercises (no data given, p>0.05).[181] The use of opioid therapies and healthcare utilization were not evaluated.

Harms

None of the trials reported serious adverse effects. Nonserious mild adverse effects included discomfort or pain during (n=5) or after Swedish massage (n=3) in one trial.[182] In the new trial of Tuina massage, the proportion of patients reporting mild adverse events was 41.3% (19/46); most included increased pain (aching muscles, n =11; headache, n=3 and point tenderness, n=1).[183] Other mild adverse events included dizziness, sleepiness, mood swings, nausea, difficulty staying asleep, difficulty moving the head and neck. In the third trial, transient neck or headache pain was reported in the neuromuscular training exercise group (n=10); there was no mention of complications for the strength training or massage groups.[181]

Figure 30. Massage versus attention control or waitlist for chronic neck pain: effects on function



AC = attention control; CI = confidence interval; CM = classic massage; NDI = Neck Disability Index; SD = standard deviation; SM = Swedish massage; WL = waitlist.

Mind-Body Practices for Chronic Neck Pain

Key Points

- Alexander Technique resulted in a small 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 fair-quality trial (SOE: low).
- There was no clear evidence that basic body awareness therapy improved function in the short term versus exercise in one fair-quality trial (SOE: low).
- There is insufficient evidence from one poor-quality trial to determine the effects of qigong on intermediate-term or long-term function or pain versus exercise; no data were available for short term outcomes (SOE: insufficient).
- Both fair-quality trials reported no serious treatment-related adverse events. The trial evaluating Alexander Technique versus usual care found no clear between-group difference for nonserious adverse events, such as pain and incapacity, knee injury, or muscle spasm (RR 2.25, 95% CI 1.00 to 5.04). The other trial reported no differences between basic body awareness and exercise in any nonserious adverse effect (RR 0.65, 95% CI 0.37 to 1.14) (SOE: low).

Detailed Synthesis

Three trials (reported in 4 publications) of mind-body practices met inclusion criteria, (Table 23 and Appendix D).[213,214,221,222] All three trials were included in the prior AHRQ report; only a newly identified publication (subanalysis)[214] of a previously included trial[213] was added for this update. One trial evaluated the Alexander Technique (a method of self-care developed to help people enhance their control of reaction and improve their way of going about everyday activities) plus usual care (N=344),[213] one trial basic body awareness therapy (N=113),[222] and one trial of qigong (N=139).[221] One trial compared mind-body techniques versus usual care[213] and two trials versus individually adjusted cervical and shoulder strengthening and stretching exercises,[221] or group-led exercises for whole body strengthening, aerobic, and coordination

exercises.[222] Two trials were conducted in Sweden[221,222] and one in England.[213] The duration of mind-body treatment ranged from 10 to 20 weeks and the number of treatment sessions ranged from 12 to 20. One trial reported outcomes during the intermediate term and long term,[221]one short-term and intermediate-term outcomes,[213] and one short-term outcomes only.[222]

Two of the trials were rated fair quality[213,222] and one trial poor quality[221] (Appendix E). In the two fair-quality trials, the main methodological limitation was the inability to blind interventions. Limitations in the other trial included the inability to blind interventions, high attrition, and unequal loss to followup between groups.

Table 39. Chronic neck pain: mind-body practices

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lansinger, 2007[221] 6 and 12 months Pain duration: >5 years, 45% Poor	A. Qigong (n=72): 10-12 group sessions of 10-15 people done 1-2 times per week over 3 months. Sessions were 1 hour and consisted of information of the philosophy of medical qigong followed by exercises based on the Biyun method B. Exercise (n=67): 10-12 sessions 1-2 times per week over 3 months. Sessions were 1 hour and individualized to target 30%-70% of a person's maximal voluntary capacity, with exercises aiming to maintain/increase circulation, endurance, and strength. All patients: Ergonomic instructions and a pamphlet containing written information on neck pain	A vs. B Age: 45 vs. 43 Female: 73% vs. 67% Physical activity: No to light exercise: 67% vs. 65% Med to hard exercise: 33% vs. 35% Baseline NDI (0-100), median: 26 vs. 22 Baseline pain (VAS, 0-10), median: 45 vs. 39	A vs. B <u>6 months</u> NDI, median: 22 vs. 18, p>0.05 Neck pain VAS (0-10), median: 2.6 vs. 2.3, p>0.05 <u>12 months</u> NDI, median: 22 vs. 18, p>0.05 Neck pain VAS, median: 2.8 vs. 2.1, p>0.05	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
MacPherson, 2015[213], Essex 2017[214] ATLAS trial 1, 7, and 12 months Duration of pain, 7 years Fair [Essex – New publication reporting healthcare utilization]	A. Alexander Technique group (n=172): up to 20 one-to-one lessons of 30 minutes' duration (600 minutes total) plus usual care, delivered weekly, with the option of being delivered twice per week initially and every 2 weeks later. B. Usual care (n=172) including general and neck pain–specific treatments routinely provided to primary care patients, such as prescribed medications and visits to physical therapists and other healthcare professionals. Treatment was 12 sessions over 5 months lasting 50 minutes.	A vs. B Age: 52 vs. 54 years Female: 69% vs. 69% White: 93% vs. 89% Employed: 61% vs. 62% P Baseline NPQ (0-100%): 39.6 vs. 40.5	A vs. B <u>1 month</u> NPQ: 35.4 vs. 40.9, difference −5.6 (95% CI −8.3 to −2.8) <u>7 months</u> NPQ: 37.1 vs. 41.0, difference −3.9 (95% CI −6.9 to −1.0)	A vs. B <u>1 month</u> SF-12v2 physical: data NR, p=NS SF-12v2 mental: data NR, p=NS <u>7 months</u> SF-12v2 physical: 0.68 (95% CI −1.1 to 2.4), p=0.44 SF-12v2 mental: 1.76 (95% CI 0.2 to 3.4), p=0.033 <u>12 months[b]</u> Mean utilization of NHS resources[c]: p>0.05, data NR Mean utilization of private healthcare (additional sessions): - Acupuncture: 0.2 vs. 0.1, p>0.05 - Alexander Technique: 0.5 vs. 0, p<0.05 - Other private appointments: 1.0 vs. 2.1, p>0.05 Mean days off work due to neck pain: 1.4 vs. 2.3, p>0.05 Mean total NHS cost (2012/13 UK £):1200 (95% CI 1000 to 1400) vs. 484 (95% CI 371 to 598), adjusted difference,[d] 667 (95% CI 472 to 896); p<0.001

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Seferiadis, 2015[222] 3 months Pain duration: 9.5 years Fair	A. Basic body awareness therapy (n=57): 1.5 hour sessions twice a week for 10 weeks. Sessions consisted of exercises based on activities of daily living, meditation, and tai chi inspired exercises aiming to improve posture and increase efficient movement patterns B. Exercise (n=56): 1.5 hour sessions twice a week for 10 weeks. Sessions consisted of 45 minutes of muscle strengthening, 15 minutes of stretching, and 20 minutes of progressive muscle relaxation	A vs. B Age: 47 vs. 49 Female: 66% vs. 77% WAD classification: 1: 0% vs. 2% 2: 23% vs. 28% 3: 77% vs. 70% Baseline NDI (0-50): 20 vs. 18.8	A vs. B <u>3 months</u> NDI: Difference from baseline −2.0 (95% CI −3.5 to −0.5) vs. −1 (95% CI −2.5 to 0.4), p>0.05	A vs. B <u>3 months</u> SF-36v2 physical functioning (0-100): Difference from baseline 7.1 (95% CI 3.7 to 11.4) vs. 0.5 (95% CI −3.2 to 4.1), p>0.05 SF-36 role-physical(0-100): Difference from baseline 17.5 (95% CI 5.9 to 29) vs. 19 (95% CI 9.3 to 28.6), p>0.05 SF-36 bodily pain(0-100): Difference from baseline 12.2 (95% CI 6.9 to 17.6) vs. 4.9 (95% CI −0.1 to 9.8), p=0.044 SF-36 general health(0-100): Difference from baseline 7.5 (95% CI 2.4 to 12.6) vs. 4.5 (95% CI −0.1 to 9), p>0.05 SF-36 vitality(0-100): Difference from baseline 7.3 (95% CI 1.0 to13.6) vs. 5.6 (95% CI −0.5 to 11.6), p>0.05 SF-36 social functioning(0-100): Difference from baseline 13.3 (95% CI 6.6 to 19.9 vs. 3.5 (95% CI −3 to 9.9), p=0.037 SF-36 role-emotional (0-100): Difference from baseline 9.3 (95% CI −2.3 to 21) vs. 4 (95% CI −8.3 to 16.4), p>0.05 SF-36 mental health (0-100): Difference from baseline 2.8 (95% CI −2 to 7.6) vs. 1.2 (95% CI −3.6 to 5.9), p>0.05

CI = confidence interval; NDI = Neck Disability Index; NHS = National Health Service; NPQ = Northwick Park Neck Pain Questionnaire; NR = not reported; SF-12 = Short-Form 12 Questionaire; SF-36 =Short-Form 36 Questionnaire; UK = United Kingdom; VAS = visual analog scale; WAD = Whiplash Associated Disorders

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

[b] 12 month data are health utilization data only from a subset of patients from the ATLAS trial (publication Essex 2017) who had full economic data N=293 (57%) [to include the acupuncture arm; details in the Acupuncture section]; no demographic data provided for the subset

[c] Across all appointment types and prescription medications; National Health Services (NHS) appointment types to include, general practitioner appointments, physiotherapy visits, hospital outpatient visits, accident and emergency admissions, hospital day case admissions, other hospital admissions. NHS prescription medication included all prescription medication and prescription items specifically for neck pain. Neck pain prescriptions t-test comparing usual care and acupuncture borderline significance (p=0.06).

[d] For baseline NHS healthcare costs and practice size.

Mind-Body Practices Compared With Usual Care

One fair-quality trial found a small improvement in function as measured by the NPQ in favor of the Alexander Technique plus usual care versus usual care alone in the short term (difference −5.56 on a 100% scale, 95% CI −8.33 to −2.78) and intermediate term (difference −3.92, 95% CI −6.87 to −0.97).[213] There were no significant differences between the intervention group and usual care for the physical component score of the SF-12 (version 2) at 1-month or 7-month followup. However, significantly larger improvements in the MCS occurred in the Alexander group versus the usual care group 7 months following treatment (difference, 2.12 on a 0-100 scale, 95% CI 0.42 to 3.82).[213]

In a new secondary economic analysis of a subset (57%) of patients from a previously included trial there were no significant differences between Alexander Technique and usual care in terms of UK National Health Service (NHS) healthcare utilization (appointments or prescription items).[214] While more people paid for extra Alexander lessons in the private healthcare setting, this represented people who attended all trial sessions and paid for extra. There were no differences in terms of utilizing other private healthcare services.

Mind-Body Practices Compared With Pharmacological Therapy

No trial of mind-body practice versus pharmacological therapy met inclusion criteria.

Mind-Body Practices Compared With Exercise

There were no differences in function as measured by the NDI between basic body awareness therapy (1 fair-quality study, n=113)[222] in the short term (mean change from baseline −2 versus −1, p>0.05) or qigong (poor-quality study, n=139)[221] in the intermediate term or long term (median 22 versus 18, p>0.05, at each time period) versus exercise therapy. The trial assessing qigong found no difference in pain at 6 or 12 months following treatment (median 2.6 versus 2.3 and 2.8 versus 2.3, p>0.05, respectively).[221] Two of the eight sections of the SF-36v2 favored basic body awareness therapy versus exercise in the short term (bodily pain and social functioning) in the fair-quality trial.[222] No other section of the SF-36v2 demonstrated a difference between groups.

No trial evaluated effects of mind-body practices on use of opioid therapies.

Harms

Two trials, one of basic body awareness therapy[222] and the other of Alexander Technique,[213] reported no serious adverse effects. One patient in the basic body awareness group and four patients in the exercise group reported that they discontinued treatment due to increased neck symptoms or pain in other joints (p=0.363). The event risk for all nonserious adverse events was 0.27 in the body awareness therapy group and 0.40 in the exercise group (RR 0.65, 95% CI 0.37 to 1.14). In the trial comparing Alexander Technique versus usual care, no clear difference was seen in the risk of any nonserious adverse event (e.g., pain and incapacity, knee injury, muscle spasm, and complications after surgery): RR 2.25 (95% CI 1.00 to 5.04).

Acupuncture for Chronic Neck Pain

Key Points

- Acupuncture was associated with small improvements in short-term and intermediate-term function versus sham acupuncture, a placebo (sham laser), or usual care (short term, 5 trials, pooled SMD −0.40, 95% CI −0.67 to −0.14, I^2=61%; intermediate term, 3 trials, pooled SMD −0.19, 95% CI −0.37 to 0.05, I^2=0%). 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).
- There were no differences in pain in trials comparing acupuncture with sham acupuncture or placebo interventions in the short term (4 trials [excluding outlier trial], pooled difference −0.27 on a 0-10 scale, 95% CI −0.59 to 0.05, I^2=2%), intermediate term (3 trials, pooled difference 0.40, 95% CI −0.45 to 1.44, I^2=19%), or long term (1 trial, difference −0.35, 95% CI −1.34 to 0.64) (SOE: low for all time periods).
- There was insufficient evidence from two small poor-quality trials to draw conclusions regarding short-term function or pain for acupuncture versus NSAIDs (SOE: insufficient).
- No serious adverse events were reported in six trials reporting harms. The most commonly reported nonserious adverse events in people receiving acupuncture included numbness/discomfort, fainting, and bruising (SOE: moderate).

Detailed Synthesis

We identified nine trials (reported in 10 publications) of acupuncture that met our inclusion criteria, (Table 24 and Appendix D).[213,214,231-237,254] All trials were included in the prior AHRQ report; only a newly identified publication (subanalysis)[214] of a previously included trial[213] was added for this update. All trials evaluated needle acupuncture to body acupoints; two also evaluated electroacupuncture.[234,237] Control groups included sham acupuncture in five trials,[231-234,236] placebo intervention (sham TENS[235] and sham laser acupuncture[237]) in two trials, usual care in one trial,[213] and pharmacological therapy (Zaltoprofen[254] and Trilisate[231]) in two trials. The duration of acupuncture therapy ranged from 2 weeks to 5 months, and the number of sessions from 5 to 14. Sample sizes ranged from 30 to 345 (total sample=1,260). Across trials, participants were predominately female (from 60% to 90%) with mean ages ranging from 37 to 53 years. One trial was conducted in the United States,[231] one in Turkey,[234] and the rest in Asia[232,233,237,254] or Europe.[213,235,236] One trial reported outcomes through long-term followup,[236] four trials through intermediate-term followup,[213,235-237] and the remainder only evaluated short-term outcomes.[231-234,254]

Seven trials were rated fair quality[213,232-237] and two trials poor quality[231,254] (Appendix E). Common limitations in the fair-quality trials included unclear allocation concealment methods and of care provider blinding; additionally, the poor-quality trials had baseline group dissimilarity (not controlled for) and high attrition.

Table 40. Chronic neck pain: acupuncture

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Birch, 1998[231] 3 months Duration of pain, 7.5 years Poor	A. Relevant acupuncture, Japanese technique (n=15): using bilateral needles on hands and feet known to be associated with treatment for neck pain and followed by Infrared lamp. B. Irrelevant acupuncture (n=16): using bilateral needles on hands and feet in areas not associated with treatment for neck pain and followed by light. C. NSAIDs only (n=15): 500mg per day of Trilisate 30 minute treatment twice per week for 4 weeks, then once per week for 4 weeks, total 14 treatments	A vs. B vs. C Age: 41 vs. 38 vs. 39 years Female: 86% vs. 77% vs. 86% Employed: 86% vs. 69% vs. 77% Baseline pain (CPEQ, 0-10) 4.8 vs. 4.7 vs. 4.9	A vs. B 3 months SF-MPQ[b] (0-33): 9.0 vs. 15.1, p=NS A vs. C 3 months SF-MPQ: 9.0 vs. 18.0, p=NS	NR
Cho, 2014[254] 1 month Duration of pain, NR Poor	A. Active acupuncture, traditional Chinese (n=15), 3x/week for 3 weeks.(length of time for each intervention not reported) B. Zaltoprofen (80mg) alone (n=15) 3x/day for 3 weeks.	A vs. B Age: 38 vs. 39 years Female: 60 vs. 80 Baseline NDI (0-50): 22.3 vs. 26.3 Baseline Pain (0-10 VAS): 6.1 vs. 7.1	A vs. B 1 month NDI: 17.3 vs. 17.7, difference −0.40 (95% CI −4.6 to 3.8) Pain VAS: 4.5 vs. 3.8, difference 0.7 (95% CI −0.7 to 2.1)	A vs. B 1 month BDI (0-63) : 28.5 vs. 27.2, p=NS SF-36 (0-100): 88.6 vs. 84.3, p=NS EQ-5D (scale unclear): 7.3 vs. 6.7, p=NS
Ho 2017[232] 1 month Duration of pain: 6 years Fair	A. Acupuncture (n=77): 30 sessions of abdominal acupuncture 3 times a week for 2 weeks. The acupuncture points CV12, CV4, KI17, and ST24 were needled for 30 minutes with infrared therapeutic lamp placed 30 cm above the naval. B. Sham acupuncture (n=77): 30 sessions of sham abdominal acupuncture 3 times a week for 2 weeks. Blunt sham needles were nonpenetrative and administered at nonacupuncture points.	A vs. B Age: 46 vs. 45 Female: 81% vs. 83% Use of pain medications: 15% vs. 13% Previous acupuncture use: 42% vs. 44% Baseline NPQ (0-100%): 41.3 vs. 41.0 Baseline pain (0-10 VAS): 6.4 vs. 6.1S	A vs. B 1 month NPQ, mean Δ (95% CI): −11.9 (−14.6 to −9.2) vs. −3.3 (−5.5 to −1.0), difference −8.7 (95% CI −12.1 to −5.2) p<0.001 Pain VAS, mean Δ (95% CI): −2.4 (−2.8 to −1.9) vs. −0.6 (−0.9 to −0.2), difference −1.8 (95% CI −2.4 to −1.2) p<0.001	A vs. B 1 month SF-36 PCS, mean Δ (95% CI): 4.1 (3.0 to 5.3) vs. 1.3 (0.1 to 2.5), difference 2.8 (95% CI 1.2 to 4.5), p=0.003 SF-36 MCS, mean Δ (95% CI): 2.0 (0.5 to 3.5) vs. −0.3 (−2.0 to 1.4), difference 2.3 (95% CI −0.0 to 4.5) p=NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Liang, 2011[233] 3 months Duration of pain: NR Fair	A. Active acupuncture, traditional Chinese, (n=93) B. Sham acupuncture (n=97) Treatment was 3x/week for 3 weeks (9 treatments total) lasting 20 minutes after needling Both groups received infrared	A vs. B Age: 37 vs. 37 years Female: 72% vs. 73% Baseline NPQ (0-100%): 32.7 vs. 33.0 Baseline Pain (0-10 VAS): 5.3 vs. 5.5	A vs. B <u>3 months</u> NPQ: 19.1 vs. 25.5, difference −6.4 (95% CI −9.9 to −2.9) Pain VAS: 2.9 vs. 3.2, difference −0.3 (95% CI −0.75 to 0.15)	A vs. B <u>3 months</u> SF-36 physical functioning (0-100): 84.3 vs. 85.9, p=0.447 SF-36 mental (0-100): 67.1 vs. 61.6, p=0.001

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
MacPherson, 2015[213], Essex, 2017[214] ATLAS trial 1, 7, and 12 months Duration of pain: 7 years Fair [Essex – New publication reporting healthcare utilization]	A. Active acupuncture, traditional Chinese, (n=173): plus usual care 2 weeks later. B. Usual care (n=172): including general and neck pain–specific treatments routinely provided to primary care patients, such as prescribed medications and visits to physical therapists and other healthcare professionals. Treatment was 12 sessions over 5 months lasting 50 minutes	A vs. B Age: 52 vs. 54 years Female: 69% vs. 69% White: 93% vs. 89% Employed: 61% vs. 62% Baseline NPQ (0-100%): 39.64 vs. 40.46	A vs. B <u>1 month</u> NPQ: 35.4 vs. 40.9, difference −5.6 (95% CI −8.3 to −2.8) <u>7 months</u> NPQ: 37.07 vs. 41.0, difference −3.9 (95% CI −6.9 to −1.0)	A vs. B <u>1 month</u> SF-12v2 physical: data NR, p=NS SF-12v2 mental: data NR, p=NS <u>7 months</u> SF-12v2 physical (0-100): difference 0.7 (95% CI 1.1 to 2.4) SF-12v2 mental (0-100): difference 1.8 (95% CI 0.2 to 3.4) <u>12 months</u>[c] Mean utilization of NHS resources[d]: p>0.05, data NR Mean utilization of private healthcare (additional sessions): - Acupuncture: 1.5 vs. 0.1, p<0.001 - Alexander Technique: 0 vs. 0, p>0.05 - Other private appointments: 0.9 vs. 2.1, p>0.05 Mean days off work due to neck pain: 0.4 vs. 2.3, p>0.05 Mean total NHS cost (2012/13 UK £): 947 (95% CI 800 to 1094) vs. 484 (95% CI 371 to 598), adjusted difference,[e] 451 (95% CI 285 to 634); p<0.001

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sahin, 2010[234] 3 months Duration of pain: NR Fair	A. Electro-acupuncture (n=15) B. Sham acupuncture (n=16) Treatment was 10 sessions, 3 sessions per week, lasting 30 minutes	A vs. B Age: 39 vs. 35 years Female: 100% vs. 81% University graduate: 54% vs. 94% BMI: 23.9 vs. 24.6 Baseline pain with motion (0-10 VAS): 7.4 vs. 6.2 Baseline pain at rest (0-10 VAS): 4.0 vs. 5.3	A vs. B <u>3 months</u> Pain with motion VAS: 4.50 vs. 5.38, difference −0.9 (95% CI −2.7 to 0.9) Pain at rest VAS: 4.0 vs. 3.5, difference 0.5 (95% CI −1.9 to 2.8)	NR
Vas, 2006[235] 6 months Duration of pain: 3.8 years Fair	A. Active acupuncture, traditional Chinese, (n=61) B. Sham TENS (n=62) Treatment was 5 sessions over 3 weeks lasting 30 minutes	A vs. B Age: 46 vs. 47 years Female: 75% vs. 89% Baseline pain with motion (0-10 VAS): 6.9 vs. 7.2 PQ (0-100%): 52.7 vs. 56.5	A vs. B <u>6 months</u> (Mean from baseline) Pain VAS with motion: 4.1 vs. 2.7, difference 1.4 (95% CI 0.3 to 2.6)	A vs. B <u>6 months</u> SF-36 PCS: (0-100): 9.3 vs. 5.3, p=0.054 SF-36 MCS: (0-100): 8.0 vs. 5.2, p=0.351 Rescue medication (none or occasional): 87% (39/45) vs. 68% (27/40), RR 1.28 (95% CI 1.01 to 1.64)
White, 2004[236] 2, 6, 12 months Duration pain: 6 years Fair	A. Active acupuncture, Western technique based on tender local and distal points (n=70) B. Sham electro-acupuncture (n=65) Treatment was 8 sessions over 4 weeks lasting 20 minutes	A vs. B Age: 54 vs. 53 years Female: 66% vs. 63% Baseline NDI (0-50): 16.8 vs. 17.2 Baseline pain (0-10 VAS): 5.0 vs. 5.4	A vs. B <u>2 months</u> NDI: 11.0 vs. 12.7, difference −1.7 (95% CI −4.3 to 0.9) Pain VAS: 1.7 vs. 2.3, difference −0.6 (95% CI −1.3 to 0.1) <u>6 months</u> NDI: 9.9 vs. 10.6, difference −0.7 (95% CI −3.6 to 2.2) Pain VAS: 1.9 vs. 2.1, difference −1.8 (95% CI −1.1 to 0.7) <u>12 months</u> NDI: 8.9 vs. 10.7, difference −1.8 (95% CI −4.84 to 1.24) Pain VAS: 2.1 vs. 2.4, difference −0.3 (95% CI −1.4 to 0.6)	A vs. B <u>2 months</u> SF-36 PCS (0-100): 42.5 vs. 43.8, p=NS SF-36 MCS (0-100): 52.5 vs. 50.3, p=NS

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Zhang, 2013[237] 3 and 6 months Duration of pain: 6.3 years Fair	A. Electro-acupuncture, traditional Chinese (n=103) B. Sham laser acupuncture (n=103): via a mock laser pen 2 minutes, with the pen at a distance of 0.5 to 1 cm from the skin. Treatment 3x/week for 3 weeks, 45 min for electro-acupuncture and 2 min per point for sham laser	A vs. B Age: 46 years (whole population) Female: 70% (whole population) Baseline NPQ (0-100%): 40.7 vs. 41.1 Baseline pain with motion (0-10 NPS): 5.5 vs. 5.2	A vs. B <u>3 months</u> NPQ: mean 32.9 (95% CI 30.3 to 35.4) vs. mean 33.3 (95% CI 30.1 to 36.5), p=0.664 Pain with motion VAS: mean 4.7 (95% CI 4.2 to 5.1) vs. mean 4.5 (95% CI 4.1 to 5.0), p=0.617 <u>6 months</u> NPQ: mean 33.6 (95% CI 30.7 to 36.4) vs. mean 34.3 (95% CI 31.1 to 37.6), p=0.808 Pain with motion: mean 4.7 (95% CI 4.2 to 5.2) vs. mean 4.4 (95% CI 3.9 to 4.8), p=0.813	A vs. B <u>3 months</u> SF-36 PCS (0-100): mean 52.8 (95% CI 53.0 to 53.7) vs. mean 53.3 (95% CI 52.4 to 54.2), p=0.982 SF-36 MCS (0-100): mean 45.9 (95% CI 46.0 to 46.8) vs. mean 45.3 (95% CI 44.2 to 46.4), p=0.444 <u>6 months</u> SF-36 PCS: mean 53.0 (95% CI 52.0 to 53.9) vs. mean 53.2 (95% CI 52.3 to 54.0), p=0.559 SF-36 MCS: mean 45.4 (95% CI 44.5 to 46.3) vs. mean 44,4 (95% CI 43.4 to 45.4), p=0.246

Δ = change; BDI = Beck Depression Inventory; CI = confidence interval; CPEQ = Comprehensive Pain Evaluation Questionnaire; EQ-5D = Euroqol 5-D; NDI = Neck Disability Index; NHS = National Health Service; NPQ = Northwick Park Neck Pain Questionnaire; NR = not reported; NS = not statistically significant; NSAID = nonsteroidal anti-inflammatory drug; SF-36 MCS = Short Form-36 questionnaire Mental Component Score; SF-36 PCS = Short Form-36 questionnaire Physical Component Score; SF-MPQ = McGill Pain Questionnaire Short Form; TENS = Transcutaneous electrical nerve stimulation; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Estimated from Figure 1 in Birch et al.[231]

[c] 12 month data are health utilization data only from a subset of patients from the ATLAS trial (publication Essex 2017) who had full economic data N=293 (57%) [to include the acupuncture arm; details in the Acupuncture section]; no demographic data provided for the subset

[d] Across all appointment types and prescription medications; National Health Services (NHS) appointment types to include, general practitioner appointments, physiotherapy visits, hospital outpatient visits, accident and emergency admissions, hospital day case admissions, other hospital admissions. NHS prescription medication included all prescription medication and prescription items specifically for neck pain. Neck pain prescriptions t-test comparing usual care and acupuncture borderline significance (p=0.06).

[e] For baseline NHS healthcare costs and practice size.

Acupuncture Compared With Sham Acupuncture, Usual Care, or a Placebo Intervention

Acupuncture was associated with small improvements in short-term and intermediate-term function versus sham acupuncture, placebo (sham laser), or usual care (short term, 5 trials,[213,232,233,236,237] pooled SMD −0.40, 95% CI −0.67 to −0.14, I^2=61%; intermediate term, 3 trials,[213,236,237] pooled SMD −0.19, 95% CI −0.37 to 0.05, I^2=0.0%) (Figure 31). Trials measured function using the NDI or the NPQ; across trials the SMD ranged from −0.78 to −0.03 in the short term and −0.29 to −0.05 in the intermediate term. None of the trials were rated poor quality. One trial reported no difference in function in the long term (SMD −0.23, 95% CI −0.61 to 0.16).[236]

Acupuncture was associated with small improvements in short-term pain versus controls (5 trials, pooled difference −0.66, 95% CI −1.46 to 0.11, I^2=78.4%), but statistical heterogeneity was large.[232-234,236,237] (Figure 32). Excluding an outlier trial (pooled difference −1.80, 95% CI −2.36 to −1.24)[232] eliminated statistical heterogeneity and resulted in a markedly attenuated effect (difference −0.27, 95% CI −0.59 to 0.05, I^2=2%). Stratified analyses according to the type of control (sham or placebo laser) resulted in similar estimates. Trials reported no differences in pain between acupuncture versus controls in the intermediate term (3 trials, pooled difference 0.40, 95% CI −0.45 to 1.44, I^2=18.7%)[235-237] or long term (1 trial, difference −0.35, 95% CI −1.34 to 0.64).[236]

In a secondary economic analysis of a subset (57%) of patients, 1 trial reported that there were no significant differences between acupuncture and usual care in terms of UK NHS healthcare utilization (appointments or prescription items).[214] While more people paid for extra acupuncture in the private healthcare setting, this represented people who attended all trial sessions and paid for extra. There were no differences in terms of utilizing other private healthcare services.

In general, acupuncture did not improve quality of life compared with sham intervention in the short term or intermediate term as reported in four trials[233,235-237] (Table 23).

No trial evaluated effects of acupuncture on use of opioid therapies.

Acupuncture Compared With Pharmacological Therapy

Two small poor-quality trials evaluated acupuncture versus NSAIDs. One trial (n=27) compared acupuncture three times per week for 3 weeks versus 80 mg of Zaltoprofen alone three times per day for 3 weeks.[254] The other trial (n=30) compared 14 sessions of acupuncture versus 500 mg of Trilisate per day for 8 weeks.[231] In the short term, one trial reported no difference in NDI (difference −0.4, 95% CI −4.6 to 3.8).[254] Both trials reported no difference between groups in pain as measured by the McGill Pain Questionnaire[231] or VAS.[254] One trial found no differences between groups in the Beck Depression Index, the SF-36, or the EQ-5D in the short term[254] (Table 23).

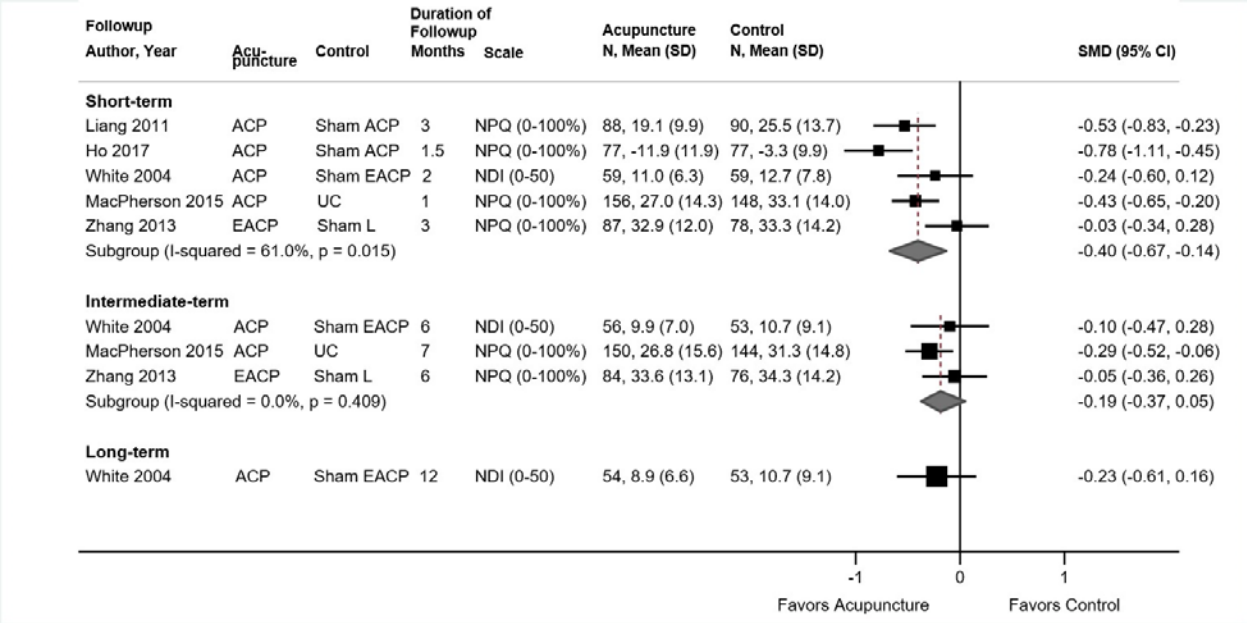
Acupuncture Compared With Exercise Therapy

No trial of acupuncture versus exercise met inclusion criteria.

Harms

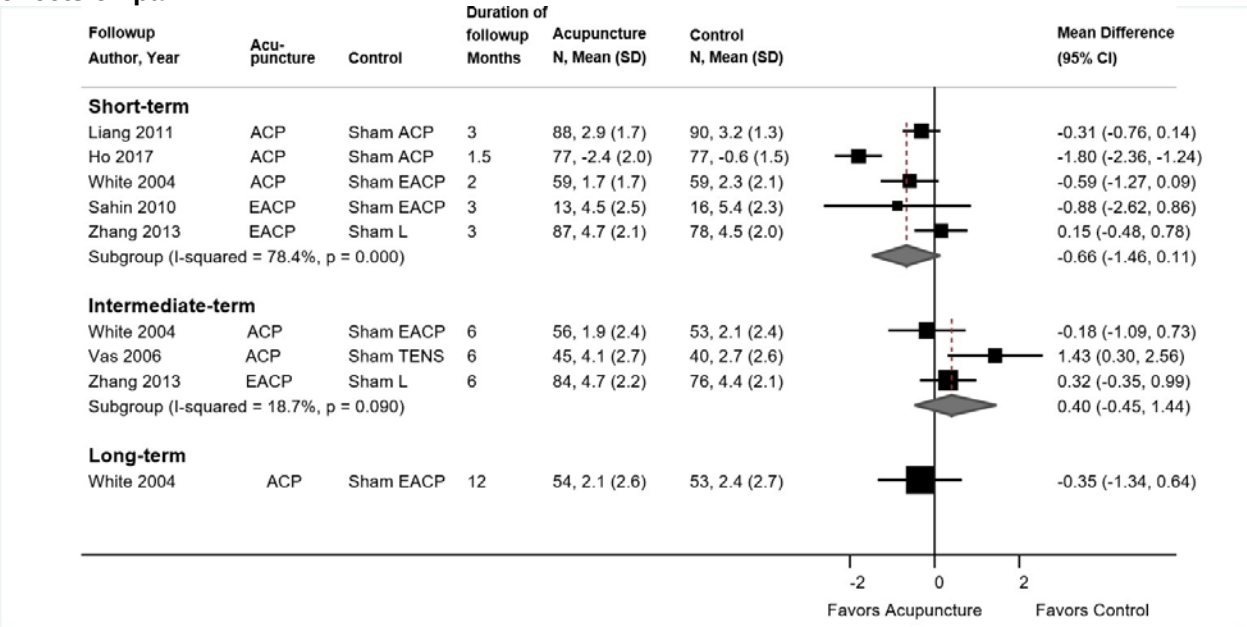
Six of the eight trials assessing acupuncture reported harms.[213,233,235-237,254] No serious adverse events (defined as involving death, hospitalization, persistent disability, or a life-threatening risk in one trial[213] and undefined in the other five studies) were reported in any trial. The most commonly reported nonserious adverse effects in people receiving acupuncture included numbness/discomfort (2.7%), fainting (1.1%), and bruising (1.1%).

Figure 31. Acupuncture versus sham acupuncture, a placebo intervention, or usual care for chronic neck pain: effects on function



ACP = traditional needle acupuncture; CI = confidence interval; EACP = electroacupuncture; NDI = Neck Disability Index; NPQ = Northwick Park Questionnaire; SD = standard deviation; Sham L = sham laser; SMD = standardized mean difference; UC = usual care.

Figure 32. Acupuncture versus sham acupuncture or a placebo intervention for chronic neck pain: effects on pain



ACP = traditional needle acupuncture; CI = confidence interval; EACP = electroacupuncture; SD = standard deviation; Sham L = sham laser; SMD = standardized mean difference; TENS = transcutaneous electrical stimulation; UC = usual care.

Key Question 3: Osteoarthritis Pain

For OA, 53 RCTs (in 56 publications) were included in the prior AHRQ report (N=6,101). Four studies were rated good quality, 31 studies fair quality, and 18 studies poor quality. The prior AHRQ report found exercise and ultrasound (US) associated with greater effects than usual care, an attention control or a sham procedure on improved function (exercise, US) or pain (exercise) for the treatment of knee OA. The strength of evidence was low or moderate, generally stronger for function than for pain, and observed at short, intermediate, and long term (with the exception of pain) for exercise but only short term for ultrasound. For hip OA, exercise and manual therapy were associated with small improvements compared with usual care and exercise for function (short and intermediate term) and pain (intermediate term). The strength of evidence was low. For hand OA, there was either no difference between treatment groups for function or pain or the evidence was insufficient to draw conclusions.

For this update, we identified nine new RCTs (in 10 publications) of knee OA (N=1,235); no new trials evaluating hip or hand OA were identified. One of the new studies was rated good quality, seven were rated fair quality, and one was rated poor quality. The new trials evaluated exercise (5 trials), psychological therapies (2 trials), and physical modalities (ultrasound) (2 trials). The Key Points summarize the main findings based on the evidence included in the prior report and new trials; the Key Points note where new trials contributed to findings.

Exercise for Osteoarthritis Knee Pain

Key Points

- Exercise was associated with a small improvement in function compared with usual care, no treatment, or sham intervention short term (8 trials [1 new trial], pooled SMD −0.29, 95% CI −0.46 to −0.11, I^2=10%) moderate improvement intermediate term (11 trials [two new trials and excluding outlier trial], pooled SMD −0.63, 95% CI −1.17 to −0.10, I^2=91%), and small improvement long term (4 trials [2 new trials], pooled SMD −0.22, 95% CI −0.34 to −0.08, I^2=0%) (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 (≥1.75 points) in VAS pain on movement (prior week) [58% (34/59) vs. 42% (27/65); RR 1.4, 95% CI 1.0 to 2.0] or VAS global improvement in pain [59% (35/59) vs. 50% (33/65); RR 1.2, 95% CI 0.8 to 1.6] in the short term.
- Exercise was associated with a small improvement in pain short term (8 trials [1 new trial], pooled difference on a 0-10 scale −0.47, 95% CI −0.86 to −0.10, I^2= 42%) versus usual care, no treatment, waitlist, or sham intervention (SOE: moderate), a moderate improvement intermediate term (11 trials [2 new trials], pooled difference −1.34, 95% CI −2.12 to −0.54, I^2=90% on a 0-10 scale) compared with usual care, an attention control, waitlist, or no treatment (SOE: low), and a small improvement long term (4 trials [2 new trials], pooled difference −0.30 on a 0 to 10 scale, 95% CI −0.49 to 0.00, I^2=0%) compared to usual care, attention control, or waitlist. (SOE: low).
- 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 (>10 point improvement on the Knee

Injury and Osteoarthritis Outcome Score [KOOS] ADL), 47% (22/47) versus 28% (13/46); RR 1.7, 95% CI 1.0 to 2.9, 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).

- Harms were not well reported. Across seven trials, one reported minor temporary increase in pain with exercise, four others found no difference in worsening pain versus controls, and one reported no difference in falls or death (SOE: moderate).

Detailed Synthesis

Twenty-three trials (in 26 publications) of exercise therapy for knee osteoarthritis (OA) met inclusion criteria (Table 25 and Appendix D).[47-71,102,103] Eighteen trials (in 21 publications) [47-67] were included in the prior AHRQ report and five (in six publications)[68-71,102,103] were added for this update. Eight trials evaluated muscle performance exercise versus attention control,[51,52,54,57,58,66] no treatment[49,53,65] or usual care (1 new trial).[71] In nine trials (3 new trials), the interventions consisted of combined exercise approaches compared with usual care,[47,55,56,60,63,68-70] an attention control[64] or no treatment.[50] Muscle performance exercises were a component of nine of these trials (3 new trials).[47,50,55,56,60,63,64,68-70] One trial had an aerobic exercise arm that consisted of a facility-based, 1-hour walking program three times per week over 3 months, and it used an attention control.[51,57,58] A single trial evaluated a mobility exercise program based on Mechanical Diagnosis and Therapy (MDT) versus a waitlist comparator, where patients were allowed to continue receiving usual care.[61] One trial evaluated gait training (guided strategies to optimize knee movements during treadmill walking with computerized motion analysis with visual feedback) versus usual care.[62] Five trials (2 new trials) tested exercise programs as a part of physiotherapy care compared to usual care or sham.[48,59,67-69] The duration of exercise programs ranged from 2 to 26 weeks; the number of exercise sessions ranged from 4 to 36. One new trial compared neuromuscular reeducation exercise with pharmacological intervention.[102,103]

Sample sizes ranged from 50 to 786 (total sample=3,633). Across the trials, the majority of patients were female (51% to 100%) with mean ages ranging from 56 to 75 years. Seven trials (2 new trials) specifically included patients with bilateral knee OA.[49,52-54,66,68,69] Six trials (1 new trials) were conducted in the United States or Canada,[51,56-58,60-63,68]eight (3 new trials) in Europe,[55,59,64,65,67,69,71,102,103] five in Taiwan,[49,52-54,66] two in Australia or New Zealand,[47,48] one in Brazil[50] and one new trial in Malaysia.[70] Most trials had short (7 trials [1 new trial])[47,55,61,62,65,67,69] or intermediate followup (13 trials [3 new trials]).[49,50,52-54,56,62-64,66,68,70,102,103] Four trials (1 new trial) reported long-term outcomes.[56-58,60,64,71]

Sixteen trials (4 new trials) were rated fair quality (one at short-term followup[62]),[47,48,51,52,54-61,65,68-70,102,103] and nine trials (1 new trial) poor quality,[49,50,53,63,64,66,67,71] including one at intermediate-term followup[62] (Appendix E). In the fair-quality trials, the main methodological limitation was a lack of blinding for the patients or care providers. Additional limitations in the poor-quality trials included unclear randomization and allocation concealment methods, unclear use of intention to treat, unclear baseline differences between intervention groups, and attrition not reported or unacceptable.

Table 41. Osteoarthritis knee pain: exercise

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Abbott, 2013[47] 9.75 months Duration of diagnosis: Mean 2.5 to 2.8 years Fair	A. Exercise (n=51/29 knee OA): 7 sessions of strengthening, stretching, and neuromuscular control over 9 weeks, with 2 booster sessions at week 16. Individual exercises prescribed as needed. Home exercise prescribed 3 times weekly B. Usual care (n=51/28 knee OA)	A vs. B (total population, includes hip OA) Age: 67 vs. 66 years Female: 52% vs. 58% Percent hip OA: 43% vs. 45% Percent knee OA: 57% vs. 55% Percent both hip OA and knee OA: 20% vs. 26% Baseline WOMAC (0−240): 95.5 vs. 93.8	A vs. B (knee OA only) A vs. C 9.75 months WOMAC mean change from baseline: −12.7 vs. −31.5	None

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Allen, 2018[68] 3, 6, and 12 months Duration of pain: NR Fair [New trial]	A. PT (n=140): Up to 8 sessions over 4 months B. IBET (n=142): Strength and stretching (3 times/week) and daily aerobic exercises C. WL (n=68) All Patients: continued to received usual care	A vs. B vs. C Age: 66 vs. 65 vs. 64 years Female: 71% vs. 69% vs. 78% Mean duration of chronicity: 11.6 vs.14.1 vs. 14.2 years Baseline WOMAC-Total (0-96): 32 vs. 31.3 vs. 33.6 Baseline WOMAC-ADL (0-68): 22.6 vs. 21.8 vs. 23.9 Baseline WOMAC-Pain (0-20): 6.1 vs. 6.0 vs. 6.2 Baseline PASE-Total (0-400): 121.4 vs. 132.3 vs. 126.9 Baseline PASE-Household: 70.4 vs. 81.6 vs. 71.8 Baseline PASE-Leisure: 20.9 vs. 22.4 vs. 21.5 Baseline PASE-Work: 29.1 vs. 30.5 vs. 34.2	A vs. C 8/12 months[b] LSM Δ in WOMAC Total (N=348): −4.4 (95% CI −6.7 to −2.2) vs. −2.8 (95% CI −5.9 to 0.3); difference −1.6 (95% CI −5.3 to 2.1), p=0.390 LSM Δ in WOMAC-ADL (N=348): −3.3 (95% CI −4.9 to −1.7) vs. −1.5 (95% CI −3.8 to 0.7); difference −1.8 (95% CI −4.4 to 0.9), p=0.1900 LSM Δ in WOMAC-Pain (N=350): −0.7 (95% CI −1.2 to −0.2) vs. −0.6 (95% CI −1.4 to 0.1); difference −0.1 (95% CI −0.9 to 0.8), p=0.900 LSM Δ in PASE-Total (N=340): 8.3 (95% CI −2.0 to 18.6) vs. 1.2 (95% CI −13.1 to 15.5); difference 7.1 (95% CI −9.7 to 23.9), p=0.410 LSM Δ in PASE-Leisure (N=344): 8.7 (95% CI 4.3 to 13.1) vs. −0.1 (95% CI −6.3 to 6.0); difference 8.8 (95% CI 1.5 to 16.1), p=0.020 LSM Δ in PASE-Household (N=345): 2.3 (95% CI −3.6 to 8.2) vs. −3.4 (95% CI −11.6 to 4.8); difference 5.7 (95% CI −3.9 to 15.4), p=0.250 LSM Δ in PASE-Work (N=349): -2.6 (95% CI -9.6 to 4.3) vs. 5.2 (95% CI −4.5, 15); difference −7.9 (95% CI −19.4 to 3.6), p=0.180	None

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Allen, 2018[68] (Continued) 3, 6, and 12 months Duration of pain: NR Fair [New trial]	(Column intentionally blank)	(Column intentionally blank)	B vs. C <u>12 months</u> LSM Δ in WOMAC-Total (N=348): −5.5 (95% CI −7.8 to −3.1) vs. −2.8 (95% CI −5.9 to 0.3); difference −2.6 (95% CI −6.4 to 1.1), p=0.170 LSM Δ in WOMAC-ADL (N=348): −3.4 (95% CI −5.1 to −1.7) vs. −1.5 (95% CI −3.8 to 0.7); difference −1.9 (95% CI −4.6 to 0.8), p=0.170 LSM Δ in WOMAC-Pain (N=350): −1.2 (95% CI −1.7 to −0.6) vs. −0.6 (95% CI −1.4 to 0.1); difference −0.5 (95% CI −1.4 to 0.4), p=0.260 LSM Δ in PASE-Total (N=340): 8.2 (95% CI −3.0 to 19.4) vs. 1.2 (95% CI −13.1 to 15.5); difference 7.0 (95% CI −10.3 to 24.4), p=0.430 LSM Δ in PASE-Leisure (N=344): 7.7 (95% CI 2.9 to 12.4) vs. −0.1 (95% CI −6.3 to 6.0); difference 7.7 (95% CI 0.3 to 15.3), p=0.040 LSM Δ in PASE-Household (N=345): −3.7 (95% CI −10.1 to 2.7) vs. −3.4 (95% CI −11.6 to 4.8); difference D −0.3 (95% CI −10.3 to 9.7), p=0.950 LSM Δ in PASE-Work (N=349): 5.3 (95% CI −2.2 to 12.7) vs. 5.2 (95% CI −4.5 to 15); difference 0.00 (95% CI −11.8 to 11.8), p=1.000	(Column intentionally blank)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bennell, 2005[48] 3 months Duration of pain: 9.6 vs. 8.7 years Fair	A. Neuromuscular Re-education (Physiotherapy) (n=73): Knee taping; exercises to retrain the quadriceps, hip, and back muscles; balance exercises; thoracic spine mobilization; and soft tissue massage. individual sessions lasting 30 to 45 minutes once weekly for 4 weeks, then fortnightly for 8 weeks. Thrice-daily standardized home exercises. B. Control (n=67) Placebo: sham ultrasound and topical nontherapeutic gel. 30 to 45 minutes once weekly for 4 weeks, then fortnightly for 8 weeks.	A vs. B Age: 67 vs. 70 years Female: 68% vs. 66% Baseline WOMAC Physical Function (0-68): 27.6 vs. 28.4 Baseline WOMAC Pain (0-20): 8.2 vs. 8.0 Baseline VAS Pain on movement (0-10): 5.3 vs. 5.2 Baseline KPS (0-36): 16.6 vs. 16.4 Baseline KPS Frequency (0-30): 23.5 vs. 22.8	A vs. B <u>3 months</u> Responders (≥1.75 point change), global improvement in pain on VAS (since start of trial): 59% (35/59) vs. 50% (33/65), RR 1.2 (95% CI 0.8 to 1.6) Responders (≥1.75 point change), VAS pain on movement (prior week): 58% (34/59) vs. 42% (27/65), RR 1.4 (95% CI 1.0 to 2.0 WOMAC, Physical Function: 20.0 vs. 21.7, difference −0.9 (95% CI −4.4 to 2.7) WOMAC, Pain: 5.8 vs. 6.0, difference −0.4 (95% CI −1.5 to 0.7) VAS pain on movement: 3.2 vs. 3.5, difference −0.5 (95% CI −1.2 to 0.3) KPS, Severity: 13.5 vs. 14.3, difference −1.0 (95% CI −2.5 to 0.6) KPS, Frequency: 19.4 vs. 20.3, difference −1.7 (95% CI −3.5 to 0.1)	A vs. B <u>3 months</u> SF-36, Physical Function (0-100): 50.5 vs. 46.2, difference 4.3 (95% CI −1.8 to 10.4) SF-36, Bodily Pain (0-100): 60.4 vs. 61.8, difference 1.8 (95% CI −6.7 to 10.3) SF-36, Role Physical (0-100): 47.0 vs. 46.5, difference 1.6 (95% CI −11.1 to 14.3) AQoL(−0.04 to 1.0): 0.52 vs. 0.48, difference 0.05 (95% CI 0.01 to 0.10) Withdrawals: 18% (13/73) vs. 3% (2/67); RR 6.0 (95% CI 1.4, 25.5) Group A: Minor skin irritation (48%), increased pain with exercises (22%), pain with massage (1%) Group B: Increased pain (2%), itchiness and pain with application of gel (2%) (All were minor and short-lived)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Chen, 2014[49] 6 months Duration of pain: 10-144 months Poor	A. Exercise (n=30): 3 sessions per week for 8 weeks. Sessions consisted of a 20 minutes of hot packs and 5 minutes of passive range of motion exercises on a stationary bike, followed by an isokinetic muscle-strengthening exercise program B. Control (n=30): Details NR	A + B Age: 63 Females: 85% A vs. B Baseline Lequesne Index (0-26): 7.8 vs. 8.0 Baseline pain VAS (0-10): 5.5 vs. 5.6	A vs. B <u>6 months</u> Lequesne Index: 5.4 vs. 7.6, (difference −2.2, 95% CI −3.1 to −1.3) Pain VAS: 4.0 vs. 6.5, (difference −2.5, 95% CI −3.3 to −1.7)	A vs. B <u>6 months</u> Intolerable knee pain: 10% (3/30) vs. 0% (0/30) RR=infinity, p=0.08
Dias, 2003[50] 6 months Duration of pain: NR Poor	A. Exercise (n=25): 12 exercise sessions twice a week for the 6 month study period in addition to three supervised walks of 40 minutes each week. Exercise sessions consisted stretching, concentric and eccentric isotonic progressive resistance exercises, and closed kinetic chain weight-bearing exercises B. Control group (n=25): Subjects were instructed to follow the instructions given at an educational session that all participants attended (see information below) All patients: One-hour educational session consisting of a lecture on disease characteristics, joint protection, pain management, and strategies to overcome difficulties in activities of daily life	A vs. B Age, median: 74 vs. 76 Female: 84% vs. 92% Baseline Lequesne Index, median (0-24): 12 vs. 12.5 Baseline HAQ, median (0-3): 1 vs. 1	A vs. B <u>6 months</u> Lequesne Index, median: 4.3 vs. 13, p=0.001 HAQ, median: 0.3 vs. 1.1, p=0.006	A vs. B <u>6 months</u> SF-36 functional capacity, median (0-100): 77.5 vs. 40, p<0.001 SF-36 physical role limitation, median (0-100): 92.5 vs. 75, p=0.001 SF-36 bodily pain, median (0-100): 100 vs. 0, p=0.002 SF-36 general health, median (0-100): 100.5 vs. 51, p=0.021 SF-36 vitality, median (0-100): 93.5 vs. 87, p=0.027 <u>Adverse Events:</u> NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Ettinger, 1997[51] (index trial) Pennix 2002[58] (substudy looking at baseline depressive symptoms) FAST trial 6 months, 15 months Duration of pain: NR Fair	A. Aerobic Exercise Program (n=144): 3-month facility-based walking program of 3 times per week for 1 hour. Each session consisted of a 10-minute warm-up and cool-down phase, including slow walking and flexibility stretches, and a 40-minute period of walking at an intensity equivalent to 50% to 70% of the participants' heart rate reserve. Followed by 15-month home-based walking program. B. Resistance Exercise Program (n=146): 3-month supervised facility-based program, with three 1-hour sessions per week, and a15-month home-based program. Each session consisted of a 10-minute warm-up and cool-down phase and a 40-minute phase consisting of 2 sets of 12 repetitions of 9 exercises. C. Attention Control (n=149): attended, during the first 3 months, monthly group sessions on education related to arthritis management, including time for discussions and social gathering. Later, participants were called bimonthly (months 4-6) or monthly (months 7-18) to maintain health updates and provide support	A vs. B vs. C Age: 69 vs. 68 vs. 69 years Female: 69% vs. 73% vs. 69% African-American: 24% vs. 28% vs. 26% Baseline function: NR	A vs. C <u>Average across all time-points:</u> FAST Physical Disability Scale Total: 1.7 vs. 1.9 Ambulation subscale: 2.2 vs. 2.6 Transfers subscale: 1.8 vs. 1.9 Pain: 2.1 vs. 2.4 B vs. C <u>Average across all time-points:</u> FAST Physical Disability Scale Total: 1.7 vs. 1.9 Ambulation subscale: 2.7 vs. 2.6 Transfers subscale: 1.7 vs. 1.9 Pain: 2.2 vs. 2.4	A vs. B vs. C Adverse Events: Falls- 14% (2/144) vs. 14% (2/146) vs. 0% (0/149); p=0.15 for both A vs. C and B vs. C Death- 0% (0/144) vs. 0% (0/146) vs. 0.7% (1/149) CES-D (<u>average across all time-points)</u> CES-D: 2.12 vs. 2.59 vs. 2.80; A vs. C, p<0.001; B vs. C, p=0.27

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Penninx, 2001[57] FAST trial (same trial as Ettinger 1997 and Pennix 2002 above): substudy in only patients with no baseline ADL disability 6 and 15 months Duration of pain: NR Fair	A. Aerobic Exercise Program (n=88): 3-month facility-based walking program of 3 times per week for 1 hour. Each session consisted of a 10-minute warm-up and cool-down phase, including slow walking and flexibility stretches, and a 40-minute period of walking at an intensity equivalent to 50% to 70% of the participants' heart rate reserve. Followed by 15-month home-based walking program. B. Resistance Exercise Program (n=82): 3-month supervised facility-based program, with three 1-hour sessions per week, and a15-month home-based program. Each session consisted of a 10-minute warm-up and cool-down phase and a 40-minute phase consisting of 2 sets of 12 repetitions of 9 exercises. C. Attention Control (n=80): attended, during the first 3 months, monthly group sessions on education related to arthritis management, including time for discussions and social gathering. Later, participants were called bimonthly (months 4-6) or monthly (months 7-18) to maintain health updates and provide support	A vs. B vs. C Age: 70 vs. 69 vs. 69 years Female: 66% vs. 72% vs. 66% African-American: 25% vs. 21% vs. 28% Baseline disability (scale NR): 1.7 vs. 1.7 vs. 1.6 Baseline pain intensity (1-6): 2.2 vs. 2.1 vs. 2.1	A vs. B vs. C <u>15 months</u> ADL Disability (overall): 36.4% vs. 37.8% vs. 52.5% Disability in transferring from a bed to a chair: 29.5% vs. 36.6% vs. 50.0% Disability in bathing: 12.5% vs. 13.4% vs. 27.5% Disability in toileting: 19.4% vs. 13.4% vs. 25.0% Disability in dressing: 5.7% vs. 7.3% vs. 17.5% Disability in eating: 0% vs. 1.2% vs. 5.0%, p=0.02 <u>15 months</u> ADL Disability (overall) A vs. C: adjusted RR 0.53 (95% CI 0.33 to 0.85), B vs. C: adjusted RR 0.60 (95% CI 0.38 to 0.97), Disability in transferring from a bed to a chair A vs. C: adjusted RR 0.46 (95% CI 0.28 to 0.76) B vs. C: adjusted RR 0.68 (95% CI 0.42 to 1.09) Disability in bathing A vs. C: adjusted RR 0.31 (95% CI 0.15 to 0.68) B vs. C: adjusted RR 0.44 (95% CI 0.21, 0.93) Disability in toileting A vs. C: adjusted RR 0.58 (95% CI 0.29 to 1.15) B vs. C: adjusted RR 0.61 (95% CI 0.28 to 1.31) Disability in dressing A vs. C: adjusted RR 0.20 (95% CI 0.07 to 0.64) B vs. C: adjusted RR 0.46 (95% CI 0.17 to 1.22) Disability in eating: incidence too small to calculate risks.	A vs. B vs. C <u>15 months</u> Increased severity of knee OA leading to withdrawal: n=3 (not reported by exercise group)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Holsgaard-Larsen 2017/2018[102,103] 10 months Duration of pain: NR Fair [New trial]	A. NEMEX (n=47): 8 weeks of twice weekly 60-minute sessions. B. Standard Pharmaceutical Care (PHARMA) (n=46): Standard recommendations of analgesics and anti-inflammatory drugs (acetaminophen and oral NSAIDs – including prescription if needed)	A vs. B Age: 58 vs. 58 Female: 62% vs. 54% Baseline KOOS-ADL (0-100): 68.2 vs. 68.4 Baseline KOOS-Symptoms (0-100): 66.1 vs. 66.6 Baseline KOOS-Sports/Recreation (0-100): 35.3 vs. 42.6 Baseline UCLA (0-10): 7.1 vs. 6.8 Baseline KOOS-Pain (0-100): 61.6 vs. 60.1	A vs. B <u>10 months</u> Mean Δ in KOOS-ADL: 11.4 vs. 7.9; difference -3.6 (95% CI −9.2 to 2.1) p=0.216 MCID KOOS-ADL: number of responders(>10 improvement): 47% (22/47) vs. 28% (13/46); RR 1.7, 95% CI 1.0 to 2.9, p=0.06 Mean Δ in KOOS-Sports/Recreation: 9.4 vs. 6.5; difference −2.9 (95% CI −11.4 to 5.5) p=0.492 Mean Δ in KOOS-Symptoms: 10.9 vs. 3.3; difference −7.6 (95% CI −12.7 to −2.6) p=0.004 Mean Δ in UCLA: 0.0 vs. 0.1; difference 0.1 (95% CI −0.6 to 0.7) p=0.852 Mean Δ in KOOS-Pain: 13.6 vs. 9.4; difference 4.2 (95% CI −10.0 to 1.6) p=0.153	A vs. B <u>10 months</u> Mean Δ in KOOS-QoL (0-100): 10.0 vs. 8.7; difference -1.3 (95% CI -7.5 to 4.9) p=0.682 Mean Δ in EuroQol-5D Health State (scale unclear): 0.3 vs. 2.9; difference 2.6 (95% CI -2.9 to 8.1) p=0.347

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Huang, 2003[53] 10 months Duration of pain: range, 0.33 (4 months) to 9 years Poor	A. Isokinetic Strengthening (n=33): 3 sessions per week for 8 weeks. 60% of average peak torque the initial dose of isokinetic exercise. An increasing dose program was used in the initial first to fifth sessions (1 set to 5 sets), and a dose of 6 sets was applied from 6th to the 24th sessions. Each set consists of 5 repetitions of concentric and eccentric contraction in angular velocity 30°/second and 120°/second for extensors, and 5 repetitions of eccentric and concentric contraction in angular velocity 30°/second and 120°/second for flexors. B. Isotonic Strengthening (n=33): same protocol as in the isokinetic exercise; the isotonic muscle strengthening exercise program consisted of 5 repetitions of concentric and eccentric the maximum velocity that the lever arm could achieve. C. Isometric Strengthening (n=33): protocol as in the isokinetic exercise; the speed of passive forward or backward motion was set at 30°/second. All intervention groups exercised 3 times weekly for 8 weeks. The patients in all groups also received 20 minutes of hot packs and passive range motion exercise by an electric stationary bike (20 cycles per minute) for 5 minutes to both knees before muscle strengthening exercise. D. Control (n=33) Description NR	A+B+C+D Age: 62 years Female: 70% A vs. B vs. C vs. D Baseline Lequesne Index (0-26): 6.9 vs. 7.1 vs. 6.8 vs. 7.2 Baseline VAS pain (0-10): 4.8 vs. 4.6 vs. 4.7 vs. 4.6	A vs. D <u>10 months</u> Lequesne Index: 3.1 vs. 7.6, difference −4.5 (95% CI −5.3 to −3.7), VAS Pain: 2.5 vs. 6.1; p<0.05 B vs. D <u>10 months</u> Lequesne Index: 3.1 vs. 7.6, difference −3.6 (95% CI −4.4 to −2.8) VAS Pain: 2.0 vs. 6.1; p<0.05 C vs. D <u>10 months</u> Lequesne Index: 4.8 vs. 7.6, difference −2.8 (95% CI −3.6 to −2.0) VAS Pain: 3.2 vs. 6.1; p<0.05	A vs. B vs. C vs. D <u>10 months</u> Withdrawals: 3% (1/33) vs. 6% (2/33) vs. 3% (1/33) vs. 18% (6/33) Withdrawals RR (95% CI): A vs. D: 0.17 (0.02, 1.3) B vs. D: 0.33 (0.07,1.53) C vs. D: 0.17 (0.02, 1.3) Stopped therapeutic exercise due to intolerable pain during exercise: 12.1% (4/33) vs. 6.1% (2/33) vs. 6.1% (2/33)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Huang, 2005[54] 10 months Duration of pain: 0.42 (5 months) to 12 years Fair	A. Isokinetic Exercise (n=35): 3 times per week for 8 weeks. Began with 60% of the mean peak torque, increasing dose program was used in the first 5 sessions (1 set to 5 sets), and a dose of 6 sets was applied from the 6th to 24th sessions, with the density rising from 60% to 80% of the mean peak torque as the patient was able. Each set consisted of 5 repetitions of concentric contraction in angular velocities of 30°/second and 120°/second for extensors, and 5 repetitions of eccentric and concentric (Ecc/Con) contractions in angular velocities of 30°/second and 120°/second for flexors. B. Control (n=35): Warm-up exercises only	A+B Age: 65 years Female: 81% A vs. B Baseline Lequesne Index (1-26): 7.6 vs. 7.4 Baseline VAS pain (0-10): 5.3 vs. 5.4	A vs. B <u>10 months</u> Lequesne Index: 5.8 vs. 8.1, difference −2.3 (95% CI −3.2 to −1.4) VAS Pain: 3.9 vs. 6.6, p<0.05	A vs. B <u>10 months</u> Withdrawals 11% (4/35) vs. 11% (4/35) Discontinuation of exercise due to intolerable pain during exercise: 14% (5/35) vs. NA
Huang 2005[52] 10 months Duration of pain: 0.5 (6 mos.) to 11 years Fair	A. Isokinetic Exercise (n=30): 3 times per week for 8 weeks. Began with 60% of the average peak torque. Intensity of isokinetic exercise increased from 1 set to 5 sets during the first through fifth sessions and remained at 6 sets for the remaining 6th through 24th sessions. Each set consisted of 5 repetitions of concentric contraction in angular velocities of 30°/s and 120°/s for extensors, and 5 repetitions of eccentric and concentric contractions in angular velocities of 30°/s and 120°/s for flexors. B. Control (n=30): Heat for 20 minutes and 5 minutes of passive range of motion on bike only.	A+B Age: 62 (range, 42-72) years Female: 81% A vs. B Baseline Lequesne Index(1-26): 6.7 vs. 7.0 Baseline VAS pain (0-10): 4.9 vs. 4.8	A vs. B <u>10 months</u> Lequesne Index: 5.1 vs. 7.8, difference −2.7 (95% CI −3.8 to −1.6) VAS Pain: 3.5 vs. 6.0; p<0.05	A vs. B <u>10 months</u> Withdrawals 13% (4/30) vs. 13% (4/30) Discontinuation of exercise due to intolerable pain during exercise: 17% (5/30) vs. NA

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lund, 2008[55] 3 months Duration of pain: 8.5 vs. 7.8 vs. 4.5 Fair	A. Aquatic Exercise (n=27): 2x per week for 8 weeks. Warm-up, strengthening and endurance exercise, balance exercise and stretching exercise. Each session lasted 50 min, comprising 10 min warm-up, 20 min resistance exercises, 10 min balance and stabilizing exercises, 5 min lower limb stretches and 5 min cool-down period. Compliance was 92%. B. Land-based Exercise (n=25): 2x per week for 8 weeks. Warm-up, strengthening/endurance exercise, balance exercise and stretching exercise. Each session lasted 50 min, comprising 10 min warm-up, 20 min resistance exercises, 10 min balance and stabilizing exercises, 5 min lower limb stretches and 5 min cool-down period. Compliance was 85%. C. Control (n=27): No exercise All 3 groups were asked to continue any other treatment as usual.	A vs. B vs. C Age: 65 vs. 68 vs. 70 years Female: 83% vs. 88% vs. 66% Baseline KOOS symptom (0-100): 50.5 vs. 50.9 vs. 50.1 Baseline KOOS pain (0-100): 47.1 vs. 41.0 vs. 37.9 Baseline KOOS Activities of Daily Living (0-100): 44.7 vs. 40.6 vs. 39.6 Baseline KOOS Sport (0-100): 79.1 vs. 75.6 vs. 70.0 Baseline KOOS Quality of Life (0-100): 63.7 vs. 57.0 vs. 60.8 Baseline VAS pain at rest (0-100): 29.8 vs. 23.3 vs. 15.5 Baseline VAS pain during walking (0-100): 59.8 vs. 53.0 vs. 48.5	A vs. C <u>3 months</u> KOOS symptom: 64.1 vs. 63.7; difference 0.5 (95% CI −6.6 to 7.6) KOOS Activities of Daily Living: 63.0 vs. 61.4; difference 1.6 (95% CI −5.7 to 8.9) KOOS sport: 24.2 vs. 23.5; difference 0.7 (95% CI −9.3 to 10.7) KOOS quality of life: 42.8 vs. 41.4; difference 1.7 (95% CI −5.4 to 8.2) KOOS pain: 60.7 vs. 62.6; difference −1.5 (95% CI −8.7 to 5.8) VAS pain at rest: 18.1 vs. 23.8; difference −5.7 (95% CI −13.3 to 2.0) VAS pain: 52.9 vs. 58.3; difference −5.4 (95% CI −16.2 to 5.4) B vs. C <u>3 months</u> KOOS symptom: 66.1 vs. 63.7; difference 2.4 (95% CI −4.8 to 9.5) KOOS Activities of Daily Living: 63.9 vs. 61.4; difference 2.5 (95% CI −5.0 to 9.9) KOOS sport: 31.6 vs. 23.5; difference 8.1 (95% CI −2.0 to 18.2) KOOS quality of life: 43.1 vs. 41.4; difference 1.7 (95% CI −5.3 to 8.7) KOOS pain: 62.0 vs. 62.6; difference −0.3 (95% CI −7.5 to 7.0) VAS pain at rest: 15.6 vs. 23.8; difference −8.1 (95% CI −15.8 to −0.4) VAS pain walking: 50.1 vs. 58.3; difference −8.2 (95% CI −19.7 to 2.7)	A vs. B vs. C <u>3 months</u> Withdrawals: 4% (1/27) vs. 20% (5/25) vs. 7% (2/27) A vs. C: RR 0.5 (95% CI 0.05, 5.2) B vs. C: RR 2.5 (95% CI 0.6, 12.7) Increased pain during and after exercise: 11% (3/27) vs. 32% (8/25) vs. NR Swollen knees: 0% (0/27) vs. 12% (3/25) vs. NR Withdrawals due to adverse events: 0% (0/27) vs. 12% (3/25) vs. NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Mat, 2017[70] Immediately post-treatment (6 months) Duration of pain: NR Fair [New trial]	A. Home Based Balance and Exercise Program [Modified Otago Exercise Program] (n=17): Encouraged to train 3 times/week, in 30 minute sessions for 6 month period. B. Usual Care (n=24)	A vs. B Age: 76 vs. 72, p=0.02 Female: 82.4% vs. 82.4% Baseline KOOS-ADL (0-100): 65.1 vs. 79.7 Baseline KOOS-Sport/Recreation (0-100): 33.8 vs. 57.1 Baseline KOOS-Symptoms (0-100): 70.5 vs. 75.9 Baseline KOOS-Pain (0-100): 73.3 vs. 80.3	A vs. B <u>6 months</u> KOOS-ADL: 75.0 vs. 80.4; difference 9.2 (95% CI NR), p=0.230 KOOS-Sport/Rec: 44.1 vs. 62.3; difference 5.0 (95% CI NR), p=0.620 KOOS-Symptoms: 80.4 (18.8) vs. 80.6; difference 5.1 (95% CI NR), p=0.430 KOOS-Pain: 81.2 vs. 80.0; difference 8.2 (95% CI NR), p=0.210	A vs. B <u>6 months</u> Short FES-I (7-28): 13.9 vs. 13.6; difference −5.2 (95% CI NR), p=0.020 KOOS-QoL (0-100): 55.9 vs. 62.0; difference 6.6 (95% CI NR), p=0.460
Messier, 2004[56] Rejeski, 2002[60] 3, 6 and18 months Duration of pain: NR Fair	A. Exercise (n=80): Three 1-hour sessions per week done at the study facility for 4 months. Option to undergo a 2 month transition phase alternating between facility and home sessions, after which they carried out the program at home. Sessions consisted of 15 minutes of aerobic exercises, 15 minutes of resistance-training, an additional 15 minutes of aerobic exercises, and a 15 minute cool down phase. B. Control (n=78): 1 hour sessions monthly for three months consisting of presentations on OA, obesity, and exercise and a question and answer session. Monthly phone contact was maintained for months 4-6 and bimonthly phone contact was maintained for months 7-18. All subjects: Instructed to continue use of all medications and other treatments as prescribed by their personal physicians	A vs. B Age: 69 vs. 69 Female: 74% vs. 68% Baseline WOMAC physical function (0-68): 24.0 vs. 26.0 Baseline WOMAC pain (0-20): 6.6 vs. 7.3	A vs. B <u>6 months</u> WOMAC physical function*: 22.0 vs. 22.0 WOMAC pain: 6.2 vs. 6.2, difference 0.0 (95% CI −0.2 to 0.2) <u>18 months</u> WOMAC physical function: 21.0 vs. 22.6 WOMAC physical function, mean change: 3.1 vs. 3.4 WOMAC pain: 6.2 vs. 6.0, difference 0.2 (95% CI 0.04 to 0.4)	A vs. B <u>3 months</u> Accident related to treatment: 1% (1/80) vs. 0% (0/78) <u>6-18 months (average; reported by Rejeski 2002)</u> SF-36 PCS: 37.1 vs. 34.4 SF-36 PCS, adjusted mean: 37.6 vs. 35.3 SF-36 MCS: 52.9 vs. 53.5 SF-36 MCS, adjusted mean: 54.1 vs. 53.7

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Quilty, 2003[59] 2.5 months, 10.5 months Duration of pain: NR Fair	A. Combination (Physiotherapy) (n=40): 9 sessions over a 10 week period. Sessions consisted of patellar taping, 7 individualized exercises, posture correction, and footwear advice. All exercises were performed 10 times each, 5 times a day B. Control (n=43): Baseline discussion with the physiotherapist concerning diagnosis, prognosis, footwear, weight reduction, and activity. General exercise was encouraged but no specific quadriceps exercises were advised	A vs. B Age: 69 vs. 67 years Baseline WOMAC Function (0-68): 27.4 vs. 27.8 Baseline VAS pain (0-100): 51.0 vs. 53.4	A vs. B <u>2.5 months</u> WOMAC function: 26.5 vs. 27.5; Adjusted difference −0.6 (95% CI −3.7, 2.4) VAS Pain: 42.8 vs. 50.5; Adjusted difference −6.4 (95% CI −15.3, 2.4) <u>10.5 months</u> WOMAC function: 29.7 vs. 28.3; Adjusted difference 1.7 (95% CI −1.8, 5.2) VAS Pain: 48.1 vs. 54.1; Adjusted difference −4.9 (95% CI −13.6, 3.8)	A vs. B Withdrawals 2% (1/43) vs. 0% (0/44) Adverse Events: None
de Rooij, 2017[69] 3 months Duration of symptoms: Mean 8.6 to 9.4 years Fair [New trial]	A. Individualized Exercise Therapy (n=63): 2 sessions of 30–60 minutes per week under the supervision of a PT for 20 weeks. Training consisted of muscle-strength training of the lower extremity, aerobic training, and training of daily activities. 86% (54/93) of patients received ≥27 of 40 sessions. B. Usual Care and Waitlist (n=63)	A vs. B Age: 63 vs. 64 years % Female: 78% vs. 73% Baseline WOMAC physical functioning (0-68): 35.1 vs. 31.0 Baseline SF-36 physical functioning (0-20): 18.4 vs. 18.8 Baseline patient-specific functioning list (PSFL) (0-10): NR Baseline NRS knee pain (0-10): 6.4 vs. 5.9 Baseline WOMAC pain (0-20): 10.1 vs. 9.4	A vs. B <u>3 months</u> WOMAC physical functioning (0–68): 23.5 vs. 31.4, difference −9.3 (95% CI −12.8 to −5.8) SF-36 physical functioning (0–20): 21.4 vs. 18.9, difference 2.1 (95% CI 0.9 to 3.3) PSFL (performance of activites 0-10): 4.1 vs. 5.9, difference −1.7 (95% CI −2.5 to −1.0) NRS knee pain severity (0–10): 4.7 vs. 6.2, difference −1.6 (95% CI −1.6 to −1.0) WOMAC pain (0–17): 6.6 vs. 8.6, difference −2.0 (95% CI −3.1 to −0.8)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Rosedale, 2014[61] 2.5 months Duration of pain: NR Fair	A. Exercise (n=120): Given end-range exercises in the direction they had responded to, to be performed 10 times every 2 to 3 hours. A nonresponder subgroup was given exercises to strengthen quadriceps and aerobic exercises. All subjects in the exercise group attended 4 to 6 physiotherapy sessions, 2 to 3 assessment sessions lasting up to 1 hour and the rest followup sessions lasting 20 minutes, over a 2 week period. B. Waiting list (n=60): Subjects were followed up in the orthopedic department at the surgeon's discretion and continued receiving their usual care.	A vs. B vs. C Age: 66 vs. 64 Female: 56% vs. 60% Median comorbidities: 3 vs. 3 Baseline KOOS function (0-100): 56 vs. 51 Baseline KOOS function in sport and recreation(0-100): 22 vs. 20 Baseline KOOS knee symptoms (0-100): 50 vs. 48 Baseline KOOS quality of life(0-100): 28 vs. 27 Baseline KOOS pain(0-100): 51 vs. 46 Baseline P4 pain scale: 21 vs. 23	A vs. B <u>2.5 months</u> KOOS function: 61 vs. 52, (adjusted difference 5, 95% CI 1 to 9) KOOS function in sport and recreation: 31 vs. 24, (adjusted difference 6, 95% CI 0 to 11) KOOS pain: 56 vs. 46, (adjusted difference 7, 95% CI 3 to 11) P4 pain scale: 24 vs. 21, (adjusted difference −2, 95% CI −4 to 1) KOOS knee symptoms: 56 vs. 52, (adjusted difference 2, 95% CI −2 to 6) KOOS quality of life: 34 vs. 32, (adjusted difference 1, 95% CI −3 to 6)	NR
Segal, 2015[62] 3 and 9 months Duration of pain: NR Fair (3 months) Poor (9 months)	A. Gait Training (n=24): guided strategies to optimize knee movements during treadmill walking; computerized motion analysis with visual biofeedback; individualized home programs from physical therapist; Twice weekly sessions (45 minutes) for 12 weeks (24 total sessions) B. Usual Care (n=18): Usual care for knee OA and were not asked to make changes in their lifestyle (e.g., annual visit to their physician, use of pain medications, knee surgery and/or physical therapy); ask to keep a diary	A vs. B Age: 70 vs. 69 years Female: 76% vs. 53% Race: NR Baseline LLFDI basic lower limb function score: 65.8 vs. 63.5 Baseline KOOS Symptoms: 60.1 vs. 63.0 Baseline KOOS Pain: 62.7 vs. 59.8	A vs. B, between group difference in change score compared with baseline <u>3 months</u> LLFDI basic lower limb function score: 2.3 (95% CI −1.8 to 6.3) KOOS Pain: 3.7 (95% CI −4.7 to 12.1) KOOS Symptoms: 6.2 (95% CI −2.9 to 15.4) <u>9 months</u> LLFDI basic lower limb function score: 1.0 (95% CI −7.4 to 9.4) KOOS Pain: 7.2 (95% CI −2.0 to 16.5) KOOS Symptoms: 6.0 (95% CI −6.2 to 18.2)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sullivan, 1998[63] 10 months Duration of pain: NR Poor	A. Exercise (n=52): 3 group sessions of 10-15 subjects per week were done for 8 weeks. Sessions were structured as a hospital-based supervised fitness walking and supportive patient education program. Sessions consisted of stretching and strengthening exercises, expert speakers, group discussions, instructions in safe walking techniques, and up to 30 minutes of walking. At the end of the 8 week treatment period, subjects were encouraged to continue walking and given guidelines for managing individualized programs of fitness walking. B. Usual care (n=50): Subjects continued to receive the standard routine medical care they had been receiving prior to enrollment in the study. Subjects were interviewed weekly during the 8 week treatment period about their functional and daily activities.	A vs. B Age: 71 vs. 68 Female: 77% vs. 90% Baseline AIMS physical activity subscale (0-10): 6.3 vs. 6.4 Baseline AIMS arthritis impact subscale (0-10): 4.6 vs. 4.5 Baseline AIMS pain subscale (0-10): 4.9 vs. 5.5 Baseline AIMS general health perception subscale (0-10): NR Baseline pain VAS (0-10): 4.1 vs. 6.3	A vs. B <u>10 months</u> AIMS physical activity subscale: 6.1 vs. 6.2, difference −0.1, (95% CI −1.7 to 1.5) AIMS arthritis impact subscale: 3.3 vs. 3.8, difference −0.5, (95% CI −1.8 to 0.8) AIMS pain subscale: 4.6 vs. 5.5, difference −0.9, (95% CI −2.2 to 0.4) Pain VAS: 5.0 vs. 5.4, difference −0.4, (95% CI −2.0 to 1.2) AIMS general health perception subscale: 3.7 vs. 3.3, difference 0.4 (95% CI −1.0 to 1.8)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Thomas, 2002[64] 6 months, 12 months, 18 months, 24 months Duration of pain: NR Poor	A. Exercise (n=470): Two year, self-paced program that started with four 30 minute visits in the first 2 months followed by visits every 6 months. Designed to maintain and improve strength of muscles around the knee, range of motion at the knee joint, and locomotor function. 121 of the 470 patients also received attention control which consisted of monthly phone calls by a study researcher that sought to monitor symptoms and offer simple advice on knee pain management. 114 of the 470 patients received the attention control and a placebo tablet in addition to the exercise program. The remaining 235 participate in the exercise program only.* B. Control (n=316): 160 subjects received attention control consisted of monthly phone calls by a study researcher that sought to monitor symptoms and offer simple advice on knee pain management. 78 subjects took a placebo tablet. 78 patients had no contact with the researchers between assessment visits.	A vs. B Age: 62 vs. 62 Female: 63% vs. 66% Baseline WOMAC physical function score (0-68): 23.2 vs. 23.0 Baseline WOMAC pain score (0-20): 7.15 vs. 7.35	A vs. B <u>6 months</u> WOMAC physical function: difference NR WOMAC pain: difference −0.6 (95% CI −1.0 to −0.2) <u>24 months</u> WOMAC physical function: difference −2.6 (95% CI −4.1 to −1.1) WOMAC pain: difference −0.82 (95% CI −1.3 to −0.3)	A vs. B <u>6 months</u> HADS: NR SF-36: NR <u>24 months</u> HADS: NR (NS) SF-36: NR (NS)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Thorstensson, 2005[65] 5 months Duration of pain: NR Fair	A. Exercise (n=30): 1 hour group exercise sessions of 2 to 9 participants, twice a week for 6 weeks. Sessions consisted of weight-bearing exercises to increase postural control and to increase endurance and strength in the lower extremity. Patients were given daily exercises to perform at home. B. Control group (n=31): Subjects were told not to make any lifestyle changes. Subjects met with the physical therapist at baseline, at 6 weeks, and at 6 months	A vs. B Age: 55 vs. 57 Female: 50% vs. 52% Baseline KOOS ADL (0-100): 69 vs. 71 Baseline KOOS Symptoms (0-100): 63 vs. 66 Baseline KOOS sports and recreation (0-100): 34 vs. 37 Baseline KOOS Pain (0-100): 60 vs. 64	A vs. B <u>5 months</u> KOOS ADL, mean change: 0.9 vs. −1.9, p=0.61 KOOS pain, mean change: 3.1 vs. −1.1, p=0.32 KOOS symptoms, mean change: 1.0 vs. −3.4, p=0.31 KOOS sports and recreation, mean change: 0.5 vs. −8.3, p=0.32	A vs. B <u>5 months</u> KOOS QOL, mean change (0-100): 5.1 vs. −2.3, p=0.02 SF-36 PCS, mean change (0-100): 3.0 vs. −0.7, p=0.09 SF-36 MCS, mean change (0-100): 0.7 vs. −0.7, p=0.40 <u>Adverse Events:</u> A vs. B Increased knee pain: 3% (1/30) vs. 0% (0/31)
Waller, 2017[71] 12 months Duration of pain: NR Fair [New trial]	A. Aquatic Exercise (n=43): Aquatic resistance training sessions (1 hour long) 3 times per week for 16 weeks (48 sessions total). Variable resistance equipment used to progress intensity B. Usual Care (n=44): Asked to continue regular leisure activities, offered two sessions (1 hour each) of light stretching, relaxation and social interaction during 12 week intervention period.	A vs. B Age: 64 vs. 64 Female: 100% vs. 100% Baseline KOOS-Symptoms (0-100): 74.4 vs. 74.8 Baseline KOOS-ADL (0-100): 84.5 vs. 85.2 Baseline KOOS-Sport/Recreation (0-100): 63.6 vs. 64.8 Baseline KOOS-Pain (0-100): 80.6 vs. 82.1	A vs. B <u>12 months</u> KOOS-ADL: 89.2 vs. 88.3; difference 1.0 (95% CI −2.6 to 4.3), p=0.397 KOOS-Sport/Rec: 71.0 vs. 68.7; difference 2.5 (95% CI −4.8 to 9.0), p=0.396 KOOS-Symptoms: 81.4 vs. 77.9; difference 3.31 (95% CI −1.2 to 7.3), p=0.119 KOOS-Pain: 86.8 vs. 85.1; difference 1.5 (95% CI −2.7 to 5.7), p=0.187	A vs. B <u>12 months</u> KOOS-QoL (0-100): 75.0 vs. 76.4; differnce 1.21 (95% CI −6.0 to 8.0), p=0.308
Weng, 2009[66] 10 months Duration of pain: 42.5 months Poor	A. Isokinetic exercise (n=33): 3 sessions a week for 8 weeks. Sessions consisted of sets of concentric and eccentric contractions at varying angular velocities and start and stop angles. Hot packs for 10 minutes and passive range of motion exercises B. No intervention (n=33): Warm-up cycling for 10 minutes. Hot packs for 10 minutes and passive range of motion exercises	A+B Age: 64 Female: 75% A vs. B Baseline Lequesne Index (0-24): 7.3 vs. 7.1 Pain VAS (0-10): 4.7 vs. 4.5	A vs. B <u>10 months</u> Lequesne Index: 6.3 vs. 7.3 Pain VAS: 3.6 vs. 5.0	A vs. B <u>10 months</u> Treatment related pain causing withdrawal: 9% (3/33) vs. 0% (0/33) RR=infinity, p=0.08

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Williamson, 2007[67] 1.5 months Duration of pain: NR Poor	A. Combination (Physiotherapy) (n=60): Groups of 6–10 patients, hourly, once a week for 6 weeks. Exercise circuit of static quadriceps contractions; inner range quadriceps contractions; straight leg raises; sit to stands, stair climbing; calf stretches; theraband resisted knee extensions; wobble board balance training; knee flexion/extension sitting on gym ball and free standing peddle revolutions. B. Control (n=61): Usual Care (home exercise and advice leaflet)	A vs. B Age: 70 vs. 70 years Female: 52% vs. 54% Baseline OKS (0-48): 39.3 vs. 40.5 Baseline WOMAC (unclear scale): 50.2 vs. 51.1 Baseline VAS pain (0-10): 6.8 vs. 6.9	A vs. B 1.5 months OKS: 38.8 vs. 40.8 WOMAC: 49.4 vs. 52.3 VAS Pain: 6.4 vs. 7.2	A vs. B 1.5 months HADS Anxiety (0-21): 7.1 vs. 6.5 HADS Depression (0-21): 6.8 vs. 7.1 Withdrawals: 17% (10/60) vs. 0% (0/61) Adverse Events: None

ADL = activity of daily living; AIMS = Arthritis Impact Measurement Scale; AQoL = Assessment of Quality of Life; CES-D = Center for Epidemiologic Studies Depression; CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; HAQ = Health Assessment Questionnaire; IBET = internet-based exercise training; ITT = intention-to-treat; KOOS = Knee Injury and Osteoarthritis Outcome Score; KPS = Knee Pain Scale; LLFDI = Late-Life Function and Disability Instrument; LSM = Least squares mean; MCS = Mental Component Score; NA = not applicable; NEMEX = neuromuscular exercise; NR = not reported; NS = not statistically significant; OA = osteoarthritis; OKS = Oxford Knee Score; PASE = Physical Activity Scale for the Elderly; PCS = Physical Component Score; PT = physical therapy; RR = relative risk; QoL = quality of life; SF-36 = Short-Form-36; VAS, visual analog scale; WL = waitlist; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

[b] Group A ceased treatment after 4 months, whereas Groups B and C continued their protocols until the 12 month F/U, therefore the '4 month F/U' for group A is actually the beginning of post-treatment, and their 12 month f/u is therefore 8 months post-treatment. For intermediate followup, only group A's '8 month F/U' is compared with group C's last F/U (12 months). Long-term followup is the comparison of 12 month followups for groups B and C only.

Exercise Compared With Usual Care, No Treatment, Sham, or an Attention Control

Functional Outcomes. Exercise was associated with a small improvement short-term in function (assessed across various measures) compared with usual care, no treatment, or sham intervention (8 trials [1 new trial], pooled SMD −0.29, 95% CI −0.46 to −0.11, I^2=9.9%),[48,55,59,61,62,65,67,69] (Figure 33). Estimates were similar following exclusion of poor-quality trials and when analyses were stratified by exercise and control type. In the short term, across three fair-quality trials,[55,61,65] a small improvement in the KOOS Sport and Recreation scale was seen with exercise compared with usual care or no treatment (pooled difference 5.88 on a 0-100 scale, 95% CI 0.28 to 11.27, $I^{2=}$0%, plot not shown) but there was no clear difference between groups in the KOOS ADL (pooled difference 5.06 on a 0-100 scale, 95% CI −1.99 to 10.65, $I^{2=}$44.6%, plot not shown).

Exercise was also associated with moderate improvement in function (assessed across various measures) versus usual care, no treatment, or attention control at intermediate term (12 trials [2 new trials], pooled SMD −0.98, 95% CI −1.86 to −0.13, I^2=96.5%),[49,50,52-54,56,59,62,63,66,68,70] (Figure 33). Substantial heterogeneity was present with one outlier trial[50] of

combination exercise versus no treatment in elderly patients (median age 75 years) which had higher (worse) baseline Lequesne Index scores compared with other studies and a larger change from baseline score in the intervention group. Removal of this poor quality trial did not improve heterogeneity but did attenuate the pooled estimate (11 trials [2 new trials], pooled SMD −0.63, 95% CI −1.17 to −0.10, I^2=90.8%). Stratification by exercise type and control type may partially explain the heterogeneity. Muscle performance exercise, but not combination exercise (5 trials), was associated with a moderate improvement in function compared with attention control or no treatment (5 trials, pooled SMD −1.44, 95% CI −2.08 to −0.79)[49,52-54,66] and when compared with attention control only (3 trials, pooled SMD −1.12, 95% CI −1.83 to −0.47)[52,54,66] and no treatment only (2 poor quality trials, pooled SMD −1.88, 95% CI −3.16 to −0.55).[49,53] No difference was seen across studies of exercise versus usual care (5 trials [1 new trial], pooled SMD 0.05, 95% CI −0.16 to 0.26).[56,59,62,63,70]

Analyses confined to trials that evaluated function on the 0-24 point Lequesne Index also suggests a moderate improvement in intermediate-term function with exercise compared with attention control or no treatment (6 trials, pooled difference −3.42, 95% CI −5.77 to −1.07, I^2=97%, plot not shown).[49,50,52-54,66] Again, removal of the poor quality outlier trial[50] did not impact the heterogeneity, but yielded a slightly lower effect estimate (5 trials, pooled difference −2.40, 95 CI −3.32 to −1.44), still consistent with a moderate effect for exercise. Results were similar when analyses were stratified according to muscle performance exercise, use of attention control, and study quality (when only the two fair-quality trials were retained).

One fair-quality trial (n=101 with knee OA)[47] compared combined exercise programs to usual care for intermediate-term function using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The exercise group had improvement in function from baseline, which was not statistically significant (mean change from baseline −12.7, 95% CI −27.1 to 1.7), while the usual care group had no change in function (mean change from baseline 1.6, 95% CI −10.5 to 13.7). Data were insufficient to determine effect size or include in the meta-analysis.

One, new fair-quality trial showed no significant difference between combined exercise and usual care at intermediate term for the KOOS Sport and Recreation (difference −18.2 on a 0-100 scale, 95% CI −41.5 to 5.1) or KOOS ADL (difference −5.4 on a 0-100 scale, 95% CI −18.3 to 7.4).[70]

One trial separately analyzed participants free of disability for ADLs at baseline (n=250) and followed them to compare cumulative incidence of disability over 15 months. The aerobic exercise group had decreased risk of disability compared to the attention control group, RR 0.53 (95% CI 0.33, 0.85), as did the muscle performance exercise group compared to the attention control group, RR 0.60 (95% CI 0.38, 0.97).[57]

A small improvement in function long-term was seen across four trials (2 new trials) of exercise compared with usual care, attention control, or waitlist (pooled SMD −0.22, 95% CI −0.34 to −0.08, I^2=0%), two fair[56,68] and two poor quality[64,71] (Figure 33). Following exclusion of the two poor quality trials the difference was slightly attenuated and no longer statistically significant (pooled SMD −0.18, 95% CI −0.38 to 0.03, I^2=0%). No difference between groups was seen when exercise was compared with a waitlist control only (2 trials, pooled difference −0.17, 95% CI −0.45 to 0.15). A single, new poor-quality trial found no long-term difference in KOOS Sport and Recreation (difference 2.3 on a 0-100 scale, 95% CI −7.9 to 12.5) or KOOS ADL (difference 0.90 on a 0-100 scale, 95% CI −4.1 to 5.9) for muscle performance exercise compared with waitlist.[71]

Pain Outcomes. One fair-quality trial found no statistical difference between exercise or sham procedure in the proportion of patients who reported clinically relevant reductions (≥1.75 points) in VAS pain on movement (prior week) [58% (34/59) vs. 42% (27/65); RR 1.4, 95% CI 1.0 to 2.0] or VAS global improvement in pain [59% (35/59) vs. 50% (33/65); RR 1.2, 95% CI 0.8 to 1.6] in the short term.[48] Exercise was associated with a small improvement in short-term pain compared with usual care, no treatment, waitlist or sham in eight (1 new) trials (pooled difference on a 0-10 scale −0.47, 95% CI −0.86 to −0.10, I^2=42%) (Figure 34). Seven trials (1 new trial) were fair quality[48,55,59,61,62,65,69] and one was poor quality.[67] The estimate was similar following exclusion of the poor-quality trial (pooled difference −0.45, 95% CI −0.86 to −0.04). Across studies comparing exercise with usual care, results were also similar (5 trials, pooled difference −0.53, 95% CI −1.07 to −0.02).[55,59,61,62,67]

Exercise was associated with moderately greater improvement in intermediate-term pain compared with usual care, attention control, waitlist or no treatment across pain measures (11 trials [2 new trials], pooled difference −1.34, 95% CI −2.12 to −0.54, I^2=90% on a 0-10 scale) across six fair-quality trials (2 new trials)[52,54,56,59,68,70] and five poor-quality trials[49,53,62,63,66] (Figure 34). Following exclusion of the poor quality trials the difference between groups was attenuated and no longer statistically significant (pooled SMD −0.98, 95% CI −2.09 to 0.12). Results differed somewhat by type of exercise and type of control. Five trials (2 new trials) showed no difference between combination exercise and usual care or waitlist[56,59,63]; however, a substantial improvement in pain was seen for muscle performance exercise compared with attention control or no treatment (5 trials, pooled difference on 0-10 scale −2.53, 95% CI −3.23 to −1.80)[49,52-54,66] and when compared with attention control only (3 trials, pooled difference −2.18, 95% CI −3.15 to −1.24)[52,54,66] and with no treatment only (2 poor quality trials, pooled difference −3.01, 95% CI −4.00 to −1.90).[49,53] No difference was seen across studies of exercise versus usual care (5 trials [1 new trial], pooled SMD −0.29, 95% CI −0.80 to 0.13).[56,59,62,63,70]

Exercise resulted in a small improvement in long-term pain versus usual care, waitlist or attention control (pooled difference −0.30 on a 0 to 10 scale, 95% CI −0.49 to 0.00, I^2=0%), in three fair-quality trials (2 new trials)[56,68,71] and one large, poor-quality trial[64] (Figure 34).

Most trials evaluated pain using a traditional 0 to 10 VAS. A small improvement in short-term pain favoring exercise was observed across four trials (3 fair [one new trial], 1 poor quality, pooled difference −0.83, 95% CI −1.49 to −0.19, I^2=33%)[48,59,67,69]; the effect estimate was similar after exclusion of the poor quality trial (pooled difference −0.84, 95% CI −1.73 to 0.02).[67] Estimates confined to combination exercise showed a slightly greater effect size and remained significant (3 trials, pooled difference −1.14, 95% CI −1.73 to −0.41).[59,67,69] Findings for intermediate-term pain showed a moderate improvement with exercise (7 trials, pooled difference −2.04, 95% CI −2.86 to −1.13, I^2=81%).[49,52-54,59,63,66] The pooled estimate was similar when four poor-quality trials[49,53,63,66] were excluded, leaving three fair-quality trials (pooled difference −1.97, 95% CI −3.45 to −0.44).[52,54,59] When results were stratified by exercise type, muscle performance exercise resulted in a large effect size (5 trials, pooled difference −2.53, 95% CI −3.23 to −1.80)[49,52-54,66] while results for combination exercise showed no difference versus usual care (2 trials, pooled difference −0.54, 95% CI −1.55 to 0.51).[59,63] Stratification by control type among studies reporting VAS pain yielded similar findings to those across multiple measures. No trial employing VAS reported on long-term pain.

Other Outcomes. Health-related quality of life (QoL) outcomes had mixed results (Table 24). Two fair-quality trials found no association between exercise and short-term QoL on the KOOS 0 to 100 scale (pooled difference 1.8, 95% CI −2.5 to 6.0, I^2=0%, plot not shown).[55,61] A fair-

quality trial (n=65) reported no differences in mean change for short term SF-36 PCS (mean change of 3.0 [95% CI −5.9 to 16.3] versus −0.7 [95% CI −14.8 to 9.8]) and SF-36 MCS (mean change of 0.7 [95% CI −18.1 to 13.2] vs. −0.7 [95% CI −16.8 to 12.8]).[65] One fair-quality trial (n=158) reported similar health-related QoL scores between a combined exercise group and usual care using averaged intermediate- and long-term scores. The adjusted mean (standard error [SE]) SF-36 PCS were 37.6 (0.9) vs. 35.3 (0.8), respectively, and adjusted mean (SE) SF-36 MCS were 54.1 (0.8) vs. 53.7 (0.8), respectively.[60] A poor-quality trial (n=50) reported intermediate-term SF-36 scores for individual domains. Functional capacity, physical role, bodily pain, general health, and vitality showed small improvement with exercise versus attention control.[50]

A fair-quality trial (n=438) reported no difference in depressive symptoms compared with attention control (2.59 vs. 2.80, p=0.27) for muscle performance exercise, while aerobic exercise was associated with fewer depressive symptoms on the Center for Epidemiologic Studies Depression (CES-D) questionnaire compared to attention control (2.12 vs. 2.80, p<0.001).[58]

There was insufficient evidence to determine effects of duration of exercise therapy or number of sessions on outcomes. No trials reported on changes in opioid use as a result of exercise programs.

Exercise Compared With Pharmacological Therapy or With Other Nonpharmacological Therapies

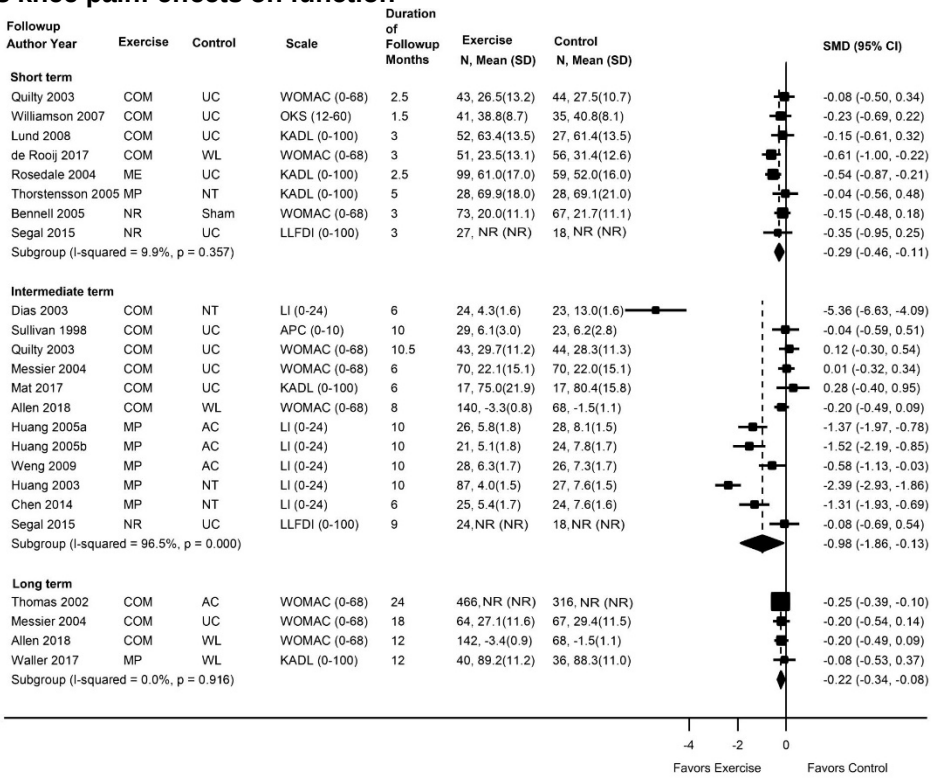
One new trial (in 2 publications) of exercise therapy versus pharmacological therapy met inclusion criteria. This fair-quality trial (N=93)[102,103] compared combined exercise with standard recommendations for analgesics and anti-inflammatory drugs and had intermediate-term followup only. More patients who received exercise versus pharmacological therapy achieved a clinically important improvement in function (>10 point improvement on KOOS ADL), 47% (22/47) versus 28% (13/46); RR 1.7, 95% CI 1.0 to 2.9; however the difference did not reach statistical significance. There was no difference between groups for change in function from baseline: KOOS ADL (difference −3.6 on a 0-100 scale, 95% CI −9.2 to 2.1) and KOOS Sport and Recreation (difference −2.9 on a 0-100 scale, 95% CI −11.4 to 5.5). There was also no difference for change in pain from baseline according to the KOOS pain measure (difference 4.2 on a 0-100 scale, 95% CI −10.0 to 1.6), but there was a small difference for change in symptoms favoring exercise, KOOS Symptoms (difference −7.6 on a 0-100 scale, 95% CI −12.7 to −2.6). No difference in change in QoL from baseline was found with the KOOS QoL (difference −1.3 on a 0-100 scale, 95% CI −7.5 to 4.9) and the EQ-5D (difference 2.6, 95% CI −2.9 to 8.1).

Findings for exercise versus other nonpharmacological therapies are addressed in the sections for other nonpharmacological therapies.

Harms

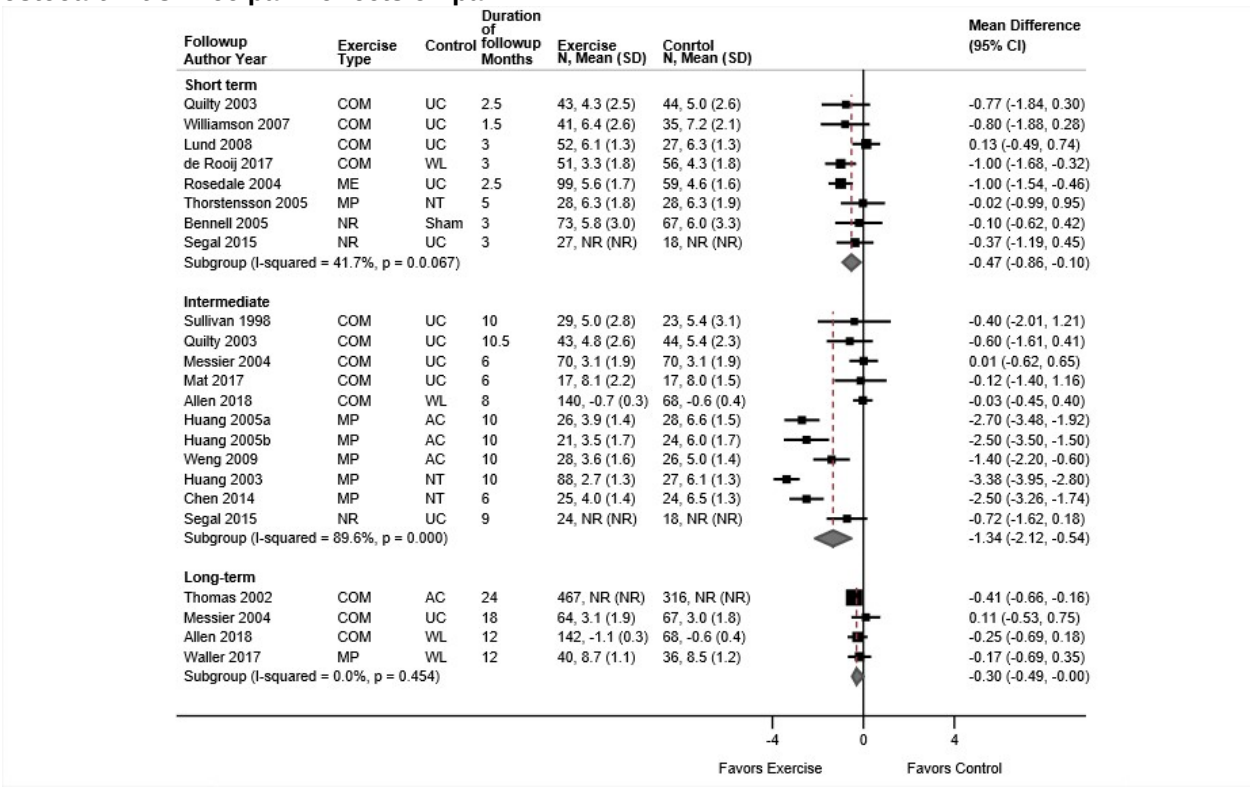
Most trials did not report harms. One trial reported greater temporary, minor increases in pain in the exercise group versus a sham group (RR 14.7, 95% CI 2.0 to 107.7); however, the confidence interval is wide.[48] Four studies found no difference in worsening of pain symptoms with exercise versus comparators.[49,53,65,66] One trial found no difference in falls or deaths.[51] No difference in adverse events (to include abdominal and intestinal symptoms, musculoskeletal symptoms, central nervous system, psychiatric symptoms, skin and subcutaneous symptoms and other) was reported for exercise compared to standard analgesics and anti-inflammatory therapy.[102,103]

Figure 33. Exercise versus usual care, no treatment, sham, or an attention control for osteoarthritis knee pain: effects on function



AC = attention control; APC = Arthritis Impact Measurement Scale (AIMS) physical activity component; CI = confidence interval; COM = combination exercise therapy; KADL = Knee Injury and Osteoarthritis Outcome Score (KOOS) ADL subscore; LI = Lequesne Index; LLFDI = Late Life Function and Disability Index Basic Lower Limb Function Score; ME = mobility exercise; MP = muscle performance exercise; NR = neuromuscular reeducation exercise; NT = no treatment; OKS = Oxford Knee Score; SD = standard deviation; SMD = standardized mean difference; UC = usual care; WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index

Figure 34. Exercise versus usual care, no treatment, sham, or an attention control for osteoarthritis knee pain: effects on pain



AC = attention control; CI = confidence interval; COM = combination exercise therapy; ME = mobility exercise; MP = muscle performance exercise; NR = neuromuscular re-education exercise; NT = no treatment; SD = standard deviation; SMD = standardized mean difference; UC = usual care

Psychological Therapy for Osteoarthritis Knee Pain

Key Points

- Two new trials of motivational interviewing and CBT versus usual care and no treatment found no differences between treatment groups in function (pooled difference −2.09 on a 0-68 WOMAC function scale, 95% CI −8.70 to 1.61, I^2=63.3%) but a small improvement in pain (pooled difference −0.6 on a 0-20 WOMAC pain scale, 95% CI −1.5 to −0.1, I^2=0.0%) 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 differences in function (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).
- One trial of pain coping skills training versus strengthening exercises found no differences in WOMAC physical function scores (0-68 scale) at short term (difference 2.0, 95% CI −2.4 to 6.4) or intermediate term (difference 3.2, 95% CI −0.6 to 7.0) or in

WOMAC pain scores (0-20 scale) at short term (difference −0.1, 95% CI −1.2 to 1.0) or intermediate term (difference 0.4, 95% CI −0.8 to 1.6) (SOE: low).

- No serious harms were reported in either trial (SOE: low).

Detailed Synthesis

Five trials of psychological therapies for knee OA met inclusion criteria (Table 26 and Appendix D).[109-112,134] Three trials were included in the prior AHRQ report[109,110,134] and two were added for this update.[111,112] Two trials (1 new trial) were conducted in the United States,[110,111] one in Finland,[109] and two (1 new trial) in Australia.[112,134] Sample sizes ranged from 67 to 155 (total sample=593). Across the trials, participants were predominately female (60% to 80%) with mean ages ranging from 58 to 64 years. Three trials (1 new trial)[109,110,112] evaluated CBT or pain coping skills training with usual care. The number and duration of psychological sessions varied between the trials (6, 2-hour sessions, 6 online sessions or e18, 1-hour sessions, respectively), as did the total duration of therapy (6 and 24 weeks). Usual care was defined as routine care provided by the patient's primary care doctor and was not well-described in any trial. Another new trial (n=155) compared motivational interviewing focused on goal setting and physical activity with no treatment.[111] Motivational interviewing consisted of a longer initial session followed by 5 brief sessions (10-15 minutes) over 24 months. The fifth trial (n=149)[134] compared pain coping skills training (PCST) (ten 45-minute sessions) with strengthening exercises (ten 25-minute sessions); all sessions were conducted on an individual basis over a treatment period of 12 weeks. Participants randomized to receive PCST were told to practice skills daily and then as needed during followup; those in the exercise group were instructed to perform exercises four times a week during 12-week intervention and three times a week during the followup period.

Four trials (2 new trials) were rated fair quality[109,111,112,134] and one was rated poor quality[110] (see Appendix E for quality ratings). The primary methodological limitation in the fair-quality trials were the inability to effectively blind care providers, outcome assessors, and/or patients. Additional methodological shortcomings in the poor-quality trial included poor treatment compliance and high attrition (32%).

Table 42. Osteoarthritis knee pain: psychological therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bennell, 2016[134] 5 and 9 months Duration of pain: 6 years Fair	A. Pain coping skills training (n=74): 10, 45-minute sessions over 12 weeks; consisted of pain education and cognitive and behavioral pain coping skills training B. Exercise (n=75): 10, 25 minute sessions over 12 week; consisted of 6 strengthening exercises.	A vs. B Age, years: 63 vs. 63 Female: 61% vs. 59% Radiographic disease severity: Grade 2: 45% vs. 40% Grade 3: 28% vs. 25% Grade 4: 27% vs. 35% Opioid use: 4% vs. 1% Baseline WOMAC physical function (0-68): 35.0 vs. 34.3 Baseline WOMAC pain (0-20): 8.7 vs. 8.6 Baseline pain overall VAS (0-100): 58.7 vs. 59.1 Baseline pain with walking VAS (0-100): 61.3 vs. 60.9	A vs. B 5 months WOMAC physical function: 23.4 vs. 21.4, difference 2.0 (95% CI −2.4 to 6.4) WOMAC pain: 6.2 vs. 6.3, difference −0.1 (95% CI −1.2 to 1.0) Pain overall VAS: 35.7 vs. 36.0, difference −0.3 (95% CI −9.0 to 8.4) Pain with walking VAS: 39.1 vs. 42.3, difference −3.2 (95% CI −12.4 to 6.0) 9 months WOMAC physical function: 21.3 vs. 18.1, difference 3.2 (95% CI −0.6 to 7.0) WOMAC pain: 5.8 vs. 5.4, difference 0.4 (95% CI −0.8 to 1.6) Pain overall VAS: 34.8 vs. 34.5, difference 0.3 (95% CI −7.8 to 8.4) Pain with walking VAS: 37.3 vs. 37.5, difference −0.2 (95% CI −9.1 to 8.7)	A vs. B 5 months DASS21 depression scale (0-42): 4.3 vs. 5.5, difference −1.2 (95% CI −4.0 to 1.6) DASS21 anxiety scale (0-42): 4.0 vs. 4.9, difference −0.6 (95% CI −3.0 to 1.2) AQoL-6D (−0.04 to 1.0): 0.79 vs. 0.76, difference 0.03 (95% CI −0.02 to 0.09) 9 months DASS21 depression scale: 3.5 vs. 4.9, difference −1.4 (95% CI −3.6 to 0.8) DASS21 anxiety scale: 3.0 vs. 4.6, difference −1.6 (95% CI −3.4 to 0.2) AQoL-6D: 0.81 vs. 0.78, difference 0.03 (95% CI −0.02 to 0.08) Percent of patients using opioids: 10% (7/72) vs. 13% (9/71), RR 0.77 (95% CI 0.3 to 1.9)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Gilbert, 2018[111] 3, 6, 12, and 24 months Mean duration of pain: NR Fair [New trial]	A. IMPAACT Motivational Interviewing (MI) (n=76) 1 initial session (45 to 60 minutes long), and 5 additional sessions (10 to 15 minutes long) B. No treatment (n=79) All patients: received brief physician consultation with recommendation to increase physical activity	A vs. B Age: 61 vs. 65 Female: 58% vs. 62% Mean duration of Chronicity: 9.6 vs. 12.1 years Baseline WOMAC Function (0-68): 18.0 vs. 17.4 Baseline WOMAC Pain (0-20): 5.9 vs. 5.5	A vs. B <u>3 months</u> WOMAC Function: 16.5 (95% CI 14.7 to 18.4) vs. 17.8 (95% CI 16.3, 19.4); difference 1.3 (95% CI −1.1 to 3.7) WOMAC Pain: 5.2 (95% CI 4.6 to 5.8) vs. 6.1 (95% CI 5.6 to 6.7); difference 1.0 (95% CI 0.2 to 1.8) <u>6 months</u> WOMAC Function: 15.1 (95% CI 13.1 to 17.2) vs. 16.7 (95% CI 15.1 to 18.3); difference 1.6 (95% CI −1.0 to 4.2) WOMAC Pain: 5.3 (95% CI 4.6 to 6.0) vs. 5.5 (95% CI 4.9 to 6.0); difference 0.18 (95% CI −0.7 to 1.1) <u>12 months</u> WOMAC Function: 13.4 (95% CI 11.1 to 15.7) vs. 16.6 (95% CI 14.6 to 18.6); difference 3.2 (95% CI 0.1 to 6.2) WOMAC Pain: 4.8 (95% CI 4.0 to 5.5) vs. 5.7 (95% CI 5.0 to 6.4); difference 0.9 (95% CI −0.1 to 1.9) <u>24 months</u> WOMAC Function: 12.5 (95% CI 10.1 to 14.9) vs. 15.3 (95% CI 12.6, 18.1); difference 2.8 (95% CI −0.8 to 6.4) WOMAC Pain: 4.0 (95% CI 3.2 to 4.7) vs. 4.7 (95% CI 3.8 to 5.7); difference 0.8 (95% CI −0.4 to 2.0)	A vs. B <u>3 months</u> SF-36 PCS (0-100): 46.0 (95% CI 44.7 to 47.3) vs. 44.7 (95% CI 43.2 to 46.2); difference 1.4 (95% CI −0.6 to 3.4) SF-36 MCS (0-100): 54.0 (95% CI 52.3 to 55.6) vs. 54.6 (95% CI 52.8 to 56.4); difference −0.6 (95% CI −3.1 to 1.8) <u>6 months</u> SF-36 PCS: 45.0 (95% CI 43.6 to 46.5) vs. 44.8 (95% CI 43.5 to 46.2); difference 0.23 (95% CI −1.8 to 2.2) SF-36 MCS: 54.3 (95% CI 52.5 to 56.1) vs. 54.1 (95% CI 52.2 to 55.9); difference 0.3 (95% CI −2.3 to 2.8) <u>12 months</u> SF-36 PCS: 46.0 (95% CI 44.6 to 47.5) vs. 44.3 (95% CI 42.6 to 46.0); difference 1.7 (95% CI −0.5 to 3.9) SF-36 MCS: 54.1 (95% CI 51.9 to 56.2) vs. 54.7 (95% CI 52.9 to 56.4); difference −0.6 (95% CI −3.4 to 2.1) <u>24 months</u> SF-36 PCS: 45.4 (95% CI 43.4 to 47.5) vs. 44.7 (95% CI 42.3 to 47.0); difference 0.78 (95% CI −2.3 to 3.9) SF-36 MCS: 54.2 (95% CI 52.0 to 56.3) vs. 52.8 (95% CI 50.0 to 55.6); difference 1.3 (95% CI −2.16 to 4.8)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Helminen, 2015[109] 31.5 to 10.5 months Duration of pain: 7.8 years Fair	Cognitive-Behavioral Training plus usual care (n=55): 2-hour groups sessions, weekly for 6 weeks (6 sessions total); included attention diversion methods (relaxation, imagery, distraction), activity-rest cycling and pleasant activity scheduling, cognitive restructuring, and homework assignments B. Usual Care (n=56)	A vs. B Age: 64.5 vs. 63 years Female: 71% vs. 68% BMI: 30 vs. 30 kg/m^2 Bilateral knee OA: 33% vs. 30% Kellgren-Lawrence grade 2: 60% vs. 61% Duration of Chronicity: 6.6 vs. 8.9 years Baseline WOMAC Function (0-100): 53.0 vs. 48.4 Baseline WOMAC Pain (0-100): 57.6 vs. 56.4 Baseline NRS pain (0-10), average past week: 6.6 vs. 6.4 Baseline NRS pain (0-10), worst past week: 8.0 vs. 7.5 Baseline NRS pain (0-10), average 3 months: 6.8 vs. 6.6 Baseline NRS pain (0-10), worst 3 months: 8.2 vs. 8.0	A vs. B <u>Post-Treatment Average (1.5 to 10.5 months)</u> WOMAC Function: 36.5 vs. 36.7, difference −0.3 (95% CI −8.3 to 7.8) WOMAC Pain: 35.6 vs. 39.5, difference −3.9 (95% CI −11.8 to 4.0) NRS pain, average past week: 5.0 vs. 4.9, difference 0.02 (95% CI −0.89 to 0.93) NRS pain, worst over week: 6.1 vs. 5.9, difference 0.1 (95% CI −0.8 to 1.1) NRS pain, average 3 months: 5.2 vs. 5.4 difference −0.2 (95% CI −1.0 to 0.6) NRS pain, worst 3 months: 6.4 vs. 6.6, difference −0.1 (95% CI −0.9 to 0.7)	A vs. B <u>Post-Treatment Average (1.5 to 10.5 months)</u> WOMAC Stiffness (0-100): 46.2 vs. 49.0 difference −2.7 (95% CI −11.4 to 5.9) BDI (0−63): 5.8 vs. 5.9, difference −0.1 (95% CI −2.2 to 2.0) BAI (0−63): 8.0 vs. 7.1, difference 0.9 (95% CI −1.3 to 3.1) HRQoL, 15D (scale NR): 0.82 vs. 0.85, difference −0.03 (95% CI −0.06 to 0.00) SF-36 Physical Functioning (scale NR): 48.0 vs. 49.4 difference −1.4 (95% CI −10.2 to 7.3) SF-36 Role-Physical: 44.4 vs. 44.5 difference −0.09 (95% CI −14.4 to 14.3) SF-36 Bodily Pain: 57.3 vs. 57.4, difference −0.1 (95% CI −8.0 to 7.7) SF-36 General Health: 53.1) vs. 58.2, difference −5.0 (95% CI −12.3 to 2.3) SF-36 Vitality: 62.7 vs. 67.5, difference −4.8 (95% CI −12.6 to 3.1) SF-36 Social Functioning: 75.0 vs. 82.8, difference −7.8 (95% CI −16.4 to 0.81) SF-36 Role-Emotional: 67.9 vs. 74.7, difference −6.7 (95% CI −20.2 to 6.8) SF-36 Emotional Well-Being: 75.3 vs. 78.5, difference −3.2 (95% CI −9.5 to 3.1) SF-36 Health Change: 46.6 vs. 47.4, difference −0.8 (95% CI −9.2 to 7.6)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
O'Moore, 2018[112] 3 months Duration of pain: NR Fair [New trial]	A. iCBT (n=43) B. Usual Care (n=24)	A vs. B Age: 63 vs. 60 years Female: 86% vs. 68% Baseline WOMAC-ADL (0-68): 32.3 vs. 30.0 Baseline WOMAC-Stiffness (0-8): 4.5 vs. 4.2 Baseline WOMAC-Pain (0-20): 9.9 vs. 9.4	A vs. B <u>3 months</u> WOMAC-ADL: 24.1 vs. 30.34; difference −6.3 (95% CI −11.9 to −0.7), p<0.05 WOMAC-Stiffness: 3.3 vs. 4.4, difference −1.1 (95% CI −2.0 to −0.3), p<0.05; WOMAC-Pain: 7.4 vs. 9.8; difference −2.34 (95% CI −4.2 to −0.5), p<0.05	NR
Somers, 2012[110] 6-12 months Duration of pain: NR *Poor*	A. Pain Coping Skills Training (n=60): 1-hour group sessions, weekly for 12 weeks then every other week for 12 weeks (total of 18 sessions over 24 weeks); consisted of informational lectures, problem solving, skills training, relaxation exercises, homework assignments, and feedback B. Usual Care (n=51)	A vs. B Age: 58 vs. 58 years Female: 67% vs. 78% Caucasian: 62% vs. 61% Mean Duration of Chronicity: NR Kellgren-Lawrence score (0-4): 2.5 vs. 2.3 Baseline WOMAC function subscale (0-100): 46.2 vs. 46.1 Baseline WOMAC pain subscale (0-100): 42.8 vs. 43.4	A vs. B <u>Post-treatment Average (6-12 months)</u> WOMAC function: 35.2 vs. 37.5, p=NS AIMS physical disability subscale: 1.5 vs. 1.4, p=NS WOMAC pain subscale: 34.5 vs. 38.0, p=NS AIMS pain subscale: 4.4 vs. 4.7, p=NS	A vs. B <u>Post-treatment Average (6-12 months)</u> WOMAC stiffness subscale (0-100): 44.5 vs. 46.4, p=NS AIMS psychological subscale (0-10): 2.6 vs. 2.5, p=NS

ADL = Activities of Daily Living; AIMS = Arthritis Impact Measurement Scale; AQoL = Assessment of Quality of Life; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CI = confidence interval; DASS21 = Depression, Anxiety, and Stress Scales 21 item quesitonaire; HRQoL = health-related quality of life; iCBT = internet-based cognitive-behavioral therapy; NR = not reported; NRS = numeric rating scale; NS = not statistically significant; OA = osteoarthritis; SF-36 MCS = Short-Form 36 Mental Component Score; SF-36 PCS = Short-Form 36 Physical Component Score; RR = risk ratio; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Psychological Therapies Compared With Usual Care

Four trials (2 new trials)[109-112] compared psychological therapies with usual care or no treatment. Only the short term results of the two new, fair quality trials (O'Moore, 2018 and Gilbert, 2018) were amenable to pooling.[111,112] There was no statistically significant difference between groups at short term for function according to the WOMAC (pooled difference −2.09 on a 0-68 scale, 95% CI −8.70 to 1.61, I^2=63.3%) (Figure 35) but there was a small improvement in pain favoring the psychological treatments compared to usual care or no treatment (pooled difference −0.60 on the 0-20 WOMAC pain scale, 95% CI −1.48 to −0.08, I^2 = 0.0%) (Figure 36).[111,112] One of these trials[111] also reported intermediate and long term results with no statistically significant differences between treatment groups in either the WOMAC pain or function subscales at any timepoint with the exception of a small difference in function favoring usual care at 12 months (difference 3.2, 95% CI 0.1 to 6.2) at 12 months. Regarding quality of life, there was no statistically significant difference between groups at short term for either the

SF-12 PCS (2 trials, pooled difference 1.3 on a 0-100 scale, 95% CI −1.1 to 3.6, I^2=0.0%)[111,112] the or the SF-12 MCS (2 trials, pooled difference 3.7 on a 0-100 scale, 95% CI −7.7 to 16.3, I^2=90.8%).[111,112]

Two other trials reported outcomes averaged over all post-treatment followup times and therefore were not able to be pooled. The trial of CBT averaged results from 1.5 to 10.5 months post-treatment (spanning short to intermediate term)[109] and the trial of pain coping skills training averaged results from 6 to 12 months post-treatment (spanning intermediate to long term).[110] Similar to the pooled results, no significant differences in function or pain were found between the psychological therapy and the usual care groups in either trial. Function was measured using the WOMAC physical function subscale (0-100) in both trials, over the short to intermediate term (difference −0.3, 95% CI −8.3 to 7.8)[109] and intermediate to long term (mean 35.2, 95% CI 31.8 to 38.6 vs. mean 37.5, 95% CI 33.9 to 41.2),[110] and using the Arthritis Impact Measurement Scale (AIMS) physical disability subscale in one trial[110] (Table 25). Both trials measured pain using the WOMAC pain subscale (0-100), one trial over short- to intermediate-term followup (difference −3.9, 95% CI −11.8 to 4.0)[109] and the other over intermediate- to long-term followup (mean 34.5, 95% CI 30.8 to 38.2 vs. mean 38.0, 95% CI 34.1 to 41.8).[110] Results were similar for the AIMS pain subscale and the numeric rating scale (NRS) pain scale, reported by one trial each (Table 25). Neither trial reported any differences between groups in any secondary outcome measure.

No trial evaluated effects of psychological therapies on use of opioid therapies or healthcare utilization.

Psychological Therapies Compared With Pharmacological Therapy

No trial of psychological therapy versus pharmacological therapy met inclusion criteria.

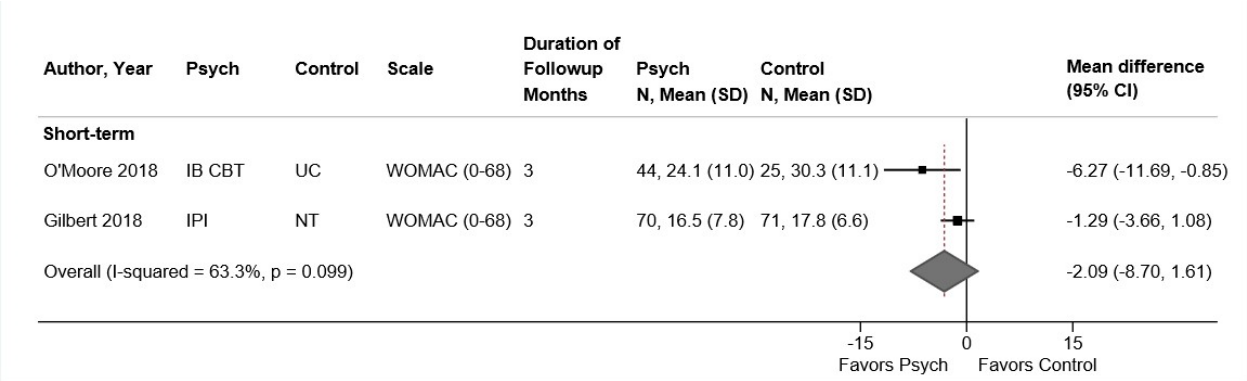
Psychological Therapies Compared With Exercise Therapy

One fair-quality trial[134] of pain coping skills training versus strengthening exercise found no between-group differences in function or pain in the short term (WOMAC physical function, difference 2.0, 95% CI −2.4 to 6.4 on a 0-68 scale and WOMAC pain, difference −0.1, 95% CI −1.2 to 1.0 on a 0-20 scale) or the intermediate term (WOMAC physical function, difference 3.2, 95% CI −0.6 to 7.0 and WOMAC pain, difference 0.4, 95% CI −0.8 to 1.6) (Table 25). Results were similar for overall pain and pain with walking, both measured on a 0-100 VAS. There were also no differences between groups on any other secondary outcome measure including opioid use at short-term or intermediate-term followup.

Harms

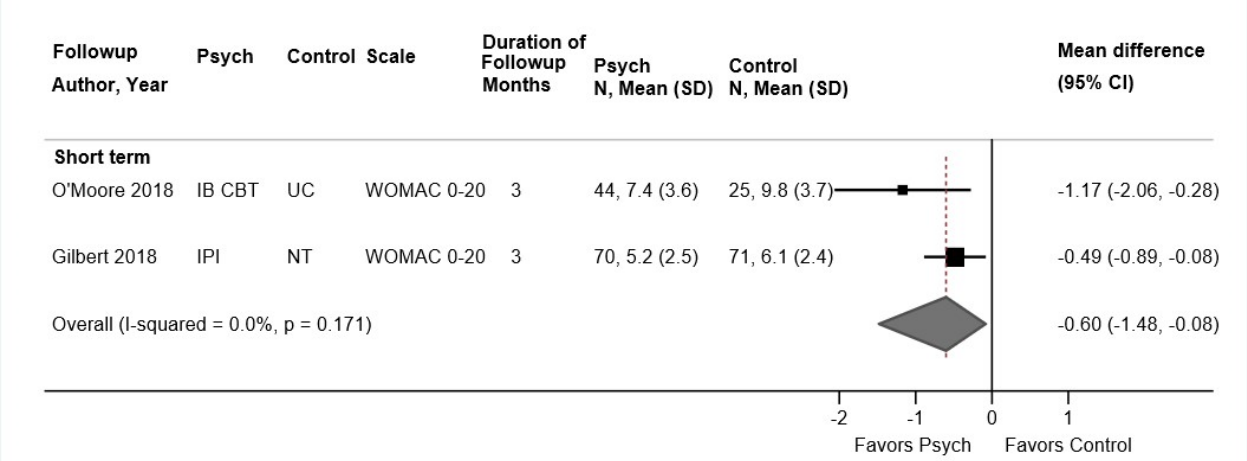
In the four trials of psychological interventions versus usual care,[109-112] no adverse events were observed. In the fifth trial,[134] fewer participants in the pain coping skills training group compared with the exercise group experienced pain in the knee (3% vs. 31%, p<0.001) and in other body regions (4% vs. 15%, p=0.02) during treatment; during followup, only the frequency of pain in other body areas differed between groups (0% vs. 11%, respectively, p<0.05; knee pain, 7% vs. 10%, p=0.53). Pain was most mostly mild and transient.

Figure 35. Psychological therapies versus usual care or no treatment for osteoarthritis knee pain: effects on function



CI = confidence interval; IB CBT = internet-based cognitive-behavioral therapy; IPI = interviewing-based lifestyle physical activity intervention; N = number; NT = no treatment; SD = standard deviation; UC = usual care; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 36. Psychological therapies versus usual care or no treatment for osteoarthritis knee pain: effects on pain



CI = confidence interval; IBCBT = internet-based cognitive-behavioral therapy; IPI = interviewing-based lifestyle physical activity intervention; N = number; NT = no treatment; SD = standard deviation; UC = usual care; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Physical Modalities for Osteoarthritis Knee Pain

Key Points

Ultrasound

- Three trials (2 new trials), one good-, one fair- and one poor-quality, found no statistically significant differences between either continuous or pulsed ultrasound or sham in short-term function (pooled difference −2.50 on a 0-24 scale, 95% CI −6.37 to 1.22, I^2=94.0%) and short-term pain intensity (pooled difference −1.2 on a 0-10 scale, 95% CI −3.7 to 1.3, I^2=91.1%) (SOE: low).

- One fair-quality trial found no 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 WOMAC function 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 WOMAC pain scale). There was also no difference between groups for VAS pain during rest or on movement (SOE: low).
- No adverse events were reported during the two trials (SOE: low).

Transcutaneous Electrical Nerve Stimulation

- One trial found no differences between TENS and placebo TENS in intermediate-term function (proportion of patients who achieved a minimal clinically important difference (MCID) on the WOMAC function subscale [≥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 the 0-100 WOMAC function subscale) 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 difference −5.6, 95% CI −14.9 to 3.6 on the 0-100 WOMAC pain subscale) (SOE: low for function and pain).
- One trial of TENS reported no difference in the risk of minor adverse events (RR 1.06 (95% CI 0.38 to 2.97) (SOE: low).

Low-Level Laser Therapy

- Evidence was insufficient from one small fair-quality and two poor-quality trials to determine effects or harms of low-level laser therapy in the short or intermediate term; No data were available for the long term (SOE: insufficient)

Microwave Diathermy

- There was insufficient evidence to determine short-term effects or harms from one small, fair-quality trial (SOE: insufficient).

Pulsed Short-Wave Diathermy

- There was insufficient evidence to determine effects or harms from one poor-quality trial in the short term or from another poor quality trial in the long term (SOE: insufficient).

Electromagnetic Field

- One fair-quality trial found pulsed electromagnetic fields were associated with small improvements in function (difference −3.48, 95% CI −4.44 to −2.51 on a 0-85 WOMAC ADL 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).
- More patients who received real versus sham electromagnetic field therapy reported throbbing or warming sensations or aggravation of pain (29% versus 7%); however, the difference was not significant (RR 1.95, 95% CI 0.81 to 4.71) (SOE: low).

Superficial Heat

- Evidence was insufficient from one small fair-quality trial to determine effects or harms of trial superficial heat versus placebo in short-term pain (SOE: insufficient).

Braces

- There was insufficient evidence from one poor-quality study to determine the effects of bracing versus usual care for intermediate-term and long-term function or pain (SOE: insufficient).
- Harms were not reported.

Detailed Synthesis

A total of 15 trials evaluating the use of a physical modality for the treatment of knee OA met inclusion criteria (Table 27 and Appendixes D and E).[150-164] Thirteen were included in the prior AHRQ report[150-162] and two were added for this update.[163,164] Physical modalities evaluated included ultrasound (both new trials), TENS, low-level laser therapy, microwave diathermy, pulsed short-wave diathermy, electromagnetic fields, superficial heat, and bracing. All but one intervention (bracing vs. usual care)[152] were compared to a sham procedure.

Table 43. Osteoarthritis knee pain: physical modalities

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Al Rashoud, 2014[150] 1.5 and 6 months Duration of pain: 11 years Fair	A. Low-level laser therapy (n=26): continuous laser (30 mW, 830 nm wavelength) applied to 5 acupuncture points over approximately of 10 sessions B. Placebo laser (n=23): placebo laser applied to 5 acupuncture points over approximately 10 sessions	A vs. B Age: 52 vs. 56 years Female: 62% vs. 65% Baseline Saudi Knee Function Scale (SKFS) (0-112), median: 61.0 vs. 60.0 Baseline pain on movement VAS (0-10): 6.4 vs. 5.9	A vs. B <u>1.5 months</u> Pain on movement VAS: 3.0 vs. 4.2[b] SKFS, median: 31 vs. 40, median difference −10 (95% CI −23 to −4) p=0.054 <u>6 months</u> Pain on movement VAS: 3.4 vs. 5.2[b] SKFS, median: 31 vs. 51, median difference −21 (95% CI −34 to −7) p=0.006	NR
Battisti, 2004[151] 1 month Duration of pain: 11 years Poor	A. Therapeutic Application of Musically Modulated Electromagnetic Field (TAMMEF) (n=30): The anatomical region treated is placed between opposing faces of low frequency electromagnets (3x4 cm). The current from amplifier B feeds a loud speaker that plays music. The music modifies parameters (frequency, intensity, waveform) of the electromagnetic field in time, randomly varying within respective ranges. 15 consecutive daily sessions, 30 minutes each B. Extremely Low Frequency (ELF) (n=30): Similar treatment as Intervention A except the electromagnetic field is stabilized at a frequency of 100Hz in a sinusoidal waveform. 15 consecutive daily sessions, 30 minutes each C. Simulated (Sham) Frequency Field (n=30): Functionally similar operation to the other groups except a simulated (noneffective) field is used, but the patients remain blinded to its effectiveness. 15 consecutive daily sessions, 30 minutes each	A + B + C Age: 58.9 (7.4) Female: 70% Race: NR Mean Duration of Chronicity: 11 (3.1) A vs. B vs. C Baseline Mean Lequesne Function Score (0-10)[c]: 3.65 vs. 4.28 vs. 3.48 Baseline Mean Lequesne Pain Score (0-10)[c]: 6.88 vs. 6.28 vs. 6.15	A vs. C <u>1 month</u> Mean Lequesne Functionality: 6.5 vs. 3.8 Mean Lequesne Pain Score: 1.4 vs. 6.9 B vs. C <u>1 month</u> Mean Lequesne Functionality: 7.1 vs. 3.8 Mean Lequesne Pain Score: 1.4 vs. 6.9	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Brouwer, 2006[152] 6 and 12 months Duration of pain: 6.7 vs. 4.9 years Poor	A. Brace (n=60): Device: Oasys brace, Innovation Sports, Irvine, CA, USA, brace allowed medial or lateral unloading; patients also received usual care B. Usual Care (n=57): patient education (adaptation of activities and/or weight loss), and (if needed) physical therapy and analgesic	A vs. B Age[f]: 59.2 Female: 48% vs. 51% Race: NR Baseline HSS Knee Function Score (0-100): 64.9 vs. 69.0 Baseline VAS pain severity (0-10): 6.6 vs. 5.5	A vs. B <u>6 months</u> HSS Knee Function: difference 3.2 (95% CI −0.6 to 7.0) VAS Pain Severity: difference −0.6 (95% CI −1.5 to 0.3) <u>12 months</u> HSS Knee Function: difference 3.0 (95% CI −1.1 to 7.1) VAS Pain Severity: difference −0.8 (95% CI −1.8 to 0.1)	A vs. B <u>6 months</u> EQ-5D: difference 0.01 (95% CI −0.08 to 0.10) <u>12 months</u> EQ-5D: difference 0.01 (95% CI −0.08 to 0.10)
Cakir, 2014[153] 6 months Duration of pain: Mean 4.0 to 5.1 years Fair	A. Continuous ultrasound (n=20): 5 times a week for 2 weeks B. Pulsed ultrasound (n=20): 5 times a week for 2 weeks C. Sham (n=20): 5 times a week for 2 weeks All patients performed home exercise program 3 days a week for 8 weeks	A vs. B vs. C Age: 57 vs. 58 vs. 57 years Female: 70% vs. 80% vs. 85% Baseline WOMAC physical mean function (0-68): 55.7 vs. 52.4 vs. 52.5 Baseline WOMAC pain (0-20):15.9 vs. 14.5 vs. 14.9 Baseline WOMAC stiffness (0-8): NR Baseline pain at rest VAS (0-10): 57.9 vs. 55.7 vs. 53.6 Baseline pain on movement VAS (0-10): 75.5 vs. 73.0 vs. 72.2 Baseline disease severity VAS (0-10): 73.9 vs. 67.9 vs. 68.4	A vs. C <u>6 months</u> WOMAC physical function: 32.6 vs. 35.5, difference −2.9 (95% CI −9.2 to 3.4) WOMAC pain: 9.5 vs. 11.1, difference −1.6 (95% CI −3.3 to 0.1) Pain at rest VAS: 21.4 vs. 22.3, difference 1.2 (95% CI −9.1 to 11.5) Pain on movement VAS: 38.7 vs. 38.1, difference 0.6 (95% CI −13.7 to 14.9) Disease severity VAS: 30.0 vs. 29.5, difference 0.5 (95% CI −6.7 to 7.7) B vs. C <u>6 months</u> WOMAC physical function: 37.1 vs. 35.5, difference 1.6 (95% CI −3.0 to 6.2) WOMAC pain: 11.3 vs. 11.1, difference 0.2 (95% CI −1.3 to 1.7) Pain at rest VAS: 20.2 vs. 22.3, difference −2.1 (95% CI −11.2 to 7.0) Pain on movement VAS: 37.5 vs. 38.1, difference −0.6 (95% CI −17.0 to 15.8) Disease severity VAS: 32.5 vs. 29.5, difference 3.0 (95% CI −4.0 to 10.0)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Fary, 2011[154] 6.5 months Duration of pain: 12 years Good	A. Pulsed electrical stimulation (TENS) (n=34): pulsed electrical stimulator worn 7 hours a day daily for 26 weeks B. Placebo electrical stimulation (n=36): placebo pulsed electrical stimulator worn 7 hours a day daily for 26 weeks	A vs. B Age: 71 vs. 69 years Female: 50% vs. 44% Baseline WOMAC total (0-100): 36 vs. 34 Baseline WOMAC function (0-100): 35 vs. 34 Baseline WOMAC stiffness (0-100): 45 vs. 41 Baseline WOMAC pain (0-100): 35 vs. 36 Baseline pain VAS (0-100): 51 vs. 52	A vs. B <u>6.5 months</u> Proportion of patients who achieved MCID (≥9.1) in WOMAC function: 38% vs. 39%, RR 1.2 (95% CI 0.6 to 2.2) Proportion of patients who achieved MCID (≥20) in pain VAS: 56% vs. 44%, RR 1.3 (95% CI 0.8 to 2.0) Mean change in WOMAC total: 6 vs. 7, MCD −1.3 (−8.8 to 6.3) Mean change in WOMAC function: 5 vs. 7, MCD −1.9 (95% CI −9.7 to 5.9) Mean change in WOMAC stiffness: 9 vs. 5, MCD 3.7 (95% CI −6.0 to 13.5) Mean change in WOMAC pain: 5 vs. 10, MCD −5.6 (95% CI −14.9 to 3.6) Mean change in pain VAS: 20 vs. 19, MCD 0.9 (95% CI −11.7 to 13.4)	A vs. B <u>6.5 months</u> Mean change in SF-36 physical component score (0-100): −1.0 vs. −2.6, MCD 1.7 (95% CI −1.5 to 4.8) Mean change in SF-36 mental component score (0-100): −1.2 vs. −2.4, MCD 1.2 (95% CI −2.9 to 5.4)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Fukuda, 2011[155] 12 months Duration of pain: NR Poor	A. Low-dose PSW (n=32): Three, 19 minute applications per week for3 weeks (9 total) Total Energy: 17 kJ Frequency: 27.12 MHz Mean Power Output: 14.5 W Pulse Duration: 400 microseconds Pulse Frequency: 145 Hz B. High-dose PSW (n=31): Treatment characteristics were identical to Group A except length of treatment (and received total energy) were doubled. Three, 38 min applications per week for3 weeks (9 total) Total Energy: 33 kJ C. Sham (n=23): Treatment characteristics were identical to Group A except the device was kept in standby mode without any electrical current applied. Three, 19 min applications per week for 3 weeks (9 total)	A vs. B vs. C Age: 62 vs. 63 vs. 57 Female: 100% Race: NR Baseline Knee Injury and Osteoarthritis Outcome Score Symptoms Subscale (0-100): 46.5 vs. 47.0 vs. 42.0 Baseline KOOS Daily Activities Subscale (0-100): 45.8 vs. 51.7 vs. 45.7 Baseline KOOS Recreational Activities Subscale (0-100): 16.6 vs. 15.3 vs. 18.2 Baseline KOOS Pain Subscale (0-100): 37.4 vs. 42.5 vs. 38.0 Baseline NRS Pain (0-10): 7.1 vs. 6.7 vs. 7.7	A vs. C <u>12 months</u> KOOS Symptoms Subscale: 61.6 vs. 40.7, difference 20.9 (95% 8.92 to 32.88) KOOS Daily Activities Subscale: 68.9 vs. 41.6, difference 27.30 (95% 13.73 to 40.87) KOOS Recreational Activities Subscale: 24.6 vs. 11.0, difference 13.6 (95% −0.73 to 27.93) KOOS Pain Subscale: 57.5 vs. 33.0, difference 24.5 (95% 12.12 to 36.88) NRS Pain: 5.7 vs. 7.5, difference −1.8 (95% −3.60 to 0.00) B vs. C <u>12 months</u> KOOS Symptoms Subscale: 54.9 vs. 40.7, difference 14.2 (95% 1.21 to 27.19) KOOS Daily Activities Subscale: 51.9 vs. 41.6, difference 10.30 (95% −1.24 to 21.84) KOOS Recreational Activities Subscale: 15.9 vs. 11.0, difference 4.9 (95% −5.32 to 15.12) KOOS Pain Subscale: 57.6 vs. 33.0, difference 24.6 (95% 14.59 to 34.61) NRS Pain: 5.2 vs. 7.5, difference −2.3 (95% −3.68 to −0.92)	A vs. C <u>12 months</u> KOOS Quality of Life Subscale (0-100): 31.8 vs. 33.0 <u>B vs. C</u> <u>12 months</u> KOOS Quality of Life Subscale: 41.2 vs. 33.0 A vs. B vs. C <u>Adverse Events:</u> Went on to have a Total Knee Replacement during 12 month followup: 3.1% (1/32) vs. 6.5% (2/31) vs. 4.3% (1/23)
Giombini, 2011[156] 3 months Duration of pain: 3 years Fair	A. Microwave diathermy (n=29): hyperthermic treatment 3 times a week for 4 weeks B. Sham diathermy (n=25): sham hyperthermic treatment 3 times a week for 4 weeks	A vs. B Age: 67 vs. 67 years Female: 66% vs. 68% Baseline WOMAC total (0-1.20): 103.1 vs. 101.3 Baseline WOMAC pain (0-25): 19.2 vs. 18.5 Baseline WOMAC stiffness (0-10): 9.7 vs. 9.7 Baseline WOMAC ADL (0-85): 74.3 vs. 73.1	A vs. B <u>3 months</u> Mean change in WOMAC total: −46.8 vs. −0.4, difference −46.4 (95% CI −58.3 to −34.5) Mean change in WOMAC pain; −8.6 vs. −0.6, difference −8.1 (95% CI −10.7 to −5.3) Mean change in WOMAC ADLs: −33 vs. 0.3, difference −33.2 (95% CI −42.0 to −24.6) Mean change in WOMAC stiffness: −5.2 vs. −0.1, difference −5.1, p<0.01	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Hegedus, 2009[157] 2 months Duration of pain NR Poor	A. Low-Level Laser Therapy (n=18): 50 mW, continuous wave laser (wavelength 830 nm). Total dose of 48 J/cm2 per session. Twice a week for 4 weeks. B. Placebo (n=17): Placebo probe (0.5 mW power output) used twice a week for 4 weeks.	Age: 49 Female: 81% A vs. B Baseline pain VAS (0-10): 5.8 vs. 5.6	A vs. B <u>2 months</u> Pain VAS: 1.2 vs. 4.1, difference −2.9 (no estimate of variability provided or calculable)	NR
Jia, 2016[163] 1 and 3 months Duration of pain: NR Good [New trial]	A. Focused Low-Intensity Pulsed Ultrasound + diclofenac sodium (FLIPUS) (n=53): 20 minute sessions, once daily for 10 days applied to both knees. B. Sham Ultrasound + Diclofenac Sodium (FLIPUS) (n=53)	A vs. B Age: 63 vs. 61 years Female: 73.6% vs. 69.8% Baseline LI (0-24): 7.56 vs. 7.10 Baseline VAS (0-10): 6.98 vs. 6.76	A vs. B <u>Short-term (3 months)</u> LI: 6.8 vs. 7.8, p=0.006; difference −1.1 (95% CI −1.9 to −0.3), p<0.01 VAS pain: 6.4 vs. 7.2, p=0.007	NR
Laufer, 2005[158] 3 months Duration of pain: NR Poor	A. Low Intensity Pulsed Shortwave Diathermy (n=38): Three, 20 min sessions per week for 3 weeks (9 total); Pulse Duration: 82 µs; Pulse Frequency: 110 Hz; Peak Power: 200 W (mean 1.8W) B. High Intensity Pulsed Shortwave Diathermy (n=32): Treatment protocol identical to Group A except with a higher intensity (pulse duration and frequency) Pulse Duration: 300 µs Pulse Frequency: 300 Hz Peak Power: 200 W (mean 18W) C. Sham Shortwave Diathermy (n=33): Identical treatment except the apparatus was turned on but the power output was not raised.	A vs. B vs. C Age: 75 vs. 73 vs. 73 Female: 82% vs. 91% vs. 67% Baseline WOMAC Overall: 5.1 vs. 4.6 vs. 5.0 Baseline WOMAC Stiffness: 4.9 vs. 4.3 vs. 4.92 Baseline WOMAC Activities of Daily Living: 5.2 vs. 4.7 vs. 5.1 Baseline WOMAC Pain: 4.9 vs. 4.4 vs. 5.0	A vs. C <u>3 months</u> WOMAC Overall: 4.8 vs. 4.6, difference 0.2 (95% CI −1.5 to 2.0) WOMAC Pain: 4.5 vs. 4.3, difference 0.2 (95% CI −1.6 to 1.9) WOMAC Stiffness: 4.4 vs. 3.6, difference 0.8 (95% CI −1.0 to 2.6) WOMAC Activities of Daily Living: 5.0 vs. 4.8, difference 0.2 (95% CI −1.5 to 1.8) B vs. C <u>3 months</u> WOMAC Overall: 4.6 vs. 4.6, difference −0.04 (95% CI −1.8 to 1.7) WOMAC Pain: 4.1 vs. 4.3, difference −0.2 (95% CI −2.0 to 1.5) WOMAC Stiffness: 3.8 vs. 3.6, difference 0.2 (95% CI −1.6 to 2.0) WOMAC Activities of Daily Living: 4.8 vs. 4.8, difference −0.02 (95% CI −1.7 to 1.6)	A vs. B vs. C <u>Adverse Events:</u> No adverse reactions to the treatment were reported by the subjects.

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Mazzuca, 2004[159] 1 month Duration of pain: NR Fair	A. Superficial Heat (sleeve) (n=25): Cotton and lycra sleeve with a heat retaining polyester and aluminum substrate, minimum 12 hours/day; continue usual pain medication(s). B. Placebo Sleeve (n=24) Placebo sleeves did not contain the heat retaining substrate layer.	A + B Age: 62.7 Female: 77% Race: 67% white Baseline WOMAC Function (17-85)[e]: 51.8 (11.8) Baseline WOMAC Stiffness (2−10)[e]: 6.5 (1.4) Baseline WOMAC Pain (5-25)[d]: 15.2 vs. 14.7*	A vs. B <u>1 month</u> WOMAC Pain: 13.7 vs. 13.9	NR
Tascioglu, 2004[160] 6 months Duration of pain: 7 years Poor	A. Active laser 3 joule (n=20) continuous laser therapy (50 mW, 830 mm wavelength) applied to 5 painful points 5 days a week for 2 weeks B. Active laser 1.5 joule (n=20): continuous laser therapy (50 mW, 830 mm wavelength) applied to 5 painful points 5 days a week for 2 weeks C. Placebo laser (n=20): sham laser therapy applied to 5 painful points 5 days a week for 2 weeks	A vs. B vs. C Age: 63 vs. 60 vs. 64 years Female: 70% vs. 75% vs. 65% Baseline WOMAC function (0-68):36.6 vs. 38.0 vs. 39.5 Baseline WOMAC stiffness (0-8): 4.1 vs. 4.6 vs. 4.5 Baseline WOMAC pain (0-20): 10.3 vs. 11.6 vs. 9.6 Baseline pain at rest VAS (0-100): 39.1 vs. 41.6 vs. 37.9 Baseline pain at activation VAS (0-100): 68.0 vs. 65.7 vs. 63.9	A vs. C <u>6 months</u> WOMAC function: 34.8 vs. 38.7, difference −3.8 (95% CI −9.8 to 2.1) WOMAC stiffness: 3.9 vs. 4.2, difference −0.3 (95% CI −1.6 to 0.9) WOMAC pain: 10.4 vs. 9.9, difference 0.6 (95% CI −1.5 to 2.7) Pain at rest VAS: 38.7 vs. 38.9, difference −0.3 (95% CI −9.8 to 9.3) Pain at activation VAS: 66.8 vs. 62.0, difference 4.8 (95% CI −4.9 to 14.5) B vs. C <u>6 months</u> WOMAC function: 38.5 vs. 38.7 WOMAC stiffness: 4.5 vs. 4.2 WOMAC pain: 11.3 vs. 9.9 Pain at rest VAS: 40.0 vs. 38.9 Pain at activation VAS: 61.8 vs. 62.0	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Thamsborg, 2005[161] 1.5 month Duration of pain: 8 years Fair	A. Pulsed Electromagnetic Fields (n=42): ±50V in 50Hz pulses changing voltage in 3 ms intervals; 2-hour sessions, daily, 5 days per week for 6 weeks (30 total) B. Sham Electromagnetic Field (n=41): noneffective placebo electromagnetic field; 2 hour sessions, daily, 5 days per week for 6 weeks (30 total)	A vs. B Age: 60 vs. 60 Female: 47.6% vs. 61% Race: NR Baseline WOMAC Activities of Daily Living (0-85): 43.83 vs. 46.49 Baseline WOMAC Stiffness (0-10): 5.74 vs. 5.85 Baseline WOMAC Joint Pain (0-25): 13.15 vs. 14.49	A vs. B <u>1.5 months</u> WOMAC Activities of Daily Living: 37.9 vs. 41.3, difference −3.5 (95% CI −4.4 to −2.5) WOMAC Stiffness: 4.8 vs. 5.2, difference −0.3 (95% CI −0.5 to −0.2) WOMAC Joint Pain: 11.4 vs. 12.2, difference −0.8 (95% CI −1.1 to −0.6)	A vs. B <u>Adverse Events:</u> throbbing sensation, warming sensations or aggravation of pain 28.5% (12/42) vs. 14.6% (6/41)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Yegin, 2017[164] 1 month Duration of pain: NR Poor [New trial]	A. Continuous Ultrasound (n=30): 8 minutes to each knee (16 minutes total), 5 days a week for 2 weeks (10 sessions total) B. Sham Ultrasound (n=32): Identical protocol but with device in off mode, and out of view of patient All patients: use of analgesics was avoided during treatment until end of first month following completed treatment.	No population details provided Baseline WOMAC-ADL (0-170): 27.3 vs. 27.7 Baseline WOMAC-Stiffness (0-20): 3 vs. 3.5 LI-ADL (0-24): 4.5 vs. 5 Baseline VAS-Mobility (0-10): 5 vs. 5.5 Baseline VAS-At Rest (0-10):1.6 vs. 2.5 Baseline LI-Pain 0-10): 5 vs. 4.5 WOMAC-Pain (0-50): 8.5 vs. 9.3	A vs. B <u>Short Term (1 month)</u> Mean WOMAC-ADL: 18.0 vs. 21.2; mean Δ −9.3 vs. −6.5, p=0.414 Median WOMAC-Stiffness: 1.0 vs. 1.5; median Δ −1.0 vs. 1.0, p=0.614 Median LI-ADL: 3.8 vs. 4.5; median Δ −1.0 vs. −0.5, p=0.490 Median VAS-Mobility: 3.5 vs. 3.0; median Δ −1.0 vs. −2.0, p=0.680 Median VAS-At Rest: 0.1 vs. 0.3; median Δ 0.0 vs. 0.0, p=0.513 Median LI-Pain: 3.0 vs. 3.0; median Δ −1.5 vs. −0.5, p=0.153 Mean WOMAC-Pain: 5.6 vs. 6.6; mean Δ −2.9 vs. −2.6, p=0.77	A vs. B <u>Short Term (1 month)</u> SF-36 PCS (0-100): 43.0 vs. 40.0; mean Δ 7.9 vs. 6.1, p=0.466 SF-36 MCS (0-100): 45.2 vs. 46.7; mean Δ −0.3 vs. −0.1, p=0.949 SF-36 Pain: 44.3 vs. 41.4; mean Δ 8.3 vs. 5.4, p=0.247 SF-36 Emotional Role: 55.3 vs. 55.3; median Δ 0.0 vs. 0.0, p=0.790 SF-36 Energy-Vitality: 43.2 vs. 44.8; mean Δ 0.6 vs. 0.7, p=0.943 SF-36 Physical Function: 44.6 vs. 44.6; median Δ 5.3 vs. 2.1, p=0.383 SF-36 Physical Role: 56.2 vs. 56.2; median Δ 0.0 vs. 0.0, p=0.597 SF-36 General Health: 40.6 vs. 40.6; median Δ 0.0 vs. 0.0, p=0.556 SF-36 Mental Health: 44.75 vs. 40.25; median Δ 4.6 vs. 0.0, p=0.072 SF-36 Social Function: 54.4 vs. 57.1; median Δ 0.0 vs. 0.0, p=0.785

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Yildiz, 2015[162] 2 months Duration of pain: Mean 2.8 to 5.1 years Fair	A. Continuous ultrasound (n=30): 5 times a week for 2 weeks B. Pulsed ultrasound (n=30): 5 times a week for 2 weeks C. Sham (n=30): 5 times a week for 2 weeks All patients performed home exercise program 3 days a week for 8 weeks	A vs. B vs. C Age: 56 vs. 55 vs. 58 years Female: 83% vs. 80% vs. 87% Baseline Lequesne Index score (0-24): 13.2 vs. 12.9 vs. 12.4 Baseline pain at rest VAS (0-10): NR Baseline pain on movement VAS (0-10): 9.0 vs. 8.6 vs. 8.9	A vs. C <u>2 months</u> Lequesne Index: 5.5 vs. 11.7, difference −6.2 (95% CI −8.4 to 4.2) Pain at rest VAS: NR Pain on movement VAS: 3.9 vs. 7.2, difference −3.3 (95% CI −4.6 to −2.0) B vs. C <u>2 months</u> Lequesne Index: 6.0 vs. 11.7, difference −5.7 (95% CI −7.7 to −3.7) Pain at rest VAS: NR Pain on movement VAS: 3.8 vs. 7.2, difference −3.4 (95% CI −4.7 to −2.0)	NR

ADL = activity of daily living; CI = confidence interval; EQ-5D = EuroQol Quality of Life Instrument 5-D; HSS = Hospital for Special Surgery; Hz = hertz; J/cm^2 – Joules per square centimeter; kJ = kilojoules; KOOS = Knee Injury and Osteoarthritis Outcome Score; LI = Lequesne Index; MCID = minimal clinically important difference; MHz = Mega Hertz; mW = mega Watts; nm = nanometer; NR = not reported; NRS = numeric rating scale; PSW = pulsed short wave; RR = risk ratio; SKFS = Saudi Knee Function Score; SF-36 MCS = Short Form 36 Questionnaire Mental Component Score; TENS = transcutaneous electrical nerve stimulation; VAS = visual analog scale; W = watts; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; μs = microsecond

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Values estimated from graph

[c] The study separated outcome values out into slight, moderate and severe disease patient groups for each treatment arm. These values are combined values for each intervention groups estimated from graphs in the study.

[d] Values estimated from graph

[e] Separate group baseline values not given for stiffness and function subscales

[f] Age only reported for population as a whole

Four RCTs (2 new trials; 1 good-quality, 2 fair-quality, and 1 poor-quality) that evaluated ultrasound for knee OA met the inclusion criteria.[153,162-164] All trials required at least grade 2 radiographic knee OA using the Kellgren–Lawrence criteria for inclusion. One (new) trial evaluated continuous ultrasound,[164] one (new) evaluated pulsed ultrasound[163] and two trials had both a continuous and a pulsed ultrasound group.[153,162] In three trials, the ultrasound groups received 1 MHz treatments five times per week for 2 weeks at an intensity of either 1 or 1.5 W/cm^2 and the sham comparators received the same protocol, but the power was switched off.[153,162,164] The forth trial applied daily pulsed ultrasound for 10 days at 0.6 MHz with an average intensity of 120 mW/cm2 and duty cycle of 20% plus participants took diclofenac sodium tablets; the comparator group received sham ultrasound (no power output) plus the diclofenac sodium tablets.[163] Compliance with the intervention protocols were not reported. Three trials reported short-term outcomes,[162-164] the other intermediate-term outcomes. The methodological shortcomings were unclear blinding of the provider or assessor,[153,163,164] unclear randomization procedures and concealment of treatment allocation[164] and unclear adherence to an intention-to-treat analysis.[162]

We found one good-quality (n=70) trial that compared active TENS with sham TENS for knee OA.[154] Inclusion criteria required a confirmed diagnosis of knee OA using the American College of Rheumatology criteria. The TENS protocol had patients wear a pulsed TENS device 7 hours daily for 26 weeks. The sham TENS groups followed the same protocol as the active

treatment, but the device turned off after 3 minutes. Compliance was unacceptable for time the TENS device was worn.

We identified three small trials (n=30, 49, and 60) that investigated low-level laser therapy versus sham laser for knee OA.[150,157,160] The mean age ranged from 49 to 64 years and most patients were female (62% to 75%). Two studies included patients meeting the American College of Rheumatology criteria for knee OA.[150,160] Two trials also required an average pain intensity of greater than 3 or 4 on a 0-10 VAS,[150] while the other trial had an additional inclusion criteria of radiographic knee OA of Kellgren–Lawrence grade of 2 or 3.[160] Treatment duration ranged from 2 to 4 weeks and the number of total sessions from 8 to 10. Low-level laser therapy protocols differed across the trials with doses ranging from 1.2 to 6 Joules per point (range, 5 to 6 points) and length of irradiation from 40 seconds to 2 minutes; all trials used a continuous laser beam. The sham laser comparison groups followed the same respective protocols, but the device was inactive. One trial was rated fair quality[150] and two poor quality.[157,160] In the fair-quality trial, blinding of the care provider was unclear. The two poor-quality trials suffered from insufficient descriptions of allocation concealment methods, unclear application of intention to treat, lack of clarity regarding patient blinding, and no reporting of or unacceptable attrition.

One small (n=63), fair-quality trial compared microwave diathermy (three 30-minute sessions per week for 4 weeks) to sham.[156] The inclusion criteria required radiographic knee OA of a Kellgren and Lawrence grade 2 or 3. The power was set to 50 watts. Sham diathermy followed the same protocol, but the machine was set to off. Compliance with the treatment regimen for each group was unclear. Methodological limitations of this study included no blinding of the care providers.

Two trials (n=86 and 115) examined pulsed short-wave diathermy compared to sham diathermy.[155,158] The mean age ranged from 62 to 75 years, and the proportion of female participants ranged from 67 to 100 percent. Both trials included patients meeting radiographic criteria for knee OA. Each trial compared two doses of short-wave diathermy to a sham diathermy group; dosages varied by intensity in one trial (mean power output of either 1.8 or 18 Watts for 20 minutes)[158] or by length of session (19 or 38 minutes at 14.5 Watts) in the other.[155] Both trials applied diathermy three times per week for 3 weeks (total of 9 sessions). Each sham diathermy group followed the same treatment protocol, but the electrical current was not applied. Compliance with the treatment regimens was acceptable for both trials. Both trials were rated poor quality due to unclear concealment of treatment allocation, a lack of care provider blinding, and unacceptable attrition.

Two trials (n=90 for both) compared the application of electromagnetic fields to sham interventions for knee OA.[151,161] The mean age of participants was 59 and 60 years, and the proportion of female participants ranged from 48 to 70 percent. The mean duration of chronicity ranged from 9 to 11 years. The good-quality trial enrolled participants meeting the American College of Rheumatology criteria for knee OA.[161] The inclusion criteria was not clearly presented in the poor-quality trial.[151] The intervention group in the good-quality study received 2 hours of pulsed electromagnetic fields 5 days a week for 6 weeks.[161] The poor-quality trial had a musically modulated electromagnetic field group that received 15 daily 30-minute sessions. Music from a connected speaker modulated the parameters of the electromagnetic field. The study also had an extremely low frequency electromagnetic field group that had 15 daily 30 minutes sessions, but the electromagnetic field was set at a frequency of 100 Hz.[151] The sham group in each trial followed the same respective treatment protocol, but used a noneffective electromagnetic field during the sessions. Compliance to the treatment sessions was acceptable

in both trials. One trial was rated fair quality[161] and the other was rated poor quality.[151] Methodological limitations in both trials included unclear methods for allocation concealment. Additionally, in the poor-quality trial, there were baseline dissimilarities between groups, no blinding of patients, providers, or outcome assessors, and attrition was not reported.[151]

A single trial compared superficial heat with placebo (n=52).[159] Participants were included if they had grade 2 or higher using the Kellgren-Lawrence grading for radiographic knee OA. Superficial heat was provided using a knee sleeve with a heat retaining polyester and aluminum substrate. Participants were instructed to wear the sleeve at least 12 hours per day. The placebo sleeves were identical and participants received the same instructions, but the sleeve did not contain the heat retaining substrate; the extent to which patients could be truly blinded is unclear (sleeve may retain body heat and feel warmer). Compliance with wearing the sleeve was acceptable. This trial was rated fair quality due to unclear concealment of treatment allocation, and a lack of clarity regarding whether it was the provider or outcomes assessor that was blinded.

We identified one trial comparing use of a knee brace to usual care (n=118).[152] Inclusion criteria required unicompartmental knee OA, and either a varus or valgus malalignment. Patients in the intervention group were fitted with a commercially available knee brace that allowed medial unloading or lateral unloading. Usual care consisted of patient education and physical therapy and analgesics as needed. Compliance with continued use of the brace was unacceptable. This trial was rated poor quality due to lack of patient, provider, or assessor blinding, and unacceptable attrition.

Physical Modalities Compared With Sham or Usual Care

Ultrasound. Three trials (2 new; one good, one fair, one poor quality) reported function using Lequesne Index and pain (during activity) using VAS over the short term.[162-164] There were no statistically significant differences between real ultrasound versus sham ultrasound in either function (3 trials, pooled difference −2.50 on a 0-24 scale, 95% CI −6.37 to 1.22, I^2=94.0%) (Figure 37) or pain intensity (3 trials, pooled difference −1.2 on a 0-10 scale, 95% CI −3.7 to 1.3, I^2=91.1%) (Figure 38) using a PL estimate likely due to heterogeneity between studies. Exclusion of the poor quality study[164] resulted slighter larger, but still nonstatistically significant, effects for function (2 trials, SMD −3.4, 95% CI −9.5 to 2.4, plot not shown) and pain (2 trials, pooled difference −1.9, 95% CI −5.1 to 1.1, plot not shown). Stratification by type of ultrasound (continuous vs. pulsed) resulted in similar conclusions regarding function and pain.

Intermediate-term results at 6 months from one fair-quality trial showed no difference on the WOMAC Physical Function subscale (0 to 100) between either the continuous or pulsed ultrasound group versus sham ultrasound (difference −4.5, 95% CI −10.34 to 1.34, and −2.9, 95% CI −9.19 to 3.39, respectively).[153] Results for pain intensity were not consistent with regard to ultrasound method. The continuous ultrasound group had a small improvement in pain on the WOMAC pain scale compared with sham (difference −1.8, 95% CI −3.34 to −0.26), but no statistical difference was seen between pulsed ultrasound and sham (difference −1.6, 95% CI −3.26 to 0.06). There was no difference between either ultrasound group versus sham ultrasound for VAS pain during rest or on movement (Table 26).

Regarding quality of life, one new trial reported no differences in the short term between the continuous and sham ultrasound groups for change from baseline on the SF-36 PCS (mean change 7.9 vs. 6.1 on a 0-100 scale, p=0.47) and the SF-36 MCS (mean change −0.3 vs. −0.1 on a 0-100 scale, p=0.95).[164]

Transcutaneous Electrical Nerve Stimulation. No effect was seen for TENS versus placebo TENS for function or pain over the intermediate term for any outcome measured in one good-quality trial.[154] Function was measured via the WOMAC-function subscale (0 to 100); the proportion of patients who achieved a MCID ≥9.1 was 38 percent versus 39 percent (RR 1.2, 95% CI 0.6 to 2.2) and the difference in mean change scores was −1.9 (95% CI −9.7 to 5.9). Pain was measured using a VAS pain scale (difference 0.9 on a scale of 0 to 10, 95% CI –11.7 to 13.4) and the WOMAC pain subscale (difference −5.6 on a 0 to 100 scale, 95% CI –14.9 to 3.6). The proportion of patients who achieved MCID (≥20) in pain VAS was 56 percent versus 44 percent (RR 1.3, 95% CI 0.8 to 2.0). Health-related quality of life measured with the SF-36 was not different between the two groups for the physical component and mental component score (Table 26).

Low-Level Laser Therapy. One fair-quality trial reported no difference between low-level laser therapy and sham for short-term function based on median Saudi Knee Function Scale scores (range 0-112 with higher scores indicating greater severity), median difference −10 (interquartile range of −23 to −4), p=0.054.[150] There were inconclusive results for intermediate-term function. One fair-quality trial reported the low-level laser therapy group had less functional severity at 6 months compared to sham on the Saudi Knee Function Scale (median difference −21.0, 95% CI −34.0 to −7.0), p=0.006.[150] For the other poor-quality trial, neither the higher dose nor the lower dose low-level laser therapy group differed from sham on the WOMAC physical function (0 to 96) subscale (difference −3.82, 95% CI −9.75 to 2.11 and −0.14, 95% CI −6.59 to 6.31, respectively).[160] However, the evidence was considered insufficient for function.

Low-level laser therapy was associated with moderately less pain over the short term in one fair-quality and one poor-quality trial (pooled difference −2.00, 95% CI −4.15 to 0.04) (Figure 39).[150,157] There was no difference between low-level laser therapy versus sham for intermediate-term pain (pooled difference −1.04, 95% CI −3.17 to 1.45).[150,160] However, the evidence was considered insufficient for pain.

Microwave Diathermy. Data were insufficient from one small, fair-quality trial evaluating microwave diathermy.[156] The microwave diathermy group showed substantial short-term improvement compared with sham for function (difference −33.2 on a 0-85 scale, 95% CI −42.0 to −24.6, WOMAC ADL subscale) and pain (difference −8.1 on a 0-25 scale, 95% CI −10.7 to −5.3, WOMAC pain subscale). Substantial imprecision was noted.

Pulsed Short-Wave Diathermy. Data were insufficient for pulsed short-wave diathermy compared with sham. There was no difference in short-term function or pain for either the low intensity or high intensity group compared to sham diathermy based on the WOMAC in one poor-quality trial.[156] There was no difference on the WOMAC function subscale (0 to 10) between either the low intensity group versus sham (difference 0.16, 95% CI −1.51 to 1.83), or the high intensity group versus sham (difference −0.02, 95% CI −1.67 to 1.63). There was also no difference on the WOMAC pain subscale (0 to 10) for either the low or high intensity group versus sham (difference 0.15, 95% CI −1.57 to 1.87 and −0.24, 95% CI −2.02 to 1.54, respectively).

The other trial found inconsistent results among the high and low dose groups for long-term function using the KOOS (0 to 100).[155] The low dose group had substantially greater improvement on the KOOS-Daily Activities subscale compared to sham (difference 27.30, 95% CI 13.73 to 40.87), but there was no difference between the high dose group and sham on the

KOOS-Daily Activities subscale (difference 10.30, 95% CI −1.24 to 21.84). Neither the low or high dose group differed from sham on the KOOS-recreational activities subscale (Table 26). Regarding pain intensity, the low dose group had moderately better pain NRS (0 to 10) that was not statistically significant (difference −1.8, 95% CI −3.60 to 0.00). The high dose group experienced substantially greater pain reduction than the sham group (difference −2.3, 95% CI −3.68 to −0.92).

Electromagnetic Fields. The fair-quality trial found use of pulsed electromagnetic fields did not appear to provide clinically meaningful short-term improvements in function or pain compared with sham, although statistical significance was achieved. The pulsed electromagnetic field group had better function on the WOMAC ADL subscale (0 to 85) compared with the sham group, (difference −3.48, 95% CI −4.44 to −2.51), and it had lower scores on the WOMAC pain subscale (0 to 25) versus sham (difference −0.84, 95% CI −1.10 to −0.58).[161] Based on estimated values from a graph for the poor-quality trial,[151] each group using electromagnetic fields had better function and substantially less pain in the short term on the Lequesne Index. The musically modulated electromagnetic field group had moderately better Lequesne Function scores (0-10) versus sham (mean of 6.5 vs. 3.8) and substantially lower Lequesne Pain scores (0 to 10) (mean of 1.4 vs. 6.9). The low frequency electromagnetic field group had similar benefits for function (mean of 7.1 vs. 3.83) and pain (mean of 1.4 vs. 6.85, standard deviation and statistical testing not reported), compared with sham.

Superficial Heat. Evidence from one small fair-quality trial was insufficient to determine the effects of superficial heat on short-term pain. WOMAC pain subscale scores were similar between the heat and placebo group at 1 month post-treatment (13.7 versus 13.9, respectively).[159]

Brace. Evidence from one small poor-quality trial was insufficient to determine the effects of brace treatment. There was no difference between bracing and usual care for intermediate-term or long-term function, pain, and quality of life outcomes.[152] Function was measured using the Hospital for Special Surgery (HSS) score (difference 3.2, 95% CI −0.58 to 6.98 for intermediate-term function and difference 3.0, 95% CI −1.05 to 7.05 for long-term function). Pain intensity was assessed using a VAS. The difference was −0.58 (95% CI −1.48 to 0.32) for intermediate-term pain and −0.81 (95% CI −1.76 to 0.14) for long-term pain. Health-related quality of life was measured using the Euro-Qol 5-Dimensions (EQ-5D) (difference 0.01, 95% CI −0.08 to 0.10 for both intermediate-term and long-term health-related quality of life).

Physical Modalities Compared With Pharmacological Therapy or With Exercise Therapy

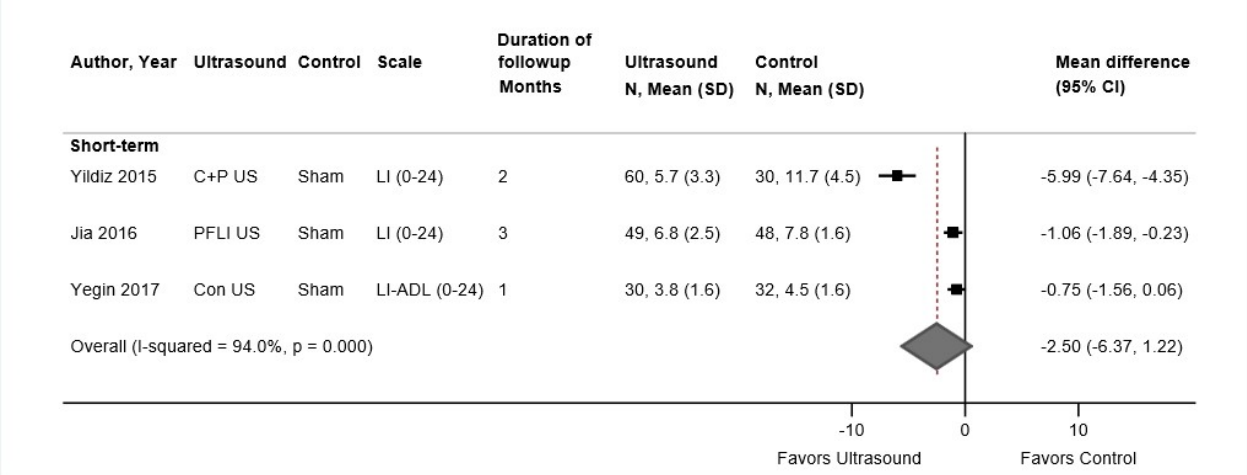
No trial of physical modalities versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

In general, harms were poorly reported across the physical modality trials. Six trials (2 of low-level laser therapy,[150,160] 2 of ultrasound therapy,[153,162] 1 of pulsed short-wave diathermy,[158] and 1 of superficial heat[159]) reported that no adverse events or side effects occurred in either group. The good-quality trial that evaluated TENS found no difference between active and sham TENS in the risk of localized, mild rashes (18% vs.17%; RR 1.06, 95% CI 0.38 to 2.97).[154] One

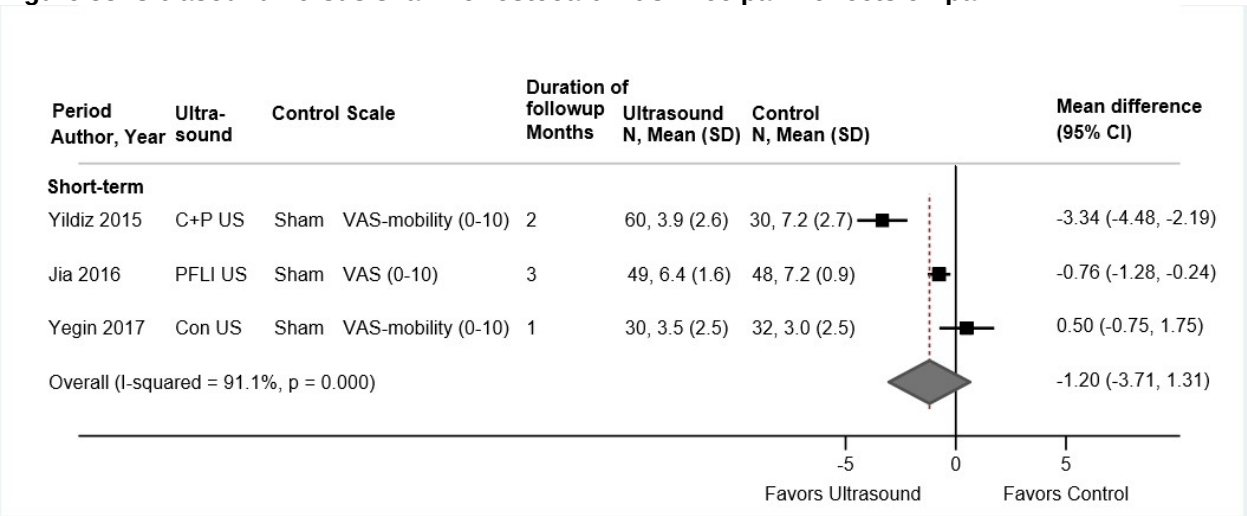
trial of microwave diathermy reported two cases of symptom aggravation in the intervention group; the events were transient and neither patient withdrew from the trial.[156] More patients who received real versus sham electromagnetic field therapy reported throbbing or warming sensations or aggravation of pain (29% versus 7%); however, the difference was not significant (RR 1.95, 95% CI 0.81 to 4.71) in one fair-quality trial.[161]

Figure 37. Ultrasound versus sham for osteoarthritis knee pain: effects on function



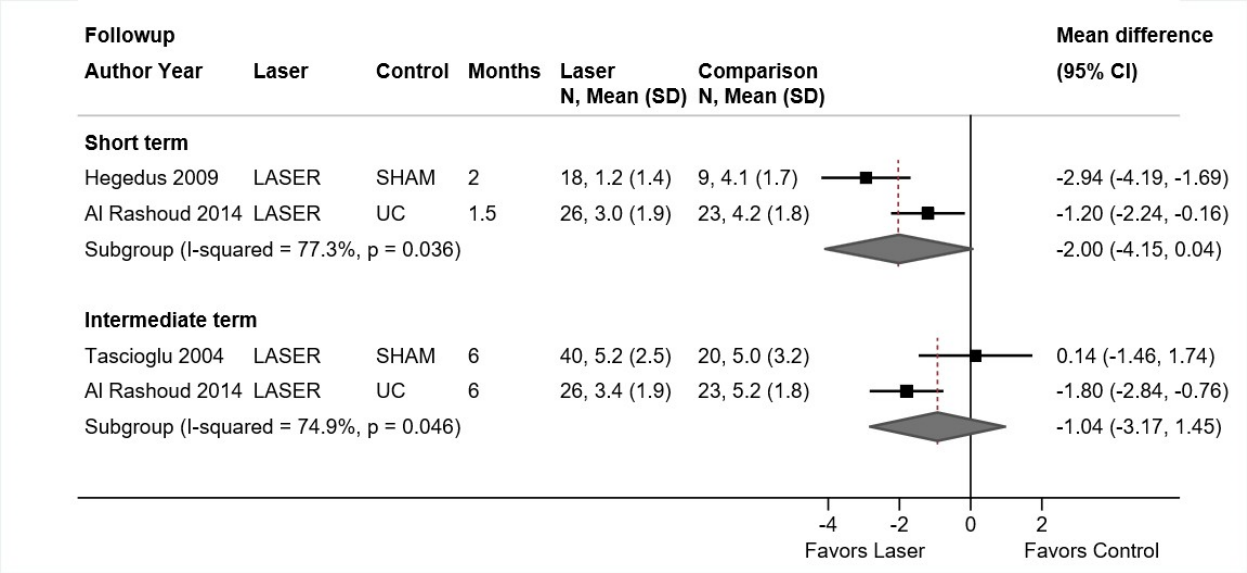
ADL = activities of daily living; CI = confidence interval; Con US = continuous ultrasound; C+P US = continuous and pulsed ultrasound combined; LI = Lequense Index; N = number; PFLI US = pulsed frequency low intensity ultrasound; SD = standard deviation.

Figure 38. Ultrasound versus sham for osteoarthritis knee pain: effects on pain



ADL = activities of daily living; CI = confidence interval; Con US = continuous ultrasound; C+P US = continuous and pulsed ultrasound combined; N = number; PFLI US = pulsed frequency low intensity ultrasound; SD = standard deviation; VAS = visual analog scale.

Figure 39. Low-level laser therapy versus usual care or sham for osteoarthritis knee pain: effects on pain



CI = confidence interval; SD = standard deviation; UC = usual care

Manual Therapies for Osteoarthritis Knee Pain

Key Points

- There was insufficient evidence from one trial to determine the effects of joint manipulation on intermediate-term function or harms versus usual care or versus exercise due to inadequate data to determine effect sizes or statistical significance (SOE: insufficient).
- There was insufficient evidence from one trial to determine the effects of massage versus usual care on short-term function, pain, or harms, or to evaluate the effect of varying dosages of massage on outcomes (SOE: insufficient).

Detailed Synthesis

Two trials were identified that met inclusion criteria and evaluated manual therapies for the treatment of knee OA,[47,184] (Table 28 and Appendixes D and E). Both trials were included in the prior AHRQ report. Patients in both trials were required to have radiographically established knee OA meeting the American College of Rheumatology criteria.

Table 44. Osteoarthritis knee pain: manual therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Abbott, 2013[47] 9.75 months Duration of diagnosis: 2.6 years Fair	A. Manual therapy (n=54/30 knee OA): 7 sessions in 9 weeks with 2 additional booster sessions B. Exercise (n=51/29 knee OA): 7 exercise sessions in 9 weeks with 2 additional booster sessions C. Usual care (n=51/28 knee OA)	A vs. B vs. C (total population, includes hip OA) Age: 67 vs. 67 vs. 66 years Female: 49% vs. 52% vs. 58% Percent knee OA: 56% vs. 57% vs. 55% Percent hip OA: 44% vs. 43% vs. 45% Percent both hip OA and knee OA: 22% vs. 20% vs. 26% Baseline WOMAC (0-240): 114.8 vs. 95.5 vs. 93.8	A vs. C (knee OA only) 9.75 months WOMAC mean change from baseline: −31.5 vs. 1.6, p=NR A vs. B 9.75 months WOMAC mean change from baseline: −31.5 vs. −12.7, p=NR	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Perlman, 2012[184] 4 months Duration of pain: NR Fair	A1. Massage Therapy Group 1 (MT) (n=25): standard Swedish massage strokes, and specified time allocated to various body regions (therapists agreed not to deviate from protocol); one, 30-minute session per week for 8 weeks (8 total sessions) A2. MT Group 2 (n=25): Identical to group A1 except differing 'dosage' of massage; two, 30-min sessions per week for 4 weeks, then once weekly for 4 weeks (12 total sessions) A3. MT Group 3 (n=25): Identical to group A1 except differing 'dosage' of massage; one, 60-min per week for 8 weeks (8 total sessions) A4. MT Group 4 (n=25): Identical to group A1 except differing 'dosage' of massage; two, 60-min sessions per week for 4 weeks, then once weekly for 4 weeks (12 total sessions) B. Usual Care (n=25): Continued current treatment without the addition of massage therapy.	A1 vs. A2 vs. A3 vs. A4 vs. B Age: 70 vs. 62 vs. 63 vs. 64 vs. 64 Female: 60% vs. 72% vs. 76% vs. 68% vs. 76% Race: 92% vs. 88% vs. 76% vs. 80% vs. 88% white Baseline WOMAC Total (0-100): 52.9 vs. 50.2 vs. 53.6 vs. 48.0 vs. 53.2 Baseline WOMAC Physical Function (0-100): 52.9 vs. 49.5 vs. 49.8 vs. 48.3 vs. 50.5 Baseline WOMAC Pain (0-100): 52.3 vs. 42.4 vs. 52.5 vs. 44.4 vs. 46.3 Baseline VAS Pain (0-100): 61.2 vs. 64.0 vs. 66.4 vs. 59.2 vs. 57.6	A1 vs. A2 vs. A3 vs. A4 vs. B <u>4 months:</u> WOMAC Total, mean change from baseline (95% CI): −14.3 (−22.9 to −5.7) vs. −7.0 (−15.6 to 1.6) vs. −14.2 (−23.4 to −5.0) vs. −15.1 (−25.1 to −5.1) vs. −6.0 (−12.6 to 0.5) WOMAC Physical Function, mean change from baseline (95% CI): −15.3 (−24.5 to 26.1) vs. −7.4 (−14.8 to 0) vs. −12.1 (−22.0 to −2.1) vs. −14.4 (−23.4 to −5.4) vs. −4.2 (−11.1 to 2.7) WOMAC Pain, mean change from baseline (95% CI): −12.2 (−22.4 to −2.0) vs. −3.9 (−12.7 to 4.9) vs. −13.7 (−23.4 to −4.0) vs. −14.2 (−24.5 to −3.8) vs. −7.5 (−16.0 to 1.1) VAS Pain, mean change from baseline (95% CI): −14.4 (−25.9, −2.8) vs. −14.0 (−24.7 to −3.3) vs. −18.5 (−29.0 to −8.1) vs. −22.8 (−35.5 to −10.1) vs. −11.5 (−21.0 to −2.0)	A1 vs. A2 vs. A3 vs. A4 vs. B <u>4 months:</u> WOMAC Stiffness (0-100), mean change from baseline (95% CI): −15.4 (−26.4 to −4.5) vs. −9.6 (−20.6 to 1.3) vs. −16.9 (−28.5 to −5.2) vs. −16.8 (−29.7 to −3.9) vs. −6.4 (−13.2 to 0.4)

CI = confidence interval; NR = not reported; OA = osteoarthritis; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Arthritis Index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

One fair-quality trial (N=117 with knee OA) compared manual therapy with usual care (continued routine care from general practitioner and other providers) and with combination exercise.[47] The manual therapy intervention consisted of nine 50-minute sessions. Seven were delivered in the first 9 weeks and two booster sessions at week 16. All participants were prescribed a home exercise program three times per week. Compliance with the intervention was acceptable in all groups, and the methodological shortcoming of this trial was a lack of blinding for the patients and care providers. Only intermediate-term outcomes were reported.

One fair-quality trial (N=125) compared four different dosages of massage therapy with usual care (continued current treatment).[184] The massage protocol consisted of standard Swedish massage strokes applied in each intervention group over 8 weeks. The dosage varied from 240 to 720 minutes based on the frequency (once or twice per week) and duration of massage (30-60 minutes per session). Compliance was acceptable in all groups, and the methodological shortcoming of this trial was a lack of blinding for the patients and care providers in the usual care arm. Only short-term outcomes were reported.

Manual Therapies Compared With Usual Care

Manual Therapy. Data were insufficient from one fair-quality trial (n=58 with knee OA)[47] to evaluate effects of joint manipulation versus usual care over the intermediate term. Although the manual therapy group showed a statistically significant improvement from baseline in function as measured by the WOMAC (mean change −31.5 on a 0-240 scale, 95% CI −52.7 to −10.3), whereas the usual care group showed no improvement (mean change 1.6, 95% CI −10.5 to 13.7), insufficient data was provided to calculate an effect estimate (number of patients with knee OA in each group were not provided). Pain outcomes were not reported.

Massage. Data were insufficient from one fair-quality trial (n=125) to evaluate the short-term effects of massage therapy (4 different dosages) compared with usual care.[184] Function was measured using the WOMAC total and physical function subscale scores (both 0 to 100 scales) and pain was measured using the WOMAC pain subscale and the VAS (both 0 to 10). No significant effects were seen in any outcome measure at 4 months postmassage treatment versus usual care (Table 27). Authors reported a trend for greater magnitude of change in function and pain with higher massage dosages versus lower massage dosages and versus usual care (statistical tests not provided).

Manual Therapies Compared With Pharmacological Therapy

No trial of manual therapy versus pharmacological therapy met inclusion criteria.

Manual Therapies Compared With Exercise Therapy

The trial evaluating manual therapy also included an exercise group that received aerobic warm-up, muscle strengthening, muscle stretching, and neuromuscular control exercises (n=59 with knee OA).[47] Both groups showed improvement from baseline in function (WOMAC) over the intermediate term, but the change was statistically significant in the manual therapy group only (mean change of −31.5, 95% CI −52.7 to −10.3 versus −12.7, 95% CI −27.1 to 1.7) for exercise. However, insufficient data was provided to calculate an effect estimate (number of patients with knee OA in each group were not provided). Pain outcomes were not reported.

Harms

No serious treatment-related adverse events occurred in either trial[47,184]; one nontrial-related death was reported in the usual care group in the trial evaluating manual therapy.[47]

Mind-Body Therapies for Osteoarthritis Knee Pain

Key Points

- Data were insufficient from two small, unblinded trials to determine the effects or harms of tai chi versus attention control in the short or intermediate terms. No data on long-term outcomes were available (SOE: insufficient).

Detailed Synthesis

Two small trials (n=31 and 40) of tai chi versus attention control in older adults met the inclusion criteria[215,216] (Table 29 and Appendix D). Both trials were included in the prior AHRQ report. Tai chi was practiced 40 to 60 minutes two or three times per week for 24 or 36 sessions. Attention control consisted of group education classes with one trial[216] including 20 minutes of stretching for sessions 18 to 24. Blinding was not possible in either trial and was the primary methodological limitation in one fair-quality trial.[216] Additional methodological concerns in the other poor-quality trial included unclear concealment of treatment allocation and high attrition[215] (Appendix E).

Table 45. Osteoarthritis knee pain: mind-body therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Brismee, 2007[215] 1.5 months Duration of pain: NR Poor	A. Tai chi (n=18): group tai chi classes for 6 weeks followed by 6 weeks of home video tai chi practice; 40 minute sessions, 3x/week for 12 weeks (36 total) B. Attention Control (n=13): group lectures and discussions covering health-related topics, no further activity past 6 week group period; 40 minutes sessions, 3x/week for 6 weeks (18 total)	A vs. B Age: 71 vs. 69 Female: 86.4% vs. 78.9% Race: NR WOMAC Total (26−13)]: 64.6 vs. 59.6 WOMAC Physical Function (17-85): 42.7 vs. 37.6 WOMAC Pain (7−35): 16.5 vs. 16.9 VAS Pain (0−10): 4.7 vs. 4.2 WOMAC Stiffness (2−10): 5.6 vs. 5.1	A vs. B 1.5 months WOMAC Total: 60.3 vs. 57.7, p=NS WOMAC Physical Function: 38.6 vs. 37.6, p=NS WOMAC Pain: 16.4 vs. 16, p=NS VAS Pain: 3.5 vs. 3.2, p=NS WOMAC Stiffness: 5.3 vs. 4.5, p=NS	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Wang, 2009[216] 3 and 9 months Duration of pain: 9.7 years Fair	A. Tai chi (n=20): group tai chi classes, 10 forms from the classic Yang style tai chi; home tai chi practice at least 20 minutes per day with a DVD. Home practice continued after group sessions ended until the 48 week followup. B. Attention Control (n=20): group classes on nutritional and medical information paired with 20 minutes of stretching. Instruction to practice at least 20 minutes of stretching exercises per day at home. In both groups, treatments were 2x/week for 12 weeks (24 total), 60 minute sessions	A vs. B Age: 63 vs. 68 Female: 80% vs. 70% Race: NR Baseline WOMAC Physical Function (0−1,700): 707.6 vs. 827 Baseline WOMAC Pain (0-500): 209.3 vs. 220.4 Baseline VAS Patient-Assessed Pain (0−10): 4.2 vs. 4.8 Baseline VAS Physician-Assessed Pain (0−10): 4.8 vs. 5.8 Baseline WOMAC Stiffness (0-200): 105.7 vs. 120.7	A vs. B <u>3 months</u> (mean change from baseline) WOMAC Physical Function: −440.5 (95% CI −574.4 to −306.6) vs. −257.3 (95% CI −391.2 to −123.4); difference −183.2 (95% CI −372.6 to 6.2) WOMAC Pain: −131.6 (95% CI −177.4 to −85.7) vs. −64.6 (95% CI −110.5 to −18.7); difference −70.0 (95% CI −131.8 to −2.1) VAS Patient Assessed Pain: −2.4 (95% CI −3.5 to −1.2) vs. −1.7 (−2.9 to −0.5); difference −0.7 (−2.3 to 1.0) VAS Physician Assessed Pain: −2.6 (95% CI −3.3 to −1.9) vs. −2.1 (95% CI −2.8 to −1.3); difference −0.5 (95% CI −1.6 to 0.5) WOMAC Stiffness: −65.0 (95% CI −86.3 to −43.7) vs. −50.2 (95% CI −71.5 to −28.9); difference −14.8 (95% CI −44.9 to 15.3) <u>9 months</u> WOMAC Physical Function: −405.9 (95% CI −539.8 to −271.9) vs. −300.6 (95% CI −434.5 to −166.6); difference −105.3 (95% CI −294.7 to −84.1) WOMAC Pain: −115.4 (95% CI −161.2 to −69.5) vs. −69.2 (95% CI −115.1 to −23.3); difference −46.2 (95% CI −111.0 to 18.7) VAS Patient Assessed Pain: −1.7 (95% CI −2.8 to −0.5) vs. −1.7 (95% CI −2.9 to −0.5); difference 0.04 (95% CI −1.6 to 1.7) VAS Physician-Assessed Pain: −2.5 (95% CI −3.3 to −1.8) vs. −1.5 (−2.3 to −0.8); difference −1.0 (95% CI −2.1 to 0.02) WOMAC Stiffness: −64.2 (95% CI −85.5 to −42.8) vs. −60.5 (95% CI −81.8 to −39.2); difference −3.7 (95% CI −33.8 to 26.5)	A vs. B <u>3 months</u> (mean change from baseline) SF-36 PCS (0−100): 10.8 (95% CI 7.3 to 14.3) vs. 6.3 (95% CI 2.8 to 9.8); difference 4.5 (95% CI −0.4 to 9.5) SF-36 MCS (0−100): 4.4 (95% CI −0.11 to 8.9) vs. 4.5 (95% CI 0.0 to 9.0); difference −0.1 (95% CI −6.5 to 6.3) CES-D (0-60): −6.4 (95% CI −9.9 to −2.9) vs. −1.1 (95% CI −4.6 to 2.4); difference −5.3 (95% CI −10.2 to −0.4) <u>9 months</u> SF-36 PCS: 10.4 (95% CI 6.9 to 13.9) vs. 4.1 (95% CI 0.6 to 7.6); difference 6.3 (95% CI 1.4 to 11.3) SF-36 MCS: 5.8 (95% CI 1.3 to 10.3) vs. 1.0 (95% CI −3.5 to 5.5); difference 4.8 (95% CI −1.6, 11.1) CES-D: −7.3 (95% CI −10.7 to −3.8) vs. 1.7 (95% CI −1.8 to 5.1); difference −8.9 (95% CI −13.8 to −4.0)

CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; MCS = Mental Component Score; NR = not reported; NS = not statistically significant; SF-36 MCS = Short-Form 36 Questionaire Mental Component Score; SF-36 PCS = Short-Form 36 Questionnaire Physical Component Score; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Mind-Body Therapies Compared With Attention Control

There is no clear difference between tai chi and an attention control on functional outcomes across the two trials over the short term on a WOMAC physical function 0- to 85-point scale (difference 1.03, 95% CI −9.87 to 11.93)[215] or WOMAC physical function 0- to 1700-point scale (difference −183.2, 95% CI −372.6 to 6.2),[216] or at intermediate term in one of the trials (difference −105.3, 95% CI −294.7 to −84.1, 0 to 1700 scale).[216] Results for short-term pain improvement were inconsistent with no difference between groups on WOMAC pain scale in one trial (difference 0.39 on a 0-35 point scale, 95% CI −4.21 to 4.99)[215] and the other marginally favoring tai chi on 0 to 500 point WOMAC pain scale (difference −67.0, 95% CI −131.8 to −2.1),[216] but demonstrating no difference between the groups in 0 to 10 VAS pain (difference −0.65, 95% CI −2.31 to 1.02).[216] There were no differences between groups at intermediate term in this latter trial (WOMAC pain 0 to 500 scale, difference −183.2, 95% CI −372.6 to 6.2).[216] One trial noted improvement in health-related quality of life (SF-36) in the intermediate term only and depression (CES-D) and self-efficacy in the short and intermediate terms.

Mind-Body Therapies Compared With Pharmacological Therapy or With Exercise Therapy

No trial of mind-body therapy versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

In the two trials of mind-body interventions, harms were poorly reported. One trial reported no serious adverse events[216] and the other reported sporadic complaints of muscle soreness and foot or knee pain.[215]

Acupuncture for Osteoarthritis Knee Pain

Key Points

- There were no 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 were no 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 −0.67 to 0.12, I^2=79%) or clinically meaningful differences in the intermediate term (4 trials, pooled SMD −0.16, 95% CI −0.32 to −0.01, I^2=0%) (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.

- Data from one poor-quality trial were insufficient to determine the effects of acupuncture versus exercise (SOE: insufficient).
- There was no difference in the risk of serious adverse events between any form of acupuncture and the control group. Worsening of symptoms (7% to 14%) and mild bruising, swelling, or pain at the acupuncture site (1% to 18%) were most common; one case of infection at an electroacupuncture site was reported (SOE: moderate).

Detailed Synthesis

Nine trials of acupuncture for knee OA were identified that met inclusion criteria[67,238-245] (Table 30 and Appendix D). All of the trials were included in the prior AHRQ report. Four trials evaluated traditional acupuncture,[67,240,242,244] four electroacupuncture,[238,239,241,243] and two laser acupuncture.[240,245] Three trials compared acupuncture with usual care (provision of educational leaflets, instructions to remain on current oral medications, or no changes to their ongoing treatments)[67,238,242] and one trial each to no treatment[240] or to waitlist control.[243] Six trials compared acupuncture with sham procedures, which consisted of inactive laser treatment (red light on but no power applied),[240,245] superficial needling, or acupuncture performed at nonmeridian sites,[239,243,244] or nonpenetrating sham acupuncture.[241] No trials of acupuncture versus pharmacological therapy or exercise were identified. Sample sizes ranged from 30 to 527 (total sample 1,811). Duration of acupuncture treatment ranged from 2 to 12 weeks, with the number of sessions ranging from 6 to 16. Four studies were conducted in Europe,[67,241,242,244] three in the United States,[238,239,243] and one study each was conducted in Australia[240] and Turkey.[245] Short-term outcomes were reported by six trials[67,238,241,243-245] and intermediate-term outcomes by four[239,240,242,244]; no trial reported outcomes over the long term.

Trials were rated good quality (for the comparison of acupuncture versus sham only).[240,243] Seven trials were rated fair quality (to include the comparison of acupuncture with no treatment/waitlist in the two trials described previously)[238-241,243-245] and two were considered poor quality[67,242] (Appendix E). The primary methodological shortcoming in the fair-quality trials was lack of blinding; additionally, the poor-quality trials suffered from unclear allocation concealment methods and high rates of attrition (30% to 35%).

Table 46. Osteoarthritis knee pain: acupuncture

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Berman, 1999[238] 1 month Duration of pain: mean 7.2 years Fair	A. Acupuncture + usual care (n=36): 20 minute treatments, 2/week for 8 weeks using Traditional Chinese Medicine theory; 9 acupoints points (5 local, 4 distal) with elicitation of de qi; electrical stimulation was used at local points (2.5 to 4 Hz, pulses of 1.0 ms); no new physiotherapy or exercise programs B. Usual care alone (n=37): current level of oral therapy throughout the trial	A vs. B Age: 66 vs. 66 Female: 47% vs. 72% Caucasian: 92% vs. 74% BMI: 32 vs. 32 Duration of symptoms: 7.5 vs. 6.9 years Baseline WOMAC total (scale unclear): 48.4 vs. 51.4 Baseline WOMAC function (scale unclear): 34.3 vs. 34.4 Baseline Lequesne Index (0-24): 11.7 vs. 12.3 Baseline WOMAC pain (scale unclear): 9.6 vs. 9.9	A vs. B <u>1 month</u> WOMAC total: 31.6 vs. 50.4, difference −18.9 (95% CI −26.5 to −11.2) WOMAC function: 23.2 vs. 36.8, difference −13.6 (95% CI −19.4 to −7.8) Lequesne Index: 9.3 vs. 12.4, difference −3.1 (95% CI −4.8 to −1.3) WOMAC pain: 5.6 vs. 9.5, difference −4.0 (95% CI −5.5 to −2.4)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Berman, 2004[239] 6 months Duration of pain: NR Fair	A. Acupuncture (n=186): electrical stimulation at knee acupoints (5 local and 4 distal) at low frequency (8 Hz and square biphasic pulses (0.5 ms pulse width) for 20 minutes. B. Sham acupuncture (n=183): modified combined insertion (at sham points in abdominal area) and noninsertion (at 3 local and 4 distal points on the knee) procedure; mock electric stimulation was attached to sham needles at the knee for 20 minutes. Both groups received 8 weeks of 2 sessions per week, followed by 2 weeks of 1 session per week, 4 weeks of 1 session every other week, and 12 weeks of 1 session per month. Total of 26 weeks, 25 possible sessions.	A vs. B Age: 65 vs. 66 years Female: 63.2% vs. 61.8% non-Hispanic white: 70% vs. 70.7% Bilateral OA: 25.0% vs. 28.9% Length of diagnosis of OA <5 years: 53.8% vs. 53% 6−10 years: 19.9% vs. 18.0% >10 years: 25.8% vs. 29.0% Using opioids: 5.5% vs. 5.0% Baseline WOMAC Function (0-68): 31.3 vs. 31.3 Baseline WOMAC Pain (0-20): 8.9 vs. 8.9	A vs. B <u>6 months</u> Δ from baseline, WOMAC Function: −12.4 vs. −9.9, p<0.01 Δ from baseline, WOMAC Pain: −3.8 vs. −2.9, p<0.01	A vs. B <u>6 months</u> Δ from baseline, SF-36 Physical Health Score: 10.7 vs. 8.2, p=0.21 Δ from baseline, Patient Global Assessment: 0.5 vs. 0.2, p=0.02

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Hinman, 2014[240] 9 months Duration of pain: mean 7.2 years Good (sham) Fair (no treatment)	A. Needle acupuncture (n=70): combination of Western and traditional Chinese acupuncture; maximum of 6 points (4 on study limb and 2 distal points) at initial session, in other sessions points were added at therapist's discretion. Needles were left in while patient rested. B. Laser acupuncture (n=71): combination of Western and traditional Chinese acupuncture; delivered to selected points using standard Class 3B laser devices (measured output 10mW and energy output 0.2 J/point) C. No treatment (n=71): did not receive acupuncture; continued in an observational study, unaware they were in an acupuncture trial D. Sham laser acupuncture (n=70): same as true laser but no laser was emitted, only red nonlaser light at the probe tip lit up. For all acupuncture and sham groups, sessions were 20 minutes in duration, 1-2 times per week for 12 weeks (8 to 12 sessions total)	A vs. B vs. C vs. D Age: 64 vs. 63 vs. 63 vs. 64 years Female: 46% vs. 39% vs. 56% vs. 56% Duration of symptoms ≥ 10 years: 41% vs. 38% vs. 27% vs. 50% Bilateral symptoms: 64% vs. 66% vs. 51% vs. 63% Opioid use: 1% vs. 3% vs. 1% vs. 1% Previous acupuncture for knee pain: 7% vs. 13% vs. 7% vs. 3% Baseline WOMAC function (0-68): 31.3 vs. 27.0 vs. 26.1 vs. 27.5 Baseline NRS activity restriction (0-10): 5.0 vs. 4.3 vs. 4.1 vs. 4.5 Baseline WOMAC pain (0-20): 9.0 vs. 8.3 vs. 7.8 vs. 8.6 Baseline NRS average pain overall (0-10): 5.3 vs. 4.9 vs. 5.1 vs. 5.0 Baseline NRS pain on walking (0-10): 5.5 vs. 4.8 vs. 4.8 vs. 5.2 Baseline NRS pain on standing (0-10): 4.6 vs. 3.8 vs. 4.1 vs. 4.3	A vs. C <u>9 months</u> WOMAC function: 22.4 vs. 23.6; adjusted difference −3.7 (95% CI −8.2 to 0.8) Activity restriction, NRS: 3.4 vs. 4.1; adjusted difference −1.1 (95% CI −2.1, −0.2) WOMAC pain: 6.7 vs. 7.4; adjusted difference −1.4 (95% CI −2.7 to 0.0) Overall Pain, NRS: 4.0 vs. 4.6; adjusted difference −0.7 (95% CI −1.6 to 0.2) Pain on walking, NRS: 4.1 vs. 4.4; adjusted difference −0.6 (95% CI −1.5 to 0.4) Pain on standing, NRS: 3.7 vs. 4.0; adjusted difference −0.5 (95% CI −1.4 to 0.5) B vs. C <u>9 months</u> WOMAC function: 22.6 vs. 23.6; adjusted difference −0.6 (95% CI −1.5 to 0.3) Activity restriction, NRS: 3.7 vs. 4.1; adjusted difference −0.4 (95% CI −1.4, 0.5) WOMAC pain: 7.1 vs. 7.4; adjusted difference −0.4 (95% CI −1.8 to 1.0) Overall Pain, NRS: 4.0 vs. 4.6; adjusted difference −0.6 (95% CI −1.5 to 0.3) Pain on walking, NRS: 4.1 vs. 4.4; adjusted difference −0.3 (95% CI −1.2 to 0.7) Pain on standing, NRS: 3.8 vs. 4.0; adjusted difference −0.2 (95% CI −1.1 to 0.8) B vs. D <u>9 months</u> WOMAC function: 22.6 vs. 21.6; adjusted difference 1.1 (95% CI −4.8 to 7.0) Activity restriction, NRS: 3.7 vs. 3.9; adjusted difference −0.1 (95% CI −1.1 to 1.0) WOMAC pain: 7.1 vs. 6.9; adjusted difference 0.0 (95% CI −1.9 to 1.9) Overall pain, NRS: 4.0 vs. 3.9; adjusted difference 0.0 (95% CI −0.9 to 1.0) Pain on walking, NRS: 4.1 vs. 4.2; adjusted difference 0.0 (95% CI −1.0 to 1.1) Pain on standing, NRS: 3.8 vs. 3.5; adjusted difference 0.5 (95% CI −0.7 to 1.6)	A vs. C <u>9 months</u> AQoL-6D (−0.04 to 1.00): 0.74 vs. 0.77; adjusted difference: −0.01 (95% CI −0.07 to 0.05) SF−12 PCS (0-100): 41.7 vs. 38.9; adjusted difference 2.3 (95% CI −1.7 to 6.3) SF-12 MCS (0-100): 51.1 vs. 54.4; adjusted difference −0.9 (95% CI −5.2 to 3.4) Opioid use: 0% (0/70) vs. 1% (1/71) B vs. C <u>9 months</u> AQoL-6D: 0.73 vs. 0.77; adjusted difference: 0.01 (95% CI −0.05 to 0.06) SF-12 PCS: 38.8 vs. 38.9; adjusted difference −0.4 (95% CI −4.4 to 3.6) SF-12 MCS: 52.1 vs. 54.4; adjusted difference −0.9 (95% CI −5.5 to 3.7) Opioid use: 2% (1/71) vs. 1% (1/71) B vs. D <u>9 months</u> AQoL-6D: 0.73 vs. 0.74; adjusted difference 0.01 (95% CI −0.05 to 0.08) SF-12 PCS: 38.8 vs. 38.2; adjusted difference 0.4 (95% CI -3.8 to 4.5) SF-12 MCS: 52.1 vs. 52.8; adjusted difference −0.6 (95% CI −5.4 to 4.2) Opioid use: 2% (1/71) vs. 0% (0/70)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Jubb, 2008[241] 1 month Duration of pain: mean 10 years Fair	A. Acupuncture (n=34): manual acupuncture (10 minutes, total of 9 points; depth of 1-1.5 cm; elicitation of de qi) and electro-acupuncture (10 minutes each on anterior and posterior part of the knee (20 minutes total); low frequency, delivered at 6 Hz at a constant current) B. Sham (n=34): sham needles, did not penetrate the skin; electrical stimulation apparatus produced sound signals but no electrical current. Both groups received 30 minute treatments, 2/week for 5 weeks, with 10 sessions in total	A vs. B Age: 64 vs. 66 years Female: 85% vs. 76% Caucasian: 74% vs. 85% Duration of symptoms: 10 vs. 9.6 years Baseline WOMAC function (0-1700): 1028 vs. 979 Baseline WOMAC pain (0−500): 294 vs. 261 Baseline Total body pain, VAS (0-100): 49 vs. 49 Baseline Night pain knee, VAS (0-100): 61 vs. 52 Baseline Overall pain knee, VAS (0-100): 63 vs. 53 Baseline Weight-bearing pain knee, VAS (0-100): 71 vs. 60 Baseline EuroQoL VAS (0-100): 63 vs. 54	A vs. B <u>1 month</u> WOMAC function: change from baseline, 137 (95% CI 20 to 255) vs. 134 (95% CI 9 to 258); difference, 4 (95% CI −163 to 171) WOMAC pain: change from baseline, 59 (95% CI 16 to 102) vs. 13 (95% CI −22 to 50); difference, 46 (95% CI −9 to 100) Weight-bearing knee pain (VAS), change from baseline, 19 (95% CI 9 to 30) vs. 8 (95% CI -1 to 16); difference, 11 (95% CI −2 to 25) Overall knee pain (VAS), change from baseline, 14 (95% CI 5 to 24) vs. 2 (95% CI −6 to 10); difference, 12 (95% CI −1 to 24) Nighttime knee pain (VAS), change from baseline, 10 (95% CI −1 to 22) vs. 5 (95% CI −3 to 14); difference, 5 (95% CI −9 to 19) General body pain (VAS), change from baseline, 5 (95% CI −5 to 15) vs. −8 (95% CI −1 to 18); difference: 13 (95% CI 0 to 27) EuroQoL-VAS: mean 63 vs. 52, p=0.98	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lansdown, 2009[242] 9.5 months Duration of pain NR Poor	A. Acupuncture + usual care (n=15): once per week for up to 10 weeks, with maximum of 10 sessions, which varied in length and content (mean number of acupoints was 12, range 4-24; de qi was usually elicited; variety of stimulation methods used including tonification and reduction; retention time for needles ranged from 10-30 minutes); auxiliary treatment included moxibustion (3/14, 21%) and acupressure massage (3/14, 21%); life style advice 11/14 (79%) B. Usual care (n=15): any appointments, medications prescribed or over the counter) and interventions sought by participants from any health practitioner	A vs. B Age: 63 vs. 64 years Female: 60% vs. 60% Caucasian: 100% vs. 100% Duration of symptoms: NR Baseline WOMAC total (0-96): 31 vs. 37.5 Baseline WOMAC function (0-68): 20.5 vs. 26.3 Baseline OKS (12-60): 30.9 vs. 30.6 Baseline WOMAC pain (0-20): 7.3 vs. 7.4	A vs. B <u>9.5 months</u> WOMAC total: 24.8 vs. 25.6, adjusted difference −2.9 (95% CI 9.5 to −15.4) WOMAC function: 17.4 vs. 17.6, adjusted difference −1.4 (95% CI 8.7, −11.4) WOMAC pain: 4.7 vs. 5.3 (3.9), adjusted difference −1.4 (95% CI 0.8 to −3.6) OKS: 24.5 vs. 28.1; difference −3.6 (95% CI −9.8 to 2.6)	A vs. B <u>9.5 months</u> (SF-36 scales are 0-100 for all) SF-36 physical functioning: 54.2 vs. 55.6, difference −1.4 (95% CI −21.8 to 19.0) SF-36 social functioning: 81.3 vs. 76.6, difference 4.7 (95% CI −10.6 to 20.0) SF-36 role physical: 71.4 vs. 57.8, difference 13.6 (95% CI −6.3 to 33.5) SF-36 role mental: 79.2 vs. 67.7, difference 11.5 (95% CI −5.8 to 28.8) SF-36 mental health: 73.1 vs. 65.0, difference 8.1 (95% CI −5.4 to 21.6) SF-36 vitality: 58.2 vs. 46.9, difference 11.3 (95% CI −0.22 to 22.8) SF-36 pain: 65.2 vs. 65.9, difference −0.7 (95% CI −15.6 to 14.2) SF-36 general health: 67.7 vs. 62.4, difference 5.3 (95% CI −4.8 to 15.4), EQ5D: 0.7 vs. 0.63, difference 0.03 (95% CI −0.13 to 0.19)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Suarez-Almazo, 2010[243] 1.5 months Duration of pain: mean 8 years Good (sham) Fair (waitlist)	A. Electro-acupuncture (n=153): Traditional Chinese Medicine points; TENS equipment emitted a dense disperse wave (50Hz, dispersed at 15 Hz, 20 cycles/minute); voltage increased from 5V to 60V until maximal tolerance achieved. Patients rested for 20 minutes with needles retaining and with continuing TENS. B. Sham (n= 302): 40Hz adjustable wave; voltage increased until the patient could feel it and then immediately turned off. Patients rested for 20 minutes with the needles retained, but without TENS stimulation; nonrelevant acupoints used and depth of needle placement was shallow C. Waitlist (n=72)	A vs. B vs. C Age: 65 vs. 65 vs. 64 Female: 66% vs. 65% vs. 58% Caucasian: 70% vs. 68% vs. 65% Mean duration of chronicity: 9.2 vs. 8.6 vs. 11.5 years Baseline WOMAC function (0-100): 42.9 vs. 44.6 vs. 40.1 Baseline WOMAC pain (0-100): 44.5 vs. 45.0 vs. 44.1 Baseline VAS pain (0-100): 58.3 vs. 57.4 vs. 54.6 Baseline J-MAP (1-7): 4.4 vs. 4.4 vs. 4.3	A vs. B <u>1.5 months</u> WOMAC function: 31.2 (vs. 32.1; difference −0.9 (95% CI −4.4 to 2.6) WOMAC pain: 30.8 vs. 31.0; difference −0.2 (95% CI −3.8 to 3.4) VAS pain: 36.2 vs. 36.7; difference −0.5 (95% CI −6.1 to 5.1) J-MAP: 3.3 vs. 3.4; difference −0.1 (95% CI −0.39 to 0.19) A vs. C <u>1.5 months</u> WOMAC function: 31.2 vs. 41.7; difference −10.5 (95% CI −15.6 to −5.5) WOMAC pain: 30.8 vs. 42.4; difference −11.6 (95% CI −16.5 to −6.7) VAS pain: 36.2 vs. 53.2; difference −17.0 (95% CI −24.7 to −9.3) J-MAP: 3.3 vs. 4.2; difference −0.9 (95% CI −1.3 to −0.5)	A vs. B <u>1.5 months</u> SF-12 PCS (0-100): 39.5 vs. 38.7; difference 0.8 (95% CI −1.1 to 2.7) SF-12 MCS (0-100): 54.1 vs. 53.2; difference 0.9 (95% CI −0.8 to 2.6) A vs. C <u>1.5 months</u> SF-12 PCS: 39.5 vs. 35.8; difference 3.7 (95% CI 1.0 to 6.4) SF-12 MCS: 54.1 vs. 51.6; difference 2.5 (95% CI 0.04, 5.0)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Williamson, 2007[67] 1.5 months Duration of symptoms: NR Poor	A. Acupuncture (n=60): conducted by a physiotherapist in a group setting (6-10 patients); needles inserted into 7 acupoints until de qi was achieved and left in place for 20 minutes; treatments were once per week for 6 weeks, with 6 sessions in total B. Combination Exercise (Physiotherapy) (n=60): supervised group (6-10 people) exercise comprised of strengthening, aerobic, stretching, and balance training; 60 minutes, once per week for 6 weeks; C. Usual care (n=61): exercise and advice leaflet; told they were enrolled in the "home exercise group"	A vs. B vs. C Age: 72 vs. 70 vs. 70 years Female: 55% vs. 52% vs. 54% BMI: 30.9 vs. 32.8 vs. 32.7 Baseline WOMAC total (scale unclear): 50.9 vs. 50.2 vs. 51.1 Baseline OKS (12-60): 40.2 vs. 39.3 vs. 40.5 Baseline pain VAS (0-10): 7.3 vs. 6.8 vs. 6.9 Baseline HAD Anxiety (0-21): 7.3 vs. 7.5 vs. 6.7 Baseline HAD Depression (0-21): 7.1 vs. 7.1 vs. 7.4	A vs. B <u>1.5 months</u> WOMAC: 48.4 vs. 49.4, difference −1.0 (95% CI −6.7 to 4.7) OKS: 38.1 vs. 38.8, difference −0.7 (95% CI −3.5 to 2.1) Pain VAS: 6.6 vs. 6.4, difference 0.22 (95% CI −0.67 to 1.11) A vs. C <u>1.5 months</u> WOMAC: 48.4 vs. 52.3, difference −3.9 (95% CI −9.5 to 1.6) OKS: 38.1 vs. 40.8, difference −2.6 (95% CI −5.4 to 0.1) Pain VAS: 6.6 vs. 7.2, difference −0.66 (95% CI −1.45 to 0.12)	A vs. B <u>1.5 months</u> HAD Anxiety: 6.9 vs. 7.1, difference −0.20 (95% CI −1.89 to 1.49) HAD Depression: 6.7 vs. 6.8, difference −0.03 (95% CI −1.30 to 1.24) A vs. C <u>1.5 months</u> HAD Anxiety: 6.9 vs. 6.5, difference 0.34 (95% CI −1.11 to 1.8) HAD Depression: 6.7 vs. 7.1, difference, −0.41 (95% CI −1.63 to 0.8)
Witt, 2005[244] 4 and 10 months Duration of pain: mean 9.4 years Fair	A. Acupuncture (n=150): semi-standardized; patients received at least 6 local and at least 2 distant Traditional Acupuncture points; elicitation of de qi; needles stimulated manually at least once during each session B. Minimal acupuncture (n=76): superficial insertion of at nonacupuncture sites away from knee; manual stimulation of the needles and provocation of de qi were avoided Both groups underwent 12 sessions of 30 minutes duration, administered over 8 weeks	A vs. B Age: 65 vs. 63 years Female: 70% vs. 65% Duration of symptoms: 9.1 vs. 9.9 years Bilateral OA: 74% vs. 77% Previous acupuncture: 9% vs. 7% Baseline WOMAC total (scale unclear): 50.8 vs. 52.5 Baseline PDI (Disability) (0-70): 27.9 vs. 27.8 Baseline VAS pain (0-100): 64.9 vs. 68.5	A vs. B <u>4 months</u> WOMAC total: 30.4 vs. 36.3; difference −5.8 (95% CI −12.0 to 0.3) WOMAC physical function: 30.4 vs. 36.5; difference −6.2 (95% CI −12.4 to 0.1) PDI: 18.6 vs. 22.8; difference −4.2 (95% CI −8.3 to −0.0) WOMAC pain: 28.9 vs. 33.8; difference −4.8 (95% CI −11.2 to 1.6) <u>10 months</u> WOMAC Total: 32.7 vs. 38.4; difference −5.7 (95% CI −12.1 to 0.7) WOMAC physical function: 33.0 vs. 38.9; difference −5.9 (95% CI −12.5 to 0.7) PDI: 20.0 vs. 23.6; difference −3.6 (95% CI −7.7 to 0.5) WOMAC pain: 30.0 vs. 33.5; difference −3.5 (95% CI −10.0 to 3.0)	A vs. B <u>4 months</u> SF-36 Physical: 35.1 vs. 33.0; difference 2.1 (95% CI −0·5 to 4.8) SF-36 Mental: 52.6 vs. 51.7; difference 0.9 (95% CI 2.3 to 4.2) ADS (Depression): 48.2 vs. 48.7; difference −0·5 (95% CI −3.6 to 2.5) <u>10 months</u> SF-36 Physical: 35.0 vs. 32.8; difference 2.2 (95% CI −0.6 to 5,1) SF-36 Mental: 52.9 vs. 51.1; difference 1.9 (95% CI −1.3 to 5.1) ADS: 48.6 vs. 49.8; difference −1.2 (95% CI −4.3 to 1.8)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Yurtkuran, 2007[245] 3 months Duration of pain: mean 5.4 years Fair	A. Laser acupuncture (n=28): applied to the medial side of the knee to the acupuncture point on the sural nerve; infrared 27 GaAs diode laser instrument (output 4 mW, 10 mW/cm2 power density, 120-sec treatment time and 0.48 J dose per session); irradiation was pulsed (duration of 1 pulse was 200 nanosecond), and only one point was treated with contact application technique. B. Sham laser acupuncture (n=27): performed in the same location and under the same conditions as the true laser acupuncture; patients could see a red light but the machine was turned off Both groups: 20 minutes sessions, 5 days per week for 2 weeks (total duration of therapy was 10 days, 10 sessions total); in addition, all patients received a home-based, standardized exercise program	A vs. B Age: 52 vs. 53 years Female: 96% vs. 96% Duration of symptoms: 5.2 vs. 5.6 months Baseline WOMAC total: 66.5 vs. 51.3 Baseline WOMAC physical function: 47.5 vs. 35.3 Baseline WOMAC pain: 13.7 vs. 11.6 Baseline VAS pain on movement (0-10): 6.5 vs. 6.1	A vs. B <u>2.5 months</u> WOMAC total: 62.4 vs. 50.6, difference 11.8 (95% CI −1.0 to 24.6) WOMAC physical function: 44.2 vs. 35.3, difference 11.9 (95% CI 2.9 to 20.9) WOMAC pain: 13.5 vs. 11.5, difference 2.0 (95% CI −1.3 to 5.3) VAS pain on movement: 5.6 vs. 4.8, difference 0.8 (95% CI −0.9 to 2.5)	A vs. B <u>2.5 months</u> NHP (0-38): 7.6 vs. 6.4. difference 1.2 (95% CI −2.1 to 4.4)

AQoL = Assessment of Quality of Life; ADS = Anxiety and Depression Scale; BMI = Body Mass Index; CI = confidence interval; HAD = Hospital Anxiety and Depression Scale; J-MAP = Joint-specific Multidimensional Assessment of Pain; NHP = Nottingham health profile; NR = not reported; NRS = numeric rating scale; OA = osteoarthritis; OKS = Oxford Knee Score; SF-12 MCS = Short Form 12 Questionaire Mental Component Score; SF-36 = Short-Form 36 Questionnaire Physical Component Score; V = volt; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Acupuncture Compared With Usual Care, Waitlist, or Sham

Functional Outcomes. There was no difference between acupuncture versus control interventions (sham acupuncture, usual care, waitlist, no treatment) on WOMAC function score in the short term (5 trials, pooled SMD −0.17, 95% CI −0.71 to 0.38, I^2=86%)[238,241,243-245] (Figure 40). All trials were considered fair quality. Removal of one outlier trial (Berman 1999)[238] attenuated the effect estimate size (4 trials, pooled SMD −0.05, 95% CI −0.32 to 0.38); results remained insignificant. No differences were found when the results were analyzed by the type of acupuncture used: electroacupuncture (3 trials, pooled SMD −0.34, 95% CI −1.17 to 0.46),[238,241,243] standard needle acupuncture (SMD −0.28, 95% CI −0.55 to 0.00),[244] or laser

acupuncture (SMD 0.55, 95% CI −0.01 to 1.10)[245] compared with control interventions. When stratified by control type no differences were found between any form of acupuncture and sham treatment (4 trials, pooled SMD −0.02, 95% CI −0.28 to 0.39);[241,243-245] however, when acupuncture was compared with waitlist and usual care, estimates suggested moderate improvement in function (2 trials, pooled SMD −0.74, 95% CI −1.40 to −0.24, plot not shown).[238,243] In one small, fair-quality trial[245] of low-level laser acupuncture the authors reported a difference in WOMAC function score that favored the sham control (Table 29).

Similarly, based on WOMAC total score, there were no differences in short-term function between acupuncture and sham, waitlist, and usual care across trials (4 trials, pooled SMD −0.30, 95% CI −0.81 to 0.21, I^2=85%, plot not shown).[67,238,244,245] Removal of one outlier trial (Berman 1999)[238] attenuated the effect estimate size (3 trials, pooled SMD −0.10, 95% CI −0.54 to 0.49); results remained insignificant. Stratification by acupuncture type, control type, and exclusion of one poor-quality trial yielded similar estimates. Results according to other measures of function were mixed. In two small, fair-quality trials authors reported significant results (Table 29), one favoring electroacupuncture compared with usual care based on the Lequesne Index (0 to 24 scale),[238] and the second favoring the sham control comparing low-level laser acupuncture based on the WOMAC total score.[245] Five additional trials reported no differences between acupuncture and any of the control conditions across other measures of function[67,240-242,244] (Table 29).

In the intermediate term, there was no difference between acupuncture versus control conditions (sham acupuncture, usual care, waitlist) on the WOMAC function score (4 trials, pooled SMD −0.15, 95% CI −0.31 to 0.02, I^2=0%),[239,240,242,244] (Figure 40). Estimates were similar when stratified by study quality, acupuncture type, and control type; however, sensitivity analyses were limited by the small number of trials. Similarly, no differences in WOMAC total score were found for standard needle acupuncture versus usual care or sham at intermediate-term followup (2 trials, pooled SMD −0.23, 95% CI −0.49 to 0.03, I^2=0%, plot not shown).[242,244] Across other measures of function, no differences were seen at intermediate term between standard needle acupuncture versus sham acupuncture on the Pain Disability Index (difference −3.5 on a 0-70 scale, 95% CI −7.7 to 0 .5) in one fair-quality trial[244] or versus usual care on the Oxford Knee Score (difference 3.6 on a 12 to 60 scale, 95% CI −9.8 to 2.6) in one small poor-quality trial.[242]

No trials reported data on long-term function.

Pain Outcomes. There was no difference between acupuncture versus control interventions (sham acupuncture, usual care, waitlist) on pain in the short term (6 trials, pooled SMD −0.27, 95% CI −0.67 to 0.12, I^2=79%)[67,238,241,243-245] (Figure 41). All but one trial used the WOMAC pain score. Removal of one outlier trial (Berman 1999)[238] attenuated the effect estimate size (5 trials, pooled SMD −0.15, 95% CI −0.29 to 0.00); results remained insignificant. Estimates were similar after exclusion of one poor-quality trial and for stratification by acupuncture type and for analyses of VAS or NRS instead of WOMAC pain score if more than one pain measure was reported. When stratified by control type, no differences were seen between acupuncture and sham acupuncture (4 trials, pooled SMD −0.06, 95% CI −0.24 to 0.14);[241,243-245] however, when acupuncture was compared with waitlist or usual care, the estimate suggested moderate effects on pain (2 trials, pooled SMD −0.68, 95% CI −1.28 to −0.15).[238,243]

There were no clinically meaningful differences between acupuncture and control interventions for pain in the intermediate term (4 trials, pooled SMD −0.16, 95% CI −0.32 to −0.01, I^2=0%)[239,240,242,244]; individually no trial reached statistical significance (Figure 41).

Stratification based on acupuncture type, type of control intervention, and study quality yielded similar results.

No trial reported data on long-term pain.

Other Outcomes. Data on the effects of acupuncture on quality of life were limited (plots not shown). A small effect favoring acupuncture versus control conditions (sham acupuncture, usual care, waitlist, no treatment) was seen for the SF-12/SF-36 PCS (0-100 scale) in both the short term (2 trials, pooled difference 1.6, 95% CI 0.08 to 3.11, I^2=0%)[243,244] and the intermediate term (2 trials, pooled difference 1.94, 95% CI 0.03 to 3.86, I^2=0%),[240,244] but no difference was seen in the SF-12/SF-36 MCS (0-100 scale) at either timepoint: short term (2 trials, pooled difference 1.14, 95% CI −0.27 to 2.56, I^2=0%)[243,244] and intermediate term (2 trials, pooled difference −0.25, 95% CI −4.05 to 3.54, I^2=70.8%).[240,244] For individual trials, the effects were small and not statistically significant for either outcome (SF-12 or SF-36 PCS or MCS). There were no differences between acupuncture and control interventions on other quality of life measures or on measures of anxiety or depression over either the short or intermediate term (Table 29).

In one trial,[240] a small (1%) change in opioid use at intermediate term was seen with needle acupuncture (decrease from 1% to 0%), laser acupuncture (decrease from 3% to 2%), and sham acupuncture (decrease from 1% to 0%) while use remained the same in the no treatment group (Table 29).

Acupuncture Compared With Pharmacological Therapy

No trial of acupuncture versus pharmacological therapy met inclusion criteria.

Acupuncture Compared With Exercise Therapy

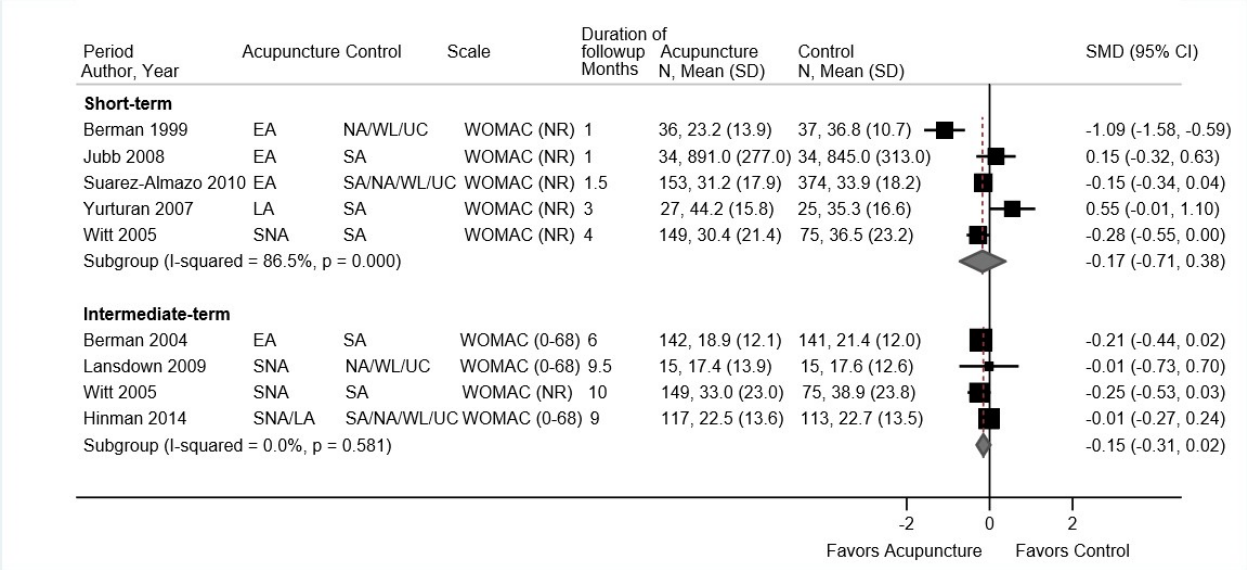
Data were insufficient from one poor-quality trial (n=120)[67] to evaluate the effects of weekly acupuncture versus 60 minutes of combination exercise (strengthening, aerobics, stretching, and balance training) for 6 weeks for knee OA (Table 29 and Appendix D). Methodological limitations included lack of patient or care provider blinding, unclear adherence, unacceptable attrition, and differential loss to followup (Appendix E). There were no differences between groups with regard to function on the Oxford Knee Score questionnaire (difference −0.7, 95% CI −3.5 to 2.1 on 12-60 scale) or WOMAC score (difference −1.0, 95% CI −6.7 to 4.7; scale not provided by author). Similarly there was no difference between treatments for VAS pain on a 0 to 10 scale (difference 0.22, 95% CI −0.67 to 1.11) or for anxiety or depression based on the Hospital Anxiety and Depression Scale.

Harms

All trials reported adverse events. One trial reported similar rates of serious adverse events in patients who received real versus sham acupuncture (2.1% vs. 2.7%, respectively; RR 0.75, 95% CI 0.13 to 4.39), to include hospitalizations and one case of death from myocardial infarction in the control group; none were considered to be related to the study condition or treatment.[244] All other events reported were classified as mild and there was no apparent difference in risk of adverse events between any form of acupuncture and the control groups. The most common adverse events reported were worsening of symptoms (7% to 14%) in three trials[240,242,243] and mild bruising, swelling, or pain at the acupuncture site (1% to 18%) in five trials.[67,240,242-244] One trial reported one case of an infection at the electroacupuncture site (n=455 for real and sham

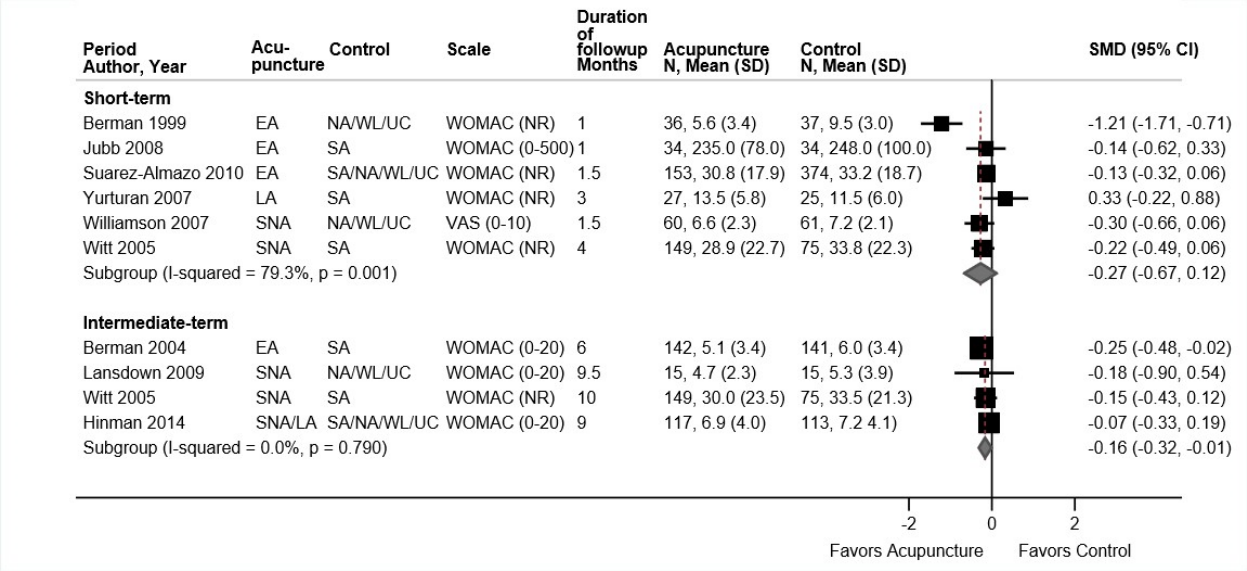
acupuncture groups).[243] In only one trial did an adverse event (not treatment related) lead to withdrawal: one patient (3%) in the acupuncture group had a flare-up of synovitis (nonseptic).[241]

Figure 40. Acupuncture versus usual care, waitlist, or sham intervention in osteoarthritis knee pain effects on function



EA = electroacupuncture; LA = laser acupuncture; NR = not reported; SA = sham acupuncture; SNA = standard needle acupuncture; SD = standard deviation; SMD = standardized mean difference; NR = not reported; UC = usual care; WL = waitlist; WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index

Figure 41. Acupuncture versus usual care, waitlist, or sham intervention for osteoarthritis knee pain: effects on pain



EA = electroacupucnture; LA = laser acupuncture; NR = not reported; SA = sham acupuncture; SNA = standard needle acupuncture; SD = standard deviation; SMD = standardized mean difference; NR = not reported; UC = usual care; WL = waitlist; WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index

Exercise for Osteoarthritis Hip Pain

Key Points

- Exercise was associated with a small improvement in function versus usual care in the short term (3 trials, pooled SMD −0.33, 95% CI −0.58 to −0.11, I^2=0%), intermediate term (2 trials, pooled SMD −0.28, 95% CI −0.55 to 0.02, I^2=0%), and long term (1 trial, SMD −0.37, 95% CI −0.74 to −0.01) (SOE: low for short and intermediate term, insufficient for long term).
- Exercise tended toward small improvement in short-term pain compared with usual care (3 trials, pooled SMD −0.30, 95% CI −0.70 to −0.02, I^2=0%) but the results were no longer significant at intermediate term (2 trials, pooled SMD −0.14, 95% CI −0.40 to 0.12, I^2=0%) or long term (1 trial, SMD −0.25, 95% CI −0.62 to 0.11) (SOE: low for short and intermediate term, insufficient for long term).
- Evidence for harms was insufficient in trials of exercise with only two trials describing adverse events. However, no serious harms were reported in either trial (SOE: insufficient).

Detailed Synthesis

Four trials of exercise therapy for hip OA met the inclusion criteria (Table 31 and Appendix D).[47,72-74] All of the trials were included in the prior AHRQ report. Three trials evaluated participants with chronic hip pain diagnosed as OA using American College of Radiology criteria[47,72,74] and one assessed participants with hip OA diagnosed clinically who were on a waitlist for hip replacement.[73] Sample sizes ranged from 45 to 203 (total sample=455). Across trials, participants were predominately female (>50%) with mean ages ranging from 64 to 69 years. Three trials were conducted in Europe[72-74] and the other in New Zealand.[47]

All trials compared exercise with usual care, defined as care routinely provided by the patient's primary care physician, which could include physical therapy referral. Two trials also provided education about hip OA to all participants.[72,74] The exercise interventions included 8 to 12 supervised sessions of 30 to 60 minutes duration once per week over 8 to 12 weeks; the interventions were comprised of strengthening and stretching exercises (all studies), as well as neuromuscular control exercises in one trial[47] and endurance exercise in another.[74] All trials reported compliance rates with the scheduled exercise sessions between 76 and 88 percent. However, in one trial,[47] although 88 percent of patients completed more than 80 percent of the scheduled sessions, only 44 percent of participants returned logbooks to demonstrate compliance with the recommended home exercises.

Three trials were rated fair quality[47,72,74] and one was rated poor quality[73] (Appendix E). In all trials, the nature of the intervention and control precluded blinding of participants and researchers; patient-reported outcomes were therefore not blinded. Additionally, in the poor-quality trial,[73] concealed allocation was unclear and outcomes were poorly reported, as were attrition rates, which were substantial for pain (68%) and function (73%) outcomes.

Table 47. Osteoarthritis hip pain: exercise

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Abbott, 2013[47] 9.75 months Duration of pain: 9 months Fair	A. Exercise therapy (n=51/22 hip OA): 7 sessions of strengthening, stretching, and neuromuscular control over 9 weeks, with 2 booster sessions at week 16. Individual exercises prescribed as needed. Home exercise prescribed 3 times weekly B. Usual care (n=51/23 hip OA): Routine care provided by patient's own GP and other healthcare providers	A vs. B (total population, includes knee OA) Age: 67 vs. 66 Females: 49% vs. 63% % hip OA: 43.1% vs. 45.1% WOMAC (0-240): 95.5 vs. 93.8	A vs. B (hip OA only) <u>9.75 months</u> WOMAC mean change from baseline: −12.4 vs. 6.6	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Juhakoski, 2011[72] 3, 9, and 21 months Duration of pain: Mean 8.3 to 8.5 years Fair	A. Exercise + usual care (n=57): 12 strengthening and stretching exercise sessions of 45 minutes once per week, with 4 booster sessions 1 year later B. Usual care (n=56): normal routine care offered by patient's own GP. All patients attended an hour-long session on basic principles of nonoperative treatment of hip OA	A vs. B Age: 67 vs. 66 years Female: 68% vs. 72% Duration of pain: 8.3 to 8.5 years Baseline WOMAC function (0-100): 24.7 vs. 28.9 Baseline WOMAC pain (0-100): 21.5 vs. 29.1	A vs. B <u>3 months</u> WOMAC function: 22.6 vs. 30.1, (difference −7.5, 95% CI −13.9 to −1.0) WOMAC pain: 23.4 vs. 28.9 (difference −5.5, 95% CI −13.0 to 2.0) <u>9 months</u> WOMAC function: 24.6 vs. 27.6 (difference −3.0, 95% CI −9.2 to 3.2) WOMAC pain: 22.9 vs. 25.0 (difference −2.1, 95% CI −9.2 to 5.0) <u>21 months</u> WOMAC function: 24.4 vs. 30.0 (difference −5.6, 95% CI −12.9 to 1.7) WOMAC pain: 24.1 vs. 27.9 (difference −3.8, 95% CI −12.0 to 4.4)	A vs. B <u>3 months</u> Weak opioid[b] use (p=0.73): Not using: 82.5% vs. 87.7% 1-6 times/week: 10.5% vs. 8.8% Daily: 7.0% vs. 3.5% <u>9 months</u> Mean doctor visits for hip OA: 0.5 vs. 0.8, p=0.07 Mean physiotherapy visits for hip OA: 1.3 vs. 2.0, p=0.05 Weak opioid[b] use (p=0.12): Not using: 81.0% vs. 93.1% 1-6 times/week: 10.4% vs. 1.7% Daily: 8.6% vs. 5.2% <u>21 months</u> Mean doctor visits (between 9 and 21 month followup) for hip OA: 0.5 vs. 1.1, p=0.05 Mean physiotherapy visits (between 9 and 21 month followup) for hip OA: 0.4 vs. 1.3, p<0.001 Weak opioid[b] use (p=0.70): Not using: 80.7% vs. 85.2% 1-6 times/week: 12.3% vs. 7.4% Daily: 7.0% vs. 7.4%
Tak,[c] 2005[73] 6 months, 3 years Duration of pain: NR Poor	A. Exercise (n=45): Eight weekly group sessions of strength training, information on a home exercise program, ergonomic advice, and dietary advice B. Usual care (n=49): Subject-initiated contact with GP. Reference group (n=NR) consisting of weekly stress management sessions for 10 weeks	A vs. B Age: 68 vs. 69 Female: 64% vs. 71% Baseline HHS (0-100): 71.1 vs. 71.0 Baseline GARS (18-72): 22.8 vs. 25.3 Baseline SIP-136 physical (0-100): 7.2 vs. 7.6 Baseline pain VAS (0-10): 3.8 vs. 4.2 Baseline HHS pain subscale (0-44): 27.9 vs. 28.8	A vs. B <u>3 months</u> HHS: 75.4 vs. 71.1, (difference 4.3, 95% CI −2.2 to 10.8) GARS: 23.7 vs. 26.3, (difference −2.6, 95% CI −6.0 to 0.8) SIP-136 physical: 5.1 vs. 8.4, (difference −3.3, 95% CI −5.3 to −1.3) Pain VAS: 3.5 vs. 5.1, (difference −1.6, 95% CI −2.6 to −0.6) HHS pain subscale: 29.6 vs. 26.9, (difference −0.9, 95% CI −4.7 to 2.9)	A vs. B <u>3 months</u> QoL VAS (0-10): 5.0 vs. 4.2, (difference 1.4, 95% CI −0.2 to 3.0) HRQoL (7-39): 28.6 vs. 27.3, (difference 0.9, 95% CI −0.4 to 2.2)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Teirlinck, 2016[74] 3 and 9 months Duration of pain: Median 1 year Fair	A. Exercise therapy (n=101): 12 sessions over 3 months consisting of strengthening, stretching, and aerobic exercise B. Usual care (n=102): Routine care provided by patient's own GP	A vs. B Age: 64 vs. 67 Females: 62% vs. 55% Pain duration median (IQR): 365 (810) vs. 365 (819) days Baseline HOOS function (0-100): 35.4 vs. 32.2 Baseline HOOS pain (0-100): 37.6 vs. 38.9 Baseline ICOAP constant pain (0-20): 5.4 vs. 5.8 Baseline ICOAP intermittent pain (0-24): 8.0 vs. 8.4 Baseline ICOAP total pain (0-100): 30.4 vs. 32.2	A vs. B <u>3 months</u> HOOS function: 30.8 vs. 35.3, (adjusted difference −2.4, 95% CI −6.7 to 1.9) HOOS pain: 34.4 vs. 37.2, (adjusted difference −2.2, 95% CI −6.2 to 1.7) ICOAP constant pain: 4.0 vs. 5.3, (adjusted difference −0.9, 95% CI −1.9 to 0.1) ICOAP intermittent pain: 7.0 vs. 7.9 , (adjusted difference −0.6, 95% CI −1.7 to 0.6) ICOAP total pain: 24.9 vs. 29.8, (adjusted difference −3.3, 95% CI −8.0 to 1.4) <u>9 months</u> HOOS function: 26.8 vs. 34.2, (adjusted difference −3.0, 95% CI −6.7 to 0.2) HOOS pain: 31.6 vs. 34.6, (adjusted difference −1.6, 95% CI −6.2 to 3.0) ICOAP constant pain: 3.6 vs. 4.7, (adjusted difference −0.7, 95% CI −1.7 to 0.4) ICOAP intermittent pain: 6.1 vs. 7.2, (adjusted difference −0.6, 95% CI −1.8 to 0.6) ICOAP total pain: 22.2 vs. 27.0, (adjusted difference −2.8, 95% CI −7.6 to 2.0)	A vs. B <u>3 months</u> EuroQol 5D−3L (−0.329−1.0): 0.77 vs. 0.76, (adjusted difference −0.01, 95% CI −0.06 to 0.04) <u>9 months</u> EuroQol 5D-3L: 0.78 vs. 0.78, (adjusted difference −0.01, 95% CI −0.06 to 0.04) Total hip replacements: 6 vs. 9

CI = confidence interval; GARS = gait abnormality rating scale; GP = general practitioner; HHS = Harris Hip Score; HOOS = hip disability and osteoarthritis outcome score; HRQoL = Health Related Quality of Life; ICOAP = intermittent and constant pain score; IQR = Inter-quartile range; NR = not reported; OA = osteoarthritis; QoL = quality of life; SIP-136 = Sickness Impact Profile-136; VAS = visual analog scale; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Authors defined weak opioids as tramadol or codeine

[c] Cluster RCT where clusters were formed from participants selecting a time that best fit their schedule

Exercise Compared With Usual Care

Exercise was associated with a small improvement in function versus usual care in the short term (3 trials, pooled SMD −0.33, 95% CI −0.58 to −0.11, I^2=0.0%),[72-74] intermediate term (2 trials, pooled SMD −0.28, 95% CI −0.55 to 0.02, I^2=0.0%)[72,74] and long term (1 trial, SMD −0.37, 95% CI −0.74 to −0.01)[72] (Figure 42). The intermediate-term findings were consistent with the additional trial not included in the meta-analysis (authors did not provide sufficient data),[47] although the small improvement in function in this trial did not reach statistical significance in those with hip OA. The small number of trials precluded meaningful sensitivity analysis.

Exercise tended toward small improvement in short-term pain compared with usual care (3 trials, pooled SMD −0.30, 95% CI −0.70 to −0.02, I^2=0%)[72-74] (Figure 43), but not at intermediate term (2 trials, pooled SMD −0.14, 95% CI −0.40 to 0.12, I^2=0%).[72,74] There was

moderate heterogeneity between studies and the short-term improvement in pain was observed in only one poor-quality study,[73] whereas the two fair-quality studies did not demonstrate any significant differences in short-term pain relief.[72,74] There were no identifiable differences in methodology between the studies to explain these inconsistent findings, although the poor-quality study only reported pain outcomes for 68 percent of participants, which may have biased results. There was no difference between exercise and usual care in the long term based on a single study (SMD −0.25, 95% CI −0.62 to 0.11).[72] The small number of trials precluded meaningful sensitivity analysis.

Data on effects of exercise on quality of life were limited and were reported in only two trials.[73,74] One fair-quality trial[74] found no differences in health-related quality of life between groups in the short term and intermediate term and one poor-quality study[73] found no differences between groups in the short term. One fair-quality study found no differences between groups in terms of opioid use at any time point (proportion of patients using tramadol or codeine daily: 7.0% vs. 3.5% at 3 months, 8.6% vs. 5.2% at 9 months, and 7.0% vs. 7.4% at 21 months, p=0.73), but did report slightly fewer followup physical therapy visits in the exercise group in the intermediate and long terms[72] (Table 30).

There was insufficient evidence to determine effects of duration of exercise therapy or number of sessions on outcomes.

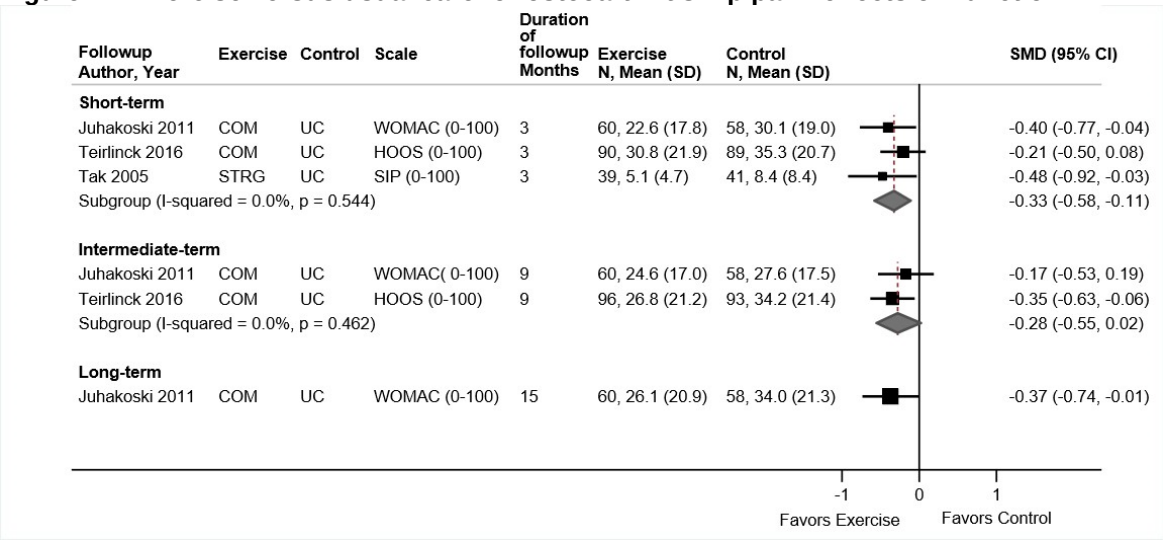
Exercise Compared With Pharmacological Therapy or With Other Nonpharmacological Therapies

No trial of exercise versus pharmacological therapy met inclusion criteria. Findings for exercise versus other nonpharmacological therapies are addressed in the sections for other nonpharmacological therapies.

Harms

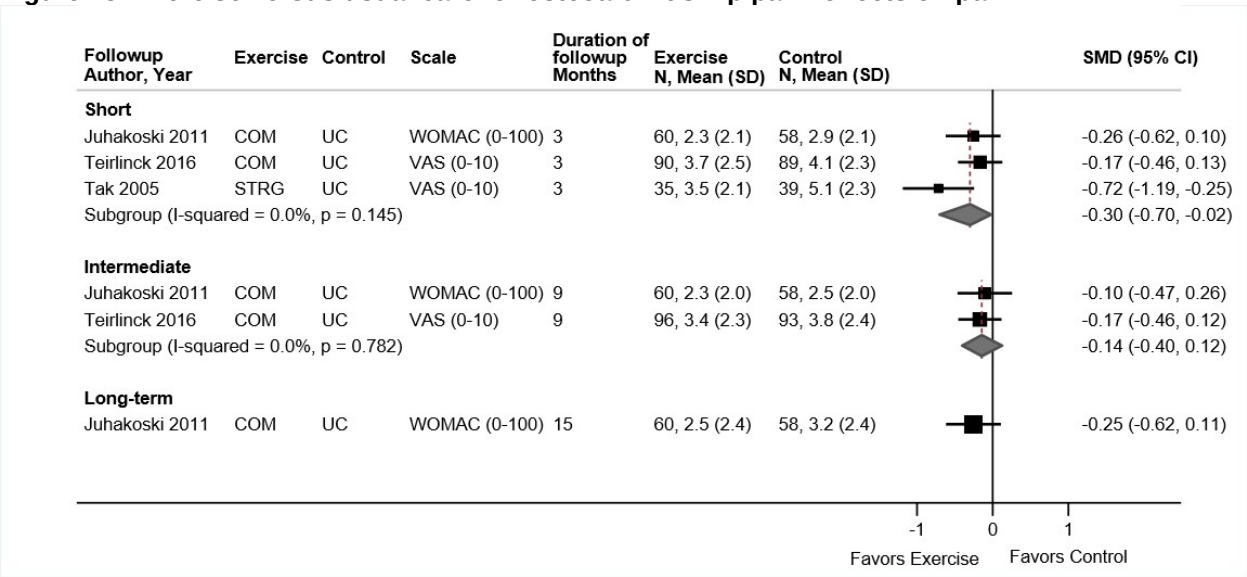
Only two exercise trials reported on harms, and neither reported adverse events in either the exercise group or usual care groups.[47,73]

Figure 42. Exercise versus usual care for osteoarthritis hip pain: effects on function



CI = confidence interval; COM = combination exercise therapy; HOOS = Hip disability and Osteoarthritis Outcomes Score; SD = standard deviation; SIP = Sickness Impact Profile physical function score; SMD = standardized mean difference; STRG = strength training exercise; UC = usual care; WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index

Figure 43. Exercise versus usual care for osteoarthritis hip pain: effects on pain



CI = confidence interval; COM = combination exercise therapy; SD = standard deviation; SMD = standardized mean difference; STRG = strength training exercise; UC = usual care; VAS = visual analog scale; WOMAC = Western Ontario and McMaster's Universities Osteoarthritis Index

Manual Therapies for Osteoarthritis Hip Pain

Key Points

- Manual therapy was associated with small improvements in short-term (difference 11.1, 95% CI 4.0 to 18.6, 0-100 scale Harris Hip Score) and intermediate-term (difference 9.7, 95% CI 1.5 to 17.9) function versus exercise (SOE: low).
- Manual therapy was associated with a small effect on pain in the short term (difference −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). The impact on pain is not clear at intermediate term; there was no difference in pain at rest (adjusted difference −7.0, 95% CI −20.3 to 5.9 , 0-100 scale) but there was small improvement in pain while walking (adjusted difference −12.7, 95% CI −24.0 to −1.9) (SOE: insufficient).
- No trials evaluated manual therapies versus pharmacological therapy.
- One trial reported that no treatment-related serious adverse events were detected and in the other, no difference in study withdrawal due to symptom aggravation was seen between manual therapy and exercise (RR 1.42, 95% CI 0.25 to 8.16) (SOE: low).
- There were insufficient data to determine the effects or harms of manual therapy compared with usual care at intermediate term. No effect size could be calculated (SOE: insufficient).

Detailed Synthesis

We identified two trials (n=69 and 109) of manual therapy for hip OA that met inclusion criteria (Table 32 and Appendix D).[47,193] Both trials were included in the prior AHRQ report. Mean patient age ranged from 66 to 72 years and females comprised 49 to 72 percent of the populations. Both trials required a diagnosis of hip OA meeting the American College of Rheumatology (ACR) criteria for inclusion. The duration of manual therapy ranged from 5 to 16

weeks with a total of nine sessions in both groups; in one trial this included seven sessions over the first 9 weeks and two booster sessions at week 16.[47] One trial compared manual therapy to usual care (continued routine care from a general practitioner and other providers)[47] and both trials compared manual therapy to combination exercise programs.[47,193] The number of exercise sessions matched the manual therapy group of that respective study. All participants were prescribed a home exercise program three times per week. One trial reported short-term outcomes[193] and both reported intermediate-term outcomes. One trial was conducted in New Zealand[47] and the other in the Netherlands.[193]

Both trials were rated fair quality (Appendix E). Compliance with the intervention was acceptable in all groups, and the methodological shortcomings of these trials included a lack of blinding for the patients and care providers.

Table 48. Osteoarthritis hip pain: manual therapy

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Abbott, 2013[47] 9.75 months Duration of diagnosis: 2.6 years Fair	A. Manual therapy (n=54/24 hip OA): 7 manual therapy sessions in 9 weeks with 2 additional booster sessions B. Exercise (n=51/22 hip OA), 7 exercise sessions in 9 weeks with 2 additional booster sessions C. Usual care (n=51/23 hip OA)	A vs. B vs. C (total population, includes knee OA) Age: 67 vs. 67 vs. 66 years Female: 49% vs. 52% vs. 58% Percent knee OA: 56% vs. 57% vs. 55% Percent hip OA: 44% vs. 43% vs. 45% Percent both hip OA and knee OA: 22% vs. 20% vs. 26% Baseline WOMAC (0-240): 114.8 vs. 95.5 vs. 93.8	A vs. B (hip OA only) 9.75 months WOMAC, mean change from baseline: −22.9 vs. −12.4, p=NR A vs. C (hip OA only) 9.75 months WOMAC, mean change from baseline: −22.9 vs. 6.6, p=NR	None

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Hoeksma, 2004[193] 3 and 6 months Duration of symptoms: NR Fair	A. Manual therapy (n=56): Sessions consisted of stretching followed by traction manipulation in each limited position (high velocity thrust technique). B. Exercise therapy (n=53): Sessions implemented exercises for muscle functions, muscle length, joint mobility, pain relief, and walking ability and were tailored to the specific needs of the patient. Instructions for home exercises were given. Both groups received 2 sessions per week for 5 weeks (9 sessions in total).	Age: 72 vs. 71 years Females: 68% vs. 72% Symptom duration of 1 month to 5 years: 76% vs. 81% Severe OA on radiography: 45% vs. 38% Baseline HHS (0-100): 54 vs. 53 Baseline pain at rest VAS (0-100): 22.5 vs. 23.0 Baseline pain walking VAS (0-100): 34.0 vs. 28.8	A vs. B <u>3 months</u> HHS: 68.4 vs. 56.0, adjusted difference 11.1, 95% CI 4.0 to 18.6 Pain at rest VAS: 19.1 vs. 26.9, adjusted difference −7.2, 95% CI −13.8 to −0.5 Pain walking VAS: 16.4 vs. 23.7, adjusted difference −12.1, 95% CI −22.9 to −2.5 <u>6 months</u> HHS: 70.2 vs. 59.7, adjusted difference 9.7, 95% CI 1.5 to 17.9 Pain at rest VAS: 14.0 vs. 21.6, adjusted difference -7.0, 95% CI −20.3 to 5.9 Pain walking VAS: 17.0 vs. 24.3, adjusted difference −12.7, 95% CI −24.0 to −1.9	A vs. B <u>3 months</u> SF-36 physical function (0-100): 45.3 vs. 46.6, adjusted difference −2.1, 95% CI −11.7 to 7.7 SF-36 role physical function: 25.4 vs. 29.8, adjusted difference −23.5 to 10.2 SF-36 bodily pain: 47.4 vs. 46.1, adjusted difference −3.2, 95% CI −13.1 to 6.8 <u>6 months</u> SF-36 physical function: 50.4 vs. 45.3, adjusted difference 3.1, 95% CI −4.1 to 10.5 SF-36 role physical function: 36.7 vs. 32.4, adjusted difference 2.2, 95% CI −16.8 to 21.1 SF-36 bodily pain: 51.4 vs. 49.9, adjusted difference −1.5, 95% CI −11.1 to 7.7

CI = confidence interval; HHS = Harris Hip Score; NR = not reported; OA = osteoarthritis; SF-36 = Short Form 36 Questionnaire; VAS = visual analog scale; WOMAC =Western Ontario and McMaster Universities Arthritis Index
[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Manual Therapies Compared With Usual Care

A single fair-quality trial (n=69 with hip OA)[47] found that manual therapy resulted in an improvement in function at intermediate term using the total WOMAC score (0 to 240) in the manual therapy group (mean change from baseline −22.9, 95% CI −43.3 to −2.6), while the usual care group showed little change from baseline (mean change −7.9, 95% CI −30.9 to 15.3). Lack of information on the number of patients precluded calculation of effect size, and results of statistical testing between groups was not presented.

Manual Therapies Compared With Pharmacological Therapy

No trial of manual therapy versus pharmacological therapy met inclusion criteria.

Manual Therapies Compared With Exercise

One trial found that manual therapy resulted in a small improvement in short-term function compared with exercise (adjusted difference on the 0-100 scale Harris Hip Score [HHS] of 11.1, 95% CI 4.0 to 18.6). Regarding intermediate-term function, manual therapy conferred a small benefit in both trials. The adjusted difference on the HHS was 9.7 (95% CI 1.5 to 17.9) in one trial.[193] The other trial compared function using the total WOMAC score (0 to 240), and the manual therapy group experienced a statistically significant improvement from baseline (mean change of −22.9, 95% CI −43.3 to −2.6), while the exercise group did not (mean change −12.4, 95% CI −27.1 to 2.3).[47]

Only one of the trials reported pain outcomes. Manual therapy was associated with a small improvement in short-term pain at rest and during walking compared with exercise (adjusted differences on a VAS (0 to 10) of −0.72, 95% CI −1.38 to −0.05, and −1.21, 95% CI −2.29 to −0.25, respectively).[193] Intermediate-term pain results were inconsistent. A moderate effect on VAS pain during walking was seen following manual therapy compared to exercise (adjusted difference −1.27, 95% CI −2.40 to −0.19), but there was no difference for pain at rest (adjusted difference −0.70, 95% CI −2.03 to 0.59).[193]

There was no difference in one trial[193] between manual therapy and exercise for short-term or intermediate-term quality of life measured with the SF-36 physical function, role physical, or bodily pain subscales (Table 31).

Harms

No trial-related serious adverse events were detected in one trial,[47] and there was no difference in symptom aggravation leading to withdrawal (5% vs. 4%; RR 1.42, 95% CI 0.25 to 8.16) in the other trial.[193]

Exercise for Osteoarthritis Hand Pain

Key Points

- Data from one poor-quality trial were insufficient to determine the effects or harms (though no serious harms were reported) of exercise versus usual care in the short term (SOE: insufficient).

Detailed Synthesis

One Norwegian trial (n=130) that evaluated the effects of strengthening and range of motion exercise (3 times weekly for 3 months plus 4 group sessions) versus usual care (treatment recommended by the patient's general practitioner) met inclusion criteria (Table 33 and Appendix D).[75] This trial was included in the prior AHRQ report and was rated poor quality due to lack of patient blinding, baseline differences in mental health conditions, and large differential attrition between groups (exercise 29% vs. usual care 7%) (Appendix E). Only short-term data was reported.

Table 49. Osteoarthritis hand pain: exercise

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Osteras, 2014[75] 3 months Duration of pain: NR Poor	A. Exercise (n=46): ROM/strength exercises, 4 group sessions supplemented by instructions for home exercise 3 times per week for 12 weeks B. Usual care (n=64): Subjects received no particular attention, referral, or treatment from the study.	A vs. B Age: 67 vs. 65 years Females: 89% vs. 91% Fulfillment of ACR criteria for hand OA 91% vs. 91% Self-reported hip OA: 39% vs. 46% Self-reported knee OA: 40% vs. 51% Other rheumatic disease: 13% vs. 15% Severe mental distress: 17% vs. 39% Baseline FIHOA (0-30): 10.8 vs. 9.8 PSFS (0-10): 3.5 vs. 3.9 Baseline hand pain NRS (0-10): 4.2 vs. 3.9	A vs. B 3 months FIHOA: 10.9 vs. 10.5; adjusted difference −0.5 (95% CI −1.9 to 0.8) Hand pain NRS: 4.3 vs. 4.3 ; adjusted difference −0.2 (95% CI −0.8 to 0.3) OARSI OMERACT no. of responders: 30% vs. 28% (NS)	A vs. B 3 months PSFS (0-10): 4.3 vs. 4.4; adjusted difference 0.1 (95% CI −0.7 to 1.0) Patient global assessment of disease activity (0-10): 4.2 vs. 4.1; adjusted difference 0.1 (95% CI −0.5 to 0.7) Patient global assessment of disease activity affecting ADL: 3.8 vs. 3.8; adjusted difference −0.2 (95% CI −0.8 to 0.4)

ACR = American College of Radiology; ADL = activity of daily living; CI = confidence interval; FIHOA = Functional Index for Hand OsteoArthritis; NR = not reported; NRS = numeric rating scale; NS = not statistically significant; OA = osteoarthritis; OARSI OMERACT = Osteoarthritis Research Society International Outcome Measures in Rheumatology; PSFS = patient-specific function scale; ROM = range of motion

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Exercise Compared With Usual Care

Data were insufficient from one poor-quality trial. No differences between exercise and usual care were observed for function according to the Functional Index for Hand OsteoArthritis (adjusted difference −0.5 on a 0-30 scale, 95% CI −1.9 to 0.8), or for pain (adjusted difference −0.2 on a 0 to 10 VAS pain scale, 95% CI −0.8 to 0.3) at 3 months.[75] Similarly, there were no differences between groups in the proportion of Osteoarthritis Research Society International Outcome Measures in Rheumatology (OARSI OMERACT) responders (30% versus 28%). There were also no differences between groups in any secondary outcome measure, including the patient-specific function scale, hand stiffness, or patient global assessment of disease activity.

The effects of exercise on use of opioid therapies or healthcare utilization were not reported. There was insufficient evidence to determine effects of duration of exercise therapy or number of sessions on outcomes.

Exercise Compared With Pharmacological Therapy or Other Nonpharmacological Therapies

No trial of exercise versus pharmacological therapy met inclusion criteria. Findings for exercise versus other nonpharmacological therapies are addressed in the sections for other nonpharmacological therapies.

Harms

In this trial,[75] no serious adverse events were reported; 8/130 (6%) patients reported increased pain (3 in hand, 5 in neck/shoulders) but adverse events were not reported by group.

Physical Modalities for Osteoarthritis Hand Pain

Key Points

- One good-quality study of low-level laser treatment versus sham found no differences in 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).
- Data were insufficient from one fair-quality trial to determine effects or harms of heat therapy using paraffin compared to no treatment on function or pain in the short term (SOE: insufficient).
- No serious harms were reported in the trial of low-level laser therapy (SOE: low).

Detailed Synthesis

We identified two trials of physical modality use for hand OA (Table 34 and Appendixes D and E).[165,166] Both were included in the prior AHRQ report. One good-quality double-blind Canadian trial (N=88)[165] compared three, 20-minute sessions of low-level laser treatment to a sham laser probe over a 6-week period. Identical treatment procedures were used in each group. All participants attended three sham laser treatment sessions prior to randomization to ensure ability to comply with the treatment protocol.

One fair-quality trial (n=46) conducted in Turkey compared 15 minutes of paraffin wrapping 5 days per week for 3 weeks with a no treatment control group.[166] Both groups received information about joint protection strategies. Methodological limitations included lack of patient blinding, unclear compliance with treatment, and poorly reported analyses.

Table 50. Osteoarthritis hand pain: physical modalities

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Brosseau, 2005[165] 4.5 months Duration of pain: NR Good	A. Low-level laser therapy (n=42): 3 J/cm^2 applied for 1 second each to the skin overlying the radial, medial and ulnar nerves (total of 15 points irradiated); 3 sessions lasting 20 minutes per week for 6 weeks B. Sham low-level laser therapy (n=46): same procedure as the active treatment but a sham laser probe was used.	A vs. B Age: 64 vs. 65 years Female: 74% vs. 83% Medication use: 60% vs. 61% Diagnosis of OA: 7.5 vs. 8.5 years Baseline AUSCAN function (0-4)[b]: 2.2 vs. 2.1 Baseline AUSCAN pain (0-4)[b]: 2.4 vs. 2.1 Baseline pain intensity VAS (0-100): 56.9 vs. 49.4	A vs. B <u>4.5 months</u> AUSCAN function: 1.9 vs. 1.7, difference 0.2 (95% CI −0.2 to 0.6) AUSCAN pain: 1.9 vs. 1.8, difference 0.1 (95% CI −0.3 to 0.5) Pain VAS: NR	A vs. B <u>4.5 months</u> Patient global assessment: Fully improved: 0% vs. 3% Partially improved: 40% vs. 33.3% No improvement: 60% vs. 52%
Dilek, 2013[166] 2.25 months Duration of pain: Mean 5.5 years Fair	A. Dip-wrap paraffin bath therapy (n=24): patients dip both hands into 50°C paraffin bath 10 times, paraffin left on for 15 minutes, treatment administered 5 days per week for 3 weeks B. Control group (n=22): Details NR; assumed to be no treatment Only paracetamol intake was permitted during the study	A vs. B Age: 59 vs. 60 years Female: 83% vs. 91% Baseline AUSCAN function (0-36)[c]: 16.2 vs. 17.1 Baseline AUSCAN pain (0-20)[c]: 10.7 vs. 9.8 Baseline Pain at rest, median (VAS 0-10): 5.0 vs. 4.0 Baseline Pain during ADL, median (VAS 0-10): 7.0 vs. 8.0	A vs. B <u>2.25 months</u> AUSCAN function: 13.8 vs. 17.8, difference −4.0 (95% CI −8.6 to 0.6) AUSCAN pain: 6.5 vs. 9.5, difference −3 (95% CI −5.5 to −0.5) Pain VAS at rest, median: 0.0 vs. 5.0, p<0.001 Pain VAS during ADL, median: 5.0 vs. 7.0, p=0.05	NR

ADL = activity of daily living; AUSCAN = Australian Canadian Osteoarthritis Hand Index; CI =confidence interval; NR = not reported; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Data for the AUSCAN was presented as an average of all responses, on a 5-point Likert scale (0-4), for both the physical function (9 items) and pain (5 items) subscale

[c] Data for the AUSCAN was presented as a sum of the values across all items within the physical function (9 items) and pain (5 items) subscales; a 5-point Likert scale (0-4) was used to rate each item resulting in score ranges of 0-36 and 0-20, respectively

Physical Modalities Compared With Sham or No Treatment

Low-Level Laser Therapy. In the one good-quality trial of low-level laser treatment versus sham (n=88),[165] there were no differences in short-term function (difference 0.2 on a 0-4 Australian Canadian Osteoarthritis Hand Index [AUSCAN] functional subscale, 95% CI −0.2 to 0.6) or pain (difference 0.1 on a 0-4 AUSCAN pain subscale, 95% CI −0.3 to 0.5) at 4.5 months. Likewise, no difference was seen between groups in improvement based on patient global assessment.

Paraffin Treatment. One fair-quality trial (N =56)[166] of paraffin heat treatment demonstrated no difference compared with no treatment on the AUSCAN function scale (0-36) (difference −4.0, 95% CI −8.6 to 0.6 at short-term [2.25-month] followup). Regarding pain, no clear difference was identified between the groups over the short term as there was inconsistency across

measures used and analyses for outcomes were poorly reported; findings were considered insufficient.[166] While heat treatment was slightly favored based on the AUSCAN pain subscale (difference −3 on a 0-20 scale, 95% CI −5.5 to −0.5), it was not statistically significant in the author's intention-to-treat (ITT) analysis (p=0.07). VAS pain at rest suggested more improvement with heat therapy versus control in the ITT analysis (median 0 vs. 5.0 on a 0-10 scale, p<0.001); however, there was no clear difference between groups on VAS pain during ADL (median 5.0 vs. 7.0, p=0.09 for per protocol analysis, p=0.05 for ITT).

No trial evaluated effects of physical modalities on use of opioid therapies or healthcare utilization.

Physical Modalities Compared With Pharmacological Therapy or With Exercise Therapy

No trial of a physical modality versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

Only the low-level laser therapy trial reported adverse events; no serious harms were reported.[165] One patient (2%) who received low-level laser treatment experienced erythema at the site.

Multidisciplinary Rehabilitation for Osteoarthritis Hand Pain

Key Points

- One fair-quality trial of multidisciplinary rehabilitation versus waitlist control found no differences between groups over the short term in function (adjusted difference 0.49, 95% CI −0.09 to 0.37 on 0-36 scale) or pain (adjusted difference 0.40, 95% CI −0.5 to 1.3 on a 0-20 scale), or with regard to the proportion of OARSI OMERACT responders (OR 0.82, 95% CI 0.42 to 1.61) (SOE: low for all outcomes).
- Data on harms were insufficient, although no serious adverse events were reported in the one trial of multidisciplinary rehabilitation versus waitlist control (SOE: insufficient).

Detailed Synthesis

One fair-quality trial (n=147) compared four, 2.5- to 3-hour group-based sessions, delivered by an occupational therapist and a specialized nurse, consisting of self-management techniques, ergonomic principles, daily home exercises, and splint (optional) versus a waitlist control,[261] (Table 35 and Appendix D). Waitlist control consisted of one 30-minute explanation of OA followed by a 3-month waiting period. Effect estimates were adjusted for baseline function or pain, body mass index (BMI), gender, and presence of erosive arthritis. Methodological limitations included lack of patient blinding and unreported compliance to treatment (Appendix E). This trial was included in the prior AHRQ report.

Of note, this intervention appeared to focus on functional restoration and while it met our broad definition of multidisciplinary rehabilitation (see footnote in Table 1), it was not consistent with how multidisciplinary rehabilitation is generally delivered clinically.

Table 51. Osteoarthritis hand pain: multidisciplinary rehabilitation

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Stukstette, 2013[261] 3 months Duration of pain: Mean 4 years Fair	A. Multidisciplinary treatment program (n=75): 4 group based therapy sessions of 2.5-3 hours duration (time period NR), supervised by a specialized nurse and occupational therapist B. Waiting list (n=72) All patients: 30 minute explanation of written information about OA	A vs. B Age: 60 vs. 58 Female: 18% vs. 16% Mean duration of diagnosis: 4 vs. 4 years Proportion taking opioids: 3% vs. 4% Baseline AUSCAN function (0-36): 21.0 vs. 21.8 Baseline AUSCAN pain (0-20):10.4 vs. 10.2	A vs. B 3 months AUSCAN function: 18.6 vs. 18.8, adjusted difference 0.5 (95% CI −0.09 to 0.4) AUSCAN pain: 9.4 vs. 9.0, adjusted difference 0.4 (95% CI −0.5 to 1.3) OARSI OMERACT responders: 33% vs. 37%, OR 0.8 (95% CI 0.4 to 1.6)	A vs. B 3 months Patient global assessment (0-100): 60.4 vs. 66.0, adjusted difference −5.2 (95% CI −11.4, 1.0) SF-36 PCS (0-100): 39.8 vs. 39.9, adjusted difference −0.14 (95% CI −1.62 to 1.35) SF-36 MCS (0-100): 50.3 vs. 51.6, adjusted difference 0.27 (95% CI −2.13 to 2.67)

AUSCAN = Australian Canadian Osteoarthritis Hand Index; OA = osteoarthritis; OARSI-OMERACT = Osteoarthritis Research Society International Outcome Measures in Rheumatology; OR = Odds ratio; SF-36 MCS = Short-Form 36 Questionnaire Mental Component ScoreSF-36 PCS = Short-Form 36 Physical Component Score

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period.

Multidisciplinary Rehabilitation Compared With Waitlist

No short-term (3 months) differences in function on the AUSCAN functional subscale (adjusted difference 0.49, 95% CI −0.09 to 0.37 on 0-36 scale) or on the AUSCAN pain subscale (adjusted difference 0.40, 95% CI −0.5 to 1.3, scale 0-20) were reported.[261]

There was no difference in the proportion of OARSI OMERACT responders (odds ratio [OR] 0.82, 95% CO 0.42 to 1.61) between groups or on any secondary outcome measure, including ADLs (Canadian Occupational Measurement Scales), health-related quality of life (SF-36), arthritis self-efficacy, pain coping, muscle strength, or joint mobility.[261]

The effect of multidisciplinary rehabilitation on use of opioid therapies or healthcare utilization was not evaluated in any of the included studies.

Multidisciplinary Rehabilitation Compared With Pharmacological Therapy or With Exercise Therapy

No trial of a multidisciplinary rehabilitation program versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

No serious adverse events were reported. One patient reported a swollen hand and increased pain after the second treatment session.[261]

Key Question 4: Fibromyalgia

For fibromyalgia, 47 RCTs (in 54 Publications) were included in the prior AHRQ report (N=4225). Three trials were rated good quality, twenty trials fair quality, and twenty-four trials poor quality. The prior AHRQ report found exercise, CBT, myofascial release, massage, tai chi,

qigong, acupuncture, and multidisciplinary rehabilitation (MDR) associated with small to moderate improvements in function and pain over the short and intermediate term compared with an attention control, sham, no treatment or usual care. Strength of evidence was low to moderate. In the long term, small improvement in function continued for MDR and in pain for massage (low strength of evidence). CBT compared with pregabalin was associated with a small improvement in function but not pain in the short term.

For this update, we identified 11 new RCTs (in 12publications) (N=1194). Ten were rated fair quality and one was rated poor quality. The new trials evaluated exercise (1 trial), psychological therapies (CBT and electromyography [EMG] biofeedback) (6 trials), mindfulness practices (1 trial), mind-body practices (Tai chi) (1 trial) and acupuncture (2 trials). The Key Points summarize the main findings based on the evidence included in the prior report and new trials; the Key Points note where new trials contributed to findings.

Exercise for Fibromyalgia

Key Points

- Exercise was associated with a small improvement in function compared with attention control, no treatment, or usual care in the short term (7 trials, pooled difference −7.68 on a 0 to 100 scale, 95% CI −13.04 to −1.84, I^2=60%) (SOE: low) and intermediate term (8 trials, pooled difference −6.04, 95% CI −9.25 to −3.01, I^2=0%) (SOE: moderate). There were no clear effects in the long term (3 trials, pooled difference −4.33, 95% CI −10.46 to 1.97, I^2=0%) (SOE: low).
- Exercise was associated with a small improvement in VAS pain (0 to 10 scale) compared with usual care, attention control, or no treatment in the short term (6 trials [excluding outlier trial], pooled difference −0.88, 95% CI −1.33 to −0.27, I^2=1.5%), and at intermediate term (8 trials [1 new], pooled difference −0.51, 95% CI −0.92 to −0.06), I^2=0%) but no effect long term (4 trials, pooled difference −0.18, 95% CI −0.77 to 0.42, I^2=0%) (SOE: moderate for all time frames).
- There was insufficient evidence from one small, poor-quality trial to determine the effects of aerobic exercise versus pharmacological therapy (paroxetine) on pain in the intermediate term (SOE: insufficient). There were no data on short- or long-term effects.
- Data on harms were insufficient. Most trials of exercise did not report on adverse events at all. One trial reported one nonstudy-related adverse event. Two trials reported no adverse events. (SOE: insufficient).

Detailed Synthesis

Twenty-two trials (reported in 24 publications) of exercise therapy for fibromyalgia met inclusion criteria[76-99] (Table 36 and Appendix D). This included one new trial not included in the prior AHRQ report.[99] The exercise interventions varied across the trials and included combinations of different exercise types (12 trials),[77,78,80,83,85,89,91,92,94-97,99] aerobic exercise (10 trials),[79,81,82,84,86-88,90,92,93,98] muscle performance exercise/strength training (1 trial),[86] and Pilates (1 trial).[76] The duration of exercise therapy ranged from 1 to 8 months across the trials and the total number of exercise sessions ranged from 4 to 96 (at a frequency of 1 to 5 times per week). Many trials also included instruction for home exercise practice. Exercise was compared to usual care in nine trials,[79,80,90-92,96-99] no treatment in six trials,[83-86,89,94,95] attention control in five trials,[76,78,81,82,87,88] and to waitlist,[77] sham (i.e., transcutaneous electrical stimulation),[93] and

pharmacological care[93] in one trial each (the latter two control conditions were separate arms of the same trial). Usual care generally included medical treatment for fibromyalgia and continued normal daily activities (which often specifically excluded the exercise intervention being evaluated). Attention control conditions consisted of fibromyalgia education sessions, social support, general guidance on coping strategies, relaxation and stretching exercises, and physical activity planning.

Sample sizes ranged from 32 to 166 across the trials (total sample=1,428). Patient mean age ranged from 35 to 57 years, and the majority were female (89% to 100%). Thirteen trials were conducted in Europe,[79,83,85,88-92,94-99] five in North America,[78,80-82,84,87] two in Brazil,[77,86] and two in Turkey.[76,93]

Twelve trials were rated fair quality[76,77,79-82,86,88,89,92,96,98,99] and 10 poor quality[78,83-85,87,90,91,93-95,97] (Appendix E). Methodological limitations in the fair-quality trials were primarily related to unclear allocation concealment methods and lack of blinding (the nature of interventions precluded blinding of participants and researchers). Additionally, poor-quality trials also suffered from unclear randomization methods and high rates of attrition and/or differential attrition.

Table 52. Fibromyalgia: exercise therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Altan, 2009[76] 3 months Duration of pain: NR Fair	A. Pilates (n=25): 1 hour session 3 times per week for 3 months: Pilates postural education, search for neutral position, sitting, antalgic, stretching and, proproceptivity improvement exercises, and breathing education B. Attention control (n=25): Instructions in home exercise relaxation/stretching program of 1 hour sessions 3 times per week for 3 months All patients: Education session about available diagnosis and treatment of FM	A vs. B Age: 48 vs. 50 years Female: 100% vs. 100% Baseline FIQ (0-100): 80.8 vs. 80.1 Baseline pain VAS (0-10): 6.1 vs. 6.3	A vs. B <u>3 months:</u> FIQ: 69.3 vs. 77.6, difference −8.3 (95% CI −21.8 to 5.2) Pain VAS: 5.2 vs. 6.5, difference −1.3 (95% CI −2.6 to 0.03)	A vs. B <u>3 months:</u> NHP (0-100): 224.2 vs. 246.3, difference −22.1 (95% CI −96.0 to 51.8)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Baptista, 2012[77] 4 months Duration of pain: NR Fair	A. Belly dance (n=40): One hour belly dance classes twice a week for 16 weeks (combination exercise) B. Waiting list control (n=40): dance offered at end of the study	A vs. B: Age: 50 vs. 49 years Female: 100% vs. 100% Race: NR Baseline FIQ (0-10): 5.9 vs. 6.3 Baseline pain VAS (0-10): 7.7 vs. 7.5	A vs. B <u>4 months</u> FIQ: 4.3 vs. 5.9; difference −1.6 (95% CI −2.5 to −0.8) Pain VAS: 4.7 vs. 7.3; difference −2.6 (95% CI −3.6 to −1.6)	A vs. B <u>4 months</u> BDI (0-63): 23.1 vs. 23.5; difference −0.40 (95% CI −7.09 to 6.29) STAI part 1: 49.4 vs. 51.8; difference −2.40 (95% CI −6.87 to 2.07) STAI part 2: 49.8 vs. 54.1; difference −4.3 (95% CI −8.72 to 0.12) SF-36 function (0-100): 56.3 vs. 39.1; difference 17.2 (95% CI 7.55 to 26.85) SF-36 limitation due to physical aspects (0-100): 36.5 vs. 13.8; difference 22.7 (95% CI 9.06 to 36.34) SF-36 pain (0-100): 46.0 vs. 29.1; difference 16.9 (95% CI 7.62 to 26.18) SF-36 mental (0-100): 52.3 vs. 46.2; difference 6.1 (95% CI −3.89 to 16.09)
Buckelew, 1998[78] 3 and 24 months Duration of symptoms: 11 years Poor	A. Combination exercise (n=30): included active range of motion exercises, strengthening exercises, low to moderate intensity aerobic exercise, proper posture and body mechanics instruction, and instructions on use of heat, cold, and massage; one 90 minute session per week for 1.5 months and instructions to train 2 additional times independently per week then 24 months of monthly 1-hour groups. B. Attention control (n=30): one 90-180 minute education session weekly for 1.5 months	A vs. B Age: 46 vs. 44 years Female: 93% vs. 90% Duration of symptoms: 12 vs. 10 years Duration of diagnosis: 3.0 vs. 2.5 years Baseline AIMS physical activity subscale (0-10): median 4.0 vs. 6.0 Baseline pain VAS (0-10): median 6.3 vs. 5.9	A vs. B <u>3 months</u>: AIMS physical activity subscale: median 4.0 vs. 6.0; median change from baseline 0 vs. 0 Pain VAS: median 5.4 vs. 5.8, median change from baseline −0.8 vs. −0.5 <u>24 months</u> AIMS physical activity subscale: median 4.0 vs. 6.0, median change from baseline 0 vs. 0 Pain VAS: median 5.5 vs. 5.4, median change from baseline −1.2 vs. −0.6	A vs. B <u>3 months</u>: SCL-90-R Global Severity Index (0-90): median 65.5 vs. 65.0, median change from baseline −3 vs. 0 CES-D (0-60): median 13.5 vs. 13.0, median change from baseline −2.5 vs. 3 Sleep scale (0-12), median 8.0 vs. 5.0, median change from baseline 0 vs. 0 <u>24 months</u> SCL-90-R Global Severity Index: median 65.5 vs. 67.0, median change from baseline −2.5 vs. −1 CES-D: median 11.5 vs. 12.0, median change from baseline −3.5 vs. −2 Sleep scale: median 7.5 vs. 6.0, median change from baseline 0 vs. 0

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Clarke-Jenssen, 2014[79] 3 and 12 months Duration of symptoms: 14 years Fair	A. Aerobic exercise (n=44): conducted on land and in warm water provided in a warm climate; also stretching, relaxation, and education; provided in groups 5 days per week for 4 weeks B. Aerobic exercise (n=44): on land and in warm water provided in a cold climate; also stretching, relaxation, education, provided in groups 5 days per week for 4 weeks C. Usual Care (n=44): no intervention	A vs. B vs. C: Age: 46 vs. 46 vs. 45 years Female: 88% vs. 93% vs. 96% Symptom duration: 17 vs. 13 vs.12 years Baseline pain VAS (mean, 0-10): 6.6 vs. 6.9 vs. 6.6	A vs. C, between-group difference in change from baseline: <u>3 months</u> FIQ: data NR, p=NS Pain VAS: −1.2 (95% CI −2.2 to −0.1) <u>12 months</u> FIQ data NR, p=NS Pain VAS: 0.1 (95% CI −0.9 to 1.1) B vs. C, between-group difference in change from baseline: <u>3 months</u> FIQ: data NR, p=NS Pain VAS: −0.9 (95% CI −1.9 to 0.2) <u>12 months</u> FIQ: data NR, p=NS Pain VAS: 0 (95% CI −1 to 1)	A vs. C, between-group difference in change from baseline: <u>3 months</u> HADS: data NR, p=NS SF-36 Physical: data NR, p=NS SF-36 Mental: data NR, p=NS <u>12 months</u> HADS: data NR, p=NS SF-36 Physical: data NR, p=NS SF-36 Mental: data NR, p=NS B vs. C, between-group difference in change from baseline: <u>3 months</u> HADS: data NR, p=NS SF-36 Physical: data NR, p=NS SF-36 Mental: data NR, p=NS <u>12 months</u> HADS: data NR, p=NS SF-36 Physical: data NR, p=NS SF-36 Mental: data NR, p=NS

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Da Costa, 2005[80] 3 and 9 months Duration of symptoms: 11 years Fair	A. Combination Exercise (n=39): aerobic exercise, stretching, and strength exercises; 4 visits (initial 90 minutes, others 30 minutes) over 12 weeks with exercise physiologist; individualized home-based program. B. Usual care (n=41): subjects asked to record exercise activity weekly during the 12-week intervention phase and monthly thereafter.	A vs. B Age, years: 49 vs. 52 Female: 100% vs. 100% Symptom duration: 10.5 vs. 11.2 years Baseline FIQ (0-100): 55.1 vs. 48.6 Baseline upper body pain VAS (0-100): 49.5 vs. 47.4 Baseline lower body pain VAS (0-100): 47.0 vs. 47.0	A vs. B, mean change from baseline <u>3 months:</u> FIQ: −7.8 (95% CI −13.9 to −1.7) vs. −0.04 (95% CI −5.2 to 5.1), p=0.05 Pain VAS, upper body: −10.6 (95% CI −17.8 to −3.4) vs. −1.9 (95% CI −6.9 to 3.2), p=0.048 Pain VAS, lower body: −8.21 (95% CI −15.7 to −0.74) vs. −2.0 (95% CI −9.4 to 5.4), p=0.24 <u>9 months</u>: FIQ: −10.1 (95% CI −16.1 to −4.0) vs. −0.024 (95% CI −4.4 to 3.9), p=0.009 Pain VAS, upper body: −7.9 (95% CI −14.3 to −1.4) vs. 2.4 (95% CI 3.7 to 8.5), p=0.02 Pain VAS, lower body: −5.6 (95% CI −13.3 to 2.2) vs. −0.29 (95% CI −8.6 to 8.0), p=0.35	A vs. B, mean change from baseline <u>3 months:</u> SCL 90-R GSI (30−81): −0.02 (95% CI −0.3 to −0.04) vs. −0.07 (95% CI −0.2 to 0.05), p=0.26 <u>9 months</u>: SCL 90-R GSI (30-81): −0.16 (95% CI −0.28 to 0.35) vs. −0.09 (95% CI −0.21 to 0.03), p=0.39
Fontaine, 2010, 2011[81,82] 6 and 12 months Duration of fibromyalgia: Mean 7.4 years Fair	A. Aerobic Exercise (n=30): Lifestyle Physical Activity; 6, 60-minute group sessions over 3 months with the goal to increase moderate-intensity physical exercise by accumulating short bursts of physical activity throughout the day to 30 minutes 5-7 days per week. B. Attention control (n=23): FM education, monthly sessions for 3 months. Included education about FM and social support.	A vs. B Age: 46 vs. 49 years Female: 94% vs. 100% Race, white: 78% vs. 82% Years since diagnosis: 5.9 vs. 9.6 Baseline FIQ (scale NR): 67.5 vs. 69.7 Baseline pain VAS (0-100): 54.6 vs. 58.9	A vs. B <u>6 months:</u> FIQ: 65.3 vs. 63.9, difference 1.4 (95% CI −10.0 to 12.8) Pain VAS: 54.9 vs. 49.4, difference 5.5 (95% CI −7.8 to 18.8) <u>12 months:</u> FIQ: 64.4 vs. 65.1, difference −0.7 (95% CI −13.6 to 12.2) Pain VAS: 51.6 vs. 50.9, difference 0.7 (95% CI −12.9 to 14.3)	A vs. B <u>6 months:</u> CES-D (scale NR): 18.1 vs. 19.9, difference −1.8 (95% CI −7.5 to 3.9) <u>12 months:</u> CES-D: 19.8 vs. 20.6, difference −0.8 (95% CI −7.1 to 5.5)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Giannotti, 2014[83] 1 and 6 months Duration of pain: NR Poor	A. Combination exercise (n=21): stretching, strengthening, active and passive mobilization, spine flexibility, and aerobic training plus education 2 days a week (60 minutes per session) for 10 weeks; instructions to perform at home the exercise program at least 3 times per week. B. No intervention (n=20)	A vs. B Age: 53 vs. 51 years Female: 95% vs. 92% Baseline FIQ (0-100): 62.7 vs. 59.1 Baseline pain VAS (0-10): 6.1 vs. 6.1	A vs. B <u>1 month:</u> FIQ: 55.5 vs. 50.9, difference 4.6 (95% CI −6.38 to 15.58) Pain VAS: 5.3 vs. 5.5, difference −0.20 (95% CI -1.87 to 1.47) <u>6 months</u> FIQ: 48.8 vs. 56.9, difference −8.1 (95% CI −20.33 to 4.13) Pain VAS: 5.8 vs. 5.4, difference 0.4 (95% CI −1.4 to 2.2)	A vs. B <u>1 month</u> Sleep VAS (0-10): 4.6 vs. 5.0, difference −0.40 (95% CI −2.51 to 1.71) <u>6 months</u> Sleep VAS (0-10): 6.3 vs. 6.1, difference 0.20 (95% CI −2.15 to 2.55)
Gowans, 2001[84] 6 months Duration of symptoms: 9 years Poor	A. Aerobic exercise (n=30): 3 pool and walking exercise classes (plus stretching) per week for 6 months B. Control group (n=27): continued ad libitum activity	A vs. B Age: 45 vs. 50 years Female: 89% vs. 87% Baseline FIQ (0-80): 57.7 vs. 56.6	A vs. B <u>6 months:</u> FIQ: 48.6 vs. 54.9, p**<0.05; difference −6.3 (95% CI −14.8 to 2.2)	A vs. B <u>6 months:</u> BDI (0-63): 16.9 vs. 21.3, p**<0.05 difference −4.4 (95% CI −10.4 to 1.6), p=0.15 STAI (20-80): 41.3 vs. 51.7, P**<0.05; difference −10.4 (95% CI −18.2 to −2.6), p=0.01
Gusi, 2006[85] 3 months Duration of symptoms: 22 years Poor	A. Combination exercise (n=18): 1-hour pool exercise (warm up, aerobic exercise, mobility and lower-limb strength exercises, cool down) 3 times per week for 12 weeks (subjects instructed to avoid physical exercise for the next 12 weeks) B. Control (n=17): Normal daily activities, which did not include any exercise related to those in the therapy.	A vs. B Age, years: 51 vs. 51 Female: 100% vs. 100% Baseline pain VAS (0-100): 63.1 vs. 63.9	A vs. B Change from baseline <u>3 months</u> Pain VAS: −1.6 (95% CI −12.7 to 0.9) vs. 0.9 (95% CI −7.3 to 9.2), p=0.69	A vs. B Change from baseline <u>3 months</u> EQ-5D (0-1): 0.14 (95% CI −0.03 to 0.32) vs. −0.02 (−0.17 to 0.13), p=0.14 EQ-5D Pain/discomfort (1-3): −0.1 (95% CI −0.4 to 0.3) vs. 0 ((95% CI −0.3 to 0.3), p=0.79 EQ-5D Anxiety/depression (1-3): −0.5 (95% CI −0.8 to −0.1) vs. 0 (95% CI −0.2 to 0.2), p=0.01

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Kayo, 2012[86] 3 months Duration of symptoms: 5 years Fair	A. Aerobic exercise (n=30): Walking program, 60 minutes 3 times per week for 16 weeks, supervised by physical therapist. B. Muscle strengthening exercise (n=30): 60 minutes 3 times per week for 16 weeks, supervised by physical therapist. C. No treatment (n=30)	A vs. B: Age: 48 vs. 47 vs. 46 years Symptom duration: 4.0 vs. 4.7 vs. 5.4 Baseline FIQ total (0-100): 63.1 vs. 67.3 vs. 63.8 Baseline pain VAS (0-10): 8.6 vs. 8.7 vs. 8.4	A vs. C <u>3 months</u> FIQ: 38.5 vs. 57.7; overall group X time interaction p=NS Pain VAS: 4.8 vs. 6.7; overall group X time interaction p=NS B vs. C <u>3 months</u> FIQ: 50.5 vs. 57.7; overall group X time interaction p=NS Pain VAS: 5.9 vs. 6.7; overall group X time interaction p=NS	NR
King, 2002[87] 3 months Duration of symptoms: 8.5 years Poor	A. Aerobic exercise (n=30): aerobic land and water activities; three, 10-40 minute supervised exercise sessions per week for 3 months B. Control (n=18): instructions on stretches and coping strategies and contacted 1-2 times during the 3 month treatment period to answer any questions	A vs. B Age: 45 vs. 47 years Female: 100% vs. 100% Duration of symptoms: 7.8 vs. 9.6 years Baseline FIQ (0-80): 52.4 vs. 55.2	A vs. B <u>3 months</u> FIQ: 47.5 vs. 51.5, difference −4.0 (95% CI −12.2 to 4.2)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Mannerkorpi, 2009[88] 6-7 months Duration of pain: NR Fair	A. Aerobic exercise (n=81): One 45 minute pool aerobic exercise session per week for 20 weeks, stretching exercise also, plus six 1 hour weekly sessions of strategies to cope with FM symptoms, plan for physical activity for the following week and short relaxation exercise B. Education control (n=85): six 1 hour weekly sessions of strategies to cope with FM symptoms, plan for physical activity for the following week and short relaxation exercise	A vs. B Age: 45 vs. 47 years Female: 100% vs. 100% Baseline FIQ (0-100): 61.6 vs. 66.6 Baseline FIQ pain subscale (0-100): 67.7 vs. 70.4	A vs. B <u>6-7 months</u> FIQ: mean change from baseline: −3.9 vs. −4.5, p=0.04 FIQ pain: mean change from baseline: −6.5 vs. −2.5, p=0.018	A vs. B <u>6-7 months</u> HADS depression scale (0-21): mean change from baseline −0.4 vs. 0.0, p=0.99 HADS anxiety scale (0-21): mean change from baseline −0.7 vs. 0.4, p=0.15 SF-36 PCS (0-100): mean change from baseline 2.9 vs. 1.3, p=0.13 SF-36 MCS (0-100): mean change from baseline 0.5 vs. 1.3, p=0.15 SF-36 physical functioning (0-100): mean change from baseline 2.2 vs. 1.3, p=0.70 SF-36 role-physical (0-100): mean change from baseline 12.1 vs. 9.3, p=0.72 SF-36 bodily pain (0-100): mean change from baseline 5.0 vs. 3.6, p=0.24
Paolucci, 2015[89] 3 months Duration of symptoms: NR Fair	A. Combination exercise (n=19): Low-impact aerobic training, agility training balance and postural exercises, hip flexor strengthening, static stretching, diaphragmatic breathing, and relaxation; 10, 60-minute sessions, twice a week for 5 weeks B. Control (n=18): No rehabilitation interventions, continued normal activities	A vs. B Age: 50 vs. 48 years Female: 100% vs. 100% Baseline FIQ total (0-100): 64.8 vs. 63.9	A vs. B <u>3 months:</u> FIQ total: 53.8 vs. 64.3, difference −10.5 (95% CI −17.8, −3.2)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sanudo, 2010[92] 6 months Duration of pain: NR Fair	A. Combination exercise (n=21): supervised aerobic, muscle strengthening, and flexibility exercises; twice-weekly sessions for 24 weeks B. Aerobic exercise (n=22): warm-up, aerobic exercise, cool down; two, 45-60 minute sessions/week for 6 months C. Usual care control (n=21): medical treatment for FM and continued normal daily activities, which did not include aerobic exercise.	A vs. B vs. C Age: 56 vs. 56 vs. 57 years Baseline FIQ (0-100): 62.2 vs. 60.9 vs. 60.5	A vs. C <u>6 months</u> FIQ: mean change from baseline −8.8 vs. NR; p<0.01 B vs. C <u>6 months</u> FIQ: mean change from baseline −8.8 vs. NR; p<0.05	A vs. C <u>6 months</u> BDI (0-63): mean change from baseline −6.4 vs. NR; p<0.01 SF-36 total (0-100): mean change from baseline 8.4 vs. NR; p<0.01 B vs. C <u>6 months</u> BDI: −8.5 vs. NR; p<0.01 SF-36 total: 8.9 vs. NR; p<0.05
Sanudo, 2012[91] 6, 18 and 30 months Duration of pain: NR Poor	A. Combination exercise (n=21): Twice-weekly 45- to 60-minute sessions of exercise (warm up, aerobic exercise, muscle strengthening exercise, flexibility exercises) for 6 months. B. Usual care (n=20): alternated between 6 months of training and 6 months with no exercise intervention (asked not to participate in any structured exercise program) for 30 months.	A vs. B Female: 100% vs. 100% Baseline FIQ (0-80): 58.6 vs. 55.6	A vs. B <u>6 months:</u> FIQ: 48.5 vs. 55.4, p<0.0005; difference −6.9 (95% CI −14.4 to 0.6), p=0.07 <u>18 months:</u> FIQ: 45.6 vs. 51.3, p=NR; difference −5.7 (95% CI −14.6 to 3.2), p=0.20 <u>30 months</u> FIQ: 38.5 vs. 49.5, p NS; difference −11.0 (95% CI −19.9 to −2.1), p=0.02	A vs. B <u>6 months:</u> SF-36 (0-100): 49.5 vs. 37.9, p=0.13; difference 4.68 (95% CI .096 to 21.104), p=0.02 BDI (0-63): 14.7 vs. 16.6, p=0.18; difference −1.9 (95% CI −6.5 to 2.7), p=0.41 <u>18 months:</u> SF-36: 51.8 vs. 41.3, p=NR; difference 10.5 (95% CI 0.5 to 20.5), p=0.04 BDI: 14.3 vs. 14.2, p=NR; difference 0.10 (95% CI −5.4 to 5.6), p=0.97 <u>30 months</u> SF-36: 60.5 vs. 42.0, p=NS BDI: 9.7 vs. 17.9, p=NS

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Sanudo, 2015[90] 6 months Duration of pain: NR Poor	A. Aerobic exercise (n=16): consisted of warm up, steady state exercise at 60-65% of predicted maximum heart rate, interval training at 75-80% of predicted maximum heart rate, and cool-down; 2, 45-60 minute sessions per week for 6 months B. Usual care (n=16): normal activities, which did not include structured exercise.	A vs. B Age: 55 vs. 58 years Female: 100% vs. 100% Baseline pain VAS (0-10): 7.4 vs. 7.2	A vs. B <u>6 months:</u> Pain VAS: 6.7 vs. 7.0, difference −0.3 (95% CI −6.3 to 5.7),	A vs. B <u>6 months</u> Anxiety VAS (0-10): 5.7 vs. 7.5, difference −1.8 (95% CI −10.8 to 7.2) Depression VAS (0-10): 5.6 vs. 6.7 (2.2), difference −1.1 (95% CI −10.1 to 7.9) Sleep disturbance VAS (0-10): 7.2 vs. 8.6 (1.9), difference −1.4 (95% CI −8.9 to 6.1)
Sencan, 2004[93] 6 months Duration of pain: 5.4 years Poor	A. Exercise group (n=14): 3 40-minute aerobic exercise sessions per week for 6 weeks B. Paroxetine (n=18): 20/mg paroxetine/day for 6 weeks C. Sham (n=20): placebo TENS with electrodes applied to two most painful tender points for 20 minutes, 3 times/week for 6 weeks. All patients instructed to take paracetamol as a rescue medication throughout the study.	A vs. B vs. C Age: 35 vs. 36 vs. 36 years Female: 100% vs. 100% vs. 100% BMI: 24 vs. 24 vs. 15 Duration of symptoms: 4.7 vs. 6.5 vs. 5.1 years Baseline VAS (0-10): 6.85 vs. 6.62 vs. 7.70 Baseline Beck Depression Index (BDI 0-60): 16.20 vs. 20.80 vs. 18.50	A vs. C 6 months VAS: 4.75 vs. 5.01, difference −0.3 (95% CI −1.5 to 0.9) A vs. B 6 months VAS:4.75 vs. 5.84, difference −1.1 (95% CI −2.4 to 0.2)	A vs. C 6 months BDI: 9.95 vs. 15.15, difference −5.2 (95% CI −7.41 to −2.99) Analgesic Consumption: 1.15 vs. 4.35, difference −3.17 (95% CI −3.79 to −2.55) A vs. B 6 months BDI: 9.95 vs. 10.12, difference −0.17 (95% CI −2.09 to 1.75) Analgesic Consumption: 1.15 vs. 2.40, difference −1.25 (95% CI −1.39 to −1.11)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Tomas-Carus, 2008/2009[94,95] 8 months Duration of symptoms: 20 years Poor	A. Combination exercise (n=17): Pool exercise in 1 hour sessions 3 times per week for 8 months (warm up, aerobic exercise, mobility and lower limb strength exercises using water resistance and upper limb strength exercises without water resistance, cool down) B. Control (n=16): normal activities for 8 months, which did not include exercise similar to that in group A.	A vs. B Age: 51 vs. 51 years Female: 100% vs. 100% Baseline FIQ Total (0-10): 6.1 vs. 6.3 FIQ Physical Baseline Function (0-10): 3.0 vs. 3.7 Baseline FIQ Pain (0-10): 5.6 vs. 6.4	A vs. B <u>8 months</u> FIQ Total: 5.2 vs. 6.5, difference −1.3 (95% CI −0.23 to −0.3) FIQ Physical Function: 2.4 vs. 3.7, difference −1.3 (95% CI −2.7 to 0.09) FIQ Pain: 5.3 vs. 6.6, difference −1.3 (95% CI −2.5 to −0.09)	A vs. B <u>8 months</u> FIQ Anxiety (0-10): 4.7 vs. 6.6, difference −1.9 (95% CI −3.7 to −0.1) FIQ Depression (0-10): 4.0 vs. 6.1, difference −2.1 (95% CI −4.1 to −0.1) STAI State Anxiety (20-80): 37.5 vs. 44.4, difference −6.9 (95% CI −13.2 to −0.6) SF-36 physical function (0-100): 54.1 vs. 36.6, difference 17.5 (95% CI 3.4 to 31.6) SF-36 bodily pain (0-100): 51.7 vs. 27.1, difference 24.6 (95% CI 11.6 to 37.6) SF-36 Mental Health (0-100): 67.3 vs. 49, difference 18.3 (95% CI 2.5 to 34.0)
van Eijk-Hustings, 2013[96] 18 months Duration of pain: NR Fair	A. Aerobic exercise (n=47): two group sessions per week for 12 weeks (warm up, aerobic exercise, resistance training to strengthen muscles, cool down). Subjects were asked to practice exercises at home with videodisc once a week. B. Usual care (n=48): individualized FM education and lifestyle advice within 1-2 consultations, plus care as usual	A vs. B Age: 44 vs. 43 years Female: 100% vs. 98% Baseline FIQ total (0-100): 60.0 vs. 55.4 Baseline FIQ physical function (0-10): 3.6 vs. 3.4 Baseline FIQ Pain (0-10): 6.2 vs. 5.5	A vs. B <u>18 months:</u> FIQ total: 52.0 vs. 56.2, ES=0.22 (95% CI −0.20 to 0.61) FIQ physical function: 3.6 vs. 3.9, ES=0.11 (95% CI −0.29 to 0.52) FIQ pain: 5.2 vs. 5.3, ES=0.05 (95% CI −0.36 to 0.44)	A vs. B <u>18 months:</u> FIQ Depression (0-10): 5.0 vs. 4.2, ES=0.09 (95% CI −0.31 to 0.49) FIQ Anxiety (0-10): 5.0 vs. 4.8, ES=−0.06 (95% CI −0.46 to 0.34) EQ-5D (−0.59 to 1): 0.54 vs. 0.51, ES=0.10 (95% CI −0.31 to 0.50) GP consultations[b]: 1.0 vs. 0.7, ES=−0.10 (95% CI −0.48 to 0.32) Medical specialist consultations[b]: −0.4 vs. 0.2, ES=−0.29 (95% CI −0.58 to 0.22) Physiotherapist consultations[b]: 0.4 vs. 2.8, ES=−0.29 (−0.58 to 0.22) Other paramedical professional consultations[b]: 2.1 vs. 0.2, ES=−0.68 (95% CI −1.00 to −0.18)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
van Santen, 2002[97] 6 months Duration of symptoms: 12 years Poor	A. Combination exercise (n=58): group sessions (60 minutes) twice a week for 24 weeks (aerobic exercises, stretching, general flexibility and balance exercises, and isometric muscle strengthening); encouraged to attend a third, unsupervised, 60 minute session weekly and to use sauna or swimming pool after all sessions. B. Usual care (n=29): analgesics NSAIDs, or tricyclic antidepressants, if appropriate; GPs informed that aerobic exercises and relaxation should not be prescribed or encouraged	A vs. B Age: 46 vs. 43 years Female: 100% vs. 100% Duration of symptoms: 9.7 vs. 15.4 years Baseline SIP physical score (mean, 0-100): 11.3 vs. 9.8 Baseline SIP total score (mean, 0-100): 14.4 vs. 11.4 Baseline AIMS (mean, 0-10): 1.9 vs. 5.4 Baseline Pain VAS (mean, 0-100): 66.8 vs. 62.4	A vs. B, mean change from baseline <u>6 months:</u> SIP physical score: −1.7 (95% CI −3.7 to 0.3) vs. −0.6 (95% CI −2.9 to 1.7), p=NS SIP total score: −1.9 (95% CI −3.9 to 0.1) vs. −1.4 (95% CI −3.4 to 0.6) p=NS AIMS: 0.1 (95% CI −0.6 to 0.8) vs. 0.8 (95% CI −1.8 to −0.2), p=NS Pain VAS: −5.5 (95% CI −10.9 to −0.1) vs. 1.3 (95% CI −4.5 to 7.1), p=NS	A vs. B, mean change from baseline <u>6 months:</u> SCL-90-R Global Severity Index (scale unclear): −6.8 (95% CI −20.1 to 6.5) vs. −8.1 (95% CI −19.8 to 3.6), p=NS SIP psychosocial score (0-100): −3.2 (95% CI −6.2 to 0.2) vs. −3.5 (95% CI -7.0 to 0.0), p=NS Patient global assessment (1-5): 0.5 (95% CI 0.2 to 0.8) vs. 0.5 (95% CI 0.2 to 0.8), p=NS
Villafaina, 2019[99] 6 months (Immediately postintervention) Duration of symptoms:NR Fair [New trial]	A. Exercise via an exergame specifically designed for patients with FM (n=28): 2, 1-hour sessions per week for 24 weeks; exercises targeting aerobic fitness, strength, mobility, postural control, and corrdination of the upper and lower limb. B. Usual Care (n=27): continued with their usual daily activities.	A vs. B Age: 54 vs. 53 years % Female: 100% vs. 100% Baseline VAS-pain: 62.14 vs. 60.37	A vs. B <u>6 months</u> VAS-pain: 58.88 vs. 68.20, effect size 0.076, p=0.04	A vs. B <u>6 months</u> VAS-EQ 5D health perception (0-100): 52.30 vs. 45.88, effect size 0.113, p=0.01 EQ-5D-5L utility (0-1): 0.56 vs. 0.52, effect size 0.04, p=0.12
Wigers, 1996[98] 48 months Duration of symptoms: 10 years Fair	A. Aerobic exercise (n=20): sessions consisted of training to music (further details not given) and aerobic games; 45 minute group sessions 3 times a week for 14 weeks B. Treatment as usual (n=20)	A vs. B Age: 43 vs. 46 years Female: 90% vs. 95% Duration of symptoms: 9 vs. 11 years Baseline pain VAS (0-100): 72 vs. 65	A vs. B <u>48 months:</u> Pain VAS: 68 vs. 69, difference −1.0 (95% CI −16.3 to 14.4)	A vs. B <u>48 months</u> Depression VAS (0-100): 32 vs. 30, difference 2.0 (95% CI −18.8 to 22.8) Global subjective improvement: 75% vs. 12%, RR 5.9 (95% CI 1.5 to 22.2)

AIMS = Arthritis Impact Measurement Scale; BDI = Beck Depression Inventory; CES-D: Center for Epidemiologic Studies Depression Scale Revised; CI = confidence interval; EQ5D = EuroQoL 5 Dimensions; ES = effect size; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; GP = general practitioner; GSI – Global Severity Index; HADS = Hospital Anxiety and Depression Scale; NHP = Nottingham Health Profile; NR = not reported; NS = not statistically significant; NSAID = nonsteroidal anti-inflammatory drug; SCL-90-R = Symptom Checklist-90-Revised; SF-36 = Short-Form 36 Questionnaire; SIP = Sickness Impact Profile; STAI = State-Trait Anxiety Inventory; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Total number of consultations over a period of 2 months prior to measurement

Exercise Compared With Usual Care, Waitlist, an Attention Control, or No Treatment

Functional Outcomes. Exercise was associated with a small improvement in function short term compared with usual care, an attention control, or no treatment based on Fibromyalgia Impact Questionnaire (FIQ) total scores, which reflect fibromyalgia impact on function as well as symptoms such as pain, fatigue, stiffness, anxiety, and depression, (7 trials, pooled difference −7.68 on a 0 to 100 scale, 95% CI −13.04 to −1.84, I^2= 59.9%)[76,77,80,83,86,87,89] (Figure 44). The estimate across fair-quality trials (i.e., not including the poor-quality trials) was somewhat higher (5 trials, pooled difference −9.91, 95% CI −15.75 to −4.07).[76,77,80,86,89]

Exercise was associated with a small improvement in intermediate-term function versus controls for FIQ total score (8 trials, pooled difference on 0-100 scale, −6.04, 95% CI −9.25 to −3.01, I^2= 0%)[80,82-84,88,91,92,94] (Figure 44). Estimates were slightly smaller across the fair-quality trials only (4 trials, pooled difference −4.04, 95% CI −7.90 to −0.03).[80,82,88,92] Stratification by exercise type yielded similar results for combination exercise (7 trials, pooled difference −5.75, 95% CI −9.29 to −2.54),[80,82,83,88,91,92,94] but there was no clear difference between aerobic exercise and no treatment or usual care (2 trials, pooled difference −8.13, 95% CI −16.24 to 0.28).[84,92] Estimates were consistent with a slightly greater effect of exercise on function when compared with usual care (3 trials, pooled difference −6.13, 95% CI −11.71 to −1.06)[80,91,92] or no treatment (3 poor quality trials, pooled difference −9.97, 95% CI −16.24 to −3.45),[83,84,94] but there was no clear difference in two fair-quality trials using attention controls (pooled difference −3.25, 95% CI −99.32 to 5.20).[82,88]

Exercise no longer had an effect on long-term function compared with controls based on the FIQ total score (3 trials, pooled difference on 0 to 100 scale, −4.33, 95% CI −10.46 to 1.97, I^2= 0%)[82,91,96] (Figure 44). There were no clear differences in estimates when analyses were stratified according to the type of exercise (2 trials of combination exercise, pooled difference −4.45, 95% CI −14.39 to 6.24),[82,91] type of comparison (2 trials of usual care, pooled difference −5.34, 95% CI −13.4 to 2.32),[91,96] or after the exclusion of one poor-quality trial (2 trials, pooled difference −3.11, 95% CI −11.26 to 5.86).[82,96] Findings are based on a small number of trials.

Pain Outcomes. Exercise had a moderately greater effect on pain (0 to 10 VAS) in the short term compared with usual care, attention control, or no treatment (7 trials, pooled difference −1.08, 95% CI −1.75 to −0.32, I^2=53.1%)[76-78,80,83,85,86] (Figure 45). Substantial heterogeneity was noted with one outlier trial of belly dance (combination exercise) versus waitlist control, reporting substantially higher estimates.[77] Excluding the outlier trial reduced heterogeneity and led to an effect size consistent with a small effect (6 trials, pooled difference −0.88, 95% CI −1.33 to −0.27, I^2=1.5%) Estimates were similar when stratified by exercise type and control type. Across the fair-quality trials, the estimate was somewhat larger (4 trials, pooled difference −1.44, 95% CI −2.4 to −0.49, including the outlier).[76,77,80,82,86]

There was a small improvement in VAS pain with exercise at intermediate term (8 trials [1 new], pooled difference −0.51, 95% CI −0.92 to −0.06), I^2=0%)[80,82,83,90,93,94,97,99] (Figure 45). Removal of poor-quality trials[83,90,93,94] and stratification by exercise and control types yielded similar estimates (pooled differences ranged from −0.40 to −0.71) with no clear differences identified.

There was no effect of exercise on pain long term (4 trials, pooled difference −0.18 on a 0-10 scale, 95% CI −0.77 to 0.42, I^2=0%)[78,82,96,98] (Figure 45). Similar estimates were obtained and no

clear differences were seen following exclusion of one poor quality-trial or for the comparisons of aerobic exercise with usual care or combination exercise with attention control; pooled differences ranged from −0.05 to −0.26.

Other Outcomes. Data on the effects of exercise on anxiety, depression, and quality of life were often poorly reported (Table 35) and results are mixed. Exercise had no clear effect in the short term on measures of mental health, depression, anxiety, psychological distress, or sleep disturbance VAS across five trials,[76-80] with only one small poor-quality trial favoring exercise on the EQ-5D anxiety/depression scale.[85] Similarly, exercise had no clear effect on quality of life.

At intermediate term, exercise was associated with a small improvement in depression measured by the Beck Depression Inventory (BDI) compared with no treatment or usual care (4 trials, pooled difference −4.9 on a 0-63 scale, 95% CI −7.55 to −2.47, I^2= 33.1%, plot not shown)[84,91-93]; three of the four trials were poor quality. Results were similar for aerobic exercise (3 trials, pooled difference −5.34, 95% CI −8.42 to −3.03) but no difference between groups was seen in the pooled estimate for the two trials using combination exercise or when any exercise was compared with usual care only (2 trials). Across various other measures, exercise had no clear effect on depression in five trials[78,79,82,88,90]; however, one poor-quality trial favored exercise based on the FIQ depression subscale versus usual care.[94] Results for anxiety were mixed: two trials (one fair- and one poor-quality)[88,90] reported no difference between groups while two small, poor-quality trials reported a greater improvement in anxiety on the State-Trait Anxiety Inventory (STAI) and the FIQ anxiety subscale with exercise versus usual care.[84,94] Exercise was associated with improved quality of life (SF-36 questionnaire) in three small trials,[91,92,95] but not in a fourth larger fair-quality trial[88] (Table 35). Exercise had no clear effect on psychological problems in two trials[78,80] or sleep in three trials.[78,83,90] One trial reported no between-group difference in analgesic medication use by 6 months, although patients randomized to aerobic exercise showed a significant reduction from baseline use.[93]

Long term, exercise had no clear effect on measures of depression, anxiety, or psychological problems in all but one poor-quality trial.[91] This same trial also reported improvement in SF-36 total scores, whereas one larger fair-quality trial did not.[79] No differences between groups in healthcare utilization were seen in the 2 months prior to the final assessment at 18 months in one trial[96] (Table 35).

Exercise Compared With Pharmacological Therapy

One small, poor-quality trial (N=32 analyzed) comparing 1.5 months of aerobic exercise (40 minutes on bicycle ergometer three times per week) versus paroxetine 20 mg daily found no between-group difference in pain on VAS at intermediate-term followup (difference −0.26 on a 0-10 scale, 95% CI −1.46 to 0.94). Regarding secondary outcomes, no differences were seen for depression (BDI) or mean analgesic consumption over the intermediate term, although the exercise group showed a greater reduction from baseline in analgesic use compared with the paroxetine group.

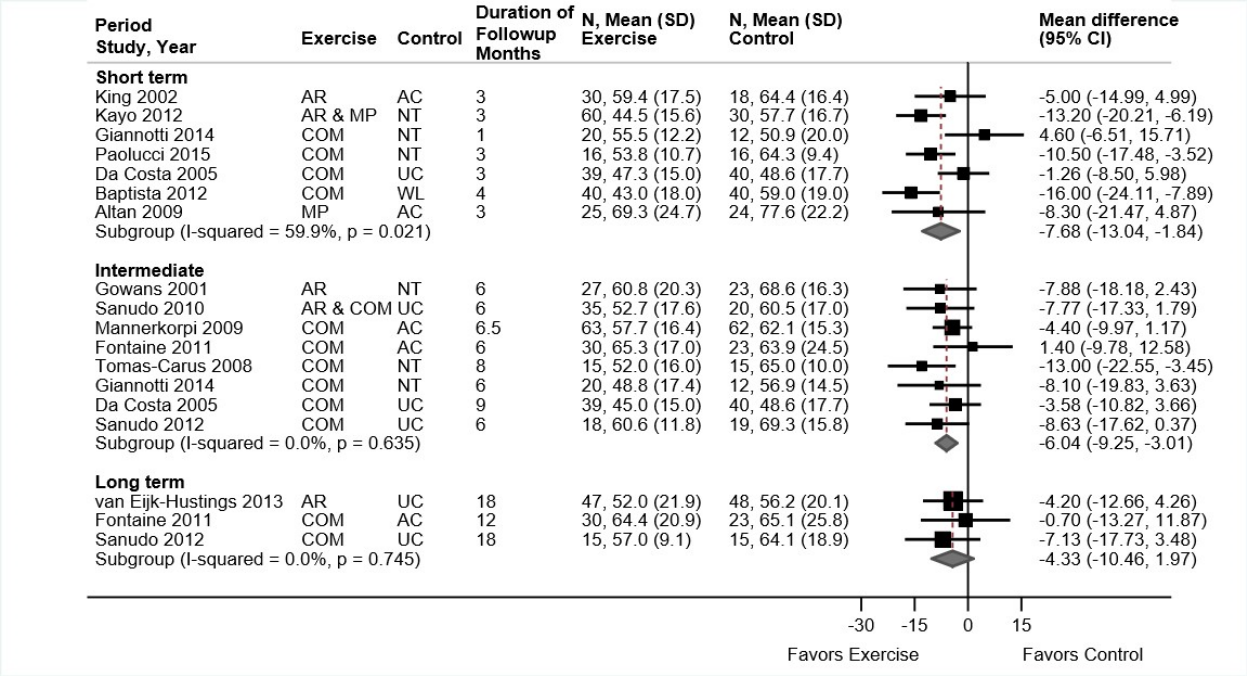
Exercise Compared With Other Nonpharmacological Therapies

Findings for exercise versus other nonpharmacological therapies are addressed in the sections for other nonpharmacological therapies.

Harms

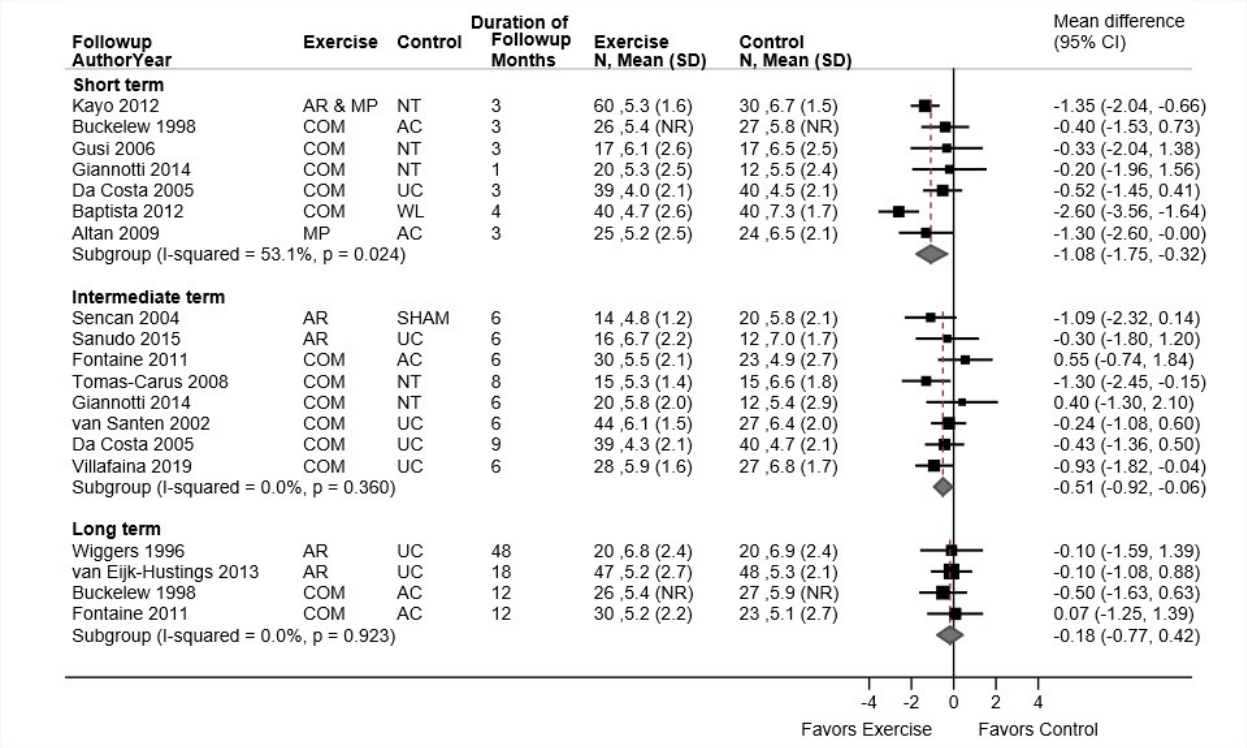
Most trials of exercise did not report on adverse events. One trial reported one nonstudy-related adverse event.[85] Two trials reported no adverse events.[86,89]

Figure 44. Exercise versus usual care, no treatment, waitlist, or an attention control for fibromyalgia: effects on function



AC = attention control; AR = aerobic exercise; AR & COM = aerobic exercise in one arm and combination exercise in another arm; AR & MP = aerobic exercise in one arm and muscle performance exercise in another arm; CI = confidence interval; COM = combination exercise therapy; MP = muscle performance exercise; MP+NR = muscle performance plus neuromuscular rehabilitation exercise; NT = no treatment; SD = standard deviation; UC = usual care; WL = waitlist

Figure 45. Exercise versus usual care, no treatment, waitlist, attention control, or sham for fibromyalgia: effects on pain



AC = attention control; AR = aerobic exercise; AR & MP = aerobic exercise in one arm and muscle performance exercise in another arm; CI = confidence interval; COM = combination exercise therapy; MP = muscle performance exercise; MP+NR = muscle performance plus neuromuscular rehabilitation exercise; NT = no treatment; SD = standard deviation; UC = usual care; WL = waitlist

Psychological Therapies for Fibromyalgia

Key Points

- There was no clear difference between CBT versus usual care or waitlist in short-term function (3 trials [1 new], pooled difference −6.14 on 0-100 FIQ total scale, 95% CI −16.86 to 3.74, I^2=70.6%). At intermediate term, CBT was associated with a moderate improvement in function (3 trials [1 new], pooled difference −12.82 on 0-100 FIQ total scale, 95% CI −24.07 to −2.44, I^2=94.2%) versus waitlist or usual care. CBT was associated with improved function intermediate term (mean difference −1.8 on 0-10 FIQ Physical Impairment Scale, 95% CI −2.9 to −0.70) compared with attention control in an additional trial, however two new trials found no difference between CBT and waitlist on the Pain Disability Index or West Haven -Yale Multidimensional Pain Inventory (MPI) pain interference subscale.. Evidence from two poor-quality trials was insufficient to determine effects on long-term function (SOE: low for short term and intermediate term, insufficient for long term).
- CBT was associated with a small improvement in pain (on a 0-10 scale) compared with usual care or waitlist in the short term (4 trials [1 new], pooled difference −0.62, 95% CI −1.08 to −0.14) but not at intermediate-term (6 trials [4 new], pooled difference −0.55, 95% CI −1.13 to 0.06). There was no difference in clinically important improvement at intermediate term (≥50% on the Brief Pain Inventory) between CBT (8.3%) or emotional

awareness and expression therpay (EAET) (22.5%) and usual care (12%) in one new fair quality trial. Evidence from one poor-quality trial was insufficient to determine effects on long-term pain (SOE: low for short term and intermediate term, insufficient for long term).

- Data were insufficient to determine the effects of EMG biofeedback on function and pain compared with attention controls in the short and long term (1 poor-quality trial and one new fair-quality trial) and with usual care in the intermediate term (1 poor-quality trial), and for the impact of guided imagery versus attention control in the short term (1 poor-quality trial) (SOE: insufficient for all comparisons and time points).
- At intermediate term, CBT was associated with a small improvement in function versus pregabalin (plus duloxetine as needed) in two trials [1 new]; differing effect size magnitudes for the trials (−4.0 vs. −15.6, FIQ total score, 0-100 scale) resulted in substantial heterogeneity for the pooled effect estimate making it unreliable (pooled difference −9.81, 95% CI −23.83 to 4.21, I^2=96%) (SOE: low). There was no difference across these trials for VAS pain at intermediate term (2 trials [1 new], pooled difference −0.31 on a 0-10 scale, 95% CI −1.15 to 0.51, I^2=63.5%) (SOE: low)
- There was insufficient evidence to determine the impact on pain and function for the following: CBT versus pharmacological treatment (amitriptyline) over the short term (fair-quality trial) and electroencephalography (EEG) biofeedback versus pharmacological treatment (escitalopram) over the short and intermediate term (poor-quality trial) (SOE: insufficient). Long-term data were not reported.
- There was insufficient evidence to determine the effects of psychological therapies versus exercise on function and pain in the short term (1 small trial of biofeedback), intermediate term (2 trials of CBT and biofeedback), and long term (3 trials of CBT, biofeedback, and relaxation for function; 4 trials of CBT [2], biofeedback, and relaxation for pain). All trials were considered poor quality (SOE: insufficient for function and pain at all time points).
- Data on harms were insufficient. Adverse events were poorly reported across the trials but were overall minor and occurred at similar frequencies between groups. In one trial, however, fewer patients randomized to stress management (4.8%) compared with usual care (50%) withdrew from the trial, citing increased depression and worsening of symptoms, respectively. In another (new) trial comparing acceptance and commitment therapy (ACT) with pregabalin (plus duloxetine as needed) several mild adverse events were noted in the pharmacological therapy group, most commonly nausea (25%) and dry mouth (23%) (SOE: insufficient).

Detailed Synthesis

A total of 20 trials (in 22 publications) of psychological therapy for fibromyalgia met inclusion criteria (Table 37 and Appendix D).[78,97,98,113-127,130,131,135,136] Fourteen trials (across 15 publications) were included in the previous AHRQ report[78,97,98,113-120,130,131,135,136] and six trials (across 7 publications)[121-124] were added for this update. Fourteen trials (5 new trials; across 16 publications) featured a CBT component,[98,113-117,119-124,126,127,130,136] four trials included biofeedback (EMG or EEG),[78,97,125,131] and one trial each included relaxation training[135] and guided imagery[118] (Table 36 and Appendix D). The various psychological interventions were compared with usual care, waitlist control or attention control groups (15 trials [5 new], 17

publications),[78,97,98,113-121,124-127] pharmacological therapy (4 trials [1 new], 5 publications),[113,122,123,130,131] or exercise therapy (5 trials).[78,97,98,135,136]

The majority of subjects in all the trials were female (range 90% to 100%, many trials were limited to females) and mean ages ranged from 32 to 56 years. Sample sizes ranged between 32 and 230 subjects (total sample=1,822). Therapy duration and frequency in CBT trials ranged from 6 weekly sessions to 20 sessions over 6 months. CBT was delivered in groups in 12 trials (4 new trials)[113,115-117,119-124,126,130,136] and by telephone[114] in another. In one trial,[127] CBT appeared to be delivered individually. Most CBT trials were of CBT as traditionally delivered for the treatment of pain problems. The exceptions included two trials (in 4 publications) ACT;[116,119,122,123] two trials that evaluated CBT for pain and CBT for pain and insomnia;[121,127] one trial of stress management therapy which that included presentations on stress mechanisms and training in pain coping and relaxation strategies;[98] and one trial of CBT for managing stress and pain.[126] These interventions were considered to be similar to standard CBT, however. Session lengths ranged from 30 minutes up to 3 hours.

In the six trials of biofeedback and associated interventions, therapy duration ranged from 4 to 16 weeks and was delivered individually in the four biofeedback trials and in groups for the remaining two trials. The frequency ranged from one to five times per week with sessions as short as 25 minutes and as long as 3 hours.

Short-term outcomes (<6 months) were reported by five trials (1 new trial) of CBT,[114-116,119,121,130] three trials (1 new trial) of biofeedback[78,125,131] and one trial of guided imagery.[118] Intermediate outcomes (6 to <12 months) were reported by eight CBT trials (4 new trials)[113,115,117,122-124,126,127,136] and one trial of biofeedback.[97] Long-term outcomes (≥12 months) were reported by four CBT trials,[98,117,120,136] one biofeedback trial[78] and one trial of relaxation therapy.[135] Studies were conducted in Spain (5 trials),[113,115,121-123,136] the United States (5 trials),[78,114,120,124,127] Sweden (3 trials),[116,119,126,135] the Netherlands (2 trials),[97,118] Germany (2 trials),[117,125] and one trial each in Brazil,[130] Norway[98] and Turkey.[131]

Among the 14 CBT trials, seven (4 new trials) were considered fair quality,[113,116,119,122-124,126,127,130] while the remaining seven (1 new trial) were rated poor quality[98,114,115,117,120,121,136] (Appendix E). Among the remaining trials of biofeedback, relaxation, and guided imagery interventions, all were rated poor quality[78,97,118,131,135] except for one new biofeedback trial which was considered to be fair-quality.[125] Methodological shortcomings included lack of blinding in fair-quality and poor-quality trials, and unclear allocation concealment methods, poor compliance, and high attrition in the poor-quality trials. In all trials, the nature of the intervention types precluded blinding of participants.

Table 53. Fibromyalgia: psychological therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Alda, 2011[113] 6 months Years since diagnosis: 12.9 vs. 11.2 vs.11.7 Fair	A. CBT (n=57): 10-12 week program; 10 weekly 90-minute group sessions of cognitive restructuring and training in cognitive and behavioral coping strategies. B. Recommended pharmacological treatment (n=56): pregabalin (300-600 mg/day); duloxetine (60-120 mg/day) for patients with major depressive disorder. C. Usual care (n=56): standard care offered by general practitioners at subjects' health centers who received a guide for the treatment of FM in primary care.	A vs. B vs. C Age: 46 vs. 47 years vs. 47 years Females: 95% vs. 93% vs. 96% Race NR Baseline FIQ (mean, 0-100): 65.9 vs. 66.4 vs. 64.5 Baseline Pain VAS (mean, 0-100): 64.2 vs. 68.1 vs. 64.7	A vs. B <u>6 months</u>: FIQ: 48.8 vs. 52.8; difference −4.0 (95% CI −7.730 to −0.270) Pain VAS: 40.7 vs. 40.5; difference 0.2 (95% CI −3.996 to 4.396) A vs. C <u>6 months:</u> FIQ: 48.8 vs. 53.3, difference −4.5 (95% CI −7.91 to −1.09) Pain VAS: 40.70 vs. 44.3, difference −3.6 (95% CI −7.617 to 0.417)	A vs. B <u>6 months</u>: HAM-D (0-50): 7.9 vs. 8.2; difference −0.3 (95% CI −1.226 to 0.626) HAM-A (0-50): 7.3 vs. 7.4; difference −0.1 (95% CI −1.247 to 1.047) A vs. C <u>6 months</u>: HAM-D: 7.9 vs. 8.6, difference −0.7 (95% CI −1.719 to 0.319) HAM-A: 7.3 vs. 7.6, difference −0.3 (95% CI −1.361 to 0.761)
Ang, 2010[114] 1.5 months Duration of fibromyalgia, years: 11.8 vs. 12.3 Poor	A. CBT (n=17): 6 weekly 30-40 minute sessions of telephone-delivered CBT (activity pacing, pleasant activity scheduling, relaxation, automatic thoughts and pain, cognitive restructuring, and stress management) B. Usual care (n=15): customary care from subject's treating physician	A vs. B Age: 51 vs. 47 years Female: 100% vs. 100% White: 81% vs. 80% Baseline FIQ total (mean, 0-100): 62.2 vs. 67.8 Baseline FIQ Physical Impairment (PI) (0-10): 5.6 vs. 5.4 Baseline FIQ Pain (0-10): 7.6 vs. 7.8	A vs. B <u>1.5 months:</u> Proportion of patients with clinically meaningful improvement from baseline FIQ total (14%): 33% vs. 15%, RR 2.2 (95% CI 0.5 to 9.3) mean change from baseline: FIQ PI: −0.6 vs. 0.5, adjusted p=0.13; FIQ Pain: −0.6 (1.6) vs. −0.3 (1.7), adjusted p=0.60	A vs. B <u>1.5 months:</u> PHQ-8 (0-24): mean change from baseline −0.9 (5.2) vs. 0.0 (4.1), adjusted p=0.80; overall effect size=0.60

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Baumueller 2017[125] 3 months Duration of symptoms: 12.4 vs. 16.4 years Fair [New trial]	A. Electromyogram-Biofeedback (n=18): 14 sessions over 8 weeks B. Attention control (n=18): 2 encounters with a therapist over 8 weeks	A vs. B Age: 55 vs. 56 years Smoking: 6% vs. 22% Baseline FIQ-total: 42.59 vs. 40.44	A vs. B <u>3 months</u> FIQ: 37.87 vs. 38.28, p=0.52	A vs. B <u>3 months</u> SF-36 Physical function: 51.64 vs. 50.9, p=0.35 SF-36: Role-physical: 15.62 vs. 20.83, p=0.57 SF-36 Bodily pain: 36.88 vs. 36.17, p=0.81 SF-36 General health: 43.50 vs. 44.44, p=0.44 SF-36 vitality: 28.63 vs. 38.80, p=0.59 SF-36 social functioning: 53.68 vs. 61.11, p=0.65 SF-36 Role-emotional: 35.42 vs. 59.26, p=0.83 SF-36 Mental health: 51.06 vs. 57.50, p=0.75 BDI: 16.91 vs. 12.30, p=0.31 SCL-90-R Global Severity Index: 66.11 vs. 63.22, p=0.27

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Buckelew, 1998[78] 3, 12, and 24 months Duration of symptoms, years: 11.6 vs. 10.0 vs. 11.6 Poor	A. Electromyographic biofeedback and relaxation training (n=29): 1 session for 1.5-3 hours per week for 6 weeks and instructions to train 2 times independently per week; taught cognitive and muscular relaxation strategies; 6-week individual training was followed by 2-year group maintenance phase of 1-hour groups once per month. B. Attention control (n=30): 1 session for 1.5-3 hours per week for 6 weeks; educational information on diagnosis and treatment of FM and general health topics information; followed by one hour groups once per month for 2 years. C. Combination Exercise (n=30): 1 session for 1.5 hours per week for 6 weeks and instructions to train 2 times independently per week. Sessions consisted of active range of motion exercises, strengthening exercises, low to moderate intensity aerobic exercise, proper posture and body mechanics instruction, and instructions on the use of heat, cold, and massage. 6-week individual training was followed by 2-year group maintenance phase of 1-hour groups once per month.	A vs. B vs. C Age: 44 vs. 44 vs. 46 years Female: 97% vs. 90% vs. 93% Race NR Baseline AIMS physical activity subscale (median, 0-10): 6.0 vs. 6.0 vs. 4.0 Baseline pain VAS (median, 0-10): 5.8 vs. 5.9 vs. 6.3	A vs. B <u>3 months:</u> AIMS physical activity subscale, median (median change from baseline): 6.0 (0) vs. 6.0 (0), NS Pain VAS, median (median change from baseline): 5.2 (−0.2) vs. 5.8 (−0.5), NS <u>24 months:</u> AIMS physical activity subscale, median (median change from baseline): 6.0 (0) vs. 6.0 (0), NS Pain VAS, median (median change from baseline): 5.2 (−1.1) vs. 5.4 (−0.6), NS A vs. C <u>3 months:</u> AIMS physical activity subscale, median (median change from baseline): 6.0 (0) vs. 4.0 (0), p≤0.05 Pain VAS, median (median change from baseline): 5.2 (−0.2) vs. 5.4 (−0.8), NS <u>24 months:</u> AIMS physical activity subscale, median (median change from baseline): 6.0 (0) vs. 4.0 (0), p≤0.05 Pain VAS, median (median change from baseline): 5.2 (−1.1) vs. 5.5 (−1.2), NS	A vs. B <u>3 months:</u> SCL-90-R Global Severity Index, median (median change from baseline): 65.0 (-2) vs. 65.0 (0), NS CES-D, median (median change from baseline): 10.0 (-2) vs. 13.0 (3), NS Sleep scale, median (median change from baseline): 7.0 (0) vs. 5.0 (0), NS <u>24 months:</u> SCL-90-R Global Severity Index, median (median change from baseline): 64.0 (−1) vs. 67.0 (−1), NS CES-D, median (median change from baseline): 10.0 (-2) vs. 12.0 (-2), NS Sleep scale, median (median change from baseline): 6.0 (-2) vs. 6.0 (0), NS A vs. C <u>3 months:</u> SCL-90-R Global Severity Index, median (median change from baseline): 65.0 (−2) vs. 65.5 (−3), NS CES-D, median (median change from baseline): 10.0 (−2) vs. 13.5 (−2.5), NS Sleep scale, median (median change from baseline): 7.0 (0) vs. 8.0 (0), NS <u>24 months:</u> SCL-90-R Global Severity Index, median (median change from baseline): 64.0 (-1) vs. 65.5 (−2.5), NS CES-D, median (median change from baseline): 10.0 (−2) vs. 11.5 (−3.5), NS Sleep scale, median (median change from baseline): 6.0 (−2) vs. 7.5 (0), NS

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Castel, 2012[115] 3 and 6 months A vs. B Pain duration, years: 13.6 vs. 11.6 Poor	A. CBT plus usual pharmacological care (n=34): CBT conducted in groups (except for one individual session); 14 weekly 2 hour sessions. CBT included education about FM and pain, autogenic training, cognitive restructuring, CBT for insomnia, assertiveness training, activity pacing, pleasant activity scheduling, goal setting, and relapse prevention. B. Usual care (n=30): usual pharmacological care, including analgesics, antidepressants, anticonvulsants, and myorelaxants	A vs. B Age: 50 vs. 49 years Female: 94% vs. 100% White: 100% vs. 100% Baseline FIQ (scale NR): 62.7 vs. 66.1 Baseline pain NRS (0-10): 6.1 vs. 6.9	A vs. B <u>3 months:</u> Proportion of patients with MCSD (≥14% improvement from baseline): FIQ: 55.9% vs. 20%; OR 5.1 (95% CI 1.7 to 15.6); RR 2.8 (95% CI 1.3 to 6.1) Pain (≥30% improvement from baseline):: 14.6% vs. 10%; RR 1.5 (95% CI 0.4 to 5.7) FIQ: 52.8 vs. 66.3; difference -13.5 (95% CI -15.5 to -11.5) Pain NRS: 5.9 vs. 6.8; difference −0.9 (95% CI -1.1 to −0.7) <u>6 months:</u> Proportion of patients with MCSD: FIQ: 58.8% vs. 20%; OR 5.7 (95% CI 1.9 to 17.8); RR 2.9 (95% CI 1.4 to 6.3) Pain: 17.6% vs. 13.3%; RR 1.3 (95% CI 0.4 to 4.2) FIQ: 50.5 vs. 68.5; difference −18.0 (95% CI −20.095 to −15.905) Pain NRS: 5.7 vs. 6.8; difference −1.1 (95% CI −1.333 to −0.867)	A vs. B <u>3 months:</u> HADS (scale NR): 15.4 (1.3) vs. 22.3 (1.4); difference −6.9 (95% CI −7.685 to −6.115) MOS Sleep quantity (scale NR): 6.9 (0.2) vs. 5.5 (0.3); difference 1.4 (95% CI 1.254 to 1.546), p <0.0001 MOS Sleep index problems (scale NR): 40.1 (1.6) vs. 28.8 (1.7); difference 11.3 (95% CI 10.340 to 12.260) <u>6 months:</u> HADS: 15.7 (1.3) vs. 23.7 (1.4); difference −8.0 (95% CI −8.785 to −7.215) MOS Sleep quantity: 6.7 (0.2) vs. 5.6 (0.3); difference 1.1 (95% CI 0.954 to 1.25) MOS Sleep index problems: 39.9 (1.5) vs. 28.0 (1.6); difference 11.9 (95% CI 10.998 to 12.802)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Falcão, 2008[130] 3 months Disease duration, years: 3.5 vs. 3.7 Fair	A. CBT plus Amitriptyline (n=30): 1 group CBT session per week for 10 weeks, consisting of progressive relaxation training with electromyographic biofeedback, cognitive restructuring, and stress management; also received amitriptyline as in control group B. Amitriptyline only (control) (n=30): amitriptyline 12.5/mg per day during first week, then increase dose to 25 mg/day; those with intolerance or side effects to amitriptyline were given cyclobenzaprine 5 mg/day in the first week and then 10 mg/day. Routine medical visits once a week for 10 weeks	A vs. B Age: 45 vs. 46 years Female: 100% vs. 100% Caucasian: 80% vs. 77% Baseline FIQ (0-100): 64.9 vs. 69.6 Baseline pain VAS (0-10): 6.9 vs. 7.0	A vs. B <u>3 months</u>: FIQ: 38.7 vs. 42.8; difference −4.1 (95% CI −18.765 to 10.565) Pain VAS: 4.4 vs. 5.1; difference −0.7 (95% CI −2.841 to 1.441)	A vs. B <u>3 months</u>: BDI (0-63): 10.6 vs. 15.6; difference −5.0 (95% CI −11.122 to 1.122) STAI-State scale (20-80): 45.8 (2.5) vs. 46.8 (2.3); difference −1.0 (95% CI −2.351 to 0.351) SF-36 Physical Capacity (0-100): 59.6 vs. 54.0; difference 5.6 (95% CI −11.905 to 23.105) SF-36 Pain (0-100): 48.4 vs. 45.5; difference 2.9 (95% CI −10.783 to 16.583) SF-36 Mental Health (0-100): 69.9 vs. 56.2; difference 13.7 (95% CI 0.070 to 27.330)
Jensen, 2012[116] Wicksell, 2013[119] 3-4 months Time since FM onset, years: 10.5 vs. 11.8 Fair	A. ACT (n=25): 12 weekly 90-minute group sessions: exposure to personally important situations and activities previously avoided due to pain and distress, training to distance self from pain and distress. B. Waiting list control (n=18)	A vs. B Age: 45 vs. 47 years Female: 100% vs. 100% Baseline FIQ (0-100): 49.3 vs. 48.7 Baseline PDI (scale NR): 40.0 vs. 39.0 Baseline pain VAS (0-100): 61 vs. 65.0 Baseline pain NRS (0-10): 4.2 vs. 4.3	A vs. B <u>3-4 months</u> FIQ: 37.4 vs. 45.7, Cohen's d=0.66 (95% CI −0.06 to 1.37); difference −8.3 (95% CI −17.056 to 0.456) PDI: 28.1 vs. 38.1, Cohen's d=0.73 (95% CI −0.00 to 1.44); difference −10.0 (95% CI −19.740 to −0.260) Pain VAS: means NR but group X time interaction p=0.26 Pain NRS: 3.9 vs. 4.8, Cohen's d= 0.82 (95% CI 0.08 to 1.54); difference −0.90 (95% CI −1.674 to −0.126)	A vs. B <u>3-4 months</u> BDI (0-63): 10.7 vs. 16.4, Cohen's d=0.64 (95% CI −0.08 to 1.35); difference −5.7 (95% CI −12.044 to 0.644) STAI-State: 39.8 vs. 45.4; Cohen's d=0.55 (95% CI −0.17 to 1.26); difference −5.6 (95% CI −12.751 to 1.551) SF-36 Mental: 46.0 vs. 34.7, Cohen's d=1.06 (95% CI 0.28 to 1.82); difference 11.3 (95% CI 3.761 to 18.839) SF-36 Physical (0−100): 28.4 vs. 31.1, Cohen's d=0.28 (95% CI −0.45 to 1.00); difference −2.7 (95% CI −9.401 to 4.001),

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Karlsson, 2015[126] 6 month (end of treatment) Duration of pain: 10.7 vs. 12 years Duration of FM diagnosis: 5.3 vs. 5 years Fair [New trial]	A. CBT stress management program (n=24): 20, 3 hour group sessions over 6 months Median attendance rate: 93% B. Waitlist (n=24)	A vs. B Age: 48 vs. 49 years Female: NR Baseline MPI pain severity: 3.85 vs. 3.38 Baseline MPI pain interference: 4.04 vs. 3.37 Baseline MADRS-S: 17.38 vs. 13.04	A vs. B <u>6 months</u> MPI pain severity: 4.20 vs. 3.37 MPI pain interference: 4.07 vs. 3.45 MADRS-S: 13.09 vs. 16.45	A vs. B <u>6 months</u> MADRS-S: 13.09 vs. 16.45
Kayiran, 2010[131] 4 to 5 months Duration of symptoms: 5 years Poor	A. EEG Biofeedback (Neurofeedback) (n=20): 5 sessions based on sensorimotor rhythm training protocol per week for 4 weeks. Each session consisted of 10 sensorimotor rhythm training periods lasting for 3 minutes for a total of 30 minutes B. Escitalopram (n=20): 10 mg/day for 8 weeks (control group)	A vs. B Age: 32 vs. 32 years Female: 100% vs. 100% Baseline FIQ (mean, 0−100): 70 vs. 74* Baseline pain VAS (mean, 0−10): 8.9 vs. 9.1	A vs. B <u>4-5 months</u>: FIQ: 19 vs. 48*, p=NR Pain VAS: 2.6 vs. 5.3; difference −2.7 (95% CI −3.7 to −1.7)	A vs. B <u>4-5 months</u>: HAM-D (0-50): 6.3 vs. 13.4; difference −7.1 (95% CI −9.1 to −5.1) BDI (0-63): 4.7 vs. 12.3; difference −7.6, 95% CI −9.7 to −5.5) HAM-A (0-56): 7.1 vs. 15.2; difference −8.1 (95% CI −11.0 to −5.2) BAI (0-63): 7.2 vs. 16.7; difference −9.5 (95% CI −13.9 to −5.1) SF-36*: Physical functioning (0-100): 77 vs. 65, p<0.05 Bodily pain: 70 vs. 45, p<0.05 Role-physical (0-100): 90 vs. 43, p<0.05 Role-emotional (0-100): 95 vs. 51, p<0.05 Social functioning (0-100): 76 vs. 65, p<0.05 General mental health (0-100): 74 vs. 59, p<0.05 General health (0-100): 72 vs. 28, p<0.05 Vitality (0-100): 70 vs. 50, p<0.05

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lami, 2017[121] 3 months Duration of symptoms: Mean 8.5 to 11.6 years Poor [New trial]	A. Cognitive Behavioral Therapy for Pain (n=24): weekly, 90-minute group sessions for 9 weeks B. Cognitive Behavioral Therapy for Pain and Insomnia (n=22): weekly, 90-minute group sessions for 9 weeks C. Usual Care (n=26)	A vs. B vs. C Age: 49 vs. 50 vs. 51 years Female: 100% vs. 100% vs. 100% Baseline FIQ (0-100): 65.5 vs. 62.0 vs. 55.6 Baseline pain VAS (0-10): 7.6 vs. 7.4 vs. 7.2; p<0.05	A vs. C <u>3 months</u> FIQ: 53.3 vs. 53.2, difference 0.1 (95% CI −8.9 to 9.1) VAS: 7.2 vs. 7.2, difference 0.0 (95% CI −0.9 to 1.0) B vs. C <u>3 months</u> FIQ: 56.5 vs. 53.2, difference 3.3 (95% CI -5.7 to 12.3) VAS: 6.6 vs. 7.2, difference −0.6 (95% CI −1.5 to 0.3)	A vs. C <u>3 months</u> PSIQ Total Sleep Quality (0-21): 13.8 vs. 11.9, difference 1.91 (95% CI −0.6 to 4.5) MFI (0-5): 4.4 vs. 4.0, difference 0.32 (95% CI −0.1 to 0.7) SCL-90-R Depression (0-4): 2.1 vs. 1.5, difference 0.6 (95% CI 0.2 to 1.1) SCL-90-R Anxiety (0-4): 1.6 vs. 1.2, difference 0.42 (95% CI −0.1 to 0.9) PCS (0-52): 22.8 vs. 24.2, difference -1.4 (95% CI −8.7 to 6.0) CPAQ (0-120): 53.5 vs. 57.5, difference −4.1 (95% CI −15.8 to 7.6) B vs. C <u>3 months</u> PSIQ Total Sleep Quality: 13.6 vs. 11.9, difference 1.7 (95% CI −0.8 to 4.2) MFI: 4.1 vs. 4.0, difference 0.0 (95% CI −0.4 to 0.4) SCL-90-R Depression: 2.0 vs. 1.5, p<0.05 SCL-90-R Anxiety: 1.6 vs. 1.18, difference 0.44 (95% CI −0.05 to 0.9) PCS: 24.1 vs. 24.2, difference −0.2 (95% CI −7.7 to 7.4) CPAQ: 53.7 vs. 57.5, difference −3.9 (95% CI −15.1 to 7.4)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Larsson, 2015[135] 13 to 18 months Duration of symptoms: 10 years Poor	A. Relaxation therapy (n=63): Two group sessions of 5-8 subjects per week for 15 weeks. The intervention was preceded by an individual meeting covering instructions and allowing for adjustments to the intervention. The sessions lasted 25 minutes and consisted of autogenic training guided by physiotherapist and were followed by stretching. B. Resistance exercise (Strength) (n=67): Two group sessions of 5-7 subjects per week for 15 weeks. The intervention was preceded by an individual meeting going over instructions on the intervention, testing, and modifications of specific exercises. Sessions were based on a resistance exercise program aiming to improve muscle strength, focusing on large muscle groups in the lower extremity.	A vs. B Age: 52 vs. 51 Female: 100% vs. 100% Baseline FIQ (0-100): 61.1 vs. 60.5 Baseline pain VAS (0-100): 52.4 vs. 49.3 Baseline PDI (0-70): 35.0 vs. 35.3	A vs. B <u>13-18 months</u> FIQ: 55.4 vs. 57.1, (difference −1.7, 95% CI −9.3 to 5.9) Pain VAS: 52.1 vs. 49.2, (difference 2.9, 95% CI −5.5 to 11.3) PDI: 33.7 vs. 33.0, (difference 0.7, 95% CI −4.0 to 5.4)	A vs. B <u>13-18 months</u> SF-36 PCS (0-100): 32.0 vs. 32.2, (difference −0.2, 95% CI −3.8 to 3.4) SF-36 MCS (0-100): 40.0 vs. 39.2, (difference 0.8, 95% CI −4.6 to 6.2) Patient global impression of change (mean, 1-7): Values NR but difference was NS

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Luciano, 2014/2017[122,123] 6 months Duration of Disease: Mean 11.4 to 14.1 years Fair [New trial]	A. ACT (n=51): Eight 2.5 hour group sessions. Additional daily 15-30 minute homework sessions. -Received eight sessions: 43.1% (22/51) -Received seven sessions: 31.4% (16/51) -Received six sessions: 9.8% (8/51) -Received three sessions: 2% (1/51) -Received two sessions: 7.8% (4/51) B. Pharmacological Treatment (n=52): Treatment with pregabalin (300–600 mg/d) was administered. In addition, patients who fulfilled the criteria for major depression also received duloxetine (60–120 mg/d). C. Waitlist (n=53)	A vs. B vs. C Age: 49 vs. 48 vs. 48 Female: 96.1% vs. 98.1% vs. 94.3% Baseline FIQ (0-100): 68.2 vs. 69.9 vs. 65.9 Baseline pain VAS (0-100): 65.4 vs. 63.0 vs. 64.0	A vs. C <u>6 months</u> FIQ: 49.5 vs. 67.5, difference −18.0 (95% CI −21.4 to −14.5) VAS: 49.6 vs. 64.4, difference −14.8 (95% CI −20.0 to −9.6) A vs. B <u>6 months</u> FIQ: 49.49 (8.77) vs. 65.11 (8.87), difference −15.6 (95% CI −19.1 to −12.2) VAS: 49.6 vs. 56.3, difference −6.7 (95% CI 11.0 to −2.3)	A vs. C <u>6 months</u> CPAQ (0-120): 58.6 vs. 39.5, difference 19.1 (95% CI 13.9 to 24.4) PCS (0-52): 23.1 vs. 30.3, difference −7.2 (95% CI −10.5 to −3.9) EQ5D (0-100): 63.3 vs. 51.2 (11.8, difference 12.2 (95% CI 7.9 to 16.5) HADS-A (0-21): 8.7 vs.12.2, difference −3.4 (95% CI −4.7 to −2.1) HADS-D (0-21): 5.8 vs. 9.3, difference −3.5 (95% CI −4.4 to −2.5) Total Cost for Treatment (in 2014 Euro): 2,267.3 vs. 4,163.6, difference −1896.3 (95% CI −3018 to −775) A vs. B <u>6 months</u> CPAQ: 58.6 vs. 42.5, difference 16.1 (95% CI 10.8 to 21.5) PCS: 23.1 vs. 28.0, difference −4.9 (95% CI −7.9 to −1.8) EQ5D: 63.3 vs. 53.8, difference 9.6 (95% CI 5.2 to 14.0) HADS-A: 8.7 vs. 9.7, difference −1.0 (95% CI −1.8 to −0.06) HADS-D: 5.8 vs. 7.5, difference −1.7 (95% CI −2.6 to −0.8) Total Cost for Treatment (in 2014 Euro): 2,267.3 vs. 2,654.6, difference −387.3 (95% CI −1205 to 430)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lumley, 2017[124] 6 months Duration of diagnosis: Mean 13.5 to 13.8 years Fair [New trial]	A. CBT (n=75): 8, 90-minute, weekly group sessions. B. Emotion and Awareness Expression Therapy (n=79): 8, 90-minute, weekly group sessions. C. Fibromyalgia Education (attention control) (n=76): 8, 90-minute, weekly group sessions. All patients continued their usual care.	A vs. B. vs. C Age: 48 vs. 49 vs. 50 years Female: 91% vs. 92% vs. 99% Baseline BPI (0-10): 5.4 vs. 5.3 vs. 5.5 Baseline WPI (1-12): 9.9 vs. 11.2 vs. 10.7 Baseline SF-12 Physical component score: 35.5 vs. vs. 35.2 vs. 34.9	6 months <u>A vs. C</u> BPI: 4.8 vs. 4.9, difference −0.12 (95% CI −0.7 to 0.5) Proportion of patients reporting at least 50% pain reduction: 8.3% vs. 12% Proportion of patients reporting much/very much pain improvement: 22.9% vs. 15.4% WPI: 8.40 vs. 9.14, difference −0.74 (95% CI −2.2 to 0.7) <u>B vs. C</u> BPI: 4.4 vs. 4.9, difference −0.54 (95% CI −1.2 to 0.1) Proportion of patients reporting at least 50% pain reduction: 22.5% vs. 12%, p=0.07 Proportion of patients reporting much/very much pain improvement: 34.8% vs.15.4%, p=0.015	6 months <u>A vs. C</u> FSS (0-31): 15.0 vs. 16.0, difference −1.1 (95% CI −3.1 to 0.9) SF-12 Physical (0-100): 39.1 vs. 36.9, difference 2.2 (95% CI −0.9 to 5.3) SWLS (0-35): 19.6 vs. 18.6, difference 1.1 (95% CI −1.4 to 3.6) PSQI (0-21): 10.1 vs. 10.7, difference −0.61 (95% CI −2.0 to 0.8) PANAS-positive score (10-50): 30.1 vs. 27.6, difference 2.5 (95% CI −0.2 to 5.3) PANAS-negative score (10-50): 18.6 vs. 19.4, difference −0.8 (95% CI −3.2 to 1.7) MASQ (0-190): 92.6 vs. 96.9, difference −4.3 (95% CI −10.5 to 1.9) CES-D (0-60): 17.3 vs.18.5, difference −1.1 (95% CI −5.0 to 2.7) GAD-7 (0-21): 5.8 vs. 7.1, difference −1.3 (95% CI −2.9 to 0.3) PROMIS-SF-F (0-100): 58.4 vs. 59.0, difference −0.62 (95% CI −2.4 to 1.2) Healthcare utilization: 3.4 vs. 4.8, difference −1.4 (95% CI −3.1 to 0.3) <u>B vs. C</u> WPI: 7.2 vs. 9.1, difference −1.9 (95% CI −3.4 to −0.4) FSS: 13.2 vs. 16.0, difference −2.9 (95% CI −4.9 to −0.8) SF−12 Physical: 39.4 vs. 36.9, difference 2.5 (95% CI −0.6 to 5.5) SWLS: 18.9 vs. 18.6, difference 0.3 (95% CI −2.3 to 2.9) PNAS−negative score: 20.0 vs. 19.4, difference 0.62 (−1.7 to 2.9) PNAS−positive score: 28.5 vs. 27.6, difference 0.97 (95% CI −1.8 to 3.7) MASQ: 94.5 vs. 96.9, difference −2.37 (95% CI −8.8 to 4.0) CES−D: 19.3 vs. 18.5, difference 0.79 (95% CI −2.9 to 4.5) GAD−7: 7.2 vs. 7.1, difference 0.12 (95% CI −1.4843 to 1.7243) PROMIS−SF−F: 58.2 vs. 59.0, difference −0.84 (95% CI −2.9 to 1.2) Healthcare utilization: 4.1 vs. 4.8, MD −0.70 (95% CI −2.6 to 1.2)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
McCrae, 2019[127] 6 months Duration of FM diagnosis: 9.5 vs. 7.9 vs. 9.1 years Fair [New trial]	A. CBT for Insomnia (n=39): 8, 50-minute sessions over 8 weeks B. CBT for Pain (n=37): 8, 50-minute sessions over 8 weeks C. Waitlist (n=37)	A vs. B vs. C Age: 54 vs. 52 vs. 52 years % Female: 100% vs. 92% vs. 100%, p=0.04 Baseline McGill Pain: 25.85 vs. 29.95 vs. 28.53 Baseline morning pain: 53.49 vs. 54.04 vs. 54.72 Baseline evening pain: 47.26 vs. 54.26 vs. 54.18 Baseline pain disability index: 34.14 vs. 37.27 vs. 37.59	A vs. C <u>6 months</u> McGill Pain: 23.62 vs. 23.30 Morning VAS: 43.29 vs. 50.60 Evening VAS: 41.99 vs. 49.26 Pain Disability Index: 27.76 vs. 34.87 B vs. C <u>6 months</u> McGill Pain: 28.99 vs. 23.30 Morning VAS: 47.78 vs. 50.60 Evening VAS: 49.77 vs. 49.26 Pain Disability Index: 36.37 vs. 34.87	A vs. C <u>6 months</u> Sleep Quality Rating (1-5): 3.27 vs. 2.65 BDI (0-63): 8.22 vs. 15.01 State-Trait Anxiety Inventory (20-80): 38.07 vs. 43.87 B vs. C <u>6 months</u> Sleep Quality Rating (1-5): 3.14 vs. 2.65 BDI (0-63): 14.38 vs. 15.01 State-Trait Anxiety Inventory (20-80): 43.86 vs. 43.87

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Redondo, 2004[136] 6 and 12 months Pain duration NR Poor	A. CBT (n=21): 1, 2.5 hour session per week for 8 weeks. Sessions included information about chronic pain and FM, relaxation techniques, and pain coping strategies training. B. Combination Exercise (n=19): 5, 45-minute sessions per week for 8 weeks. Each week included 1 session of aquatic exercises, 2 sessions of flexibility and endurance exercises, and 2 sessions of cardiovascular exercises. All subjects: Offered ibuprofen or diclofenac, 25 mg of amitriptyline a day, and acetaminophen.	A vs. B Age NR Female: 100% vs. 100% Baseline FIQ total (mean, 0-80): 52.0 vs. 52.0 Baseline FIQ pain (mean, 0-10): 7.3 vs. 6.8	A vs. B <u>6 months:</u> FIQ total: 47.4 vs. 48.0, (difference −0.6, 95% CI −12.6 to 11.4) FIQ pain: 5.9 vs. 6.9, (difference −1.0, 95% CI −2.8 to 0.8) <u>12 months:</u> FIQ: 47.8 vs. 47.7; (difference 0.1, 95% CI −10.5 to 10.7) FIQ pain: 6.3 vs. 6.6; (difference −0.3, 95% CI −2.0 to 1.3)	A vs. B <u>6 months:</u> FIQ depression (0-10): 5.2 vs. 5.3, (difference −0.1, 95% CI −2.6 to 2.4) FIQ anxiety (0-10): 6.0 vs. 5.8, (difference 0.2, 95% CI −2.2 to 2.6) BAI: 25.2 vs. 22.1, (difference 3.1, 95% CI −5.1 to 11.3) BDI (0-63): 17.1 vs. 15.0, (difference 2.1, 95% CI −6.6 to 10.8) SF-36 physical functioning (0-100): 52.2 vs. 43.9, (difference 8.3, 95% CI −6.4 to 23.0) SF-36 physical role (0-100): 22.4 vs. 18.3, (difference 4.1, 95% CI −21.2 to 29.4) SF-36 bodily pain (0-100): 31.4 vs. 32.9, (difference −1.5, 95% CI −16.1 to 13.1) SF-36 social functioning (0-100): 66.4 vs. 66.9, (difference −0.5, 95% CI −21.6 to 20.6) SF-36 emotional role (0-100): 68.4 vs. 66.0, (difference 2.4, 95% CI −28.2 to 33.0) SF-36 mental health (0-100): 48.9 vs. 51.8, (difference −2.9, 95% CI −19.3 to 13.5) <u>12 months:</u> FIQ depression: 5.4 vs. 4.9; (difference 0.5, 95% CI −2.0 to 3.0) FIQ anxiety: 6.0 vs. 5.8; (difference 0.2, 95% CI −2.1 to 2.5) BAI: 20.0 vs. 20.0; (difference 0.0, 95% CI −7.4 to 7.4) BDI: 13.0 vs. 13.6; (difference −0.6, 95% CI −7.9 to 6.7) SF-36 physical functioning: 38.9 vs. 41.6; (difference −2.7, 95% CI −19.5 to 14.1) SF-36 physical role: 26.1 vs. 31.0; (difference −4.9, 95% CI −27.9 to 18.1) SF-36 bodily pain: 33.8 vs. 34.3; (difference −0.5, 95% CI −20.9 to 19.9) SF-36 social functioning: 60.7 vs. 57.2; (difference 3.5, 95% CI −17.2 to 24.2) SF-36 emotional role: 66.7 vs. 58.7; (difference 8.0, 95% CI −19.2 to 35.2) SF-36 mental health: 56.5 vs. 53.8; (difference 2.7, 95% CI −19.1 to 24.5)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Thieme, 2006[117] 6 and 12 months Duration of symptoms, years: 9.1 vs. 8.7 Poor	A. CBT (n=42): 2-hour group sessions weekly for 15 weeks. Sessions focused on changing patients' thinking and problem-solving, stress and pain coping strategies, and relaxation exercises performed during and between sessions. B. Attention control (n=40): 2-hour group sessions weekly for 15 weeks: general discussions about medical and psychosocial problems of fibromyalgia.	A vs. B Age: 49 vs. 47 years Female: 100% vs. 100% Baseline FIQ physical impairment (mean, 0-10): 4.4 vs. 4.2 Baseline WHYMPI pain intensity (mean, 0-6): 4.2 vs. 3.8	A vs. B <u>6 months</u> FIQ physical impairment: 3.0 vs. 4.8; difference −1.8 (95% CI −2.899 to −0.701) WHYMPI pain intensity: 3.7 vs. 4.1; difference −0.4 (95% CI −0.841 to 0.041) <u>12 months</u> FIQ physical impairment: 3.4 vs. 5.2; difference −1.8 (95% CI −2.855 to −0.745) WHYMPI pain intensity: 3.2 vs. 4.1; difference −0.9 (95% CI −1.537 to −0.263)	A vs. B <u>6 months</u> WHYMPI affective distress: 2.6 vs. 4.0; difference −1.4 (95% CI −1.952 to −0.848) <u>12 months</u> WHYMPI affective distress: 2.6 vs. 4.2; difference −1.6 (95% CI −2.172 to −1.028)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Van Santen, 2002[97] Post 6-month intervention Duration of symptoms, years: 10.1 vs. 15.4 vs. 15.4 Poor	A. Electromyographic biofeedback (n=56): Progressive muscle relaxation and frontalis EMG biofeedback; 30-minute individual sessions 2 times per week for 8 weeks; subjects encouraged to practice at home twice daily for the 8 weeks then for 16 more weeks. Subjects randomized to education aimed at compliance with biofeedback training (6 90-minute sessions over 24 weeks). B. Usual care (n=29): General physicians informed not to prescribe or encourage aerobic exercises and relaxation. Intervention duration: 6 months C. Combination Exercise (n=58): 60-minute group sessions of twice a week for 24 weeks; aerobic exercises, postural strengthening, general flexibility and balance exercises, and isometric muscle strengthening; subjects encouraged to attend third, unsupervised, 60-minute session and to use sauna or swimming pool after sessions.	A vs. B Age: 44 vs. 43 vs. 46 years Female: 100% vs. 100% vs. 100% Race NR Baseline SIP Physical score (0-100): 11.4 vs. 9.8 vs.11.3 Baseline SIP Total score (0-100): 14.0 vs. 11.4 vs. 14.4 Baseline AIMS (0-10): 3.1 vs. 5.4 vs. 1.9 Baseline pain VAS (0-100): 59.1 vs. 62.4 vs. 66.8	A vs. B <u>6 months:</u> SIP physical score, mean change: −1.6 (95% CI −3.4 to 0.2) vs. −0.6 (95% CI −2.9 to 1.7) SIP total score, mean change: −2.3 (95% CI −4.3 to −0.3) vs. −1.4 (95% CI −3.4 to 0.6) AIMS, mean change: 0.4 (95% CI −0.1 to 0.9) vs. 0.8 (95% CI −1.8 to −0.2) SIP total score, mean change: −2.3 (95% CI −4.3 to −0.3) vs. −1.4 (95% CI −3.4 to 0.6) Pain VAS, mean change: −0.6 (95% CI −6.5 to 5.3) vs. 1.3 (95% CI −4.5 to 7.1) A vs. C <u>6 months:</u> SIP physical score, mean change: −1.6 (95% CI −3.4 to 0.2) vs. −1.7 (95% CI −3.7 to 0.3), NS SIP total score, mean change: −2.3 (95% CI −4.3 to −0.3) vs. −1.9 (95% CI −3.9 to 0.1) AIMS, mean change: 0.4 (95% CI −0.1 to 0.9) vs. 0.1 (95% CI −0.6 to 0.8) Pain VAS, mean change: −0.6 (95% CI −6.5 to 5.3) vs. −5.5 (95% CI −10.9 to −0.1), NS	A vs. B <u>6 months:</u> SIP psychosocial score (0-100), mean change: −3.7 (95% CI −4.9 to −2.5) vs. −3.5 (95% CI −7.0 to 0.0) Patient global assessment of well-being, mean change: 0.3 (95% CI 0.0 to 0.6) vs. 0.5 (95% CI 0.2 to 0.8) A vs. C <u>6 months:</u> SIP psychosocial score, mean change: −3.7 (95% CI −4.9 to −2.5) vs. −3.2 (95% CI −6.2 to 0.2) Patient global assessment of well-being, mean change: 0.3 (95% CI 0.0 to 0.6) vs. 0.5 (95% CI 0.2 to 0.8)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Verkaik, 2014[118] 1.5 months Duration of symptoms, NR Poor	A. Guided imagery (n=33): Two 1.5 hour group sessions of 6-12 subjects. The first sessions consisted of group discussion, the theoretical background of guided imagery, and instructions to practice at least one exercise daily for 4 weeks. Each exercise was a CD and contained relaxation techniques, music, positive imagery, and pain management techniques. The second group session took place after the 4 weeks and consisted of a group discussion. B. Attention control (n=37): Two 1.5 hour group sessions of 6-12 subjects held 4 weeks apart. Group sessions were a group discussion and did not contain any information or training on guided imagery.	A vs. B Age: 47 vs. 48 Female: 100% vs. 97% Baseline FIQ(0-100): 53.7 vs. 56.4 Baseline pain VAS (0-10): 5.9 vs. 5.8	A vs. B <u>1.5 months</u> FIQ: 54.2 vs. 53.0, difference 1.2, 95% CI −0.2 to 2.6) Pain VAS: NR	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Wigers, 1996[98] 48 months Fibromyalgia duration A vs. B vs. C Mean: 11 vs. 9 years Poor	A. Stress management (n=20): 90 minute group sessions of 10 patients done 2 times a week for 6 weeks followed by 1 session per week for the next 8 weeks. Sessions consisted of equal portions of presentations stress mechanisms and strategies for improving quality of life, group discussions on patients' experiences of stress and coping with pain, and relaxation training aimed at helping cope with stress and pain. B. Usual care (n=20): Subjects continued treatments they had been using at baseline. C. Aerobic exercise (n=20): 45 minute group sessions of 10 patients done 3 times a week for 14 weeks. The exercise program involved the whole body and aimed to minimize eccentric muscle strain. Sessions consisted of training to music (further details not given) and aerobic games.	A vs. B Age: 44 vs. 46 vs. 43 years Female: 90% vs. 95% vs. 90% Baseline pain VAS (0-100): 72 vs. 65 vs. 72	A vs. B <u>48 months</u> Pain VAS: 70 vs. 69, (difference 1, 95% CI −12.6 to 14.6) A vs. C <u>48 months</u> Pain VAS: 70 vs. 68, (difference 2, 95% CI −11.6 to 15.6)	A vs. B <u>48 months</u> Depression VAS (0-100): 40 vs. 30, (difference 10, 95% CI −8.9 to 28.9) Global subjective improvement: 47% (6/13) vs. 12% (2/16), (RR 3.7, 95% CI 0.9 to 15.3) A vs. C <u>48 months</u> Depression VAS: 40 vs. 32, (difference 8, 95% CI −11.9 to 27.9) Global subjective improvement: 47% (6/13) vs. 75% (11/15), (RR 0.6, 95% CI 0.3 to 1.2)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Williams, 2002[120] 12 months Fibromyalgia duration, 8.6 years Poor	A. Group CBT plus Usual Care (n=76): 6 1-hour group sessions over 4-week period: progressive muscle relaxation, imagery, activity pacing, pleasant activity scheduling, communication skills and assertiveness training, cognitive restructuring, stress management and problem-solving. B. Usual Care (n=69): Standard pharmacological management (typically low-dose tricyclic antidepressant medication, analgesics, and/or antidepressants) plus suggestions to engage in aerobic fitness.	A + B Age, mean, years: 47.7 Females: 90% Race: White non-Hispanic 88%, black non-Hispanic 9%, Hispanic 2%, Asian American 1% Baseline MPQ-Sensory (scale NR): 14.8 Baseline MPQ-Affective pain score (scale NR): 4.6	A vs. B 12 months Mean (SD): NR Proportion of subjects who improved more than 12 points from baseline on MPQ-Sensory scale: 3.9% vs. 7.2%; RR 0.54 (95% CI 0.14 to 2.2)	A vs. B 12 months Mean (SD) NR Proportion of subjects who improved more than 6.5 points from baseline on SF-36 PCS Score: 25% vs. 11.6%, OR 2.9; RR 2.2 (95% CI 0.98 to 4.99) Proportion of subjects who improved more than 5 points from baseline on MPQ-Affective scale: 9.2% vs. 8.7%, RR 1.1 (95% CI 0.37 to 3.0)

ACT = acceptance and commitment therapy; AIMS = Arthritis Impact Measurement Scales; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BPI = Brief Pain Inventory; CBT = cognitive-behavioral therapy; CES-D = Center for Epidemiologic Studies Depression Scale; CI = confidence interval; CPAQ = Chronic Pain Acceptance Questionnaire; EEG = electroencephalogram; EMG = electromyography; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; FSS = Fatigue Severity Scale; GAD-7 = Generalized Anxiety Disorder 7-item scale; HAM-D = Hamilton Rating Scale for Depression; HAM-A = Hamilton Anxiety Rating Scale; HADS-A = Hospital Anxiety and Depression Scale, Anxiety; HADS-D = Hospital Anxiety and Depression Scale, Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; MASQ = Mood and Anxiety Symptom Questionnaire; MCS = Mental Component Summary Score; MCSD = Minimal Clinically Significant Difference; MFI = Modified Fatigue Impact Scale; mg = milligrams; MOS = Medical Outcomes Study; MPI = West Haven-Yale Multidimensional Pain Inventory; MPQ = McGill Pain Questionnaire; NR = not reported; NRS = numerical rating scale; NS = not statistically significant; OR = odds ratio; PANAS = Positive and Negative Affect Schedule; PCS = Physical Component Summary Score; PDI = Pain Disability Index; PHQ = Patient Health Questionnaire; PI = Physical Impairment; PSQI = Pittsburg Sleep Qualtiy Index; RR = risk ratio; SCL-90-R = Symptoms Checklist 90-Revised; SD = standard deviation; SIP = Sickness Impact Profile; SF-12 = Short-Form 12 questionaire; SF-36 = Short-Form 36 questionnaire; SWLS = Satisfaction With Life Scale; STAI = State-Trait Anxiety Inventory; VAS = visual analog scale; WHYMPI = West Haven-Yale Mulidemensional Pain Inventory; WPI = Widespread Pain Index

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Psychological Therapies Compared With Usual Care, Waitlist, or Attention Control

Fifteen trials (5 new trials) compared psychological interventions versus usual care, waitlist, or attention control.[78,97,98,113-121,124-127] Nine trials were considered poor quality and six [5 new trials][116,119,122-127] were considered fair quality. ACT is considered a form of CBT and was included in CBT-specific analyses.

Functional Outcomes. Across all types of psychological interventions, two poor quality trials reported on clinically meaningful improvement in short-term function (Table 37). Significantly more patients in the CBT group attained a clinically important improvement (≥14% on the FIQ

total, 0-100 scale) from baseline compared with usual care (RR 2.8, 95% CI 1.3 to 6.1) in one trial,[115] but there was no significant difference in a smaller trial (RR 2.2, 95% CI 0.5 to 9.3).[114]

Examining mean differences in followup scores short-term, there was no clear difference in function across psychological therapies versus usual care, waitlist or attention control (5 trials [2 new], pooled difference −2.82 on a 0-100 FIQ total scale, 95% CI −9.79 to 2.81, I^2=70.6%).[115,116,118,119,121,125] Analysis confined to CBT trials (including ACT) showed no clear difference in function compared with usual care or waitlist in the short term (3 trials [1 new], pooled difference −6.14 on a 0-100 scale, FIQ total, 95% CI −16.86 to 3.74, I^2=70.6%).[115,116,119,121] Two trials were fair quality (Figure 46). Analysis of differences in change scores on the FIQ were similar in magnitude (data not shown). The prior AHRQ review reported a small improvement in function with CBT versus usual care or waitlist based on two trials.[115,116,119] No differences between groups were seen in the trials of guided imagery (difference 1.2 on a 0-100 FIQ total scale, 95% CI −0.2 to 2.6)[118] and EMG biofeedback. In one study of EMG biofeedback versus attention control, median change from baseline was 6.0 for both groups on the Arthritis Impact Measurement Scales (AIMS) physical activity subscale (0-10 scale).[78] In a new fair-quality trial of EMG biofeedback,[125] there was no difference on the FIQ as compared with an attention control condition.

At intermediate term, one poor quality trial reported that substantially more CBT patients achieved a clinically important functional improvement (≥14% on the FIQ total, 0-100 scale) compared with usual care (RR 2.9, 95% CI 1.9 to 17.8).[115] For analysis of mean differences in intermediate term scores, CBT/ACT was associated with moderate improvement in function (3 trials [1 new], pooled difference −12.82 on 0-100 scale, FIQ total, 95% CI −24.07 to −2.44, I^2=94.2%)[113,115,122,123] versus waitlist or usual care. All trials favored CBT (2 fair, 1 poor quality) but differed in magnitude of benefit. Pooled effect size was attenuated (small improvement with CBT) and no longer significant due to heterogeneity across the two trials of CBT versus usual care in the prior report (pooled difference −9.35, 95% CI −26.95 to 5.02, I^2=84.5%).[113,115] Both trials individually showed CBT had a statistically greater effect on function than usual care, but the effects differed in magnitude and we reported as a small improvement in function in the prior report (Figure 46). Findings from an additional trial suggested a greater improvement in function with CBT compared with attention control based on a 0 to 10 FIQ Physical Impairment Scale (difference −1.8, 95% CI −2.9 to −0.70).[117] A new fair-quality trial[127] of CBT for pain and CBT for insomnia versus waitlist found no difference between groups on the Pain Disability Index. A new fair-quality trial[126] of a CBT stress management program versus waitlist also found no difference on the West Haven-Yale Multidimensional Pain Inventory (MPI) pain interference subscale. There was no clear difference between biofeedback and usual care on function on the Sickness Impact Profile (SIP) physical score in one trial (mean change −1.6, 95% CI −3.4 to 0.2 versus −0.6, 95% CI −2.9 to 1.7, respectively, on a 0-100 scale).[97]

Data from two poor-quality trials were insufficient to determine the long-term effects of psychological therapies on function. One trial reported that CBT resulted in greater improvement compared with attention control on the FIQ Physical Impairment Scale (difference −1.8 on a 0-10 scale, 95% CI −2.85 to −0.745).[117] A trial of biofeedback versus usual care reported the same median change in the AIMS Physical Activity subscale (6.0) in both groups.[78]

Pain Outcomes. Psychological interventions (CBT/ACT and EMG biofeedback) were associated with a small improvement in pain compared with usual care, waitlist, or attention control, based on mean differences at short-term followup (5 trials [1 new], pooled difference −0.62, 95% CI −1.02 to −0.20, I^2=0%)[78,114-116,119,121] (Figure 47). Results based on the mean difference of

change scores were similar, but not statistically significant (data not shown). The estimate was similar when only trials of CBT were considered (4 trials [1 new], pooled difference −0.62, 95% CI −1.08 to −0.14, plot not shown).[114-116,119,121] One poor quality trial reported no difference between CBT and usual care in the proportion of patients with clinically important improvement in pain short-term (≥30% improvement on 0-10 NRS, RR 1.5, 95% CI 0.4 to 5.7).[115] The addition of the new poor quality CBT trial[121] resulted in no changes in conclusions from the prior AHRQ report for short term results.

At intermediate term, one poor quality trial reported no difference in the proportion of patients showing a clinically important improvement in pain (≥30% on 0-10 NRS, RR 1.3 95% CI 0.4 to 4.2)[115]; similarly, one new fair quality trial reported no differences in clinically important improvement (≥50% on Brief Pain Inventory) with CBT (8.3%) or EAET (22.5%) versus usual care (12%).[124] In analyses based on mean differences in scores, psychological interventions (CBT, ACT, EMG biofeedback, and combined CBT and EAET) were associated with a small benefit for pain compared with usual care, attention control or waitlist (7 trials [4 new], pooled difference −0.62, 95% CI −1.14 to −0.09, I^2=65.7%),[97,113,115,122-124,126,127] (Figure 47). Effect sizes at intermediate term were slightly smaller in a subanalysis of therapies versus usual care only (3 trials [1 new], pooled difference −0.52, 95% CI −1.4 to −0.15).[97,113,115] Pooling only the six CBT trials, the effect was slightly smaller (6 trials [4 new] pooled difference −0.55, 95% CI −1.12 to 0.06)[113,115,122-124,126,127] with no clear difference between CBT and usual care, waitlist or attention control. Similarly, there was no clear difference in a subanalysis confined to the five fair quality trials, all of which were of CBT (5 trials [4 new], pooled difference −0.48, 95% CI −1.11 to 0.24).[113,122-124,126,127] In the prior AHRQ report, there was no clear difference between CBT and usual care across two studies although each tended to favor CBT. The addition of the four new fair quality studies does not change the conclusion of no clear difference. In one new trial, the author-developed EAET, compared with attention control, was not associated with lower pain intensity at intermediate term based on the proportion of patients achieving a 50 percent or greater reduction in pain (22.5% vs. 12.0%, p=0.07) or the mean difference in pain scores using the Brief Pain Inventory 0-10 scale (−0.54, 95% CI −1.2 to 0.1), but was associated with improved fibromyalgia symptoms (difference −2.9, 95% CI −4.9 to −0.8 on the FM symptom scale, scale unclear).[124]

Three trials[78,98,120] reported long term effects on pain. A pooled analysis of two of these trials found no difference between these psychological therapies (CBT or biofeedback/relaxation training) and attention control or usual care (2 trials, pooled difference 0.04, 95% CI −0.89 to 0.98, I^2=0%)[78,98]; however, evidence across these two poor-quality trials was considered insufficient (Figure 47). The third trial found no difference between CBT and usual care in the proportion of participants achieving a clinically meaningful change of 12 points from baseline on the McGill Pain Questionnaire (MPQ) Sensory Scale (RR 0.54, 95% CI 0.14 to 2.2).[120]

Other Outcomes. Results for secondary outcomes were mixed across trials of CBT and ACT on secondary outcomes (Table 36). Five trials were fair quality;[116,119,122-124,126,127] the rest were poor quality.

In one fair-quality trial of ACT versus waitlist there were no differences between groups over the short term on the BDI, STAI-State scale or Short-Form-36 (SF-36) PCS; ACT was associated with improvement in the SF-36 MCS.[116,119] In a new fair-quality trial of EMG biofeedback,[125] there was no difference on SF-36 scores compared with an attention control condition.

Five fair-quality trials of CBT/ACT reported intermediate term outcomes. A comparison of CBT versus usual care found no differences on the Hospital Anxiety and Depression Scale

(HAM-D) and Hamilton Anxiety Rating Scale (HAM-A).[113] A new trial of ACT versus waitlist found a benefit of ACT for the 0-100 EQ5D VAS health status rating (difference 12.2, 95% CI 7.9 to 16.5), Hospital Anxiety and Depression Scale-Anxiety (HADS-A) (difference −3.42, 95% CI −4.7 to −2.1), and Hospital Anxiety and Depression Scale-Depression (HADS-D) (difference −3.5, 95% CI −4.4 to −2.5).[122,123] A new trial of CBT versus education attention control[124] found no difference on the Short Form-12 Physical scale, Satisfaction with Life Scale, Pittsburgh Sleep Quality Index (PSQI), Positive Affect Negative Affect Schedule (PANAS)-positive score, PANAS-negative score, Center for Epidemiologic Studies Depression Scale (CES-D), Generalized Anxiety Disorder-7, or PROMIS Fatigue Short-Form. A new fair-quality trial of CBT for insomnia, CBT for pain, and waitlist found benefits of both CBT interventions for measures of sleep, but not depression or anxiety.[127] A new fair-quality trial of CBT stress management versus waitlist found benefits of CBT for measures of affective distress and depression, but not sleep.[126] Across the poor-quality trials, results were mixed across various secondary outcomes measures (Table 36).

Two poor-quality studies compared EMG biofeedback to attention control conditions; neither found differences on secondary outcomes, including the Symptoms Checklist 90-Revised Global Severity Index, SIP psychosocial score, global assessment of well-being, CES-D, and a sleep scale.[78,97]

Psychological Therapies Compared With Pharmacological Therapy

Three fair-quality trials[113,122,123,130] and one poor-quality trial[131] compared a psychological therapy with pharmacological treatment. Two small trials reported functional outcomes over the short term with differing results. No effect was seen for CBT (plus amitriptyline) compared with amitriptyline alone at 3 months in one fair-quality trial (difference −4.10, 95% CI −18.40 to 10.20 on the FIQ total score [0 to 100 scale]).[130] One poor-quality trial, comparing EEG biofeedback with escitalopram, reported improved mean FIQ total scores (0-100 scale) in the biofeedback group at 4 to 5 months followup (difference −29.00, 95% CI −38.58 to −19.42).[131] Substantial heterogeneity of the interventions, the medication comparators and quality of the trials precluded meaningful pooling for this outcome (Figure 48).

Intermediate-term function was reported by two fair-quality trials (1 new trial)[113,122,123]; both found benefits for CBT (including ACT) compared with pregabalin (plus duloxetine for depressed patients) according to the FIQ Total scale (0-100). One found a small improvement in function favoring CBT (difference −4.00 on a 0-100 scale, 95% CI −7.44 to −0.56)[113]; the other found a moderate improvement for function associated with CBT (difference −15.62, 95% CI −19.03 to −12.21).[122,123] The pooled estimate suggests a small improvement in function (pooled difference −9.81, 95% CI −23.83 to 4.21, I^2=96% but substantial heterogeneity due to the differences in effect magnitudes is noted) (Figure 48). It is unclear how many patients in the pharmacological group received concomitant duloxetine for major depressive disorder.

No differences in pain short-term were seen between groups in the trial of CBT versus amitriptyline (difference −0.7 on a 0-10 VAS, 95% CI −2.8 to 1.4),[130] whereas a moderate improvement was seen for EEG biofeedback compared with escitalopram (difference −2.7 on a 0-10 VAS, 95% CI −3.7 to −1.7) in the poor-quality trial.[131] Trials were not pooled given heterogeneity of both the intervention and medication comparators.

At intermediate-term, no difference between CBT/ACT versus pregabalin was observed (2 trials [1 new] pooled difference −0.31, 95% CI −1.15 to 0.51, I^2= 63.5%).[113,122,123]

Regarding secondary outcomes, EEG biofeedback was associated with significantly better outcomes on various measures of anxiety, depression, and quality of life compared with escitalopram short term in the poor-quality trial.[131] The two fair-quality trials evaluating CBT (versus amitriptyline and versus pregabalin)[113,130] found no differences between groups over the short or intermediate term, with the exception of a benefit of CBT for SF-36 Mental Health scores at short-term followup in one trial (difference 13.7 on a 0-100 scale, 95% CI 0.07 to 27.3).[130] In the fair quality trial of ACT versus pregabalin (plus duloxetine for patients who were depressed), at intermediate term there was a benefit of ACT on the EQ-5D VAS measure of self-assessed health state (0-100 scale, with higher scores indicating better health; difference 9.6, 95% CI 5.2 to 14.0); the 0-21 HADS-A anxiety scale (difference −1.0, 95% CI −1.8 to −0.06); and the 0-21 HADS-D depression scale (difference −1.7, 95% CI −2.6 to −0.8). Across the two studies of CBT versus pregabalin (plus duloxetine as needed),[113,122,123] there was no difference between therapies on depression (measured by the HADS depression scale and the Hamilton Depression scale) intermediate term (difference −0.43, 95% CI −1.13 to 0.28, I^2=93%). Two trials examined effects of pregabalin (plus duloxetine as needed) on measures of anxiety, with no difference across these studies at intermediate term followup (difference −0.23, 95% CI −0.69 to 0.23, I^2= 0%).

Psychological Therapies Compared With Exercise

Five poor-quality trials compared psychological interventions with exercise; two trials evaluated CBT,[98,136] two trials evaluated biofeedback,[78,97] and one evaluated relaxation training[135] (Table 36). All trials were included in the prior AHRQ report.

Data were insufficient from one poor-quality trial to determine the effects of biofeedback versus combination exercise on function. The trial reported improved function based on the AIMS physical activity subscale (median change from baseline 6.0 versus 4.0, p<0.05).[78] Intermediate-term data from two poor-quality trials were insufficient to determine effects of psychological therapies on function and no clear differences in function were seen for CBT (difference −0.6, 95% CI −12.6 to 11.4 on 0-100 FIQ total score)[136] or biofeedback (mean change −1.6, 95% CI −3.4 to 0.2 vs. −0.6, 95% CI −2.9 to 1.7 on 0-100 SIP Physical score)[97] versus combination exercise. Similarly, no clear differences between psychological therapies and exercise were seen across three trials at longer term and evidence was considered insufficient. Results from two trials were not statistically significant (CBT vs. combination exercise [difference 0.1, 95% CI −10.5 to 10.7 on 0-100 FIQ total scale][136] and relaxation training versus strength training [difference −1.7, 95% CI −9.3 to 5.9, on 0-100 FIQ Total Score]).[135] The third trial of biofeedback versus combination exercise reported improvement in function, but limited data were provided (median change from baseline, 6.0 versus 4.0, p<0.05).[78]

Data were insufficient from one poor-quality trial to determine the effects of biofeedback versus combination exercise pain (median change from baseline, 5.2 vs. 5.4 on 0-10 VAS).[78] Across two poor-quality trials at intermediate term, no clear differences were seen for CBT (difference −1.0, 95% CI −2.8 to 0.8)[136] or biofeedback (mean change −0.6, 95% CI −6.5 to 5.3 vs. −5.5, 95% CI −10.9 to −0.1, p=not statistically significant [NS])[97] compared with combination exercise; evidence was considered insufficient. There were no clear differences between any of the psychological therapies and exercise for pain on a 0 to 10 scale across four trials long term, including CBT versus combination exercise (difference 0.3, 95% CI −2.0 to 1.3)[136] or aerobic exercise (difference 2, 95% CI −11.6 to 15.6),[98] biofeedback versus

combination exercise (median change: 5.2 vs. 5.5, p=NS),[78] and relaxation training versus strength training (difference 2.9, 95% CI −5.5 to 11.3).[135]

There were generally no significant differences on measures of mental health, depression or anxiety, or on SF-36 scales, at any time frame across five poor-quality trials.[78,97,98,135,136] Some trials did not provide data for determination of effect sizes between treatment groups or report results of significance tests (Table 36).

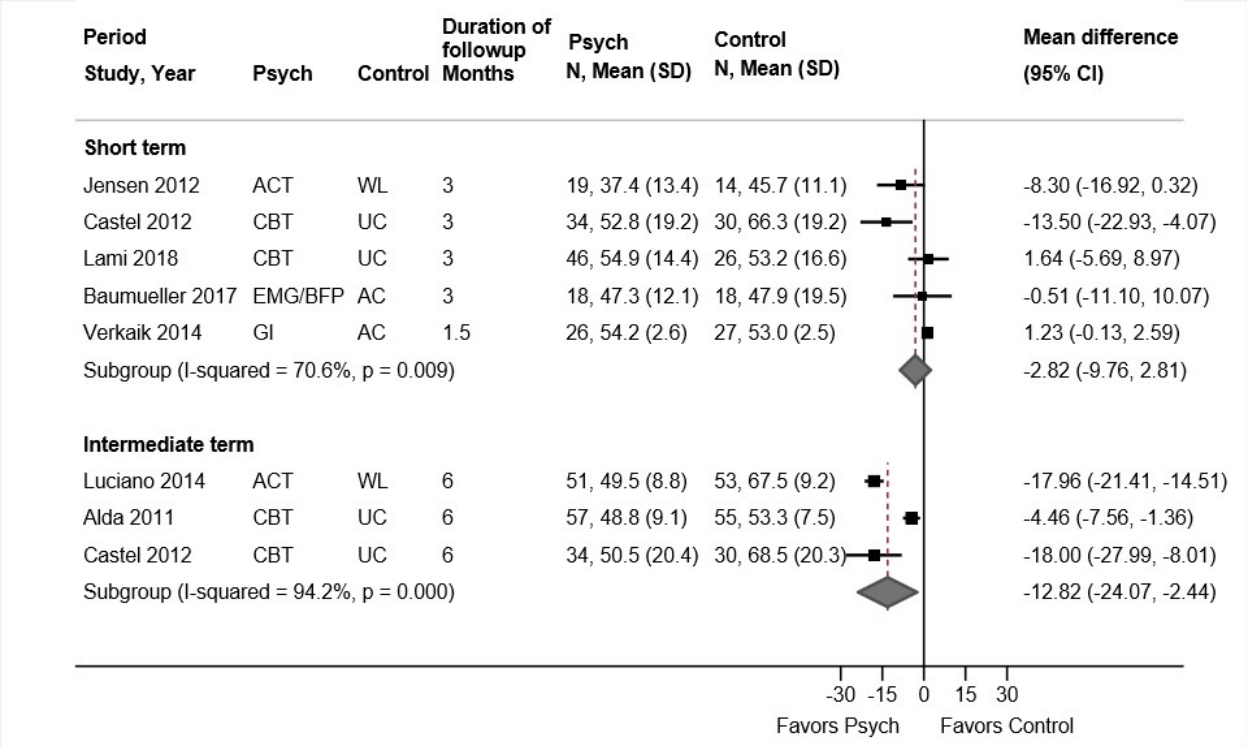
Harms

Only seven trials (3 fair-quality and 4 poor-quality, 2 new) reported harms, which were poorly described in general. Two trials compared CBT with usual care; in one, there were no withdrawals due to adverse events in the CBT group compared with two (3.6%) in the control group (not further described)[113] and in the other there were two withdrawals, one in each group, due to painfulness of the nociceptive flexion reflex test used as an outcome measure (not as part of treatment).[114] Two trials compared psychological therapies with attention controls. One trial reported that 4.8 percent of patients in the CBT group versus 50 percent in the control group withdrew from the study (withdrawal attributed to depression [CBT group] and symptom worsening [control group]).[117] The other trial (a new trial) reported no adverse events for CBT or attention control (education) but did note that brief symptom exacerbation (i.e., increased pain or sleep problems) was occasionally reported by patients who received the EAET intervention[124]; 4% of patients in the CBT and EAET groups (vs. 2.6% in the control group) withdrew due to treatment not of interest or fit and one (1.3%) patient in the CBT group withdrew after being diagnosed with cancer. In another trial that compared CBT with waitlist,[122,123] 5.9% and 3.9% of CBT patients withdrew due to lack of efficacy or patient decision, respectively, compared with no patients in the waitlist group. One trial of stress management versus usual care reported one withdrawal due to cancer (unrelated to the treatment) in the intervention group compared with no withdrawals or adverse events in the control group.[98]

Two of the above trials also compared psychological therapy to pharmacological therapy, specifically pregabalin (with duloxetine as needed). One trial evaluated CBT and reported no withdrawals due to adverse events in the CBT group compared with three (5.5%) in the pharmacotherapy group (2 due to digestive problems and 1 due to dizziness).[113] An additional new trial compared ACT versus pregabalin and reported withdrawal due to lack of efficacy (5.9% vs. 1.9, respectively) or patients decision (3.9% vs. 0%, respectively); adverse events reported in the pregabalin group only included nausea (25%), dry mouth (23%), drowsiness, headache and fatigue (21% each) and constipation (19%).[122,123]

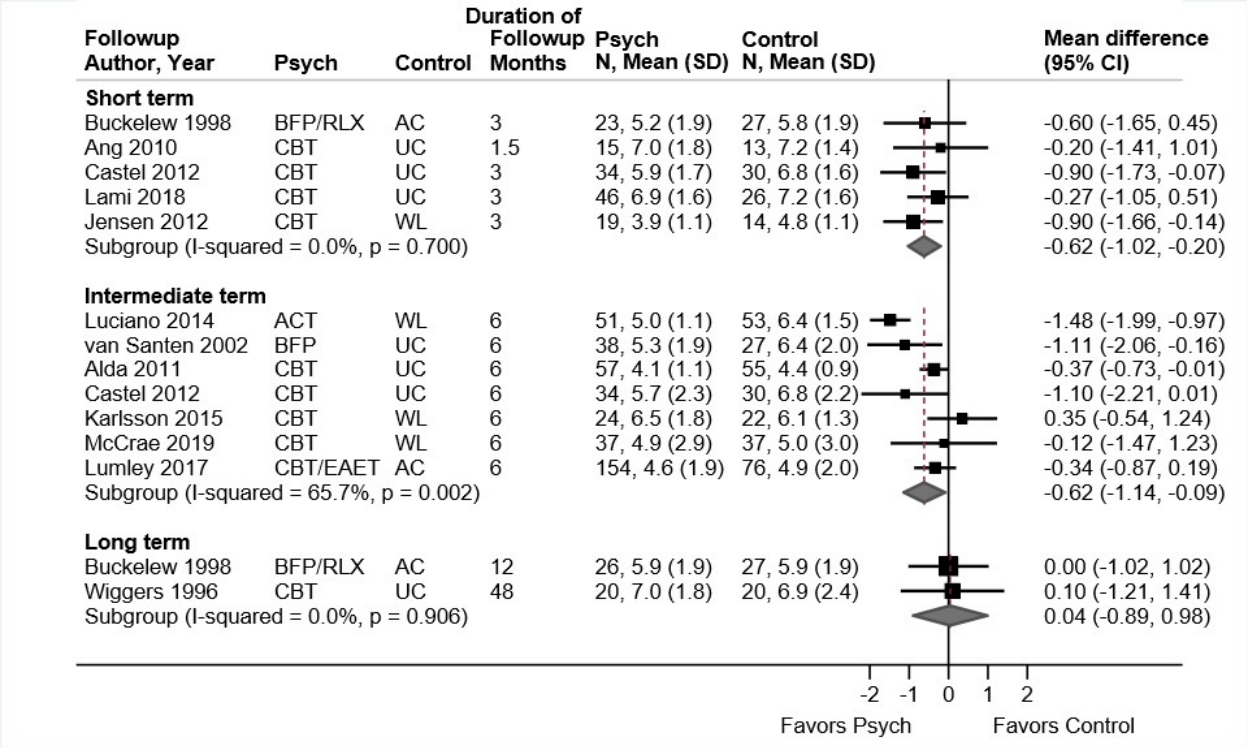
Two trials of psychological therapies versus exercise reported harms. One trial reported no adverse effects with relaxation therapy, but five (7.5%) adverse effect reports following strengthening exercises (due to increased pain), resulting in three withdrawals (out of 67 randomized) from the trial.[135] The other trial reported one withdrawal due to cancer (unrelated to the treatment) in the intervention group compared with three withdrawals in the exercise group (1 death, 1 gastritis, 1 ischialgia).[98]

Figure 46. Psychological therapies versus usual care, waitlist, or attention control for fibromyalgia: effects on function



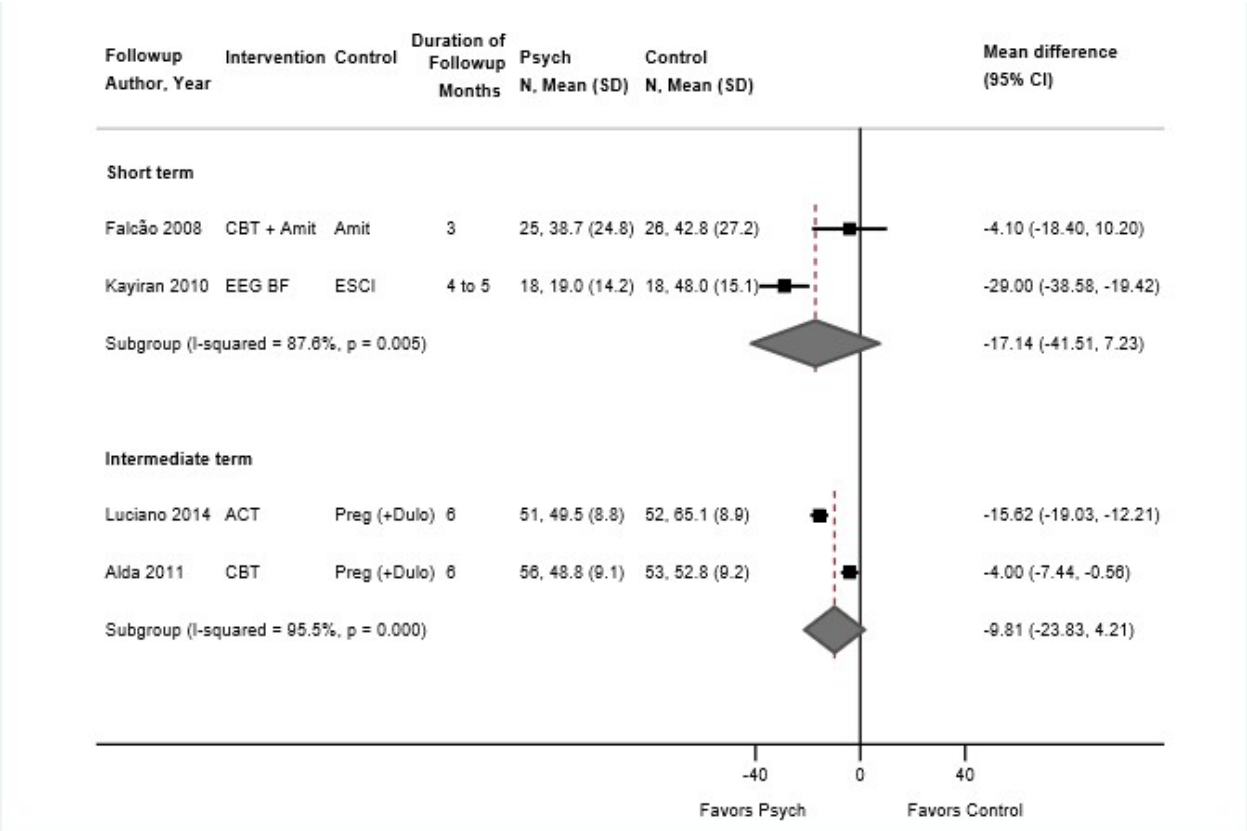
AC = attention control; ACT = acceptance and commitment therapy; CBT = cognitive-behavioral therapy; CI = confidence interval; GI = guided imagery; SD = standard deviation; UC = usual care; WL = waitlist

Figure 47. Psychological therapies versus usual care, waitlist, or attention control for fibromyalgia: effects on pain



AC = attention control; ACT = acceptance and commitment therapy; BFP = biofeedback; BFP/RLX = Biofeedback with a Relaxation component; CBT = cognitive-behavioral therapy; CI = confidence interval; EAET = emotional awareness and expression therapy; SD = standard deviation; UC = usual care; WL = waitlist

Figure 48. Psychological therapies versus pharmacological therapy for fibromyalgia: effects on function



ACT = acceptance and commitment therapy; Amit = amitriptyline; CBT = cognitive-behavioral therapy; CI = confidence interval; Dulo = duloxetine; EEG BF = Electroencephalographic Biofeedback; ESCI = escitalopram; Preg = pregabalin; SD = standard deviation.

Physical Modalities for Fibromyalgia

Key Points

- One fair-quality parallel trial found no differences between magnetic mattress pads compared with sham or usual care in intermediate-term function (difference on the 0 to 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 to 10 NRS) (SOE: low). Data from one small, poor-quality crossover trial were insufficient to determine the effects of a magnetic mattress versus sham on function and pain in the short term (SOE: insufficient).
- There were no differences in adverse events between the functional and sham magnetic mattress pad groups (data not reported); none of the events were deemed to be related to the treatments (SOE: low).

Detailed Synthesis

Two trials,[167,168] one parallel and one cross-over design, evaluating the efficacy of magnetic fields for the treatment of fibromyalgia met inclusion criteria (Table 38 and Appendix D). Both

trials were included in the prior AHRQ report. In both trials, the majority of patients were female (93% and 100%) and the mean ages were 45 and 50 years; symptom duration was 6 years in one trial and was not reported by the other trial. Due to the differences in trial designs we could not pool the data; therefore, these trials are reported separately.

One parallel trial (N=119),[167] conducted in the United States, compared two different magnetic mattress pads (one with a low, uniform magnetic field of negative polarity and the other a low, static magnetic field that varied spatially and in polarity) versus sham (mattress pads with demagnetized magnets) and versus usual care (management by primary care provider). All pads were used for 6 months and outcomes were measured immediately post-treatment. This trial was rated fair quality due to deviations from the randomization protocol and high attrition rate (21%) (Appendix E).

A second small, crossover trial (N=33)[168] evaluated the effects of an extremely low frequency magnetic mattress compared with a sham mattress (no magnetic field delivered). The trial was conducted in Italy. The intervention periods were 1 month and the washout period between the first and second period was 1 month; no further information was provided about the washout period. Outcomes were measured 1 month after the end of each treatment cycle (i.e., at the beginning of the second treatment cycle, after a 1 month washout, and 1 month after the end of the second treatment cycle).This trial was rated poor quality due to unclear randomization sequence generation and allocation concealment, and loss-to-followup of greater than 20% through the second treatment period; additional sources of bias in this crossover trial include no details regarding handling of missing data and no analysis of carryover effect.

Table 54. Fibromyalgia: physical modalities

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Alfano, 2001[167] 6 months Duration of pain: >3 months (mean NR) Fair	A. Magnetic mattress pad designed to expose body to a uniform magnetic field of negative polarity (n=37) B. Magnetic mattress pad exposing body to magnetic field that varied spatially and in polarity (n=33) C. Sham magnetic field (n=32): combined group of 2 sham magnetic mattress pads; identical in appearance to real magnetic pads but contained demagnetized magnets. D. Usual care (n=17): maintain current treatment under PCP, refrain from new treatments Treatment period was 6 months for all groups.	A vs. B vs. C vs. D Age: 44 vs. 47 vs. 46 vs. 45 years Female: 92% vs. 87% vs. 96% vs. 100% Baseline FIQ (0-80): 51.6 vs. 55.5 vs. 51.5 vs. 53.9 Baseline pain intensity FIQ NRS (0-10): 7.1 vs. 7.0 vs. 6.7 vs. 7.0	A + B vs. C <u>Post 6-month intervention</u> FIQ: 42.9 vs. 47.9, difference −5.0 (95% CI −14.1 to 4.1) Pain intensity NRS: 5.6 vs. 6.2, difference −0.6 (95% CI −1.9 to 0.7) A + B vs. D <u>Post 6-month intervention</u> FIQ: 42.9 vs. 48.4, difference −5.5 (95% CI −14.4 to 3.4) Pain intensity NRS: 5.6 vs. 6.6, difference −1.0 (95% CI −2.2 to 0.2) A vs. C <u>Post 6-month intervention</u> FIQ: 38.3 vs. 47.9, difference −9.6 (95% CI −20.0 to 0.8) Pain intensity NRS: 4.8 vs. 6.2, difference −1.4 (95% CI −2.8 to 0.05) B vs. C <u>Post 6-month intervention</u> FIQ: 47.4 vs. 47.9, difference −0.5 (95% CI −11.2 to 10.2) Pain intensity NRS: 6.3 vs. 6.2, difference 0.1 (95% CI −1.4 to 1.6) A vs. D <u>Post 6-month intervention</u> FIQ: 38.3 vs. 48.4, difference −10.1 (95% CI −21.9 to 1.7) Pain intensity NRS: 4.8 vs. 6.6, difference −1.8 (95% CI −3.4 to −0.2) B vs. D <u>Post 6-month intervention</u> FIQ: 47.4 vs. 48.4, difference −1.0 (95% CI −13.0 to 11.0), Pain intensity NRS: 6.3 vs. 6.6, difference −0.3 (95% CI −2.0 to 1.4)	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Paolucci, 2016[168] 1 month Duration of pain: Poor	A. Extremely low-frequency magnetic field first (n=16): three 30-minute sessions per week for 4 weeks (12 sessions total). Patients laid on a bed with multi-low-frequency mattress that delivered a magnetic field at an intensity of 100 uT and a multifrequency of 1 to 80 Hz. B. Sham extremely low-frequency magnetic field first (n=17): three 30-minute sessions per week for 4 weeks (12 sessions total). Patients laid on a bed with multi-low-frequency mattress but no magnetic field was delivered. Washout period: 1 month	A vs. B Age, years: 50 vs. 51 Female: 100% vs. 100% Fibromyalgia duration, years: 7 vs. 5 Baseline FIQ: 58.7 (11.3) vs. 57.2 (12.3) Baseline FIQ pain: NR Baseline pain VAS: 4.9 (1.4) vs. 4.8 (1.2) Baseline FAS (0−10): 6.1 (1.7) vs. 6.4 (1.4)	A vs. B, mean <u>1 month</u> FIQ: 19.2 vs. 57.9, p<0.001 Percent change from baseline in FIQ: −67.3% vs. 2.9%, p<0.001 FIQ pain: values NR, p<0.001 Pain VAS: 2.2 vs. 5.3, p<0.001 Percent change from baseline in pain VAS: −54.1% vs. 6.3%, p<0.001 FAS: 3.2 vs. 6.1, p<0.001 Percent change from baseline in FAS: −46.5% vs. −4.5% p<0.001 B vs. A (after cross-over) <u>1 month</u> FIQ: 25.1 vs. 53.9, p<0.001 Percent change from baseline in FIQ: −56.0% vs. −8.1%, p<0.001 Pain VAS: 3.1 vs. 4.6, p=0.02 Percent change from baseline in pain VAS: −39.7% vs. −9.1%, p=0.006 FAS: 3.5 vs. 6.2, p=0.002 Percent change from baseline in FAS: −46.9% vs. −1.2%, p<0.001	A vs. B <u>1 month</u> HAQ (0-3): 0.3 vs. 1.1, p=0.03 Percent change from baseline in HAQ: NR B vs. A (after cross-over) <u>1 month</u> HAQ: 0.7 vs. 0.8, p=0.41 Percent change from baseline in HAQ: NR

CI = confidence interval; FAS = Fibromyalgia Assessment Status; FIQ = Fibromyalgia Impact Questionnaire; HAQ = Health Assessment Questionnaire; Hz = Hertz; NR = not reported; NRS = numeric rating scale; PCP = primary care physician; uT = microtesla; VAS = Visual Analog Scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Physical Modalities Compared With Usual Care or Sham

The magnetic mattress pads offered no intermediate-term benefit for either function or pain compared with both sham and usual care in the one parallel trial.[167] The difference between groups on the 0 to 80 scale FIQ at 6 months was −5.0 (95% CI −14.1 to 4.1) (versus sham) and −5.5 (95% CI −14.4 to 3.4) (usual care). Regarding pain, the between-group differences were −0.6 (95% CI −1.9 to 0.7) and −1.0 (95% CI −2.2 to 0.2), respectively, on a 0 to 10 NRS. When the intervention groups were considered separately, only the magnetic mattress pad designed to expose the body to a uniform magnetic field of negative polarity resulted in lower FIQ and NRS pain scores compared with controls; however, the differences between groups were not statistically significant.

The crossover trial[168] reported statistically significant improvement in both function and pain favoring the magnetic mattress 1 month after the end of both treatment periods (i.e., over the short term); however, the evidence is considered insufficient. For patients that received magnetic therapy during the first and second (i.e. after crossing-over) treatment periods, mean FIQ scores

were 19.2 and 25.1 on a 0-100 scale, respectively, compared with 57.9 and 53.9 for those receiving sham during the same treatment periods (p<0.001 for both). For VAS pain, respective scores were 2.2 and 3.1 versus 5.3 and 4.6 on a 0-10 scale (p<0.001 for both). Results were similar for both the Fibromyalgia Assessment Scale and the Health Assessment Questionnaire (Table 37).

Physical Modalities Compared With Pharmacological Therapy or Exercise

No trial of physical modality versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

In the parallel trial, there were no differences in adverse events between the magnetic mattress pad and sham pad groups.[167] Type of adverse events was not reported, but none of the events were judged to be due to magnetic treatments. The crossover trial only stated that no side effects were recorded during the study.[168]

Manual Therapies for Fibromyalgia

Key Points

- Myofascial release therapy was associated with a small improvement in intermediate-term function as measured by the FIQ (mean 58.6 [standard deviation, SD, 16.3] vs. 64.1 [SD 18.1] on a 100 point scale, p=0.048 for the group effect in repeated measures analysis of variance [ANOVA]), but not long-term function (mean 62.8 [SD 20.1] vs. 65.0 [SD 19.8], p=0.329), compared with sham in one fair-quality trial (SOE: low). Short-term function was not reported.
- There was insufficient evidence to determine the effects of myofascial release therapy on short-term pain (1 poor-quality trial) and intermediate-term pain (1 fair-quality and 1 poor-quality trial) compared with sham; there were inconsistencies in effect estimates between the intermediate-term trials (SOE: insufficient).
- Myofascial release therapy was associated with small improvement in pain long term compared with sham, based on the sensory domain (mean 18.2 [SD 8.3] vs. 21.2 [SD 7.9] on a 0-33 scale, p=0.038 for group by repeated measures ANOVA) and evaluative domain (mean 23.2 [SD 7.6] vs. 26.7 [SD 6.9] on a 0-42 scale, p=0.036) of the MPQ in one fair-quality trial; there were no differences for the affective domain of the MPQ or for VAS pain (SOE: low).
- Data were insufficient for harms; however, no adverse effect occurred in one fair-quality trial (SOE: insufficient)

Detailed Synthesis

Two trials (N=64 and 94)[185,186] evaluating myofascial release therapy versus sham therapy for fibromyalgia met inclusion criteria (Table 39 and Appendix D). Both trials were included in the prior AHRQ report. Mean patient ages were 48 and 55 years. Baseline pain history characteristics were poorly described in both trials. The duration of myofascial release therapy was 20 weeks in both trials; sessions ranged in length from 60 to 90 minutes and were conducted twice or once a week. The sham conditions included short-wave and ultrasound electrotherapy or sham (disconnected) magnotherapy. Both trials reported intermediate-term outcomes; short-term

and long-term outcomes were also reported by one trial each. One trial was rated fair quality and the other poor quality (Appendix E). Unclear allocation concealment methods and lack of blinding were the major methodological shortcoming in both trials. Additionally, the poor-quality trial did not describe the randomization process employed.

Table 55. Fibromyalgia: manual therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Castro-Sanchez, 2011a[185] 6 and 12 months Duration of pain, NR Fair	A. Myofascial Release (n=47): myofascial release (across 10 pain regions) administered by a physiotherapist; 60 minutes sessions twice weekly for 20 weeks B. Sham short-wave and ultrasound electrotherapy (n=47): both applied to the cervical, dorsal and lumbar regions using disconnected equipment; 30 minute sessions (10 minutes each region), twice weekly for 20 weeks	A vs. B Age: 55 vs. 54 years Female: NR Race: NR Mean duration of pain: NR FIQ total (0-100): 65.0 vs. 63.9 Pain (FIQ, 0-10): 9.2 vs. 8.9 Pain (VAS, 0-10): 9.1 vs. 8.9 MPQ sensory dimension (0-33): 19.3 vs. 19.9 MPQ affective dimension (0-12): 5.6 vs. 4.9 MPQ evaluative (sensory + affective) dimension (0-45): 24.9 vs. 25.3	A vs. B <u>6 months</u> FIQ Total: 58.6 vs. 64.1, p=0.048 FIQ pain: 8.5 vs. 8.0, p=0.042 VAS pain: 8.25 vs. 8.94, p=0.043 MPQ sensory: 17.3 vs. 20.7, p=0.042 MPQ affective: 4.5 vs. 5.2, p=0.042 MPQ evaluative: 21.9 vs. 26.2, p=0.022 <u>12 months</u> FIQ Total: 62.8 vs. 65.0, p=0.329 FIQ pain: 8.8 vs. 8.7, p=0.519 VAS pain: 8.74 vs. 8.92, p=0.306 MPQ sensory: 18.2 vs. 21.2, p=0.038 MPQ affective: 4.8 vs. 5.1, p=0.232 MPQ evaluative: 23.2 vs. 26.7, p=0.036 p-values are from authors' ANOVA[b]	A vs. B <u>6 months</u> Clinical Global Impression Severity Scale (Likert, 1-7): 5.3 vs. 6.0, p=0.048 Clinical Global Impression Improvement Scale (Likert, 1-7): 5.6 vs. 6.3, p=0.046 <u>12 months</u> Clinical Global Impression Severity Scale: 5.5 vs. 6.2 p=0.147 Clinical Global Impression Improvement Scale: 5.8 vs. 6.5, p=0.049 p-values are from authors' ANOVA[b]

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Castro-Sanchez, 2011b[186] 1 and 6 months Duration of pain, NR Poor	A. Massage-Myofascial Release (n=32): Massage-Myofascial release therapy (across 18 pain regions) administered by a physiotherapist; weekly 90-minute session for 20 weeks. B. Sham magnotherapy (n=32): weekly 30-minute session of disconnected magnotherapy (applied on cervical and lumbar area for 15 minutes each) for 20 weeks.	A vs. B Age: 49 vs. 46 years Female: 94% vs. 96% Race: NR Mean duration of pain: NR Pain Intensity (VAS, 0-10)[c]: 9.1 vs. 9.6	A vs. B <u>1 month</u> VAS pain[c]: 8.4 vs. 9.4, p<0.043 <u>6 months</u> VAS pain[c]: 8.8 vs. 9.7, p=NS p-values are from authors' ANOVA[b]	A vs. B <u>1 month</u> STAI state anxiety (20-80)[c]: 21.5 vs. 22, p=NS STAI trait anxiety (20-80)[c]: 25.1 vs. 26.3, p=NS BDI (0-63)[c]: 2.1 vs. 2.5, p=NS SF-36 physical function (0-100): 46.8 vs. 49.6, p=0.049 SF-36 physical role (0-100): 24.6 vs. 29.0, p=0.047 SF-36 bodily pain (0-100): 75.1 vs. 89.9, p=0.046 SF-36 general health (0-100): 66.8 vs. 68.4, p=0.093 SF-36 vitality (0-100): 61.6 vs. 59.2, p=0.055 SF-36 social function (0-100): 60.6 vs. 63.6, p=0.081 SF-36 emotional role (0-100): 50.5 vs. 47.0, p=0.057 SF-36 mental health (0-100): 75.0 vs. 78.3, p=0.082 PSQI, sleep duration, p=0.041[d]: patients with severe problems, 60% vs. 83%; moderate problems, 37% vs. 10%; and no problems, 3% vs. 7% <u>6 months</u> BDI[c]: 2.3 vs. 2.5, p=NS STAI state anxiety[c]: 22.0 vs. 23.0, p=NS STAI trait anxiety[c]: 25.8 vs. 26.2, p=NS SF-36 physical function: 48.2 vs. 51.2, p=0.281 SF-36 physical role: 25.5 vs. 27.5, p=0.213 SF-36 body pain: 75.6 vs. 77.8, p=0.293 SF-36 general health: 67.5 vs. 68.1, p=0.401 SF-36 vitality: 62.2 vs. 58.9, p=0.312 SF-36 social function: 61.3 vs. 63.9, p=0.088 SF-36 emotional role: 49.1 vs. 46.9, p=0.219 SF-36 mental health: 76.5 vs. 80.0, p=0.126 PSQI, sleep duration, p=0.047[d]: patients with severe problems, 57% vs. 93%; moderate problems, 37% vs. 0%; and no problems, 7% vs. 7% p-values are from authors' ANOVA[b]

ANOVA = repeated-measures analysis of variance; BDI = Beck Depression Inventory; FIQ = Fibromyalgia Impact Questionnaire; MPQ = McGill Pain Questionnaire; NR = not reported; NS = not statistically significant; PSQI = Pittsburgh sleep quality index; SF-36 = Short-Form 36 health questionnaire; STAI = State-Trait Anxiety Inventory; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Changes in scores were analyzed by using a 2 (groups: experimental and placebo) X 4 (time points: baseline, immediately postintervention, at 1 and 6 months) repeated-measures analysis of variance

[c] Values estimated from figures in the article.

[d] For all other dimensions of the PSQI (subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbance, daily dysfunction), there were no statistically significant difference between groups in the proportion of patients experiencing severe, moderate or no problems in the authors' analysis of variance (ANOVA).

Myofascial Release Therapy Compared With Sham

Myofascial release therapy was associated with a small improvement in intermediate-term function compared with sham as measured by the FIQ (mean 58.6 [standard deviation, SD 16.3] vs. mean 64.1 [SD 18.1] on a 100 point scale, p=0.048 for the group by time effect in repeated measures ANOVA) in one fair-quality trial[185]; this effect did not persist to the long term (62.8 [SD 20.1] vs. 65.0 [SD 19.8], p=0.329, at 12 months). Function was not reported over the short term.

Regarding pain outcomes, one poor-quality trial reported a small effect for myofascial release compared with sham therapy over the short term (mean 8.4 vs. mean 9.4 on a 0-10 VAS at 1 month, p=0.048 for group by time repeated measures ANOVA).[186] Intermediate-term results were inconsistent across the trials as measured on a 0 to 10 VAS pain scale with one fair-quality trial reporting a small improvement in pain for myofascial release versus sham (mean 8.25 [SD 1.13] vs. mean 8.94 [SD 1.34], p=0.043)[185] at 6 months and the other (poor quality) reporting no significant difference between groups (8.8 vs. 9.7, p=NS) (Figure 49).[186] Additional pain measures were reported over the intermediate-term by the fair-quality trial, all of which showed a small benefit in favor of myofascial release: FIQ pain (8.5 [SD 0.7] vs. 8.0 [SD 1.3], p=0.042 for group by time repeated measures ANOVA) and the MPQ sensory (17.3 [SD 7.8] vs. 20.7 [SD 7.1] on a 0-33 scale, p=0.04), affective (4.5 [SD 2.9] vs. 5.2 [SD 3.8] on a 0-12 scale, p=0.04) and evaluative (21.9 [SD 7.2] vs. 26.2 [SD 6.8] on a 0-42 scale, p=0.02) dimensions.[185] This effect persisted at long-term followup for the sensory and evaluative dimension of the MPQ only; no differences were seen between groups regarding VAS pain of the affective dimension of the MPQ at long term following in this trial (Table 38).

Depression, anxiety, and sleep outcomes were evaluated in one poor-quality trial, with significant improvement seen short term in the myofascial release versus the sham group on some subscales of the Short-Form-36 and on the sleep duration subscale of the PSQI,[186] but no differences between groups on the STAI or BDI (Table 38); at intermediate followup, only PSQI sleep duration was significantly improved following myofascial release versus sham.

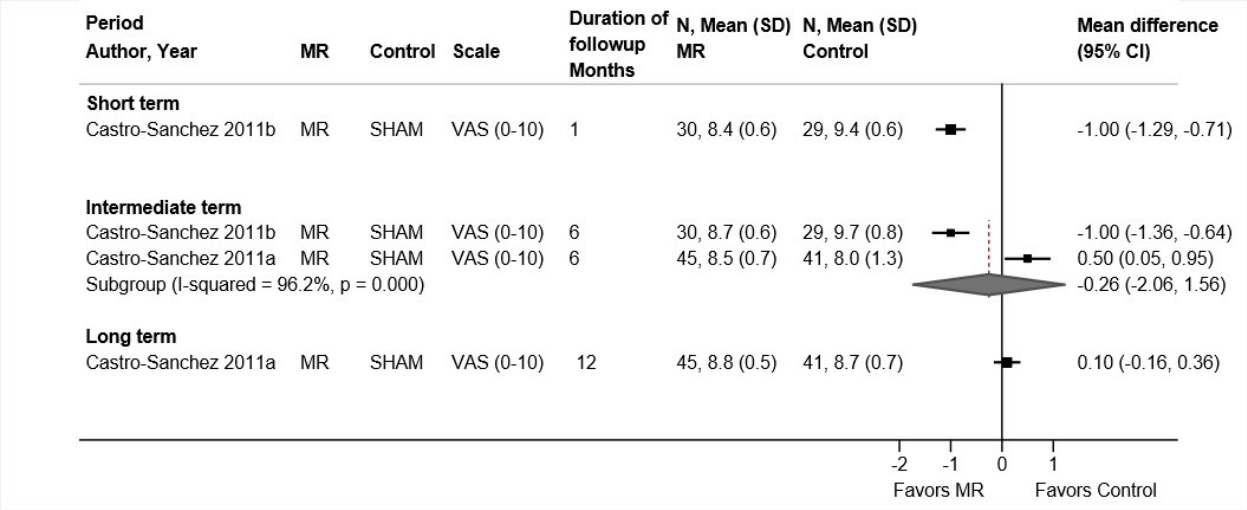
Manual Therapy Compared With Pharmacological Therapy or Exercise

No trial of manual therapy versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

In one trial, no patient experienced an adverse effect (details not reported).[185] No information on harms was reported by the other trial.

Figure 49. Myofascial release versus sham for fibromyalgia: effects on pain



CI = confidence interval; MR = myofascial release; SD = standard deviation

Mindfulness Practices for Fibromyalgia

Key Points

- No clear short-term effects of MBSR were seen on function compared with waitlist or attention control (difference 0 to 0.06 on a 0-10 scale) in two trials (one fair and one poor quality). Clinically meaningful improvement in function (≥14% on the FIQ total, 0-100 scale) was not different for MBSR versus either comparator (SOE: moderate).
- No clear short-term effects of MBSR were seen on pain (difference 0.1 on a 0-100 VAS pain scale in one poor quality trial; 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 fair-quality trial) compared with waitlist or attention control in two trials (SOE: moderate). Intermediate-term and long-term outcomes were not reported.
- In one new trial, meditation awareness training (MAT) was associated with a small intermediate-term improvement in function (adjusted difference −7.9, 95% CI −8.2 to −4.3 on FIQ 0-100 scale) and a small improvement in pain (adjusted difference −3.0, 95% CI −4.1 to −1.9 on the 0-45 SF-MPQ Pain Perception Index) versus attention control (SOE: low).
- No trial of mindfulness practices versus pharmacological therapy or versus exercise met inclusion criteria.
- Harms were not reported.

Detailed Synthesis

We identified three trials (4 publications) of mindfulness practices for fibromyalgia that met inclusion criteria (Table 40 and Appendix D).[200-203] Two trials (3 publications)[200-202] of mindfulness-based stress reduction (MBSR) practices were included in the prior AHRQ report and one new trial[203] of "Meditation Awareness Training" (MAT) was included for this update. In both MBSR trials, the intervention was modeled after the program developed by Kabat-Zinn. The intervention lasted 8 weeks, with weekly 2.5-hour sessions, daily homework assignments,

and a single 7-hour session. Sample sizes ranged from 90 to 168 (total sample=406), age ranged from 48 to 53 years, and all participants were female. Both studies compared MBSR versus waitlist control; one trial[201] also compared MBSR to an attention control group that consisted of education, relaxation, and stretching. Both studies reported only short-term outcomes. One study was conducted in the United States[200,202] and the other in Germany.[201] The third trial (N=148, mean age 47, 83% female) compared MAT, a mindfulness-based intervention, with an attention control condition (education only).[203] MAT consisted of one 2-hour session per week for 8 weeks plus a CD of guided meditations to facilitate daily practice. Weekly sessions included a presentation, a facilitated group discussion, and guided educational exercises, with no practice or discussion of meditation. This trial was conducted in England.

Two trials (1 MBSR and 1 MAT) were considered fair quality[201,203] and the other MBSR trial was considered poor quality[200,202] (Appendix E). Methodological shortcomings in all trials were the lack of long-term followup and the inability to blind patients and providers. The poor-quality study also had a high rate of overall attrition as well as differential attrition between the groups.

Table 56. Fibromyalgia: mindfulness practices

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cash 2015,[200] Sephton, 2007[202,b] 2 months Duration of pain NR Poor	A. Mindfulness-based Stress Reduction (n=51): 8-week group-based program with one 2.5 hour session/week including instruction in techniques, meditation, and simple yoga positions to encourage relaxation. Participants were asked to complete daily practices with workbook and audiotapes for 45 min a day for 6 days a week. B. Waitlist (n=39)	A vs. B Age: 48 vs. 48 years Female: 100% vs. 100% Caucasian: 94% vs. 93% Baseline FIQ Physical Functioning (0-10): 1.3 vs. 1.2 Baseline pain VAS (0-100): 68.1 vs. 69.2 Baseline FIQ Severity (0-100)[c]: 67.5 vs. 62.5	A vs. B <u>2 months:</u> FIQ Physical Functioning: 1.2 vs. 1.2; difference 0.0 (95% CI −0.32 to 0.32) Pain VAS: 65.2 vs. 65.1; difference 0.1 (95% CI −9.96 to 10.16) FIQ Severity[c]: 62.0 vs. 66.7; difference −4.7 (95% CI -12.24 to 2.84)	A vs. B <u>2 months</u> BDI Total[b]: 13.3 vs. 14.8; difference −1.5 (95% CI −4.76 to 1.76) BDI Cognitive Subscale[b]: 5.3 vs. 6.4; difference −1.1 (95% CI −2.98 to 0.78) BDI Somatic Subscale[b]: 7.4 vs. 7.7; difference −0.3 (95% CI −1.73 to 1.13) PSS: 20.2 vs. 20.8; difference −0.60 (95% CI −3.37 to 2.17) SDQ: 8.4 vs. 9.5; difference −1.10 (95% CI −2.58 to 0.38) FSI: 5.5 vs. 6.0; difference −0.50 (95% CI −1.28 to 0.28)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Schmidt, 2011[201] 2 months Duration of fibromyalgia, years: 14 years Fair	A. Mindfulness-based Stress Reduction (n=53): 8-week group-based program; 1, 2.5 hour session/week and one 7 hour all-day session covering training in specific exercises and topics of mindfulness practices. Participants were asked to complete daily practices of 45-60 minutes each B. Active-control Intervention (n=56) Controlled for nonspecific aspects of the MBSR program with similar meeting structure and format to MBSR treatment arm. Equivalent levels of social support and weekly topical education was provided along with Jacobson Progressive Muscle Relaxation training and fibromyalgia-specific gentle stretching exercises. Participants were asked to complete daily homework assignments with the same duration as MBSR group. C. Waitlist (n=59)	A vs. B vs. C Age: 53 vs. 52 years Female: 100% (all female study) Race: NR A vs. C Baseline FIQ Total (0-10): 5.8 vs. 5.7 Baseline PPS Affective (scale unclear): 35.5 vs. 34.8 Baseline PPS Sensory (scale unclear): 22.4 vs. 22.6	A vs. B <u>2 months</u> Proportion of patients with >14% improvement in FIQ scores (MCID): 30% vs. 25%; RR 1.21 (95% CI 0.79 to 1.82) FIQ: 5.23 vs. 5.33; difference −0.10 (95% CI −0.84 to 0.64) PPS Affective: 30.79 vs. 32.17; difference −1.38 (95% CI −4.79 to 2.03) PPS Sensory: 21.16 vs. 21.87; difference −0.71 (95% CI −2.77 to 1.34) A vs. C <u>2 months</u> Proportion of patients with >14% improvement in FIQ scores (MCID): 30% vs. 22%; RR 1.37 (95% CI 0.83 to 1.94) FIQ: 5.23 vs. 5.29; difference −0.06 (95% CI −0.75 to 0.63) PPS Affective: 30.79 vs. 32.38; difference −1.59 (95% CI −5.01 to 1.83) PPS Sensory: 21.16 vs. 21.44; difference −0.28 (95% CI −2.30 to 1.74)	A vs. B <u>2 months</u> Proportion of Patients who saw Clinically Relevant Improvement (score of <23) in CES-D scores: 28% vs. 23%; RR 0.53 (95% CI 0.54 to 1.12) CES-D: 21.70 vs. 22.55; difference −0.85 (95% CI −4.66 to 2.96) STAI Trait Subscale: 47.86 vs. 48.44; difference −0.58 (95% CI −4.42 to 3.26) Proportion of Patients with PSQI score <5 indicates good sleep): 17%vs. 7%; RR 2.38 (95% CI 0.85 to 2.34) PSQI: 10.01 vs. 10.25; difference −0.24 (95% CI −1.71 to 1.23) FMI: 37.66 vs. 35.14; difference 2.52 (95% CI 0.04 to 5.00) GCQ: 42.63 vs. 43.91; difference −1.28 (95% CI −6.51 to 3.95) PLC: 12.83 vs. 12.16; difference 0.67 (95% CI −0.60 to 1.94) A vs. C <u>2 months</u> Proportion of Patients who saw Clinically Relevant Improvement (score of <23) in CES-D scores: 28% vs. 19%; RR 1.52 (95% CI 0.85 to 2.04) CES-D: 21.7 vs. 24.0; difference −2.3 (95% CI −5.96 to 1.36) STAI Trait Subscale: 47.9 vs. 49.2; difference −1.32 (95% CI −5.02 to 2.38 Proportion of Patients with PSQI score <5 indicates good sleep): 17% vs. 10%; RR 1.67 (95% CI 0.80 to 2.14) PSQI: 10.0 vs. 10.4; difference −0.36 (95% CI −1.8 to 1.1) FMI: 37.7 vs. 36.1; difference 1.5 (95% CI −0.9 to 3.91) GCQ: 42.6 vs. 45.3; difference −2.7 (95% CI −7.8 to 2.5) PLC: 12.8 vs. 12.3; difference 0.5 (95% CI −0.7 to 1.7)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Van Gordon, 2017[203] 6 months Duration of pain: NR Fair [New trial]	A. Meditation Awareness Training (MAT) (n=74): MAT is a second-generation mindfulness-based intervention (SG-MBI); 1, 2-hour session per week for 8 weeks in addition to receiving a CD of guided meditations to facilitate daily self-practice B. "Cognitive Behavior Therapy for Groups" (CBTG) (attention control) (n=74): designed to be educational only and an attention control condition.	A vs. B Age (mean): 46 vs. 47 years Female: 82% vs. 84% Baseline FIQ-R (0-100): 55.2 vs. 54.0	A vs. B 6 months FIQ-R: 45.7 vs. 52.4, adjusted difference −7.9 (95% CI −8.2 to −4.3), p<0.001	A vs. B 6 months PSQI (0-21): 11.4 vs. 13.6, adjusted difference −2.3 (95% CI −2.9 to −1.6), p<0.001 SF-MPQ (0-45): 23.8 vs. 26.4, adjusted difference v3.0 (95% CI −4.1 to −1.9), p<0.001 DASS (0-100): 20.7 vs. 25.2, adjusted difference -4.9 (95% CI −6.3 to −3.4), p<0.001 NAS (0-42): 22.8 (5.4) vs. 19.1, adjusted difference 3.6 (95% CI 2.5 to 4.6), p<0.001

BDI = Beck Depression Inventory; CES-D = Center for Epidemiological Studies Depression Scale; CI = confidence interval; DASS = Depression Anxiety Stress Scale; FSI= Fatigue Symptom Inventory; FIQ = Fibromyalgia Impact Questionnaire; FMI = Freiburg Mindfulness Inventory; FSI = Fatigue Symptom Inventory; GCQ = Giessen Complaint Questionnaire; MCID = minimal clinically important difference; PLC = Profile for the Chronically Ill; PPS = Pain Perception Scale; PSQI = Pittsburgh Sleep Quality Index; PSS = Perceived Stress Scale; RR = risk ratio; SF-MPQ = Short-Form McGill Pain Questionaire; SDQ = Stanford Sleep Disorders Questionnaire; STAI = State-Trait-Anxiety-Inventory; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Sephton is the same population as Cash 2015 but the focus of the study was on depression (Beck Depression Inventory).

[c] FIQ symptom severity is comprised of visual analog ratings of pain, fatigue, morning sleepiness, stiffness, anxiety, and depression

Mindfulness Practices Compared With Waitlist or Attention Control

There were no clear short-term effects of MBSR on any function or pain measure reported compared with waitlist or attention control. Both trials compared MBSR to waitlist and reported function using the FIQ; one reported the physical function subscale (difference 0 on a 0-10 scale, 95% CI −0.32 to 0.32)[200] and the other reported the total score (difference −0.06 on a 0-10 scale, 95% CI −0.75 to 0.63).[201] The latter fair-quality trial also reported the proportion of patients who achieved a 14percent or greater improvement in FIQ total scores: 30 percent versus 22 percent, RR 1.37 (95% CI 0.83 to 1.94).[201] Regarding pain, one trial reported a mean difference of 0.1 (95% CI −9.96 to 10.16) on a 0 to 100 VAS pain scale[200] between the MBSR and waitlist groups, while the other reported on affective (difference −1.59, 95% CI −5.01 to 1.83) and sensory (difference −0.28, 95% CI −2.30 to 1.74) domains of the Pain Perception Scale (scale not reported).[201] Estimates for function and pain were similar for the comparison of MBSR versus attention control in the fair-quality trial[201] (Table 39). The new fair-quality trial of MAT versus educational attention control reported only intermediate term outcomes. There were small improvements in function on the 0-100 FIQ-R (adjusted difference −7.9, 95% CI −8.24 to −4.25) and in pain on the 0-45 SF-MPQ Pain Perception Index (adjusted difference −3.0, 95% CI −4.1 to −1.9) associated with MAT compared with attention control.[203]

Secondary outcomes (measures of depression, anxiety, sleep, fatigue) did not differ significantly between MBSR and waitlist or attention control in either trial[200-202] (Table 39). The

fair-quality trial compared medication use (analgesics, anti-depressants, and sleep medication) between baseline and short-term followup; only antidepressant medication was reduced significantly from baseline (46% to 35%, p=0.01) but there was no group effect (data not reported).[201] In the trial of MAT versus education attention control ,[203] there was an intermediate-term benefit for MAT on the 0-21 PSQI sleep measure (adjusted difference −2.3, 95% CI −2.9 to −1.6) and the 0-100 DASS measure of depression, anxiety and stress (adjusted difference −4.9, 95% CI −6.3 to −3.4).

Mindfulness-Based Stress Reduction Therapy Compared With Pharmacological Therapy or Exercise

No trial of MBSR versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

Neither trial reported harms.

Mind-Body Therapy for Fibromyalgia

Key Points

- Over the short term, two trials of mind-body practices reported small improvement in function for qigong compared with waitlist (difference −7.5, 95% CI −13.3 to −1.68) and for tai chi compared with attention control (difference −23.5, 95% CI −30 to −17) based on 0 to 100 scale total FIQ score; heterogeneity may be explained by duration and intensity of intervention and control conditions. 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 small effect (SOE: low).
- Qigong and tai chi were associated with moderately greater improvement in pain (0-10 scale) compared with waitlist and attention control in the short term (2 trials, pooled difference −1.44, 95% CI −2.96, −0.23, I^2=46%). 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 small effect (SOE: low).
- There was no evidence regarding effects of mind-body practices versus waitlist or attention control in the intermediate or long term.
- In one new trial, compared with aerobic exercise, tai chi was associated with a small improvement in function 3 to 6 months postintervention (difference in change scores −5.5, 95% CI −0.6 to −10.4, FIQ-R 0-100 scale), but the effect did not persist from intermediate to longer term (6-12 months) (difference in change scores −2.7, 95% CI −2.3 to 7.7) (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 (difference in change scores −16.2, 95% CI −8.7 to −23.6, 0-100 FIQ-R scale) that was sustained long-term (difference in change scores −11.1, 95% CI −2.7 to −19.6). There were no differences between tai chi overall and exercise with regard to opioid use at intermediate (OR 0.89, 95% CI 0.28 to 2.80) or long term (OR 1.08, 95% CI 0.33 to 3.51).
- Data for harms were insufficient. However, one trial reported two adverse events (in two patients) judged to be possibly related to qigong practice: an increase in shoulder pain and plantar fasciitis; neither participant withdrew from the study. One trial of tai chi

reported no adverse events while the second (new) trial reported that, across all intensities of tai chi vs. aerobic exercise, there were no severe treatment-related adverse events and 5.3% (8/151) versus 5.3% (4/75) mild/moderate treatment-related adverse events, respectively (SOE: insufficient).

Detailed Synthesis

Three trials[217,218,223] that evaluated mind-body therapies for fibromyalgia met inclusion criteria (Table 41 and Appendix D). Two trials were included in the prior AHRQ report[217,218] and one was added for this update.[223] Sample sizes ranged from 66 to 226 (total sample=392). Across trials, the participants were predominately female (87% to 96%), with mean ages between 51 to 52 years. Prior to study enrollment, participants in both trials were being treated with several drugs from major analgesic and adjuvant drug groups such as analgesics/NSAIDs (53% to 73%), antidepressants (35% to 48%), and anticonvulsants (21% to 27%); in one trial, approximately 30 percent of participants were taking opioids and many participants had tried a variety of other therapies (including acupuncture, chiropractic, naturopathic/homeopathic/osteopathic therapies, massage therapy, and psychological therapies).[217]

One trial compared Qigong (3 consecutive half-day training sessions, then weekly practice/review sessions for 8 weeks plus daily at-home practice for 45 to 60 minutes) to a waiting list control condition.[217] Another trial compared tai chi (two 60-minute sessions/week for 12 weeks) to an attention control condition (40 minutes of wellness education and 20 minutes of supervised stretching exercises).[218] In the Qigong trial, the mean self-reported practice time per week for all participants who completed the trial was 4.9 hours at 2 months, 2.9 hours at 4 months, and 2.7 hours at 6 months.[217] In the tai chi study, the average percent of sessions attended during the 12-week intervention was 77 percent for the tai chi group and 70 percent for the control group.[218] The third trial[223] compared three different intensities (one 60-minute session/week for 12 weeks vs. two 60-minute sessions/week for 12 weeks vs. one 60-minute session/week for 24 weeks vs. two 60-minute sessions/week for 24 weeks) of Yang style tai chi to an aerobic exercise intervention consisting of two 60-minute sessions per week for 24 weeks. Patients in the tai chi group attended 62% of all possible classes (67% vs. 65% vs. 57% vs. 58% by intensity, respectively) and those in the exercise group attended 40%. In all three trials, patients were instructed to continue the practice at home throughout the followup period. The two trials comparing Qigong and tai chi with a waitlist and an attention control reported only short-term outcomes while the third trial comparing tai chi with exercise reported only long-term outcomes. Both tai chi trials were conducted in the United States[218,223] and the Qigong trial in Canada.[217]

All trials were rated fair quality (Appendix E). Due to the nature of the intervention and control groups, blinding was not possible in these trials. Other methodological concerns included unacceptable attrition overall (30% at 12 months) and differential attrition (e.g., 11% in the most frequent tai chi group vs. 24% in the comparable exercise group at 12 months) in the new tai chi trial and differential attrition between groups in the Qigong trial (intervention 19% vs. waitlist 4% at 6 months).[217]

Table 57. Fibromyalgia: mind-body therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Lynch, 2012[217] (N=100) 4 months Duration of fibromyalgia, mean: 9.6 years Fair	A. Qigong (n=53): Chaoyi Fanhuan Qigong; 3consecutive half-day training sessions then weekly practice sessions for 8 weeks plus daily at-home practice for 45 to 60 minutes. B. Waitlist (n=47): continued with usual care; offered qigong after the trial ended	A vs. B Age: 53 vs. 52 years Female: 94% vs. 98% Previous opioid therapy: 42% vs. 30% Current opioid therapy: 36% vs. 23% Current NSAID therapy: 49% vs. 57% FIQ (0-100): 65.5 vs. 61.8 NRS pain (0-10): 6.5 vs. 6.6 SF-36 PCS (0-100): 30.0 vs. 32.6 SF-36 MCS (0-100): 38.1 vs. 40.4 PSQI (0-21): 13.8 vs. 13.1	A vs. B 4 months Mean change from baseline: FIQ: −16.1 vs. −4.8; difference −11.3 (95% CI −19.3 to −3.3) NRS pain: −1.21 vs. −0.27; difference −0.9 (95% CI −1.7 to −0.1)	A vs. B 4 months Mean change from baseline: SF-36 PCS: 4.6 vs. 0.2; difference 4.4 (95% CI 1.5 to 7.3) SF-36 MCS: 4.4 vs. 0.7; difference 3.7 (95% CI −0.3 to 7.7) PSQI: −3.3 vs. −1.1; difference −2.2 (95% CI −3.6 to −0.8)
Wang, 2010[218] (N=66) 3 months Duration of fibromyalgia pain: 11 years Fair	A. Tai chi (n=33) Classic Yang style tai chi; at home practice for at least 20 minutes a day; encouraged to maintain tai chi practice using an instructional video. B. Attention control (n=33): 40 minutes of education then 20 minutes of supervised stretching (upper body, trunk, and lower body); plus 20 minutes of daily at-home stretching Both groups had 60-minute sessions twice a week for 12 weeks and continued regular medications and routine activities.	A vs. B Age: 50 vs. 51 years Female: 85% vs. 88% Analgesic use: 88% vs. 73% FIQ (0-100): 62.9 vs. 68.0 VAS pain (0-10): 5.8 vs. 6.3 CES-D (0-60): 22.6 vs. 27.8 SF-36 PCS (0-100): 28.5 vs. 28.0 SF-36 MCS (0-100): 42.6 vs. 37.8 PSQI (0-21): 13.9 vs. 13.5	A vs. B 3 months Proportion with clinically meaningful improvement: FIQ[b]: 81.8% vs. 51.5%; RR 1.6 (95% CI 1.1 to 2.3) VAS pain[c]: 54.5% vs. 27.3%; RR 2.0 (95% CI 1.1 to 3.8) Mean change from baseline: FIQ: −28.6 vs. −10.2; difference −18.3 (95% CI −27.1 to −9.6) VAS pain: −2.4 vs. −0.7; difference −1.7 (95% CI −2.7 to −0.8)	A vs. B 3 months Proportion with clinically meaningful improvement: CES-D[d]: 69.7% vs. 39.4%; RR 1.8 (95% CI 1.1 to 2.9) SF-36 PCS[e]: 51.5% vs. 15.2%; RR 3.4 (95% CI 1.4 to 8.1) SF-36 MCS[f]: 48.5% vs. 24.2%; RR 2.0 (95% CI 1.0 to 4.0) PSQI[g]: 45.5% vs. 18.2%; RR 2.5 (95% CI 1.1 to 5.6) Mean change from baseline: CES-D: −6.5 vs. −2.4; difference −4.1 (95% CI −8.2 to 0.1) SF-36 PCS: 8.4 vs. 1.5; difference 7.0 (95% CI 2.9 to 11.0) SF-36 MCS: 8.5 vs. 1.2; difference 7.3 (95% CI 1.9 to 12.8) PSQI: −4.2 vs. −1.2; difference −3.0 (95% CI −5.2 to −0.9)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Wang, 2018[223] All groups were assessed at 12, 24, and 52 weeks from the start of treatment Duration of pain: Mean 11.1 to 13.8 years Fair [New trial]	A. Yang style tai chi (n=39): one 60-minute session/week for 12 weeks. Mean adherence rate (SD): 66.7% (28.7%) B. Yang style tai chi (n=37): two 60-minute sessions/week for 12 weeks. Mean adherence rate (SD): 65.1% (26%) C. Yang style tai chi (n=39): one 60-minute session/week for 24 weeks. Mean adherence rate (SD): 57.2% (27.9%) D. Yang style tai chi (n=36): two 60-minute sessions/week for 24 weeks. Mean adherence rate (SD): 57.8% (33.3%) E. Aerobic exercise (n=75): two 60-minute sessions/week for 24 weeks. All groups received educational information about the importance of physical activity and home practice; encouraged to integrate at least 30 minutes of tai chi or aerobic exercise into their daily routine; asked to continue exercise after completing their 12 week or 24 week sessions, as well as throughout 52 weeks of followup.	A vs. B vs. C. vs. D vs. E Age: 53 vs. 52 vs. 51 vs. 52 vs. 51 years Female: 85% vs. 81% vs. 97% vs. 100% vs. 96% Baseline FIQ-R (0-100): 52.4 vs. 53.8 vs. 56.5 vs. 60.4 vs. 57.3	All results reported as mean change from baseline (95% CI) C vs. E <u>6 months</u> FIQ-R: −16.7 (−23.4 to −10.1) vs. −9.2 (−14.3 to −4.1) <u>12 months</u> FIQ-R: −13.6 (−20.4 to −6.8) vs. −11.7 (−16.7 to −6.6) D vs. E <u>6 months</u> FIQ-R: −25.4 (−32.3 to −18.4) vs. −9.2 (−14.3 to −4.1); difference 16.2 (8.7 to 23.6), p<0.001 <u>12 months</u> FIQ-R: −22.7 (−30.0 to −15.4) vs. −11.7 (−16.7 to −6.6); difference 11.1 (2.7 to 19.6), p=0.01 Any tai chi vs. E 3-6 months FIQ-R; differnce 5.5, (0.6 to 10.4) p=0.03 6-12 months (FIQ-R, differnce -2.7, 95% CI -2.3 to 7.7)	All results reported as mean change from baseline (95% CI) C vs. E <u>6 months</u> SS (0-12): −1.8 (−2.6 to −1.0) vs. −0.8 (−1.4 to −0.2) PGAS (0-10): −1.6 (−2.4 to −0.8) vs. −0.4 (−1.0 to 0.2) HAQ (0-100): −3.9 (−8.6 to 0.9) vs. −4.1 (−7.8 to −0.5) BDI (0-63): −7.5 (−10.8 to −4.1) vs. −5.2 (−7.7 to −2.7) HADS-D (0-21): −1.4 (−2.6 to 0.3) vs. −0.6 (−1.5 to 0.4) HADS-A (0-21): −1.4 (−2.5 to −0.2) vs. 0.0 (−0.9 to 0.9) SF-36 MCS (0-100): 5.3 (1.9 to 8.7) vs. 0.9 (−1.8 to 3.6) SF-36 PCS (0-100): 5.0(2.5 to 7.6) vs. 4.0 (2.0 to 6.0) PSQI (0-100): −1.9 (−3.2 to −0.6) vs. −1.1 (−2.1 to −0.1) <u>12 months</u> SS: −1.4 (−2.3 to −0.6) vs. −1.1 (−1.8 to −0.4) PGAS: −1.4 (−2.2 to −0.5) vs. −0.3 (−0.9 to 0.3) HAQ: −3.5 (−8.8 to 1.8) vs. −3.9 (−7.8 to 0.0) BDI: −5.5 (−9.4 to −1.6) vs. −6.4 (−9.3 to −3.5) HADS-D: −0.9 (−2.2 to 0.5) vs. −0.6 (−1.6 to 0.4) HADS-A: −1.3 (−2.7 to 0.0) vs. −0.4 (−1.4 to 0.6) SF-36 MCS: 3.8 (−0.5 to 8.0) vs. 3.0 (−0.1 to 6.0) SF-36 PCS: 6.9 (3.9 to 9.9) vs. 2.6 (0.4 to 4.7) PSQI: −1.1 (−2.6 to 0.4) vs. −1.2 (−2.3 to −0.1)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Wang, 2018[223] (Continued) All groups were assessed at 12, 24, and 52 weeks from the start of treatment Duration of pain: Mean 11.1 to 13.8 years Fair [New trial]				<u>D vs. E</u> <u>6 months</u> SS: −1.7 (−2.5 to −0.8) vs. −0.8 (−1.4 to −0.2); difference 0.9 (−0.1 to 1.9), p=0.09 PGAS: −2.0 (−2.8 to −1.2) vs. −0.4 (−1.0 to 0.2); difference 1.6 (0.7 to 2.5), p=0.0006 HAQ: −6.7 (−12.0 to −1.3) vs. −4.1 (−7.8 to −0.5); difference 2.4 (−4.3 to 9.0), p=0.48 BDI: −9.5 (−13.0 to −6.0) vs. −5.2 (−7.7 to −2.7); difference 4.3 (0.0 to 8.5), p=0.049 HADS-D: −2.7 (−4.1 to 1.4) vs. −0.6 (−1.5 to 0.4); difference 2.1 (0.5 to 3.7), p=0.01 HADS-A: −2.1 (−3.4 to −0.8) vs. 0.0 (−0.9 to 0.9); difference 2.1 (0.6 to 3.6), p=0.008 SF-36 MCS: 7.4 (3.6 to 11.2) vs. 0.9 (−1.8 to 3.6); difference 6.2 (1.9 to 10.6), p=0.006 SF-36 PCS: 5.9 (3.1 to 8.8) vs. 4.0 (2.0 to 6.0); difference 2.0 (−1.3 to 5.3), p=0.24 PSQI: −2.1 (−3.5 to −0.7) vs. −1.1 (−2.1 to −0.1); difference 1.0 (−0.6 to 2.5), p=0.22

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Wang, 2018[223] (Continued) All groups were assessed at 12, 24, and 52 weeks from the start of treatment Duration of pain: Mean 11.1 to 13.8 years Fair [New trial]				12 months SS: −1.8 (−2.8 to −0.9) vs. −1.1 (−1.8 to −0.4); difference 0.7 (−0.3 to 1.8), p=0.18 PGAS: −1.7 (−2.7 to −0.8) vs. −0.3 (−0.9 to 0.3); difference 1.5 (0.4 to 2.5), p=0.008 HAQ: −5.0 (−10.8 to 0.7) vs. −3.9 (−7.8 to 0.0); difference 1.8 (−5.9 to 9.4), p=0.65 BDI: −11.1 (−15.2 to −6.9) vs. −6.4 (−9.3 to −3.5); difference 4.6 (−0.5 to 9.7), p=0.08 HADS-D: −2.2 (−3.7 to 0.8) vs. −0.6 (−1.6 to 0.4); difference 1.6 (0.0 to 3.2), p=0.05 HADS-A: −2.1 (−3.6 to −0.7) vs. −0.4 (−1.4 to 0.6); difference 1.6 (0.1 to 3.1), p=0.04 SF-36 MCS: 5.4 (0.8 to 9.9) vs. 3.0 (−0.1 to 6.0); difference 2.2 (−2.7 to 7.1), p=0.38 SF-36 PCS 5.4 (2.2 to 8.6): vs. 2.6 (0.4 to 4.7); difference 3.0 (−0.7 to 6.8), p=0.11 PSQI: −2.0 (−3.6 to −0.4) vs. −1.2 (−2.3 to −0.1); difference 0.9 (−0.7 to 2.5), p=0.26 Any tai chi vs. E: Change in narcotics use: 24 weeks: OR 0.89 (0.28, 2.80) 52 weeks: OR 1.08 (0.33, 3.51)

BDI = Beck Depression Inventory; CES-D = Center for Epidemiologic Studies Depression index; CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Score; MCS = Mental Component Summary; NRS = numeric rating scale; NSAIDs = nonsteroidal anti-inflammatory drugs; PCS = Physical Component Summary; PSQI = Pittsburgh Sleep Quality Index; RR = risk ratio; SF-36 = Short-Form-36 Questionaire; SS = Symptom Severity; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] A reduction of ≥8.1 points from baseline on the FIQ was considered a clinically meaningful improvement

[c] A reduction of ≥2 points from baseline on the VAS was considered a clinically meaningful improvement

[d] A reduction of ≥6 points from baseline on the CES-D was considered a clinically meaningful improvement

[e] An increase of ≥6.5 points from baseline on the SF-36 PCS was considered a clinically meaningful improvement

[f] An increase of ≥7.9 points from baseline on the SF-36 MCS was considered a clinically meaningful improvement

[g] A reduction of >5 points from baseline on the PSQI was considered a clinically meaningful improvement

Mind-Body Therapies Compared With Waitlist or Attention Control

All trials were included in the prior AHRQ report. Short-term improvement in function on 0 to 100 scale total FIQ score was reported for qigong (small improvement, difference −7.51, 95%

CI −13.33 to −1.69)[217] and for tai chi (substantial improvement, difference −23.50, 95% CI −29.98 to −17.02)[218] compared with waitlist or attention control. Substantial heterogeneity (I^2=92%) precluded meaningful pooling for this outcome (Figure 50). Significantly more participants in the tai chi group also showed clinically meaningful improvement (reduction of ≥8.1 points from baseline) on total FIQ (RR 1.6, 95% CI 1.1 to 2.3), consistent with a small effect. Tai chi and qigong were associated with a moderate improvement in pain (0 to 10 scale) compared with wait list or attention control (2 trials, pooled difference −1.44, 95% CI −2.96 to −0.23, I^2=45.6%) (Figure 51). Significantly more participants in the tai chi group also showed clinically meaningful improvement (reduction of ≥2 points from baseline) in VAS pain (RR 2.0, 95% CI 1.1 to 3.8), consistent with a small effect. Heterogeneity may in part be due to differences in duration and intensity of the intervention.

Mind-body therapy resulted in significant improvement in most secondary outcomes measured. Tai chi participants showed clinically meaningful improvement in depressive symptoms as measured by the CES-D (RR 1.8, 95% CI 1.1 to 2.9), in sleep quality as measured by the PSQI (RR 2.5, 95% CI 1.1 to 5.6), and in quality of life as measured by the SF-36 PCS (RR 3.4, 95% CI 1.4 to 8.1) and MCS (RR 2.0, 95% CI 1.0 to 4.0) compared with controls; similar results were seen for mean followup scores on these measures (Table 40).[218] In the second trial,[217] compared to a waitlist control, qigong resulted in significantly improved quality of life as measured by the SF-36 PCS (difference in change from baseline 4.4, 95% CI 1.5 to 7.3) and in sleep quality as measured by the PSQI (difference in change from baseline −2.2, 95% CI −3.6 to −0.8). The change in SF-36 MCS scores did not differ between groups.

Mind-Body Therapies Compared With Pharmacological Therapy or Exercise

No trials comparing mind-body therapies with pharmacological therapy met inclusion criteria in the prior report; no new studies were identified for this update.

One new trial of different frequencies and durations of tai chi versus aerobic exercise was identified.[223]Tai chi was associated with a small improvement in function 3 to 6 months postintervention (difference in change scores −5.5, 95% CI −0.6 to −10.4, FIQ-R, 0-100 scale) when all tai chi groups were combined versus twice weekly aerobic exercise at 6 months. At 12 months (6 to 12 months postintervention), there was no difference between the combined tai chi groups and the exercise group (difference in change scores −2.7, 95% CI −2.3 to 7.7). When analysis was confined to two 60-minute sessions of tai chi per week for 24 weeks, a moderate improvement in function based on 0-100 FIQ-R at intermediate term (difference in change scores −16.2, 95% CI −8.7 to −23.6) was seen and improvement was sustained long-term (difference in change scores −11.1, 95% CI −2.7 to −19.6) versus a comparable number of sessions/weeks of aerobic exercise. Once-weekly tai chi for 24 weeks was also associated with improved function at intermediate term and long term versus twice-weekly aerobics for 24 weeks but effect sizes were slightly smaller versus twice-weekly sessions (−7.5 and −1.9 respectively, CI's not reported) and consistent with small improvement in function.

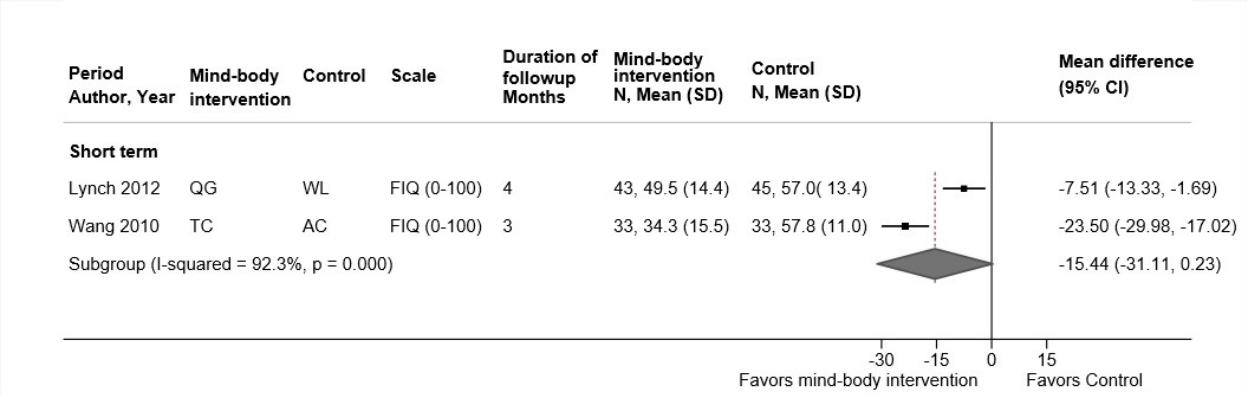
There were no differences between tai chi overall and exercise with regard to opioid use at intermediate (OR 0.89, 95% CI 0.28, 2.80) or long term (OR 1.08, 95% CI 0.33, 3.51). Two weekly 60 minute tai chi sessions, versus a comparable number of aerobic exercise sessions, were associated with improved HADS-A anxiety (difference 1.6, 95% CI 0.1 to 3.1) and 0-10 PGAS global assessment (difference 1.5, 95% CI 0.4 to 2.5), but no difference on the SS symptom severity (difference 0.7, 95% CI −0.3 to 1.8), HAQ (difference 1.8, 95% CI −5.9 to 9.4), BDI depression (difference 4.6, 95% CI −0.5 to 9.7), HADS-D depression (difference 1.6,

95% CI 0.0 to 3.2), SF-36 MCS (difference 2.2, 95% CI −2.7 to 7.1), SF-36 PCS (difference 3.0, 95% CI −0.7 to 6.8) or PSQI (difference 0.9, 95% CI −0.7 to 2.5) measures.

Harms

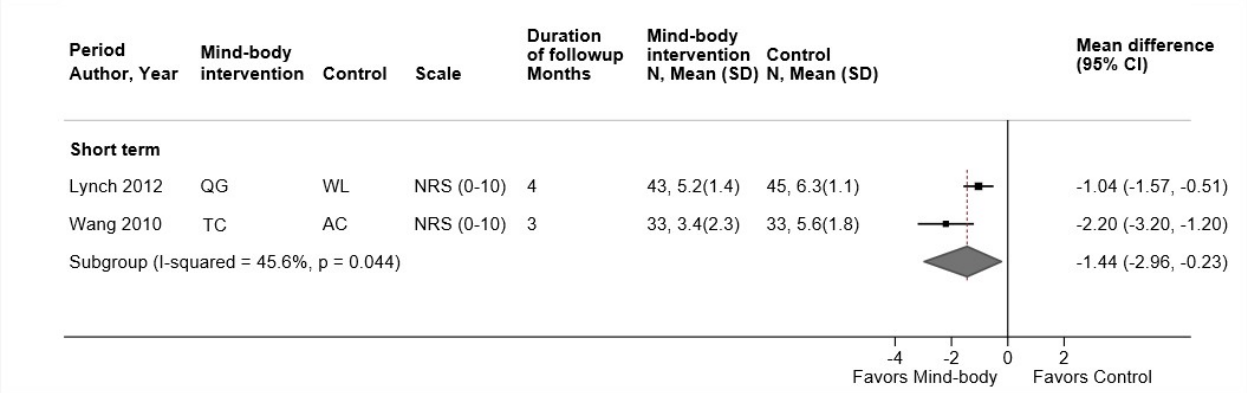
In the trial of qigong,[217] there were two adverse events judged to be possibly related to the practice. One participant reported an increase in shoulder pain and another experienced plantar fasciitis; neither participant withdrew from the study. In the trial of tai chi, no adverse events were reported.[218] In the new trial,[223] across all intensities of tai chi versus aerobic exercise, there were no severe treatment-related adverse events and 5.3% (8/151) versus 5.3% (4/75) mild/moderate treatment-related adverse events, respectively.

Figure 50. Mind-body therapies versus waitlist or attention control for fibromyalgia: effects on function



AC = attention control; CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; QG = qigong; SD = standard deviation; TC = tai chi; WL = waitlist

Figure 51. Mind-body therapies versus waitlist or attention control for fibromyalgia: effects on pain



AC = attention control; CI = confidence interval; QG = qigong; SD = standard deviation; TC = tai chi; WL = waitlist

Acupuncture for Fibromyalgia

Key Points

- Acupuncture was associated with a small improvement in function compared with sham acupuncture as evaluated by the FIQ Total Score (0 to 100) at short-term (3 trials [1 new], pooled difference −9.21, 95% CI −13.65 to -5.78, I^2=0%) and intermediate-term followup (2 trials, pooled difference −9.82, 95% CI −14.35 to −3.01, I^2=27.4%) (SOE: moderate).
- There was no effect of acupuncture versus sham acupuncture on pain (0 to 10 scale) in the short term (4 trials [1 new], pooled difference −0.86, 95% CI −2.73 to 0.92, I^2=88.9%) or intermediate term (3 trials, pooled difference −0.65, 95% CI −1.15 to 0.17, I^2=45.5%). Across control conditions (sham or attention control), there was also no effect of acupuncture (5 trials [two new], pooled difference −1.14, 95% CI −2.66 to 0.33, I^2=91.6%) (SOE: low).
- Results for secondary outcomes across trials of acupuncture versus sham were inconsistent.
- No data on long-term effects were reported.

- Discomfort and bruising were the most common adverse events. Across two trials, discomfort was reported by 37% to 70% of those receiving true or sham acupuncture. Across two trials, bruising was reported in 6% (1/16) to 30% (29/96) of patients who received true or sham acupuncture. Vasovagal symptoms (occurring in 4% of participants who received acupuncture in one trial) and dizziness/nausea were less common adverse events associated with acupuncture (SOE: moderate).

Detailed Synthesis

Five trials of acupuncture for fibromyalgia were identified that met inclusion criteria (Table 42 and Appendix D).[246-250] Three trials[246-248] were included in the prior AHRQ report and two trials[249,250] were added for this update. Four trials (2 new trials) evaluated traditional Chinese needle acupuncture[246,248-250] and the fifth evaluated acupuncture with electrical stimulation.[247] Four studies compared acupuncture to sham[246-249]; the fifth compared it to an education attention control.[250] One study[246] employed three different types of sham treatments (needling for an unrelated condition, sham needling, and simulated acupuncture); one employed two different types of sham procedures (sham needling and simulated acupuncture)[249]; one used sham needling[247]; and one used simulated acupuncture.[248] Sample sizes ranged from 30 to 164 (total sample=412), mean ages from 35 to 56 years, and the proportion of females ranged from 95 percent to 100 percent. The duration of acupuncture treatment ranged from 3 to 12 weeks, with the total number of sessions ranging from six to 24. All studies except two reported short-term and intermediate-term outcomes; the two new trials reported only short-term outcomes.[249,250] No trial had long-term followup. Three trials were conducted in the United States,[246,247,250] one in Spain[248] and one in Turkey.[249]

All trials except two were considered good quality; the two new trials were considered fair-quality[249,250] (Appendix E). The primary limitation across trials was lack of acupuncturist blinding to treatment allocation; for one new fair-quality trial, the intention-to-treat principle was not followed.[249] No trial reported long term outcomes.

Table 58. Fibromyalgia: acupuncture

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Assefi, 2005[246] 3 and 6 months Mean duration of pain: 9 to 12 years Good	A. Acupuncture (n=25): in accordance with Traditional Chinese Medicine B. Sham Acupuncture (n=24): Needling for Unrelated Condition C. Sham Acupuncture (n=24): Sham Needling D. Sham Acupuncture (n=23): Simulated Acupuncture Treatment protocol: 24 sessions (2/week for 12 weeks)	A vs. B vs. C vs. D Mean age: 46 vs. 46 vs. 49 vs. 48 years Female: 88% vs. 96% vs. 100% vs. 96% Race (white): 96% vs. 88% vs. 96% vs. 92% Mean duration of pain: 12 vs. 9 vs. 9 vs. 10 years Baseline pain Intensity VAS (0-10): 7.0 vs. 6.9 vs. 6.8 vs. 7.3	A. vs. B vs. C vs. D <u>3 months</u> Pain Intensity VAS[b]: 6.0 vs. 5.4 vs. 5.4 vs. 4.5 <u>6 months</u> Pain Intensity VAS[b]: 5.7 vs. 6.0 vs. 5.2 vs. 5.2 A vs. B+C+D <u>Across all timepoints[c]</u> Pain intensity VAS: adjusted difference 0.5, (95% CI −0.3 to 1.2)	A. vs. B vs. C vs. D <u>3 months</u> SF-36 PCS (0-100)[b]: 31 vs. 39 vs. 31.5 vs. 40 SF-36 MSC (0-100)[b]: 46 vs. 46.5 vs. 48.5 vs. 47 Sleep Quality VAS (0-10)[a]: 4.3 vs. 4.1 vs. 5.2 vs. 5.5 Overall Well-Being VAS (0-10)[b]: 4.9 vs. 4.9 vs. 5.0 vs. 6.3 <u>6 months</u> SF-36 PCS[b]: 31 vs. 36 vs. 31. vs. 39 SF-36 MCS[b]: 43 vs. 45 vs. 50 vs. 46.5 Sleep Quality VAS[b]: 4.3 vs. 3.4 vs. 5.4 vs. 5.5 Overall Well-Being VAS[b]: 4.6 vs. 4.6 vs. 5.7 vs. 5.7 A vs. B+C+D <u>Across all time-points[c]</u> SF-36 PCS: adjusted difference −0.4 (95% CI −2.3 to 1.5) SF-36 MCS: adjusted difference −1.5, (95% CI −4.0 to 1.0) Sleep Quality VAS: adjusted difference −0.5, (95% CI −1.3 to 0.2) Overall Well-Being VAS: adjusted difference −0.3, (95% CI −1.0 to 0.3)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Karatay, 2018[249] 1 and 3 months Duration of pain: Mean 3.9 to 5.0 years Fair [New trial]	A. Acupuncture (n=24): 18 acupoints using 0.25x25 mm stainless steel needles; 2, 30 minute sessions per week for 4 weeks (8 total) B. Sham acupuncture (n=25): 2, 30 minute sessions per week for 4 weeks (8 total) C. Simulated acupuncture (n=23): 2, 30 minute sessions per week for 4 weeks (8 total)	A vs. B vs. C Age: 35 vs. 34 vs. 35 years Duration of disease: 4.4 vs. 3.9 vs. 5 years Baseline FIQ (0-100): 70.8 vs. 65.9 vs. 57.4 Baseline pain VAS (0-10): 8.1 vs. 7.7 vs. 8.7 Baseline NHP pain (0-100): 82.6 vs. 65.2 vs. 67.9	A vs. B <u>3 months</u> FIQ (0-100): 43.6 vs. 58.4, difference −14.8 (95% CI −26.5 to −3.0) VAS (0-10): 4.5 vs. 7.0, difference −2.5 (95% CI −4.1 to −1.0) NHP pain (0-100): 18.6 vs. 57.9, difference −39.3 (95% CI −59.4 to −19.1) A vs. C <u>3 months</u> FIQ: 43.6 vs. 55.6, difference −11.94 (95% CI −23.1 to −0.8) VAS: 4.5 vs. 8.2, difference −3.7 (95% CI −5.1 to −2.4) NHP pain: 18.6 vs. 72.3, difference −53.6 (95% CI −72.3 to −34.9)	A vs. B <u>3 months</u> NHP physical mobility: 15.4 vs. 33.1, difference −17.7 (95% CI −31.4 to −4.0) NHP energy: 29.3 vs. 69.7, difference −40.4 (95% CI −65.8 to −15.0) NHP sleep: 9.7 vs. 47.9, difference −38.2 (95% CI −55.9 to −20.6) NHP social isolation: 8.1 vs. 29.0, difference −20.9 (95% CI −38.2 to −3.6) NHP emotional reactions: 20.6 vs. 56.4, difference −35.9 (95% CI −56.8 to −14.9) BDI: 10.1 vs. 31.4, difference −21.2 (95% CI −29.5 to −13.0) A vs. C <u>3 months</u> NHP physical mobility: 15.4 vs. 52.8, difference −37.4 (95% CI −53.1 to −21.7) NHP energy: 29.3 vs. 71.4, difference −42.1 (95% CI −66.9 to −17.4) NHP sleep: 9.7 vs. 63.3, difference −53.6 (95% CI −71.6 to −35.7) NHP social isolation: 8.1 vs. 48.8, difference −40.7 (95% CI −57.9 to −23.5) NHP emotional reactions: 20.6 vs. 59.32, difference −38.74 (95% CI −59.4 to −18.1) BDI: 10.1 vs. 35.4, difference −25.2 (95% CI −32.4 to −18.1)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Martin, 2006[247] 1 and 7 months Duration of pain: NR *Good*	A. Acupuncture (n=25): 6 treatments over 2 to 3 weeks B. Sham Acupuncture (n=25): sham needling; 6 treatments over 2 to 3 weeks	A vs. B Age: 48 vs. 52 years Female: 100% vs. 96% Race: 96% vs. 100% white Baseline FIQ total (0-80): 42.4 vs. 44.0 Baseline FIQ Physical Function (0-10): 4.1 vs. 3.6 Baseline MPI Interference (scale NR): 42.6 vs. 36.9 Baseline MPI General Activity Level (scale NR): 55.7 vs. 56.6 Baseline MPI Pain Severity (scale NR): 40.4 vs. 43.0 Baseline FIQ Pain (0-10): 6.2 vs. 6.5	A vs. B <u>1 month</u> FIQ Total: 34.8 vs. 42.2, difference −4.9 (95% CI −8.7 to −1.2) FIQ Physical Function: 3.7 vs. 3.3, difference –0.4 (95% CI –1.1 to 0.3) MPI Interference: 38.3 vs. 34.9, difference 0.1 (95% CI –3.4 to 3.6) MPI General Activity Level: 55.4 vs. 58.3, difference –1.2, (95% CI –3.8 to 1.4) MPI Pain Severity: 34.2 vs. 41.6, difference –4.6 (95% CI –8.7 to –0.5) FIQ pain: 4.7 vs. 5.9, difference –0.8, (95% CI –1.8 to 0.2) <u>7 months</u> FIQ Total: 38.1 vs. 42.7, difference –4.3 (95% CI –7.7 to –0.9) FIQ Physical Function: 3.5 vs. 3.3, difference –0.3 (95% CI –0.9 to 0.3) MPI Interference: 37.7 vs. 35.5, difference 0.1 (95% CI –3.2 to 3.4) MPI General Activity Level: 58.1 vs. 59.5, difference –0.6 (95% CI –3.1 to 1.8) MPI Pain Severity: 37.3 vs. 41.4, difference –3.8 (95% CI –7.5 to –0.2) FIQ Pain: 5.5 vs. 6.4, difference –0.7 (95% CI –1.5 to 0.3)	A vs. B <u>1 month</u> FIQ Anxiety (0-10): 2.6 vs. 5.1, difference –1.1 (95% CI –2.0 to –0.2) FIQ Depression (0-10): 2.0 vs. 3.7, difference –0.7 (95% CI –1.6 to 0.3) FIQ Sleep (0-10): 5.9 vs. 6.8, difference –0.7 (95% CI –1.8 to 0.5) FIQ Well-Being (0-10): 4.6 vs. 3.1, difference 0.8 (95% CI –0.4 to 2.0) <u>7 months</u> FIQ Anxiety: 3.3 vs. 4.8, difference –1.1 (95% CI –1.9 to –0.2) FIQ Depression: 2.2 vs. 3.6, difference –0.7 (95% CI –1.6 to 0.2) FIQ Sleep: 6.1 vs. 6.3, difference –0.3 (95% CI –1.3 to 0.6) FIQ Well-Being: 3.8 vs. 3.6, difference 0.4 (95% CI –0.6 to 1.4)
Mist, 2018[250] 1 month Duration of symptoms: NR Fair [New trial]	A. Group acupuncture (n=16): 20, 45-minute long treatments over 10 weeks B. Education attention control (n=14)	A vs. B Age: 52 vs. 56 years BMI: 33 vs. 33 kg/m^2 Baseline VAS-pain (from FIQR): 6.2 vs. 6.3	A vs. B <u>1 month</u> VAS: 4.0 vs. 6.2, p<0.001	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Vas, 2016[248] 3.75 and 9.75 months Duration of pain: NR Good	A. Acupuncture (n=82): 1, 20 minute session per week for 9 weeks B. Sham Acupuncture (n=82): simulated acupuncture; 1, 20 minute session per week for 9 weeks All patients received pharmacological treatment as prescribed by GP.	A vs. B Age: 52.3 vs. 53.2 years Female: 100% vs. 100% Baseline FIQ (0-100): 71.7 vs. 70.1 Baseline Pain Intensity VAS (0-100): 79.3 vs. 75.8	A vs. B <u>3.75 months</u> FIQ % mean relative change: −25.0 vs. −11.2, Cohen's d=0.58 Pain Intensity VAS % mean relative change: −23.6 vs. −16.6, Cohen's d=0.28 <u>9.75 months</u> FIQ % mean relative change (%): −22.2 vs. −4.9, Cohen's d=0.80, Pain intensity VAS % mean relative change: −19.9 vs. −6.2, Cohen's d=0.62	A vs. B <u>3.75 months</u> HDRS % mean relative change: NR SF-12 MCS % mean relative change: 30.6 vs. 13.9, Cohen's d=0.38 SF-12 PCS % mean relative change: 37.0 vs. 15.5, Cohen's d=0.56 <u>9.75 months</u> HDRS % mean relative change: −19.1 vs. −5.9, Cohen's d=0.22 SF-12 PCS % mean relative change: 37.2 vs. 11.4, Cohen's d=0.58 SF-12 MCS % mean relative change: 23.0 vs. 9.4, Cohen's d=0.36

BDI = Beck Depression Inventory; CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; GP = general practitioner; HDRS = Hamilton Depression Rating Scale; MCS = Mental Component Score; MPI = Multidimensional Pain Inventory; NHP = Nottingham Health Profile; NR = not reported; PCS = Physical Component Score; SF-12 = Short-Form-12 questionaire; SF-36 = Short-Form 36 questionaire; VAS = visual analog scale

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Outcome values were estimated from graphs.

[c] Authors combined the three sham control groups and calculated the adjusted least-square mean difference between the acupuncture group and combined control groups. Treatment-by-time interaction was not included in the models; therefore data reflects results across all time-points.

Acupuncture Compared With Sham or Attention Control

Acupuncture was associated with a small improvement in function compared with sham acupuncture as evaluated by the FIQ Total Score (0 to 100) at short-term followup (3 trials, pooled difference −9.21, 95% CI −13.65 to −5.78, I^2=0%)[247-249] and intermediate-term followup (2 trials, pooled difference on 0-100 scale, −9.82, 95% CI −14.35 to −3.01, I^2=27.4%)[247,248] (Figure 52). There was, however, no effect of acupuncture versus sham acupuncture on pain (0-10 scale) in the short term (4 trials, pooled difference −0.86, 95% CI −2.73 to 0.92, I^2=88.9%)[246-248] or intermediate term (3 trials, pooled difference −0.65, 95% CI −1.15 to 0.17, I^2=45.5%)[246-248] (Figure 53). Results based on mean difference in change scores were similar (data not shown). These conclusions are the same as in the previous report. All trials versus sham, except one, were considered good quality; the new trial[249] was considered fair quality. In the new trial, acupuncture was also compared with simulated acupuncture; at short term, a moderate improvement in function (difference −11.9, 95% CI −23.1 to −0.8, FIQ 0-100) and large improvement in pain (difference −3.7, 95% CI −5.1 to −2.4, VAS 0-10) were reported.[249] Another new, small trial of group acupuncture versus education attention control found a benefit at short term on VAS pain[250]; however, across control conditions (sham or attention control), there was no effect of acupuncture short term (5 trials [2 new], pooled difference −1.14, 95% CI −2.66 to 0.33, I^2=91.6%).[246-250] Substantial heterogeneity was noted and may be due to a variety

of factors including differences in intervention delivery across studies and lack of blinding (attention control).

Results for secondary outcomes across trials of acupuncture versus sham were inconsistent. In the trial of acupuncture versus three different types of sham acupuncture,[246] there was no significant benefit of acupuncture versus the combined sham groups on the SF-36 MCS score, a measure of sleep quality, or a measure of overall well-being. In the trial of six acupuncture treatments over 2 to 3 weeks, there was a benefit for true versus sham acupuncture at 1 and 7 months on the FIQ subscale of anxiety, but not depression, sleep, or well-being.[247] In the trial of one 20-minute session per week for 9 weeks plus pharmacological treatment as prescribed by a general practitioner, there was a benefit for true versus sham acupuncture at 1 month for the SF-12 MCS scale (mean relative change 30.6%, 95% CI 19.7 to 41.5 vs. 13.9%, 95% CI 5.4 to 22.5; Cohen's d=0.38, p=0.01), and at 9.75 months for the Hamilton Rating Scale for Depression (mean relative change −19.1%, 95% CI −34.2 to −3.9 vs. −5.9%, 95% CI −16.6 to −4.8, Cohen's d=0.22, p=0.01) and the SF-12 Mental Component scale (mean relative change, 23.0%, 95% CI 13.7 to 32.4 vs. 9.4%, 95% CI 1.9 to 16.9; Cohen's d=0.36, p=0.01).[248] In the new trial of acupuncture versus sham and simulated acupuncture,[249] comparing acupuncture versus sham short-term, there was a benefit for acupuncture on the 0-100 NHP sleep measure (difference −38.2, 95% CI −55.9 to −20.6) and the 0-40 BDI depression measure (difference −21.2, 95% CI −29.5 to −13.0). Comparing acupuncture versus simulated acupuncture short-term, there was a benefit of acupuncture on the NHP sleep scale (difference −53.6, 95% CI −71.6 to −35.7) and 0-63 BDI (difference −25.2, 95% CI −32.4 to −18.1).[249]

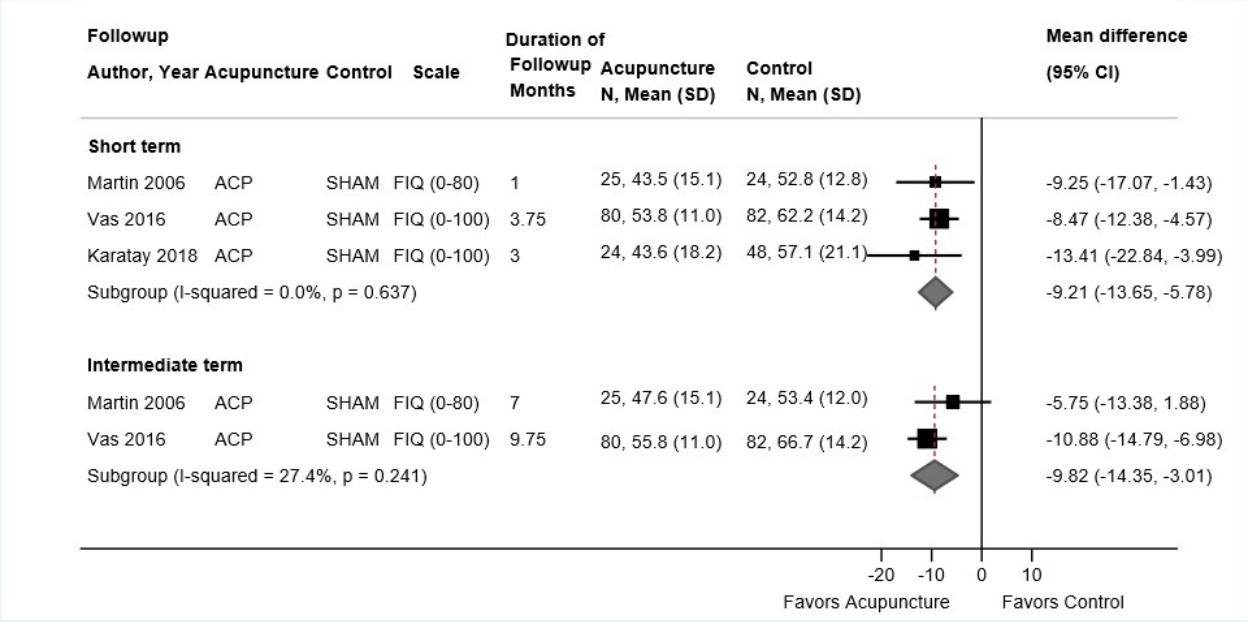
Acupuncture Compared With Pharmacological Therapy or Exercise

No trial of acupuncture versus pharmacological therapy or versus exercise met inclusion criteria.

Harms

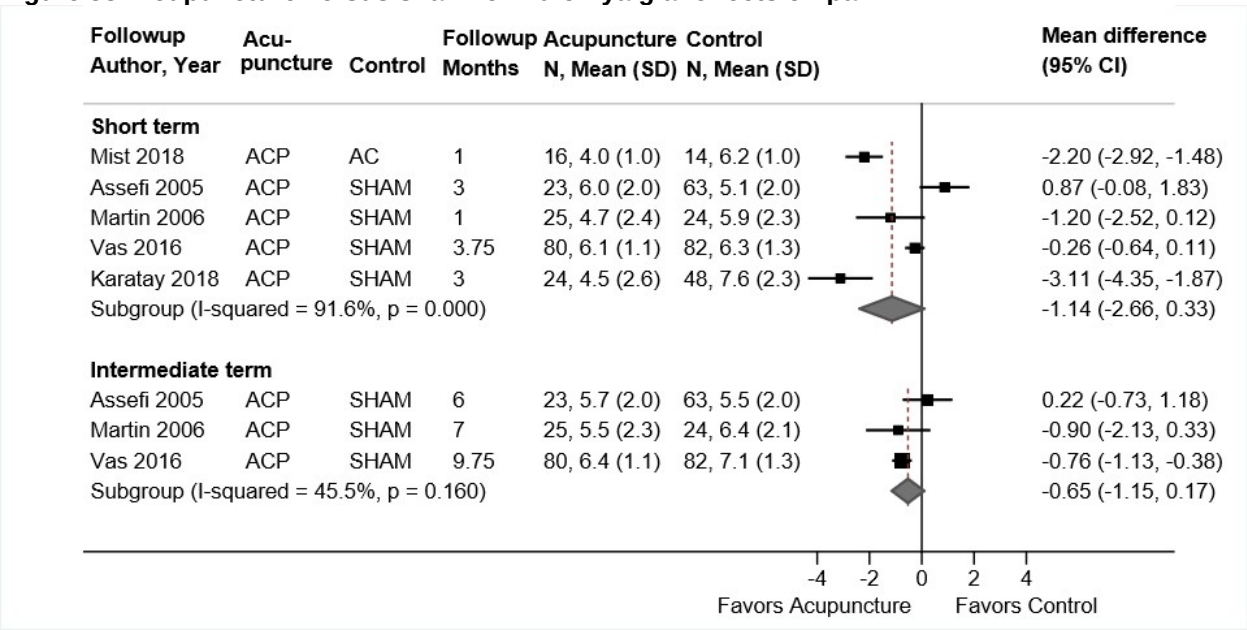
Discomfort and bruising were the most common reported adverse events. In one trial,[246] 89 of 96 treated (true or sham acupuncture) participants reported adverse events; 35 of 96 (37%) reported discomfort at needle insertion sites, 29 of 96 (30%) reported bruising, 3 of 96 (3%) reported nausea, and one of 96 (0.3%) felt faint at some point during the study. For patients assigned to simulated acupuncture, five of 19 (29%) had significantly less discomfort than those in directed acupuncture (14 of 23, 61%), acupuncture for unrelated condition (15 of 22, 70%) or sham needling (14 of 22, 64%); p=0.02. In one trial,[247] two of 50 (4%) experienced mild vasovagal symptoms and 1 of 50 (2%) experienced a pulmonary embolism believed to be unrelated to treatment. Mild bruising and soreness were reported to be more common in the true acupuncture group, but rates were not reported. In one study,[248] 2.6 percent of sessions led to aggravation of fibromyalgia symptoms and 0.5 percent led to headache. In the true acupuncture group, pain, bruising, and vagal symptoms presented after 4.7 percent of sessions. In one new trial, no serious adverse events were reported but some patients experienced discomfort and bruising at the sites of needle insertion.[249] In the other new trial, bruising and dizziness were reported in one patient following acupuncture (of 16 randomized or 6%) versus no patients randomized to attention control.[250]

Figure 52. Acupuncture versus sham for fibromyalgia: effects on function



ACP = acupuncture; CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; SD = standard deviation

Figure 53. Acupuncture versus sham for fibromyalgia: effects on pain



ACP = acupuncture; CI = confidence interval; SD = standard deviation

Multidisciplinary Rehabilitation for Fibromyalgia

Key Points

- More multidisciplinary treatment participants experienced a clinically meaningful improvement in FIQ total score (≥14% change) 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 poor-quality trial. Multidisciplinary treatment

was associated with a small improvement in function (based on a 0-100 FIQ total score) versus usual care or waitlist in the short term (3 trials, pooled difference −6.08, 95% CI −14.17 to 0.16, I^2=49%), and versus usual care at intermediate term (3 trials, pooled difference −7.77, 95% CI −12.22 to −3.83, I^2=0%) and long term (2 trials, pooled difference −8.54, 95% CI −15.00 to −1.30, I^2=0%) (SOE: low for short, intermediate and long term).

- Multidisciplinary treatment was associated with a small improvement in pain compared with usual care or waitlist at intermediate term (3 trials, pooled difference −0.68, 95% CI −1.10 to −0.27, 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 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 difference −0.25, 95% CI −0.79 to 0.36, I^2=0%) (SOE: low for short, intermediate and long term).
- There were no differences between multidisciplinary pain treatment versus aerobic exercise at long term in one trial for function (difference −1.10, 95% CI −8.40 to 6.20, 0-100 FIQ total score) or pain (difference 0.10, 95% CI −0.67 to 0.87, 0-10 FIQ pain scale) (SOE: low).
- Data were insufficient for harms. However, one poor-quality study reported on adverse events, stating that 19 percent of participants randomized to multidisciplinary treatment withdrew (versus 0% for waiting list) and two of these 16 patients gave increased pain as the reason. Reasons for other withdrawals were not given and there was not systematic reporting of adverse events (SOE: insufficient).

Detailed Synthesis

We identified six trials (across 8 publications) of multidisciplinary treatments that met inclusion criteria (Table 43 and Appendix D).[96,262-268] All the trials were included in the prior AHRQ report. Across trials, sample sizes ranged from 66 to 203 (total sample=801) and participants were predominantly (>90%) female with mean ages between 40 to 50 years. The multidisciplinary treatments included physical therapy or exercise training in all trials, as well as CBT and pharmacological therapy (2 trials)[263,266]; CBT and an educational program (1 trial)[268]; sociotherapy, psychotherapy, and creative arts therapy (1 trial)[96]; relaxation exercises (1 trial)[265]; and education and group discussions (1 trial).[262] All trials compared multidisciplinary treatment with usual care or waitlist; in addition, one trial compared it with exercise.[96] Treatment duration ranged from 2 to 12 weeks and the frequency of sessions from once a week to daily (total number of sessions ranged from 12 to 24 with durations between 1.5 to 5 hours). One of the trials included two intervention arms.[268] The long-term multidisciplinary arm (2 days of education and exercise followed by 10 weeks of CBT) was determined to be most consistent with interventions employed by the other trials and was included in the pooled estimates below; results for the short-term group (2 days of education, exercise, and CBT programs) were similar to those of the long-term group and can be found in Table 42. Three trials reported outcomes over the short term (3 to 5.5 months),[262,263,268] three over the intermediate term (6 months),[263,265,266] and two over the long term (12 and 18 months).[96,263] Five trials were conducted in Europe[96,262-267] and one trial in Turkey.[268]

Three trials were judged to be of fair quality[96,262,268] and three trials were rated poor quality[263,265,266] (Appendix E). The nature of the intervention precluded blinding of participants and of people administering the treatments. Additional methodological shortcomings in the poor

quality trials included unclear allocation concealment methods and high rates of overall attrition (21% to 43%) and differential attrition (12% to 13%) between groups.

Table 59. Fibromyalgia: multidisciplinary rehabilitation

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Amris, 2014[262] 5.5 months Duration of pain: median 10 to 11 years Fair	A. Multidisciplinary treatment (n=84): 3- 5 hours of education, sleep hygiene, group discussions, and physical therapy per day over 2 weeks B. Wait list (n=86)	A vs. B Age: 44 vs. 44 years Female: 100% vs. 100% Baseline Fibromyalgia Impact Questionnaire Total (FIQ, 0-100): 64.0 vs. 65.7 Baseline FIQ pain VAS (0-10): 7.1 vs. 7.4	A vs. B <u>5.5 months</u> Change in FIQ total from baseline: −1.3 vs. −1.4, difference 0.1 (95% CI −3.6 to 3.8) Change in FIQ pain VAS from baseline: 0.1 vs. −0.1, difference 0.2 (95% CI −0.3 to 0.7)	A vs. B <u>5.5 months</u> Change in Generalized Anxiety Disorder-10 from baseline (scale NR): −0.8 vs. −0.5, difference −0.2 (95% CI −2.0 vs. 1.5) Change in Major Depression Inventory from baseline (0-50): −1.7 vs. −0.5, difference −1.3 (95% CI −3.3 to 0.8) Change in SF-36 physical component score from baseline (0-100): 1.4 vs. 0.8, difference 0.6 (95% CI −1.0 to 2.1) Percent responders in SF-36 physical component score: 27% vs. 23% Change in SF-36 mental component score from baseline (0-100): 2.3 vs. 1.2, difference 1.1 (95% CI −1.5 to 3.8) Percent responders in SF-36 mental component score: 27% vs. 27% Change in SF-36 physical functioning from baseline (0-100): 1.1 vs. 1.6, difference −0.5 (95% CI −3.9 to 3.0)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Castel, 2013[263] Salvat, 2017[267] 3, 6 and 12 months Duration of pain: Mean 10.8 to 12.5 years Poor	A. Multidisciplinary treatment (n=53), conventional pharmacological treatment, 24 sessions of group CBT and physical therapy over 12 weeks. B. Usual care (n=35): conventional pharmacological treatment including analgesics, antidepressants, benzodiazepines, and nonbenzodiazepine hypnotics	A vs. B Age: 49 vs. 49 years Female: 100% vs. 100% Baseline FIQ (0-100): 64.6 vs. 66.6 Baseline pain NRS (0-10): 6.8 vs. 7.1	A vs. B <u>3 months</u> FIQ: 55.5 vs. 64.6, difference −9.1 (95% CI −14.9 to −3.3) Proportion with clinically significant FIQ improvement (≥14% change): 48% vs. 23%, OR 3.1 (95% CI 1.6 to 6.2) Pain NRS: 6.4 vs. 6.8, difference −0.40 (95% CI −0.98 to 0.18) Proportion with clinically significant NRS pain improvement (≥30% change): 14% vs. 11% <u>6 months</u> FIQ: 55.8 vs. 67.8, difference −12.0 (95% CI −18.2 to −5.8) Proportion with clinically significant FIQ improvement (≥14% change): 42% vs. 19%, OR 3.1 (95% CI 1.5 to 6.4) Pain NRS: 6.4 vs. 7.0, difference −0.60 (95% CI −1.2 to 0) Proportion with clinically significant NRS pain improvement (≥30% change): 16% vs. 5%, OR 3.3 (95% CI 1.0 to 10.8) <u>12 months</u> FIQ: 58.8 vs. 69.6, difference −10.8 (95% CI −16.8 to −4.8) Proportion with clinically significant FIQ improvement (≥14% change): 27% vs. 4%, OR 8.8 (95% CI 2.5 to 30.9) Pain NRS: 6.7 vs. 7.1, difference −0.40 (95% CI −0.94 to 0.14) Proportion with clinically significant NRS pain improvement (≥30% change): 8.6% vs. 0%, OR 0.5 (95% CI 0.4 to 0.6)	A vs. B <u>3 months</u> HADS (0-42): 15.2 vs. 20.6, difference −5.4 (95% CI −8.2 to −2.6) MOS sleep scale (scale NR): 40.5 vs. 31.2, difference 9.3 (95% CI 6.1 to 12.5) WONCA, mean (95% CI): total score: 23.7 (22.5 to 25.0) vs. 26.5 (25.1 to 27.9), p<0.005; physical function: 2.71 (2.51 to 2.95) vs. 3.20 (2.95 to 3.41), p=NR; daily activities: 2.88 (2.70 to 3.05) vs. 3.20 (3.00 to 3.39), p=NR <u>6 months</u> HADS: 16.2 vs. 21.5, difference −5.3 (95% CI −8.1 to −2.5) MOS sleep scale: 38.7 vs. 29.0, difference 9.7 (95% CI 6.6 to 12.8) WONCA, mean (95% CI): total score: 23.6 (22.4 to 24.9) vs. 27.3 (25.9 to 28.6), p<0.005; physical function: 2.69 (2.48 to 2.90) vs. 3.38 (3.12 to 3.60), p=NR; daily activities: 2.97 (2.80 to 3.15) vs. 3.28 (3.10 to 3.47), p=NR <u>12 months</u> HADS: 17.1 vs. 22.8, difference −5.7 (95% CI −8.7 to −2.7) MOS sleep scale: 36.3 vs. 28.8, difference 7.5 (95% CI 4.3 to 10.7) WONCA, mean (95% CI): total score: 23.5 (22.1 to 24.8) vs. 26.4 (24.9 to 27.9), p<0.005; physical function: 2.72 (2.49 to 2.96) vs. 3.33 (3.05 to 3.62), p=NR daily activities: 2.87 (2.69 to 3.06) vs. 3.32 (3.10 to 3.55), p=NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Cedraschi, 2004[265] 6 months Duration of pain: Mean 8.4 to 9.5 years Poor	A. Multidisciplinary treatment (n=84): 12 group pool sessions of physiotherapy, relaxation exercises, and exercise over 6 weeks B. Usual care (n=80): Regular care, including physical therapy, drug treatment and, in some cases, psychotherapy.	A vs. B Age: 49 vs. 50 years Female: 93% vs. 93% Baseline FIQ total (0-10): 5.5 vs. 5.6 FIQ physical function (0-10): 4.2 vs. 4.5 Baseline FIQ pain (0-10): 6.3 vs. 6.0	A vs. B <u>6 months</u> FIQ total: 4.9 vs. 5.5, difference −0.6 (95% CI −1.1 to −0.09) FIQ physical function: 4.3 vs. 4.8, difference −0.5 (95% CI −1.3 to 0.3) FIQ pain: 6.1 vs. 6.6, difference −0.5 (95% CI −1.2 to 0.2) Regional Pain Score: 62.6 vs. 68.4, difference −5.8 (95% CI −12.1 to 0.5)	A vs. B <u>6 months</u> Psychological General Wellbeing Index total (0-110): 51.1 vs. 43.8, difference 7.3 (95% CI 0.2 to 14.3) Psychological General Wellbeing Index anxiety (0-25): 13.0 vs. 10.3, difference 2.7 (95% CI 0.6 to 4.8) Psychological General Wellbeing Index depression (0-15): 9.0 vs. 7.7, difference 1.3 (95% CI −0.1 to 2.7) SF-36 physical function (0-100): 42.2 vs. 43.9, difference −1.7 (95% CI −8.6 to 5.2) FIQ depression (0-10): 4.6 vs. 6.1 FIQ anxiety (0-10): 5.1 vs. 6.7, difference −1.6 (95% CI −2.6 to −0.6)
Martin, 2012[266] 6 months Duration of pain: Mean 14 to 15 years Poor	A. Multidisciplinary treatment (n=54): conventional pharmacological treatment, 12 sessions of CBT, education, and physiotherapy over 6 weeks B. Usual care (n=56): conventional pharmacological treatmentincluding amitriptyline, paracetamol, and tramadol	A vs. B Age: 49 vs. 52 years Female: 91% vs. 91% Baseline FIQ total (0-100): 76.3 vs. 76.2 Baseline FIQ physical functioning (0-10): 5.5 vs. 5.4 Baseline FIQ pain (0-10): 7.5 vs. 7.5	A vs. B <u>6 months</u> FIQ total: 70.3 vs. 76.8, difference −6.5 (95% CI -12.3 to −0.7) FIQ physical function: 5.2 vs. 5.9, difference −0.7 (95% CI -1.4 to −0.04) FIQ pain: 7.2 vs. 8.2, difference -1.0 (95% CI -1.7 to −0.3)	A vs. B <u>6 months</u> Hospital Anxiety and Depression Scale anxiety (HADS, 0-21): 13.4 vs. 12.8, difference 0.66 (95% CI −1.02 to 2.34) HADS depression (0-21): 9.8 vs. 10.2, difference −0.43 (95% CI −2.00 to 1.14)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Saral, 2016[268] 6 months; 4 months based on intervention group[b] Duration of pain: 7.5 years Fair	A. Long term interdisciplinary group (n=22): educational program (1 full day), exercise program (1 full day), and CBT (1, 3-hour session per week for 10 weeks); plus home strengthening and stretching exercises and relaxation B. Short term interdisciplinary group (n=22): education, exercise, and CBT over 2 full days; plus home strengthening and stretching exercises and relaxation C. Usual care (n=22): Patients continued current medical treatments, normal daily living, and current physical activity levels	A vs. B vs. C Age, years: 38 vs. 43 vs. 44 Female: 100% vs. 100% vs. 100% Symptom duration, months: 69 vs. 113 vs. 88 Baseline FIQ (0-100): 71.6 vs. 67.7 vs. 65.5 Baseline pain VAS (0-10): 8.2 vs. 7.6 vs. 7.5	A vs. C 4 months[b] FIQ: 53.9 vs. 65.5, difference −11.6 (95% CI −21.9 to −1.29) Percent change from baseline in FIQ: −22.1% vs. 3.2% Pain VAS: 5.1 vs. 7.6, difference −2.5 (95% CI −3.78 to −1.22) Percent change from baseline in VAS pain: −38.3% vs. 1.5% B vs. C 4 months[b] FIQ: 54.5 vs. 65.5, difference −11.0 (95% CI −19.5 to −2.5) Percent change from baseline in FIQ: −18.9% vs. 3.2% Pain VAS: 5.8 vs. 7.6, difference −1.8 (95% CI −2.6 to −1.0) Percent change from baseline in VAS pain: −22.8% vs. 1.5%	A vs. C 4 months[b] BDI: 16.6 vs. 18.7, difference −2.1 (95% CI −8.2 to 4.0) SF-36 PCS: 39.9 vs. 34.3, difference 5.6 (95% CI 0.61 to 10.6) SF-36 MCS: 40.7 vs. 37.6, difference 3.1 (95% CI −4.1 to 10.3) Sleep VAS: 3.0 vs. 4.9, difference −1.9 (95% CI −3.8 to −0.04) B vs. C 4 months[b] BDI: 15.0 vs. 18.7 (9.5), difference −3.7 (95% CI −10.2 to 2.8) SF-36 PCS: 39.6 vs. 34.3, difference 5.3 (95% CI −0.03 to 10.6) SF-36 MCS: 40.2 vs. 37.6, difference 2.6 (95% CI −4.0 to 9.2) Sleep VAS: 3.1 vs. 4.9 difference −1.8 (95% CI −3.6 to 0.02)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Van Eijk-Hustings, 2013[96] 18 months Duration of pain: Mean of 6.1 to 7.1 years Fair	A. Multidisciplinary intervention (n=108): 36 days of sessions of sociotherapy, physiotherapy, psychotherapy, and creative arts therapy over 12 weeks B. Aerobic exercise (n=47): 24 sessions over 12 weeks C. Usual care (n=48): education and lifestyle advice in addition to usual care	A vs. B vs. C Age: 41 vs. 39 vs. 43 years Female: 93% vs. 100% vs. 98% Baseline FIQ physical function (0-10): 4.2 vs. 3.6 vs. 3.4 Baseline FIQ total (0-100): 64.5 vs. 60.0 vs. 55.4 Baseline FIQ pain (0-10): 6.3 vs. 6.2 vs. 5.5	A vs. B[c] <u>18 months</u> FIQ physical function: 3.6 vs. 3.6, difference 0 (95% CI −0.79 to 0.79) FIQ total: 50.9 vs. 52.0, difference −1.10 (95% CI −8.40 to 6.20) FIQ pain: 5.3 vs. 5.2, difference 0.10 (95% CI −0.67 to 0.87) A vs. C <u>18 months</u> FIQ physical function: 3.6 vs. 3.9, ES 0.12 (−0.22 to 0.46) FIQ total: 50.9 vs. 56.2, ES 0.25 (95% CI −0.09 to 0.59) FIQ pain: 5.3 vs. 5.3, ES −0.01 (95% CI −0.35 to 0.34)	A vs. B[c] <u>18 months</u> FIQ Depression: 3.9 vs. 5.0, difference −1.1 (95% CI −2.2 to 0.01) FIQ Anxiety: 4.7 vs. 5.0, difference −0.30 (95% CI −1.41 to 0.81) EQ-5D (−0.59 to 1): 0.6 vs. 0.5, difference 0.01 (95% CI −0.10 to 0.12) GP consultations[d]: 0.9 vs. 1.0, difference −0.10 (95% CI −0.89 to 0.69) Medical specialist consultations[d]: 0.3 vs. 0.4, difference −0.10 (95% CI −0.43 to 0.23) Physiotherapist consultations[d]: 2.6 vs. 0.4, difference 2.20 (95% CI 0.69 to 3.71) Other paramedical professional consultations[d]: 1.0 vs. 2.1, difference −1.10 (95% CI −2.21 to 0.01) A vs. C <u>18 months</u> FIQ depression: 3.9 vs. 4.2, ES 0.10 (95% CI −0.24 to 0.44) FIQ anxiety: 4.7 vs. 4.8, ES 0.03 (95% CI −0.31 to 0.37 EQ-5D: 0.55 vs. 0.51, ES 0.12 (95% CI −0.22 to 0.46) GP consultations[d]: 0.9 vs. 0.7, ES=−0.11 (95% CI −0.45 to 0.23) Medical specialist consultations[d]: 0.3 vs. 0.2, ES=−0.14 (95% CI −0.48 to 0.20) Physiotherapist consultations[d]: 2.6 vs. 2.8, ES=0.04 (95% CI −0.30 to 0.38) Other paramedical professional consultations[d]: 1.0 vs. 0.2, ES=−0.28 (95% CI −0.62 to 0.06)

BDI = Beck Depression Inventory; CBT = cognitive behavioral therapy; CI = confidence interval; ES = effect size; EQ-5D = EuroQol-5D; FIQ = Fibromyalgia Impact Questionnaire; GP = general practitioner; HADS = Hospital Anxiety and Depression Scale; MOS = Medical Outcomes Study; NR = not reported; NRS = Numeric Rating Scale; OR = odds ratio; SF-36 MCS = Short-Form 36 Mental Component Scale; SF-36 PCS = Short-Form 36 Physical Component Scale; VAS = visual analog scale; WONCA = World Organization of Family Docotors

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Long term multidisciplinary group was followed up at 4 months from end of intervention and the short term multidisciplinary and control groups were followed up at 6 months from end up intervention

[c] Authors did not provide effect estimates for the comparison of multidisciplinary rehabilitation versus exercise; mean differences were calculated by the EPC

[d] Total number of consultations over a period of 2 months prior to measurement

Multidisciplinary Rehabilitation Compared With Usual Care or Waitlist

Clinically important FIQ improvement (≥14% change) was significantly more common for multidisciplinary treatment 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 followup (OR 8.8, 95% CI 2.5 to 30.9) in one poor-quality trial.[263] Multidisciplinary treatment for fibromyalgia was associated with a small improvement in function versus usual care or waitlist based on a 0 to 100 FIQ total score in the short term (3 trials, pooled difference −6.08, 95% CI −14.17 to 0.16, I^2=48.9%),[262,263,268] and versus usual care in the intermediate term (3 trials, pooled difference −7.77, 95% CI −12.22 to −43.83, I^2=0%)[263,265,266] (Figure 54). The short-term estimate for trials of multidisciplinary treatment versus usual care only was similar (2 trials, pooled difference −9.74, 95% CI −16.38 to −3.83).[263,268] The slightly smaller effect of multidisciplinary rehabilitation versus usual care persisted over the long term (2 trials, pooled difference on 0-100 scale −8.54, 95% CI −15.00 to −1.30, I^2=0%).[96,263] Only one poor-quality trial reported short-term, intermediate-term, and long-term effects on function, showing a significant result for each time frame.[263]

Clinically important improvement in pain (≥30% change on a 0-10 scale) was more common for multidisciplinary treatment compared with usual care at intermediate-term followup in one poor-quality trial (OR 3.4, 95% CI 1.0 to 10.8)[263]; no statistically significant differences were seen between groups at short- or long-term followup. There were no clear effects of multidisciplinary treatment for fibromyalgia on pain versus usual care or waitlist in the short term (3 trials, pooled difference on a 0-10 scale −0.84, 95% CI −2.56 to 0.64, I^2=83.6%),[262,263,268] but statistical heterogeneity was very large (Figure 55). Excluding an outlier trial (difference −2.50, 95% CI −3.73 to −1.27)[268] reduced the statistical heterogeneity and resulted in an attenuated effect (pooled difference −0.24, 95% CI −0.63 to 0.15, I^2=0%). At intermediate term, multidisciplinary treatment was associated with a small improvement in pain compared with usual care (3 trials, pooled difference 0−10 scale −0.68, 95% CI −1.10 to −0.27, I^2=0%).[263,265,266] Long term, there were no clear effects of multidisciplinary treatment on pain versus usual care (2 trials, pooled difference −0.25, 95% CI −0.79 to 0.36, I^2=0%).[96,263] Only one poor-quality trial reported short-, intermediate-, and long-term effects on pain, showing a significant result for each time frame.[263]

Results were mixed across the six trials for effects of multidisciplinary treatment on secondary outcomes. Three trials were fair quality.[96,262,268] Across the three fair-quality trials, there were no significant differences between multidisciplinary treatment and usual care or waitlist on measures of anxiety (Generalized Anxiety Disorder−10, FIQ anxiety subscale) in two trials[96,262] and depression (Major Depression Inventory, FIQ depression subscale, BDI) in three trials[96,262,268] over short-term or long-term followup. Regarding quality of life, two of these trials reported no differences between groups on the SF-36 PCS and MCS and the EQ-5D[96,262] while the third reported significant improvement on the SF-36 PCS but not the MCS.[268] One trial reported no difference in healthcare utilization between groups during the 2 months prior to the final measurement at 18 months.[96]

Multidisciplinary Rehabilitation Compared With Pharmacological Therapy

No trial of multidisciplinary rehabilitation versus pharmacological therapy met inclusion criteria.

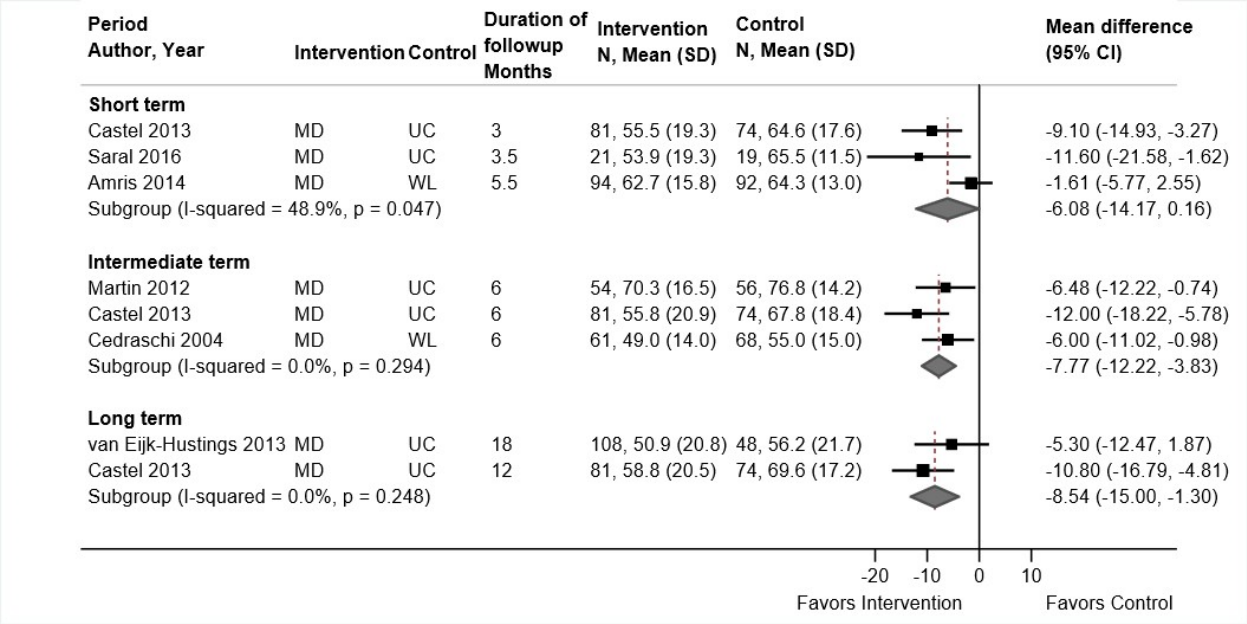
Multidisciplinary Rehabilitation Compared With Exercise

There was no clear effect of multidisciplinary pain treatment versus aerobic exercise at long term in one fair-quality trial[96] for physical function on the FIQ physical function scale (difference 0 on a 0−10 scale, 95% CI −0.79 to 0.79) or the FIQ total score (difference −1.10 on a 0−100 scale, 95% CI −8.40 to 6.20). Similarly, there were no significant differences on the FIQ pain scale (difference 0.10 on a 0−10 scale, 95% CI −0.67 to 0.87), or secondary outcomes of quality of life, depression or anxiety, or healthcare utilization, with the exception of physiotherapist consultations, which was higher for the multidisciplinary group in the 2 months prior to the final measurement at 18 months (Table 42).

Harms

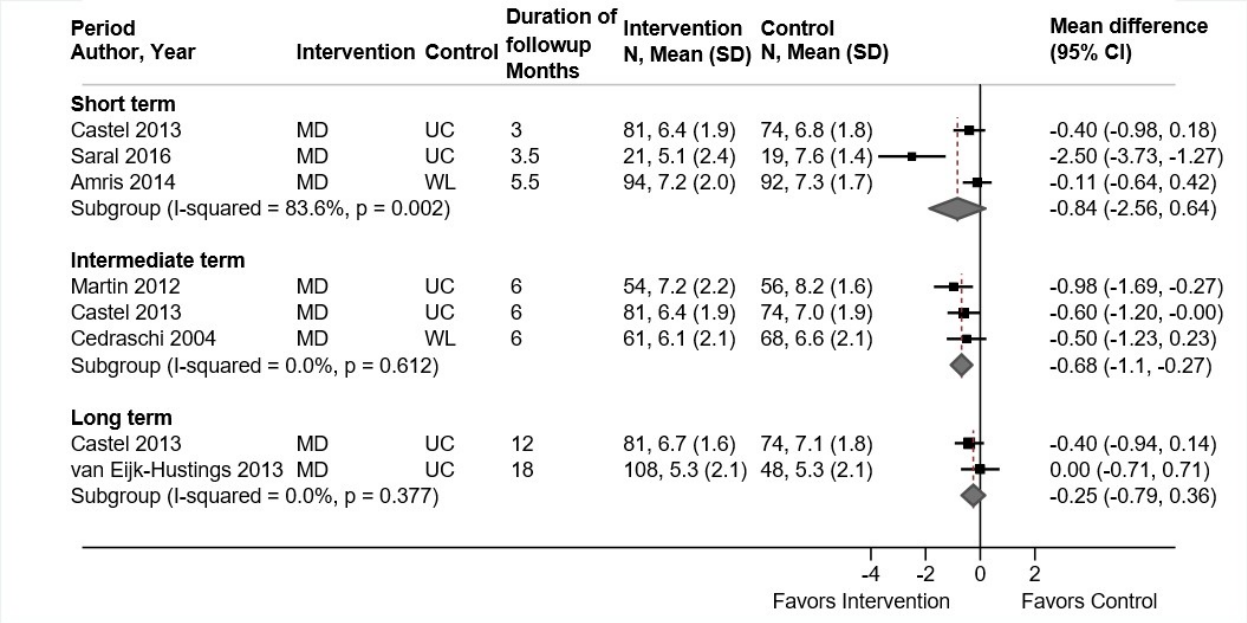
Adverse events were poorly reported by the included trials. One trial that compared multidisciplinary treatment (group pool sessions of physiotherapy, relaxation exercises, and exercise) with usual care (physical therapy, drug treatment and, in some cases, psychotherapy)[265] reported that 16 of 84 (19%) multidisciplinary participants withdrew (versus 0% for waiting list) and two of these gave increased pain as the reason. Reasons for other withdrawals were not given and there was not systematic reporting of adverse events.

Figure 54. Multidisciplinary rehabilitation versus usual care or waitlist for fibromyalgia: effects on function



CI = confidence interval; MD = multidisciplinary rehabilitation; SD = standard deviation; UC = usual care; WL = waitlist

Figure 55. Multidisciplinary rehabilitation versus usual care or waitlist for fibromyalgia: effects on pain



CI = confidence interval; MD = multidisciplinary rehabilitation; SD = standard deviation; UC = usual care; WL = waitlist.

Key Question 5: Chronic Tension Headache

No new trials that evaluated nonpharmacological treatments for chronic tension headache that met our inclusion criteria were identified for this update.

Psychological Therapies for Chronic Tension Headache

Key Points

- There is insufficient evidence from three poor quality trials to determine the effects of psychological therapies (CBT, relaxation) on short-term or intermediate-term function or pain compared with waitlist, placebo, or attention control (SOE: insufficient).
- There is insufficient evidence from two poor-quality trials to determine the effects of CBT on short-term or intermediate-term function or pain compared with antidepressant medication (SOE: insufficient).
- No long-term outcomes were reported and no trials comparing psychological therapies to biofeedback were identified that met inclusion criteria.
- Data were insufficient for harms. Results were mixed across two poor-quality trials comparing CBT with antidepressant medication, with one trial reporting a lower risk of "at least mild" adverse events in the CBT group (0% vs. 59%), four of which led to withdrawal from the trial, and the second trial reporting a similar low risk of withdrawal due to adverse events (2% to 6% across groups to include placebo) (SOE: insufficient).

Detailed Synthesis

Three trials, all conducted in the United States,[128,129,132] of CBT for chronic tension headache met inclusion criteria (Table 44 and Appendix D). Sample sizes ranged from 36 to 104 (total

sample=198); the mean age across trials varied from 32 to 42 years and most participants were female (56% to 80%). Duration since the onset of headache pain ranged from 10.7 to 14.5 years. All trials either excluded patients with concomitant migraines or required that they suffer from no more than one migraine per month. Two trials also specifically excluded patients with medication overuse (analgesic-abuse) headaches and required that patients be free from prophylactic headache medication upon study entry.[129,132]

All three trials evaluated some variation of stress management therapy/cognitive coping skills training with a relaxation component; one trial (n=77) also included an additional relaxation only arm.[128] In two trials (n=41, 150), patients received three 60-minute sessions of CBT and training in home-based relaxation,[129,132] and in the third trial (n=77), patients underwent 11 sessions (1-2 per week) of CBT plus progressive muscle relaxation training (session duration varied from 45 to 90 minutes).[128] In all trials, the interventions were administered by a psychologist or counselor over a 2-month period. Two trials compared CBT with placebo (placebo pill),[129] attention control (pseudomeditation/body awareness training)[128] and waitlist (monitoring via phone and clinical visits) control groups.[128] Two trials compared CBT with amitriptyline (25-75 mg/day).[129,132] All trials reported short-term results; one trial also provided outcomes at intermediate-term followup.[129]

All three trials were considered poor quality (Appendix E) due to lack of blinding and large differential attrition between groups (in one trial, overall attrition was also substantial[129]). Additionally, randomization, concealment, and intention-to-treat processes were unclear in one trial.[132]

Table 60. Chronic tension headache: psychological therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Blanchard, 1990[128] 1 month Duration of pain: mean 14.2 years Poor	A. Cognitive Stress Coping Training + PMR (n=17): 11, 45-90 minute sessions once or twice per week for 8 weeks B. PMR alone (n=22): 10, 30-70 minute sessions twice weekly for 3 weeks followed by once weekly for 3 weeks with a final session at week 8 C. Pseudomeditation (attention control) (n=19): body awareness and mental control training; 11 sessions over 8 weeks, 40-45 minutes each D. Waitlist (n=19): monitoring via phone, clinical visits and patient diaries.	A vs. B vs. C vs. D Age: 38 vs. 43 vs. 39 vs. 37 years Female: 56% vs. 58% vs. 45% vs. 66% Mean duration of chronicity: 13.0 vs. 13.9 vs. 15.3 vs. 14.3 years Baseline Headache Index Scores: mean 5.82 vs. 5.63 vs. 5.23 vs. 5.05 Baseline Medication Index Scores: mean 39.8 vs. 16.9 vs. 12.1 vs. 24.0	A vs. C <u>1 month</u> ≥50% improvement (i.e., reduction) in headache frequency: 62.5% vs. 43.7%; RR 1.43 (95% CI 0.81 to 1.97) Headache Index Scores: 3.2 vs. 4.6; difference −1.4 (95% CI −4.3 to 1.5) A vs. D <u>1 month</u> ≥50% improvement (i.e., reduction) in headache frequency: 62.5% vs. 20.0%; RR 3.13 (95% CI 0.91 to 2.45) Headache Index Scores: 3.2 vs. 4.5; difference −1.3 (95% CI −3.9 to 1.4) B vs. C <u>1 month</u> ≥50% improvement (i.e., reduction) in headache frequency: 31.6% vs. 43.7%; RR 0.72 (95% CI 0.65 to 1.69) Headache Index Scores: 3.8 vs. 4.6; difference −0.8 (95% CI −3.2 to 1.6) B vs. D <u>1 month</u> ≥50% improvement (i.e., reduction) in headache frequency: 31.6% vs. 20%; RR 1.58 (95% CI 0.75 to 2.11) Headache Index Scores: 3.8 vs. 4.5; difference −0.6 (95% CI −2.7 to 1.5)	A vs. C <u>1 month</u> Medication Index Scores: 20.7 vs. 8.3; difference 12.4 (95% CI −6.8 to 31.6) A vs. D <u>1 month</u> Medication Index Scores: 20.7 vs. 22.5; difference −1.8 (95% CI −23.8 to 20.2) B vs. C <u>1 month</u> Medication Index Scores: 9.8 vs. 8.3; difference 1.5 (95% CI −6.8 to 9.8) B vs. D <u>1 month</u> Medication Index Scores: 9.8 vs. 22.5; difference −12.7 (95% CI −25.6 to 0.21)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Holroyd, 1991[132] 1 month Duration of pain: mean 10.7 years Poor	A. CBT (n=19): 3, 1 hour sessions over 8 weeks B. Amitriptyline therapy (n=17): Individualized dosage at 25, 50, or 75 mg/day for 8 weeks	A + B Age: 32.3 years Female: 80% A vs. B Baseline % of Headache-free days: 18.0 vs. 18.5 Baseline Headache Index scores (0−10): 2.17 vs. 2.04 Baseline Headache Pain Peak scores (0−10): 6.41 vs. 6.36	A vs. B <u>1 month</u> Proportion with >66% reduction in headaches (substantial improvement): 37% vs. 18%; RR 2.09 (95% CI 0.79 to 2.23) Proportion with 33-66% reduction in headaches (moderate improvement): 53% vs. 35%; RR 1.49 (95% CI 0.80 to 2.03) % of Headache-free days: 54.7 vs. 42.3; difference 12.4 (95% CI −8.06 to 32.86) Headache Index scores: 0.96 vs. 1.49; difference −0.53 (95% CI −1.14 to 0.08) Headache Peak scores: 4.33 vs. 4.55; difference −0.22 (95% CI −1.70 to 1.26)	A vs. B <u>1 month</u> BDI (0-63): 5.16 vs. 5.56; difference −0.4 (95% CI −3.96 to 3.16) STPI Anxiety (20-80): 18.37 vs. 19.06; difference −0.69 (95% CI −3.99 to 2.62) STPI Anger (20-80): 19.47 vs. 17.44; difference 2.03 (95% CI −1.98 to 6.04) WPSI (scale NR): 16.05 vs. 20.50; difference −4.45 95% CI −9.78 to 0.87) Analgesic Tablets: 0.26 vs. 0.82; difference −0.56 (95% CI −1.16 to 0.04)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Holroyd, 2001[129] 1 and 6 months Duration of pain: mean 11.8 years Poor	A. Stress Management Therapy + Placebo (n=34): 3, 1 hour sessions B. Placebo (n=26) Treatment Protocol: identical to group C C. Antidepressant Medications (n=44): Low starting dose (12.5 mg/day increased to 25mg, then 50mg) with the possibility to switch to nortriptyline	A vs. B vs. C Age: 37 vs. 38 vs. 36 years Female: 80% vs. 79% vs. 66% Caucasian: 91% vs. 98% vs. 98% Duration of pain: 12.3 vs. 11.1 vs. 11.9 years Headache frequency, days/month: 26.5 vs. 26.1 vs. 25.1 Baseline Headache Index (0−10): 2.8 vs. 2.7 vs. 2.8 Baseline Days/month with at least moderately severe headache (≥5 on 0−10 scale): 13.5 vs. 13.5 vs. 14.1	A vs. B <u>1 month</u> Days/month with at least moderately severe headache: difference 2.5 (95% CI −0.1 to 5.2) Headache Disability Inventory (0−100): difference 7.3 (95% CI 1.6 to 13.0) Headache Index: difference 0.46 (95% CI 0.02 to 0.89) <u>6 months</u> Patients who experienced ≥50% reductions in Headache Index Scores: 35% vs. 29%; RR 1.18 (95% CI 0.79 to 1.79) Days/month with at least moderately severe headache: difference 5.1 (95% CI 2.3 to 8.0) Headache Disability Inventory: difference 9.3 (95% CI 3.5 to 15.1) Headache Index: difference 0.79 (95% CI 0.30 to 1.28) A vs. C <u>1 month</u> Days/month with at least moderately severe headache: difference −3.5 (95% CI −6.1 to −0.9) Headache Disability Inventory: difference 0.1 (95% CI −5.6 to 5.7) Mean Headache Index: difference −0.54 (95% CI −0.97 to −0.012) <u>6 months</u> Patients who experienced >50% reductions in Headache Index Scores: 35% vs. 38%; RR 0.92 (95% CI 0.71 to 1.54) Days/month with at least moderately severe headache: difference 0.1 (95% CI −2.7 to 2.9) Headache Disability Inventory: difference 2.4 (95% CI −3.3 to 8.0) Headache Index: difference −0.13 (95% CI −0.61 to 0.35)	A vs. B <u>1 month</u> Weighted analgesic use: difference −1.7 (95% CI −12.0 to 8.6) <u>6 months</u> Weighted analgesic use: difference 11.8 (95% CI 1.5 to 22.1) A vs. C <u>1 month</u> Weighted analgesic use: difference −19.4 (95% CI −29.5 to −9.3) <u>6 months</u> Weighted analgesic use: difference −6.2 (95% CI −16.2 to 3.8)

BDI = Beck Depression Inventory; CBT = cognitive-behavioral therapy; CI = confidence interval; NR = not reported; PMR = Progressive Muscle Relaxation; RR = risk ratio; STPI = State-Trait Personality Inventory; VAS = visual analog scale; WPSI = Wahler Physical Symptom Inventory

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Psychological Therapy Compared With Waitlist, Placebo, or Attention Control

There was insufficient evidence from three poor-quality trials to draw conclusions regarding the effects of psychological therapies compared with waitlist, placebo, or attention control over the short term or intermediate term.

CBT plus placebo was associated with a small improvement in both short-term and intermediate-term function compared with placebo alone as measured by the Headache Disability Inventory (HDI) (scale 0−100) in one trial (difference 7.3, 95% CI 1.6 to 13.0 at 1 month and 9.3, 95% CI 3.5 to 15.1 at 6 months.[129] Long-term function was not reported.

Various pain measures were reported across trials. In general, CBT (plus relaxation), but not relaxation alone, appeared to have a small effect on short-term pain compared with waitlist, placebo, or attention control (Table 43). CBT plus relaxation was associated with a small improvement in pain on the Headache Index (HI) at 1 month compared with waitlist, attention control, or placebo across two trials (pooled SMD −0.40, 95% CI −0.79 to 0.00, I^2=0%)[128,129] (Figure 57). Relaxation only conferred no benefit for short-term pain compared with waitlist or attention control in one of these trials (difference −0.21 on a 0-20 HI scale, 95% CI −0.78 to 0.36).[128] Almost twice as many patients who received CBT plus relaxation achieved at least a 50 percent improvement in headache frequency compared with usual care or waitlist (risk ratio [RR] 1.94, 95% CI 1.03 to 3.66) over the short term in one trial; however, there was no difference between groups when the intervention was relaxation alone (RR 0.98, 95% CI 0.42 to 2.26)[128] (Figure 56). One trial reported similar favorable results regarding pain over the intermediate-term for CBT plus placebo compared with placebo alone (difference −0.65, 95% CI −1.06 to −0.24) (Figure 57), with the exception of "success" (≥50% improvement from baseline in HI score), which did not differ between groups (Table 43).[129]

Medication use did not differ significantly between the CBT and relaxation therapy groups and waitlist, placebo, or attention control groups over the short-term in two trials.[128,129] Over the intermediate-term, CBT plus placebo resulted in a significant reduction in analgesic use compared with placebo alone (difference 11.8, 95% CI 1.5 to 22.1).[129]

Psychological Therapy Compared With Pharmacological Therapy

There was insufficient evidence from two poor-quality trials to draw conclusions regarding the effect of CBT versus pharmacological therapy through intermediate-term followup.

There was no effect for CBT plus placebo versus antidepressant medication over the short-term or intermediate-term for function as measured by the HDI (scale 0−100) in one trial (difference 0.1, 95% CI −5.6 to 5.7 at 1 month and 2.4, 95% CI −3.3 to 8.0 at 6 months).[129] Long-term function was not reported.

Regarding short-term pain, two trials reported HI index scores with differing results. One trial found that CBT plus placebo resulted in less improvement compared with antidepressant medication at 1 month (SMD 0.50, 95% CI 0.11 to 0.89),[129] whereas the other trial showed an improvement with CBT versus amitriptyline by 1 month, although the difference did not reach statistical significance (SMD −0.59, 95% CI −1.26 to 0.08)[132] (Figure 57); due to the significant heterogeneity between groups we did not use the pooled estimate. There were no significant differences between CBT and pharmacological treatment for any other pain outcome reported over the short term in both trials[129,132] or over the intermediate-term in one trial[129] (Table 43).

Short-term results were mixed regarding medication use with one trial reporting no difference between CBT and amitriptyline[132] and the other reporting a significant difference

between groups favoring antidepressant therapy[129]; however, this difference did not persist to the intermediate term in the latter trial (Table 43).

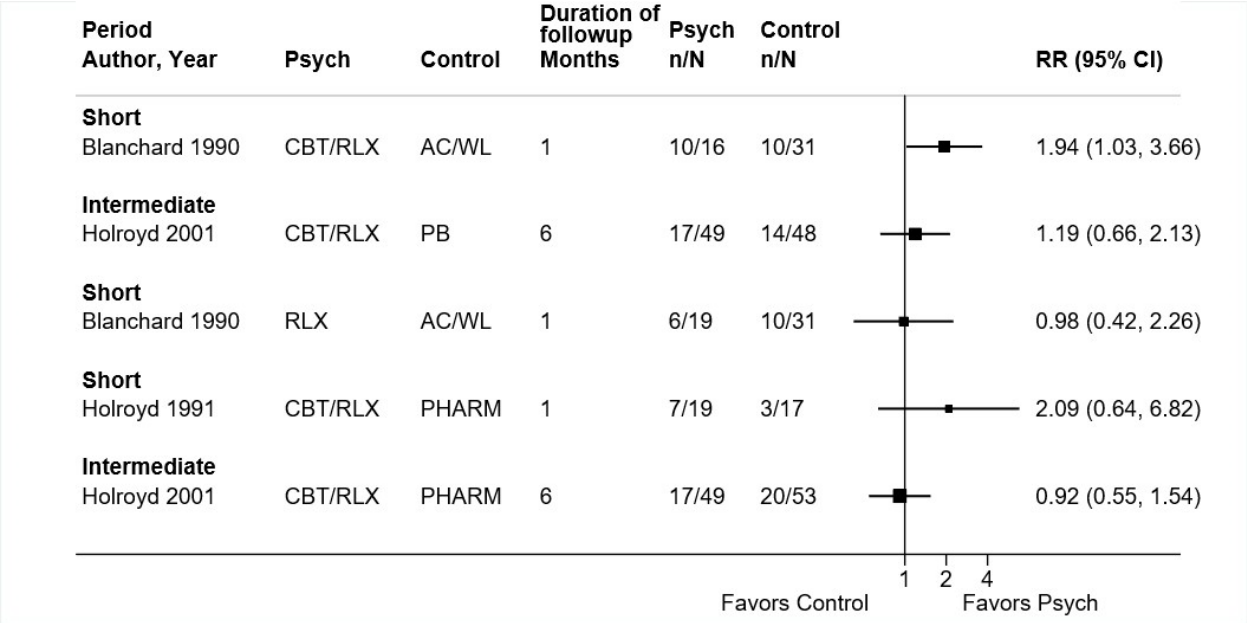
Psychological Therapy Compared With Biofeedback

No trial of psychological therapy versus biofeedback met inclusion criteria.

Harms

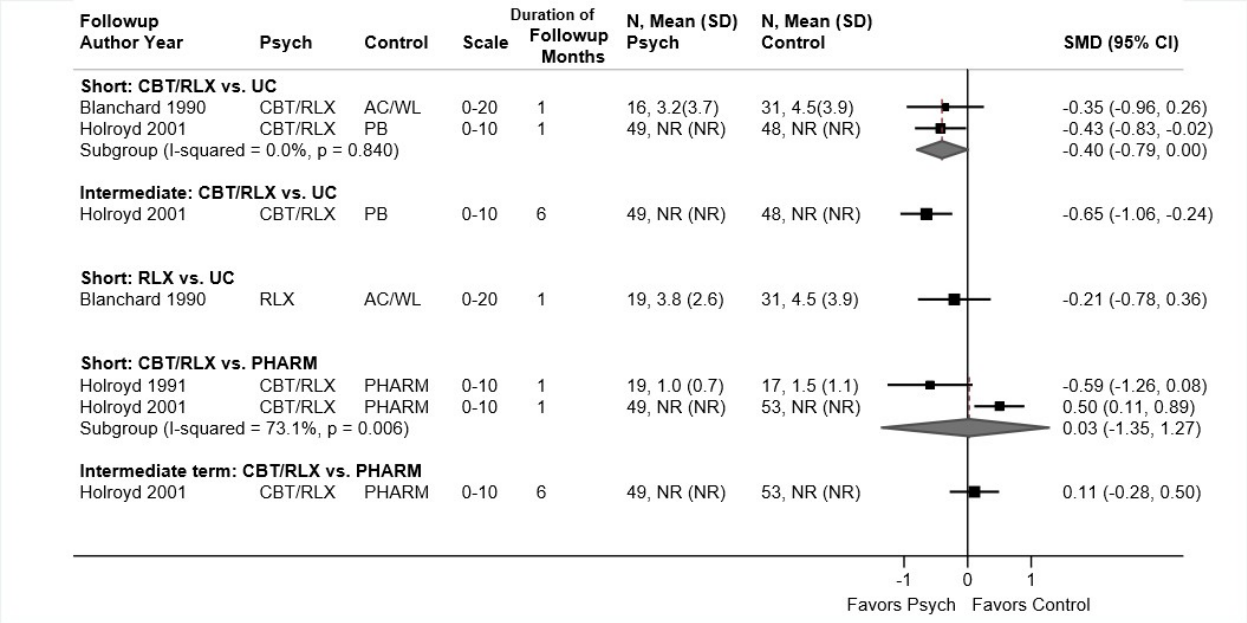
Harms were reported by the two poor-quality trials comparing CBT with antidepressant medication,[132] and with placebo in one.[129] No patient who underwent CBT experienced an adverse effect versus 10 of 17 (59%) of those who took medication in one trial;[132] six events were classified as mild, two as moderate, and two as substantial (no further details provided). Four of these patients withdrew from the trial. The risk of withdrawal due to adverse events was similar across groups in the second trial: CBT (2%) versus antidepressant medication (2%) and placebo (6%); no other information was provided.[129]

Figure 56. Psychological therpies versus waitlist, attention control, placebo intervention, or pharmacological treatment for chronic tension headache: effects on pain (success)



AC/WL = an attention control arm and a waitlist arm; CBT = cognitive-behavioral therapy; CBT/RLX = cognitive-behavioral therapy with a relaxation component; CI = confidence interval; PB = placebo (pill); PHARM = standard pharmacological therapy; RLX = relaxation therapy; RR = risk ratio; UC = usual care

Figure 57. Psychological therapies versus waitlist, attention control, placebo intervention, or pharmacological treatment for chronic tension headache: effects on pain (mean difference)



AC/WL = an attention control arm and a waitlist arm; CBT = cognitive-behavioral therapy; CBT/RLX = cognitive-behavioral therapy with a relaxation component; CI = confidence interval; PB = placebo (pill); PHARM = standard pharmacological therapy; RLX = Relaxation therapy; SMD = standardized mean difference; UC = usual care

Physical Modalities for Chronic Tension Headache

Key Points

- There is insufficient evidence from one poor-quality trial to determine the effects occipital transcutaneous electrical stimulation (OTES) on short-term function or pain compared with sham (SOE: insufficient).
- No longer-term outcomes were reported and no trials comparing physical modalities to pharmacological therapy or to biofeedback were identified that met inclusion criteria.
- Data were insufficient for harms; however, no adverse events occurred in either the real or the sham OTES group in one poor-quality trial (SOE: insufficient).

Detailed Synthesis

Only one Italian trial[169] was identified that investigated the efficacy of OTES versus sham (Table 45 and Appendix D). Patients were excluded if they had undergone prophylactic treatment in the prior 2 months or had previous treatment with OTES. Acute medications use was permitted during the study period, but other methods of pain control or new preventive treatments were prohibited. At baseline, 46 percent of patients were overusing medications. Identical devices and procedures were used for both the real and the sham OTES, and treatment consisted of 30-minute sessions, three times per day for two consecutive weeks. Limited information on the timing of outcomes was provided, but it was assumed that data was collected at 1 and 2 months post-treatment. This trial was rated poor quality due to unclear randomization sequence, failure to control for dissimilar proportion of females between groups, and no

reporting of attrition (Appendix E). The focus of the trial was on allodonia, which was not of interest to this report.

Table 61. Chronic tension headache: physical modalities

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Bono, 2015[169] 1 month, 2 months Duration of pain: >2 years (mean NR) Poor	A. Occipital TES (n=54): Electro-stimulator generated biphasic impulses via electrodes placed on occipital region bilaterally; pulse width: 250 µs; frequency: 40 Hz; intensity 20 mA. B. Sham (n=29): Same device and procedure, but no current was delivered. Treatment protocol: 30 minute sessions 3 times daily for two consecutive weeks (42 sessions total)	A vs. B Age: 42 vs. 40 years Female: 81% vs. 66% Race: NR Headache frequency: mean 29.0 days/month Medication overuse: 43% vs. 52% Baseline MIDAS (0-21+): 63 vs. 50 Baseline VAS pain (0−10): 8 vs. 8	A vs. B <u>1 month</u> Patients who achieved >50% reduction in headache days: 85% vs. 7%; RR 12.4 (95% CI 3.2 to 47.3) <u>2 months</u> MIDAS: 16 vs. 51; difference −35.0 (95% CI −42.6 to −27.4) VAS pain (0−10): 3 vs. 8; difference −5.0 (95% CI −5.8 to −4.2) Proportion of patients still overusing medications: 7% vs. 48%; RR 0.15 (95% CI 0.06 to 0.42)	A vs. B <u>2 months</u> BDI-II: 7 vs. 8; difference −1.0 (95% CI −2.2 to 0.2) HAM-A: 6 vs. 7; difference −1.0 (95% CI −1.9 to −0.1)

BDI-II = Beck Depression Inventory-II; CI = confidence interval; HAM-A = Hamilton Anxiety Rating Scale; Hz = Hertz; mA = milliamps; MIDAS = Migraine Disability Assessment Questionnaire; NR = not reported; RR = risk ratio; SD = standard deviation; TES = transcutaneous electrical stimulation; VAS = visual analog scale; µs = microsecond

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

Physical Modalities Compared With Sham

There was insufficient data from one poor-quality trial to determine the short-term effects of OTES compared with sham.[169] OTES resulted in greater improvement in function at 2 months as measured by the Migraine Disability Assessment Questionnaire (difference −35.0, 95% CI −42.6 to −27.4, scale 0-21+) and in pain intensity as measured by VAS (difference −5.0 on a 0−10 scale, 95% CI −5.8 to −4.2) The proportion of patients who achieved a 50 percent or greater reduction in headache days also favored OTES (RR 12.4; 95% CI 3.2 to 47.3). Measures of depression and anxiety were both somewhat better following OTES compared with sham at 2 months, however, the between-group difference was only statistically significant for anxiety (Table 44). The proportion of patients overusing medications at 2 months was also significantly lower in the OTES group.

Physical Modalities Compared With Pharmacological Therapy or Biofeedback

No trial of physical modalities versus pharmacological therapy and versus biofeedback met inclusion criteria.

Harms

Authors report that neither adverse events nor side effects occurred in either the real or the sham OTES group in one poor-quality trial.[169]

Manual Therapies for Chronic Tension Headache

Key Points

- Spinal manipulation therapy, compared with usual care, was associated with small and moderate improvements, respectively, 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 to 100) and pain intensity (difference −1.4 on a 0-10 NRS scale, 95% CI −2.69 to −0.16) over the short term in one fair-quality trial (SOE: low). Approximately 25 percent of the patients had comorbid migraine.
- There is insufficient evidence from one poor-quality trial to determine the effects of spinal manipulation therapy on short-term pain compared with amitriptyline (SOE: insufficient).
- No longer-term outcomes were reported and no trials comparing physical modalities to pharmacological therapy or to biofeedback were identified that met inclusion criteria.
- No adverse events occurred in the trial comparing spinal manipulation to usual care, but significantly fewer adverse events were reported following manipulation versus amitriptyline in the other poor-quality trial (4.3% vs. 82.1%; RR 0.05, 95% CI 0.02 to 0.16). The risk of withdrawal due to adverse events was not significantly different (1.4% vs. 8.9%; RR 0.16, 95% CI 0.02 to 1.33). Common complaints were neck stiffness in the manipulation group and dry mouth, dizziness, and weight gain in the medication group (SOE: low).

Detailed Synthesis

Two trials (n=75 and n=126)[187,188] that evaluated spinal manipulation therapy (SMT) for the treatment of chronic tension headache met inclusion criteria (Table 46 and Appendix D). The majority of patients in both trials were female (61% to 78%) with mean ages ranging from 40 to 42 years and a mean headache duration of 13 years. Both trials included patients with comorbid migraine as long as their headache problem was determined by a physician to be predominantly tension-type in nature (this included 26% of patients in one trial,[187] proportion not reported in the other trial). In one trial, patients were specifically excluded if they met the criteria for medication overuse or if they had received manual therapy in the 2 months prior to enrollment.[187] At baseline, prophylactic medication use was common. Current or past use of other treatments was not reported.

One Dutch trial compared a maximum of nine, 30-minute sessions of SMT over 8 weeks with usual care (information, reassurance and advice, discussion of lifestyle changes, and analgesics or NSAIDs provided by a general practitioner).[187] The second trial, conducted in the United States, compared 12 SMT sessions of 20 minutes over a 6-week treatment period versus amitriptyline (maximum dose 30 mg/day).[188] Both trials reported only short-term outcomes. One trial was rated fair quality[187] and one poor quality[188] (Appendix E). Due to the nature of the interventions, blinding of patients and researchers was not possible. Additionally, the poor trial had a high rate of differential attrition (7% SMT and 27% amitriptyline).

Table 62. Chronic tension headache: manual therapies

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Boline, 1995[188] 1 month Duration of pain: 13.5 years Poor	A. Spinal Manipulative Therapy (n=70): short-lever, low-amplitude, high-velocity thrust techniques on cervical, thoracic or lumbar spinal segments. Moist heat and light massage preceded manipulation; 12, 20 minute sessions (2 per week for 6 weeks) B. Amitriptyline (n=56): dose titration of amitriptyline for 6 weeks. Nighttime, daily doses began at 10mg/day for first week, then increased to 20mg/day in the second, followed by 30mg/day in the third week and after; continued use of OTC medications as-needed.	A vs. B Age: 41 vs. 42 years Female: 54% vs. 70% Race: NR Baseline Daily headache intensity (0-20)[b]: 5.6 vs. 5.0 Baseline Weekly headache frequency (0-28)[c]: 12.4 vs. 10.8	A vs. B <u>1 month</u> Daily headache intensity[b]: adjusted means 3.8 vs. 5.2; difference 1.4 (95% CI 0.3, 2.3) Weekly headache frequency[c]: adjusted means 7.6 vs. 11.8; difference 4.2 (95% CI 1.9, 6.5)	A vs. B <u>1 month</u> SF-36 Function Health Status Global Score (% points): adjusted means 78.8 vs. 73.9; difference 4.9 (95% CI 0.4, 9.4) OTC medication usage: adjusted means 1.3 vs. 2.2; difference 0.9 (95% CI 0.3, 1.5)

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Castien, 2011[187] 4.5 months Duration of pain: 13 years Fair	A. Spinal Manipulation (n=38): combination of 3 approaches at the therapist discretion: mobilizations of the cervical and thoracic spine, craniocervical muscle exercises and posture correction; maximum of 9, 30-minute sessions over 2 months B. Usual Care (n=37): 2-3 general practitioner visits over 2 months	A vs. B Age, years: 40 vs. 40 years Female: 78% vs. 78% Race: NR Mean frequency of headache (days/month): 24 vs. 24 NSAID use: 29% (mean 3 pills/week); Analgesic use: 59% (mean 1.5 pills/week) Baseline HIT-6 (36-78): 62.6 vs. 61.2 Baseline HDI (0-100): 39.6 vs. 44.2 Baseline Pain intensity, NRS (0-10): 6.3 vs. 5.7	A vs. B <u>4.5 months</u> Proportion of patients with ≥50% reduction in headache frequency: 81.6% vs. 40.5%; RR 2.01 (95% CI 1.32 to 3.05) HIT-6, mean change from baseline: −10.6 vs. −5.5; difference 5.0 (95% CI −9.02 to −1.16) HDI, mean change from baseline: −20.0 vs. −9.9; difference −10.1 (95% CI −19.5 to −0.64) Headache frequency (days/14 days), mean change from baseline: −9.1 vs. −4.1; difference −4.9 (95% CI −6.95 to −2.98) Pain intensity mean change from baseline: −3.1 vs. −1.7; difference −1.4 (95% CI −2.69 to −0.16) Headache duration (hrs./day), mean change from baseline: −7.0 vs. −3.5; difference −3.5 (95% CI −7.71 to −0.63)	A vs. B <u>4.5 months</u> Resource use, proportion who used: ≥1 sick leave day: 7.9% vs. 32.4%; RR 0.23 (95% CI 0.07 to 0.79) Any additional healthcare: 13.2% vs. 59.4%; RR 0.22 (95% CI 0.09 to 0.52) Additional physical therapy: 2.6% vs. 40.5%; RR 0.06 (95% CI 0.01 to 0.47) Additional medical specialist care: 2.6% vs. 16.2%; RR 0.16 (95% CI 0.02 to 1.28) Additional "other" healthcare": 7.8% vs. 2.7%; RR 2.9 (95% CI 0.3 to 26.8)

CI = confidence interval; HDI = Headache Disability Index; HIT-6 = Headache Impact Test-6; mg = milligram; NR = not reported; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drugs OTC = over-the-counter; RR = risk ratio; SF-36 = Short-Form-36 Questionnaire

[a] Unless otherwise noted, followup time is calculated from the end of the treatment period

[b] Headache intensity was calculated as the total ratings per period and divided by the number of days per period

[c] Headache frequency was calculated by summing all headache ratings 2 and above for the month

Manual Therapies Compared With Usual Care

Only short-term data from one fair-quality trial were reported. SMT resulted in small to moderate improvements in function compared with usual care at 4.5 months post-treatment as measured by the Headache Disability Inventory (HDI, scale 0 to 100) and the Headache Impact Test (HIT-6, scale 36 to 78), respectively (difference between groups in change scores from baseline, −10.1, 95% CI −19.5 to −0.64 and −5.0, 95% CI −9.02 to −1.16).[187] Regarding pain outcomes, twice as many patients who received SMT experienced a ≥50% reduction from baseline in the number of headache days (per 2 weeks) compared with usual care: 81.6% versus 40.5%; RR 2.0 (95% CI 1.3, 3.0).[187] Similarly, a statistically greater reduction in the number of headache days (difference between groups in change scores from baseline, −4.9; 95% CI −6.95 to −2.98) and in headache pain intensity (difference in change scores from baseline, −1.4 on a 0 to 10 NRS scale, 95% CI −2.69 to −0.16) was seen following SMT. Given that 29 percent of SMT patients and 22 percent of usual care patients had comorbid migraine, it is unclear how the coexistence of these headache types may have affected the outcome.

The proportion of patients who used any additional healthcare services (e.g., physical therapy, medical specialists, other) was statistically lower in the SMT group compared with the

usual care group (Table 45).[187] Authors report no statistically significant differences between treatments in analgesic or NSAID use; data were not provided.

Manual Therapies Compared With Pharmacological Therapy

The evidence was insufficient from one poor-quality trial to determine the effects of spinal manipulation compared with amitriptyline over the short term.[188] The spinal manipulation group showed more improvement compared with the amitriptyline group in daily headache intensity (adjusted difference −1.4, 95% CI −2.3 to −0.3), weekly headache frequency (adjusted difference −4.2, 95% CI −6.5 to −1.9), Short Form-36 Function score (adjusted difference 4.9, 95% CI 0.4 to 9.4), and over-the-counter medication use (difference −0.9, 95% CI −1.5 to −0.3) at 1 month. Attrition in the amitriptyline group was 27 percent, compared with 7 percent in the manipulation group.

Manual Therapies Compared With Biofeedback

No trial of physical modalities versus biofeedback met inclusion criteria.

Harms

No adverse events occurred in the trial comparing spinal manipulation to usual care.[187] The other poor-quality trial reported significantly fewer adverse events following spinal manipulation compared with amitriptyline (4.3% vs. 82.1%; RR 0.05, 95% CI 0.02 to 0.16) but the risk of withdrawal due to adverse events was not significantly different (1.4% vs. 8.9%; RR 0.16, 95% CI 0.02 to 1.33).[188] Patients in the manipulation group complained of neck stiffness which resolved in all cases and common side effects in the amitriptyline group included dry mouth, drowsiness, and weight gain.

Acupuncture for Chronic Tension Headache

Key Points

- There is insufficient evidence from two poor quality trials to determine the effects of Traditional Chinese needle acupuncture on short-term (2 trials), intermediate-term (1 trial), or long-term (1 trial) pain compared with sham acupuncture (SOE: insufficient).
- Laser acupuncture was associated with a small 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 fair-quality trial (SOE: low).
- No trials comparing acupuncture to pharmacological therapy or to biofeedback were identified that met inclusion criteria.
- The fair-quality trial evaluating laser acupuncture reported that no adverse events occurred in either group (SOE: low).

Detailed Synthesis

Three small trials (N=30 to 50; total sample=119)[251-253] that evaluated acupuncture versus sham treatment for chronic tension headaches met inclusion criteria (Table 47 and Appendix D). Two trials employed traditional Chinese needle acupuncture,[252,253] while one used low-energy laser acupuncture.[251] The number of acupoints ranged from 6 to 10 across studies. The duration of treatment ranged from 5 to 10 weeks, with the total number of sessions ranging from 8 to 10

(20 to 30 minutes duration, 1 to 3 times per week). Sham treatment consisted of irrelevant acupuncture (superficial needle insertion in areas without acupuncture points) and sham acupuncture (blunt needle that simulates puncturing of the skin, laser power output set to zero).

Across trials, participants were primarily female (49% to 87%), mean ages ranged from 33 to 49 years, and headache frequency from 18 to 27 days per month. Two trials specifically excluded patients with other causes of chronic headache[251,252]; the third trial did not note if any of the patients had concomitant headaches.[253] One trial required patients to abstain from all other prophylactic therapies (with the exception of rescue analgesics),[253] and one trial excluded patients who had received any treatment for their headache in the 2 weeks prior to enrollment.[251] Concomitant (nonnarcotic) medication was permitted in two trials,[252,253] the third stated that no patient took concomitant analgesics.[251] All trials assessed outcomes over the short term; one trial additionally provided intermediate- and long-term data.[253]

One trial was rated fair quality[251] and two poor quality[252,253] (Appendix E). In all three trials, random sequence generation and concealment of allocation were not clearly reported and the care providers were not blinded to treatment. Additional methodological concerns in the poor quality trials included unclear application of intention-to-treat methods, and failure to control for disproportionate baseline characteristics or to account for loss to followup in one trial each.

Table 63. Chronic tension headache: acupuncture

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Ebneshahidi, 2005[251] 3 months Duration of pain: NR Fair	A. Low-Energy Laser Acupuncture (n=25): 4 acupoints (two local and two distal), bilaterally (8 total): intensity 1.3J, output 100%, continuous mode, using vertical contact with pressure and a duration of 43 seconds. B. Sham Laser Acupuncture (n=25): Identical procedure to real electroacupuncture except power output set to 0 Treatment Protocol: 3 sessions per week for a total of 10 sessions (session length: NR)	A vs. B Age: 33 vs. 39 years Female: 80% vs. 80% Race: NR Baseline Number of headache days per month (0-28), median: 20 vs. 18 Baseline Pain intensity on VAS (0-10), median: 10 vs. 10 Baseline Duration of attacks, (hours), median: 10 vs. 8	A vs. B <u>3 months</u> Headache Days/Month, median change from baseline: −8 vs. 0, p<0.001 Headache Intensity (VAS), median change from baseline: −2 vs. 0, p<0.001 Duration of attacks (hours), median change from baseline: −4 vs. 0, p<0.001	NR

Author, Year, Followup,[a] Pain Duration, Study Quality	Intervention	Population	Function and Pain Outcomes	Other Outcomes
Karst, 2000[252] 1.5 months Duration of pain: NR Poor	A. Acupuncture (n=21) Traditional Chinese acupuncture; maximum of 15 needles, 10 acupoints B. Sham Acupuncture (n=18): blunt placebo needles and elastic foam were used to simulate puncturing and shield needle type. Treatment Protocol: 30-minute sessions twice weekly for 5 weeks (10 sessions total)	A vs. B Age: 50 vs. 47 years Female: 38% vs. 61% Race: NR Headache frequency: 27 vs. 27 days/month VAS (0-10): 6.2 vs. 6.3 Analgesic Intake/Month: 8.3 vs. 10.2	A vs. B <u>1.5 months</u> Frequency of headache attacks/month: 22.1 vs. 22.0; difference 0.1 (95% CI −6.6 to 6.8) Headache Severity, VAS: 4.0 vs. 3.9; difference 0.1 (95% CI −11.9 to 12.1)	A vs. B <u>1.5 months</u> Analgesic Intake/Month: 13.7 vs. 21.2; difference −7.5 (95% CI −22.2 to 7.2)
Tavola, 1992[253] 1, 6, 12 months Duration of pain: 8 years Poor	A. Acupuncture (n=15): Traditional Chinese acupuncture; 6-10 acupoints chosen on an individual basis; insertion depth 10-20 mm; needles were left in place without the use of any manual or electrical stimulation B. Sham Acupuncture (n=15): same number of needles, inserted more superficially (depth 2-4 mm), in the same region used in real acupuncture group but in areas without acupuncture points Treatment Protocol: 20-minute sessions once per week for 8 weeks (8 sessions total)	A vs. B Age: 33 vs. 33 years Female: 87% vs. 87% Mean frequency of headache attacks per month: 18 vs. 17 Mean analgesic use: 12 vs. 12 units/month Mean HI (intensity X duration X frequency/30): 4.3 vs. 4.5 Mean duration of attacks (sum of the hours of headache in a month/number of attacks): 3.3 vs. 4.4	A vs. B <u>1 month</u> Responders, ≥33% improvement in HI: 86.7% vs. 60.0%; RR 1.44 (95% CI 0.91 to 2.28) Responders, ≥50% improvement in HI: 53.3% vs. 46.7%; RR 1.14 (95% CI 0.56 to 2.35) HI, mean[b]: 2.4 vs. 3.0; difference −0.60 (95% CI −6.12 to 4.92) Mean decrease in HI from baseline: 58.3% vs. 27.8% Mean decrease in headache attack frequency from baseline: 44.3% vs. 21.4% <u>6 months</u> HI, mean[b]: 2.2 vs. 3.1; difference −0.90 (95% CI −7.15 to 5.35), <u>12 months</u> Responders, ≥33% improvement in HI: 53.3% vs. 46.7%; RR 1.14 (95% CI 0.56 to 2.35) Responders, ≥50% improvement in HI: 40.0% vs. 26.7%; RR 1.50 (95% CI 0.53 to 4.26) HI, mean[b]: 3.2 (2.1) vs. 3.7 (2.2); difference −0.50 (95% CI −6.73 to 5.73)	A vs. B <u>1 month</u> Mean decrease in analgesic consumption from baseline: 57.7% vs. 21.7%

CI = confidence interval; HI = headache index; J = joule; NR = not reported; RR = risk ratio; VAS = visual analog scale
[a] Unless otherwise noted, followup time is calculated from the end of the treatment period
[b] Means and standard error of the means (not shown) estimated from graphs.

Acupuncture Compared With Sham

None of the trials reported on function. All three trials reported pain outcomes, although the specific measures varied across the trials. The results were mixed depending on the type of acupuncture used. No significant differences were found between needle acupuncture and sham

for any pain outcome evaluated during the short term in two small poor-quality trials,[252,253] or at intermediate and long-term followup in one of these trials[253] (Table 46). In the third small fair-quality trial,[251] laser acupuncture resulted in a significant reduction in the number of headache days per month (median −8, interquartile range [IQR] 21.5), in pain intensity on a 0 to 10 VAS scale (median −2, IQR 6.3), and in the duration of attacks (median −4 hours, IQR 7.5) over the short term compared with the sham group, which reported no improvement from baseline on any outcome at the 3-month followup ($p<0.001$ for all). Substantial heterogeneity ($I^2=91\%$) precluded meaningful pooling for this outcome (Figure 58).

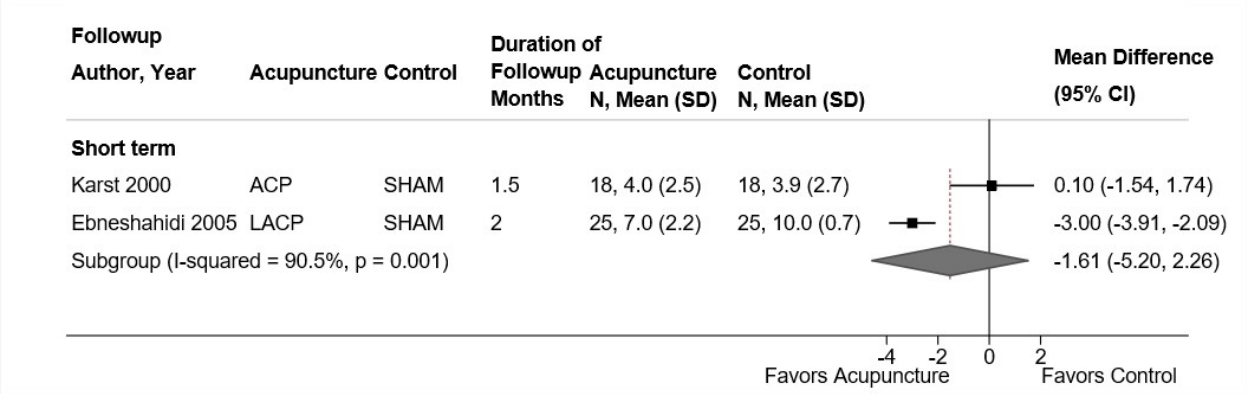
Acupuncture Compared With Pharmacological Therapy or Biofeedback

No trial of acupuncture versus pharmacological therapy and versus biofeedback met inclusion criteria.

Harms

Harms were generally not reported. The trial evaluating laser acupuncture reported that no adverse events occurred in either group.[251]

Figure 58. Acupuncture versus sham for chronic tension headache: effects on pain



ACP = standard needle acupuncture; CI = confidence interval; LACP = laser acupuncture; SD = standard deviation; WMD = weighted mean difference

Key Question 6: Differential Efficacy

RCTs that stratified on patient characteristics of interest, permitting evaluation of factors that might modify the effect of treatment, were considered for inclusion. Factors included age, sex, presence of comorbidities (e.g., emotional or mood disorders) and degree of nociplasticity/central sensitization. If a comparison is not listed below there was either no evidence identified that met the inclusion criteria or the included trials did not provide information on differential efficacy or harms. Studies likely had insufficient sample size to evaluate differential efficacy or harms, and evidence was considered insufficient.

Osteoarthritis Knee Pain

Key Point

- There is insufficient evidence from one fair-quality trial (across 3 publications) that age, sex, race, BMI, baseline disability, pain, or depression status modify the effects of exercise in patients with OA of the knee. Sample sizes in the subgroup analyses from the Fitness, Arthritis and Seniors Trial (FAST) were likely inadequate to effectively test for modification.

Exercise Compared With Attention Control

One fair-quality trial (n=439) reported across three publications of the FAST[51,57,58] included in Key Question 3 compared muscle performance (i.e., resistance training) and aerobic exercise programs to an attention control and formally evaluated factors that may modify treatment in patients with OA of the knee. Details regarding these study populations are available in the Results section for Key Question 3 and in Appendix D. Two of the reports performed formal tests for interaction; none of the demographic or clinical variables evaluated were found to modify the effect of either type of exercise.[57,58] One trial explored whether age, sex, race, BMI, baseline disability, or baseline pain modified the effects of exercise on function based on ADL disability measures in a subgroup of patients who were free of ADL disability upon enrollment; however, no data were provided for evaluation.[57] A second publication looked at whether the effects of exercise on pain, disability, and depression were modified by baseline depression status, that is, high versus low depressive symptomology according to the Center for Epidemiologic Studies Depression scale over time (using an adjusted repeated measures analysis of variance). However, the authors do not provide results that directly examined modification by baseline depression without the time component.[58] The third FAST publication stratified on age, sex, race, and BMI and did not perform a formal statistical test for interaction.[51] Upon visual inspection, the point estimates across groups and strata are similar, suggesting that the effect of exercise on physical disability and knee pain was not modified by any patient characteristic evaluated.

Osteoarthritis Hip Pain

Key Point

- There is insufficient evidence from one fair-quality trial that age, sex, baseline pain, and the presence of radiographic OA modify the effects of exercise in patients with OA of the hip. Study authors only reported on effects that include evaluation of these factors over time. Sample size was likely inadequate to effectively test for modification.

Exercise Compared With Usual Care

One fair-quality trial (n=203) included for Key Question 3 compared combination exercise therapy (strengthening, stretching, and endurance exercises) to usual care and stratified on age, sex, race, and BMI, but it did not formally test for interaction.[74] Details regarding this study population are available in the Results section for Key Question 3 and in Appendix D. Age, sex, education, self-reported knee OA, and baseline pain and Kellgren & Lawrence radiographic OA scores were defined *a priori* as subgroups of interest. Although older patients (age ≥65 years), women, patients with a lower NRS pain score at baseline, and patients with radiographic OA

showed somewhat larger effects of exercise therapy on function and pain, data were not systematically reported and, based on the data provided, overlapping confidence intervals suggest that the effect of exercise was not modified by any of these variables.

Fibromyalgia

Key Point

- There was insufficient evidence from one poor-quality trial that baseline BMI (normal, overweight, obese) modifies the effects of multidisciplinary rehabilitation in patients with fibromyalgia. Study authors only report on effects that include evaluation of these factors over time. Sample size was likely inadequate to effectively test for modification.

Multidisciplinary Rehabilitation Compared With Usual Care

An additional publication (n=130)[264] of a poor-quality trial[263] included for Key Question 4 that compared multidisciplinary rehabilitation to usual care assessed potential modification of treatment based on baseline BMI (normal, overweight, obese). No significant interactions were found for the effect of BMI on exercise over time for any pain or function measure evaluated; however, the authors do not provide results that exclude effects of time. Details regarding this study population are available in the section on efficacy and in Appendix D.

Discussion

Key Findings and Strength of Evidence

This report updates the prior 2018 Agency for Healthcare Research and Quality (AHRQ) report. The key findings of this review, including strength of evidence (SOE) ratings, are summarized for each chronic pain condition in Tables 48-63 and reflect the totality of evidence from the 2018 review combined with new evidence from this update (interventions and comparators with no evidence for either function or pain outcomes are not shown). Changes to effect size or SOE based on integration of new trials with the 2018 evidence base are footnoted in the tables. Domains used to determine the overall SOE are shown in Appendix G. All outcomes were considered direct. The SOE was low or insufficient for many interventions and was limited by small numbers of trials for specific comparisons and for our specified time frames, particularly for long term. We focused on evaluating the persistence of effects for therapies 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 effects for long-term outcomes; 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 with very few trials employing pharmacological treatments or exercise as comparators; only three new trials of interventions versus active comparators were 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 the 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 intervention on opioid use. In our concurrent review on opioid medications for chronic pain management, opioids were associated with small effects on pain and function during treatment compared with placebo (effects would not be expected to persist) but evidence is primarily from short-term (≤3 month) trials.[13,19,28,284] There were no differences in pain, function or other outcomes for opioid compared with nonopioid medications.

Harms were poorly reported across interventions and reported harms varied in scope and specification. No serious intervention-related adverse events (e.g., leading to death, disability or requiring intensive medical attention) were identified; reported adverse events were generally minor (e.g., muscle soreness or increased pain with exercise, bruising or discomfort 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 randomized controlled trials [RCTs]) or acupuncture versus sham, placebo, or usual care (neck pain, 6 RCTs; knee osteoarthritis, 9 RCTs; fibromyalgia, 4 RCTs). Evidence was low or insufficient for other adverse events. Table 64 summarizes reported adverse events for each intervention.

Table 64. Chronic low back 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[b] ++	none +	none +	moderate[c] +	small +	moderate +
Psychological Therapies: CBT Primarily	small ++	small ++	small ++	small ++	small ++	small ++
Physical Modalities: Short-Wave Diathermy	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
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 +

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 65. 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
Psychological Therapies: Operant Therapy	no evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence
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 66. Chronic neck 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	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
Physical Modalities: Traction, Electromagnetic field	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
Manual Therapies: Massage	small[b] +	none +	no evidence	moderate[c] +	no evidence	no evidence

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

Table 67. Chronic neck pain: 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: Versus NSAIDs + Muscle Relaxants	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence
Exercise (Pilates): Versus Acetaminophen[b]	small +	no evidence	no evidence	large +	no evidence	no evidence
Acupuncture: Versus NSAIDs	insufficient evidence	no evidence	no evidence	insufficient 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; NSAIDs = nonsteroidal anti-inflammatory drugs; 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. Due to differences in the types of drugs used, the two trials comparing exercise with pharmacological treatments were not amenable to pooling.

Table 68. 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
Mind-Body Practices: Qigong	no evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient 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 69. 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: Microwave Diathermy	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
Physical Modalities: Pulsed Short-Wave Diathermy	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence	insufficient evidence
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: Low-Level Laser Therapy	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence
Physical Modalities: Electromagnetic Field	none +	no evidence	no evidence	none +	no evidence	no evidence

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: Superficial Heat	no evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
Physical Modalities: Braces	no evidence	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence	no evidence
Manual Therapies: Joint Manipulation	no evidence	insufficient evidence	no evidence	no evidence	no evidence	no evidence
Manual Therapies: Massage	no evidence	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence
Mind-Body Practices: Tai Chi	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient 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 report.
[c] Effect size downgraded one level from prior report.

Table 70. Osteoarthritis knee pain: 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 71. Osteoarthritis knee 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: Pain Coping	none +	none +	no evidence	none +	none +	no evidence
Manual Therapies: Joint Manipulation	no evidence	insufficient evidence	no evidence	no evidence	no evidence	no evidence
Acupuncture	insufficient evidence	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; SOE = strength of evidence

Table 72. Osteoarthritis hip 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	small +	small +	insufficient evidence	small +	none +	insufficient evidence
Manual Therapies	no evidence	insufficient 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; SOE = strength of evidence

Table 73. Osteoarthritis hip 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
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 74. Osteoarthritis hand 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	insufficient evidence	no evidence	no evidence	no evidence	no evidence	no evidence
Physical Modalities: Low-Level Laser Therapy	none +	no evidence	no evidence	none +	no evidence	no evidence
Physical Modalities: Heat Therapy	insufficient evidence	no evidence	no evidence	no evidence	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 75. Fibromyalgia: 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 ++	none ++	none ++
Psychological Therapies: CBT	none[b] +	moderate[c] +	insufficient evidence	small[d] +	small[c] +	insufficient evidence
Psychological Therapies: Biofeedback, Imagery	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence	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

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
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 76. Fibromyalgia: effects of psychological therapies 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: Versus Paroxetine	no evidence	no evidence	no evidence	no evidence	insufficient evidence	no evidence
CBT Plus Amitriptyline: Versus Amitriptyline	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
Biofeedback: Versus Escitalopram	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
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 77. 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
Psychological Therapy: CBT, Biofeedback, Relaxation	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence	insufficient evidence
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
CBT = cognitive-behavioral therapy; 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 78. 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
Psychological Therapies: CBT Plus Relaxation	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence
Psychological Therapies: Relaxation Only	no evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
Physical Modalities: OTES	insufficient evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence
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
CBT = cognitive-behavioral therapy; OTES = occipital transcutaneous electrical stimulation; SOE = strength of evidence

Table 79. Chronic tension headache: 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
Psychological Therapies: CBT	insufficient evidence	insufficient evidence	no evidence	insufficient evidence	insufficient evidence	no evidence
Manual Therapies: Manipulation	no evidence	no evidence	no evidence	insufficient evidence	no evidence	no evidence

Short-Term: 1 to <6 months; Intermediate-Term: ≥6 to <12 months; Long-Term: ≥12 months
CBT = cognitive-behavioral therapy; SOE = strength of evidence

Table 80. Overview of reported treatment-related adverse events/harms from included trials

Intervention	Reported Adverse Events
Exercise vs. usual care, waitlist, no treatment, attention control, sham treatment, acetaminophen, standard analgesics and anti-inflammatory therapy.	No statistical differences between exercise and any comparator were identified for any condition. One RCT in older patients with knee OA pain reported six SAEs; five were in the exercise group [4 falls (1 resulting in distal radius fracture); 1 foot fracture from dropping a dumbbell]. Sudden death was reported in one attention control participant. No other intervention-related SAEs requiring medical intervention were reported across trials of exercise for LBP, neck pain, OA pain or FM. Reported AEs included minor and/or temporary increases in pain with exercise ranging from 3% to 22% versus 0% to 3% for comparators. Withdrawal for worsening pain ranged between 3% and 10% compared with 0% in usual care or no treatment groups.
Psychological therapies vs. usual care, waitlist, no treatment, attention control, exercise	No intervention-related SAEs requiring medical intervention were reported for psychological therapies vs. usual care, waitlist or attention control for LBP, knee OA pain, or CTTH. Harms were not reported in neck pain trials. Withdrawal due to an AE (claim that physiotherapist hurt participant or participant did not benefit) was similar for psychological therapies versus usual care (0.2% vs. 0.4%, 1 in each group) in one LBP trial. For CTTH, withdrawal and risk of intervention-related AEs (not specified) was 2% in one small trial. For FM, AEs were more commonly reported in control groups (attention control, waitlist, usual care, pregabalin with duloxetine and exercise). Intervention-specific withdrawal due to depression (2 patients) was reported in one trial; another reported brief, occasional exacerbation of symptoms (pain, sleep problems). Most trials reported that there were no AEs.
Ultrasound vs. sham ultrasound **Interferential therapy** vs. sham	For LBP, risk of SAEs (not defined, not considered to be intervention related) was similar for ultrasound and sham [3 patients (1.3%) vs. 6 patients (2.7%), respectively] as was risk of any AE (6.0% vs. 5.9%) in one trial. No AEs were identified across trials in knee OA pain. In one trial of interferential therapy, withdrawal due to any AE (not defined) was similar (4% in each group).
Low-level laser therapy vs. sham or exercise	No AEs were reported vs. sham or exercise in LBP patients or vs. sham in knee OA patients. Erythema was experienced by one patient with hand OA. In patients with neck pain, in one trial, AEs in the intervention group included mild (78%) or moderate (60%) increased neck pain, increased pain elsewhere (78%), mild headache (60%) and tiredness (24%).
Diathermy vs. sham **Electromagnetic field** vs. sham	For knee OA, two cases of transient symptom aggravation with microwave diathermy were reported (1 RCT) and 24 patients reported throbbing sensation or warming sensations or aggravation of pain with electromagnetic field treatment (1 RCT).

Intervention	Reported Adverse Events
Spinal manipulation vs. Usual care, attention control, placebo, exercise or pharmacological treatment	For LBP, no SAEs or withdrawal due to AEs (not defined) were observed (10 RCTs); primary nonserious AEs reported included mild to moderate increase in pain, local discomfort and tiredness (2 RCTs). For CTTH, temporary neck stiffness occurred; 1.4% of patients withdrew from the manipulation group vs. 8.9% from the amitriptyline group in one trial.
Massage vs. sham, usual care, attention control, exercise	No serious intervention-related adverse events requiring medical intervention were reported with massage for LBP, neck pain, OA pain or FM. Nonserious AEs included discomfort, aching muscles, headache, and tenderness; reports of increased pain ranged from <1% to 26% for LBP.
MBSR vs. usual care	For LBP in one trial, 29% of MBSR patients reported temporarily increased pain.
Mindbody practices (yoga, tai chi, Qigong) vs. usual care, attention control, waitlist, exercise	For LBP, three SAEs were reported in one yoga patient each: cellulitis and a herniated disc in one RCT (0.8% for both, unclear if these were treatment-related) and severe back pain possibly or probably related to yoga in another RCT (1%). No trial of neck pain, knee OA pain or FM reported SAEs due to mindbody practices in their populations. Nonserious AEs reported across studies: for LBP, range 7% to 16% across four RCTs of yoga or Qigong, mostly related to increased back/joint pain, muscle soreness or dizziness; for neck pain, knee injury and muscle spasms (0.6%; one case each) in one RCT of Alexander Technique and an event risk of 0.27 in one RCT of body awareness therapy (primarily due to increased pain); for knee OA pain, mild muscle soreness and foot or knee pain was reported with tai chi in one RCT (no data provided); and for FM, mild to moderate treatment-related AEs occurred in 4% (tai chi) and 5% (Qigong) of patients in 2 RCTs; shoulder pain, plantar fasciitis were specified others were not.
Acupuncture vs. sham, usual care, attention control, placebo, pharmacological therapy	Treatment-related SAEs were rare (across 5 LBP, 5 neck pain, 4 FM, 1 knee OA, and 1 CTTH trial); only one event (needle insertion site pain lasting1 month) in a LBP patient (<1%) in one trial was considered related to treatment, SAEs not considered to be related to acupuncture or the study conditions (range 0% to 9% across 5 LBP, 5 neck pain, 4 FM, 1 knee OA, and 1 CTTH trial). These included hospitalization (primarily) or outpatient treatment; reasons were not specified. The most commonly reported nonserious AEs: swelling, bruising, bleeding or pain at the acupuncture site (1% to 61%, 12 RCTs; or 1% to 18% excluding an outlier trial)); numbness, discomfort, pain or increase in symptoms (1% to 14%; 11 RCTs), dizziness, nausea, fainting (1% to 7%, 7 RCTs), headache (1% to 2%; 4 RCTs), vasovagal symptoms (1% to 4%; 2 RCTs), respiratory problems, chest discomfort (1%; 2 neck pain RCTs), and infection at needle insertion site [1%; 1 RCT (knee OA)]
MDR vs. usual care, waitlist, exercise pharmacological therapy	No intervention-related SAEs requiring medical intervention were reported. Specified nonserious AEs included transient worsening of pain (3 patients) including one report of a painful swollen hand after a treatment session and mood alteration (2 patients). One trial reported that 19% of MDR recipients with FM withdrew with two patients attributing withdrawal to increased pain.

AE = adverse event; CTTH = chronic tension-type headache; FM = fibromyalgia; LBP = low back pain; MBSR = mindfulness-based stress reduction; MDR = multidisciplinary rehabilitation; OA = osteoarthritis; RCT = randomized controlled trial; SAE = serious adverse event.

The findings below reflect integration of trials from the prior report (2018) with new trials for this update. Changes to SOE and/or effect size based on inclusion new trials are footnoted in the tables.

Low Back Pain. For chronic low back pain (LBP), compared with usual care, attention control, sham, or placebo, there was moderate evidence of small improvement in function, at least in the short term, for exercise, massage, psychological therapies (cognitive-behavioral therapy [CBT]) and moderate improvement with yoga (SOE: moderate). There was low evidence of small

functional improvement for acupuncture, low-level laser therapy, spinal manipulation, and multidisciplinary rehabilitation (MDR) (SOE: low). With the exception of spinal manipulation, these interventions also showed small improvement (acupuncture, massage, psychological therapies, MDR; SOE: low) or moderate improvements (exercise, yoga, low-level laser therapy, SOE: low) in pain short term. Interferential therapy did not improve function or pain short term (SOE: low). The small improvements in function compared with controls were sustained into the intermediate term for yoga, spinal manipulation, psychological therapies, and MDR, with low strength of evidence for all but the psychological therapies, for which SOE was moderate. No clear improvement in function was seen at intermediate term for exercise, acupuncture, massage or low-level laser therapy (SOE: low for all).

Improvements in pain were seen in the intermediate term for exercise, yoga and mindfulness-based stress reduction (MBSR) (small effects, SOE: low for all) as well as spinal manipulation, psychological therapies and MDR (small effects, SOE: moderate). Long-term evidence was available for four intervention categories: psychological therapies, MDR, exercise, and acupuncture. The strongest evidence was for psychological therapies (CBT primarily), which were associated with small improvements versus usual care or attention control in both function and pain at short, intermediate, and long term (SOE: moderate for all time frames). Neither exercise nor acupuncture was associated with improved function long term, even though both demonstrated continued pain improvement (SOE: low for all). For MDR, effects on function from earlier time frames were not sustained in the long term versus usual care (SOE: low). High intensity MDR (≥20 hours/week or >80 hours total) was not clearly better than nonhigh intensity programs. Short-term effects on function and pain were somewhat larger with high intensity MDR than with nonhigh intensity interventions but the tests for interaction were not statistically significant. At intermediate term, estimates were similar for high intensity and nonhigh intensity programs.

In people with chronic LBP, there were no clear differences in short-term function for comparisons of qigong, yoga, or spinal manipulation with exercise even though small improvements in pain were seen for yoga (SOE: low for all). MDR was associated with small effects on function short term as well as pain (SOE: moderate). For Qigong, results for intermediate-term function and short-term pain slightly favored exercise (SOE: low for all). Again, MDR was associated with small improvements in function and pain at intermediate term (SOE: moderate), but this was not sustained in the long term (SOE: low). Long-term data were only available for MDR.

Neck Pain. For chronic neck pain, in the short term, moderate effects on function and pain were seen for low-level laser therapy (SOE: moderate). Massage conferred a small improvement in function and moderate improvement in pain short term; the functional improvement did not persist into intermediate term (SOE: low for all). In the short term and intermediate term, acupuncture and Alexander Technique were associated with a small improvement in function compared with usual care (both interventions), sham acupuncture or sham laser (SOE: low). The effect of acupuncture was not sustained long term (SOE: low) compared with sham acupuncture, sham laser, or usual care, and no improvement in pain was seen at any time frame (SOE: low). There were no clear improvements in function or pain at short or intermediate term across types of exercise or for psychological therapies (physical therapist–led relaxation training alone) compared with usual care, sham procedures, or attention controls (SOE: low for all). A small improvement in function was associated with exercise long term versus attention control (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 small benefit in function and pain versus waitlist or attention control over the short term. Exercise (Pilates) was associated with a small functional improvement and large improvement in pain short term compared with acetaminophen (SOE: low).

Knee Osteoarthritis Pain. For knee osteoarthritis (OA), exercise was associated with small functional improvement in the short term compared with usual care, attention control, or sham procedure; the effect size was small for exercise (SOE: moderate). The small effects of exercise on function persisted into the intermediate term as moderate but were small at long term (SOE: low for both). A similar pattern for improvement in pain was observed; small effect (SOE: moderate) at short term, moderate at intermediate term and small at long term (SOE: low for intermediate and long term.) There were no clear benefits to ultrasound at short or intermediate term (SOE: low). With the exception of a small improvement in short term pain, no clear differences between psychological interventions (pain coping skills training, CBT) and usual care were observed (SOE low). There were no clear differences in function or pain associated with electromagnetic fields (short-term, SOE: low), or with acupuncture at short (SOE: moderate) or intermediate term (SOE: low) versus usual care, attention control, or sham procedure. There was no difference in function or pain between pain coping skills training and exercise at short term or intermediate term in one trial (SOE: low). There was no intermediate term improvement in function or pain with exercise versus acetaminophen and nonsteroidal anti-inflammatory drugs (SOE: low).

Hip and Hand Osteoarthritis Pain. Evidence was sparse on interventions for hip and hand OA. Exercise was associated with small improvements in function compared with usual care at short and intermediate-term (SOE: low), but data were insufficient to determine long-term effects. For pain, a small effect was seen only at short term; no differences were seen at the other time points (SOE: low for short term and intermediate term, insufficient for long term). Compared with exercise, a small effect on function was seen with manual therapy in the short and intermediate term, and small improvement in pain short term (SOE: low for all). For hand OA, no clear differences were seen for low-level laser therapy versus sham or for MDR versus waitlist control at short term for either function or pain (SOE: low).

Fibromyalgia. Short term, in patients with fibromyalgia (FM), there was low-quality evidence of small improvements in function were associated with exercise, MDR, and mind-body practices of tai chi and qigong (SOE: low for all) compared with wait list and attention control, and moderate-quality evidence with acupuncture compared with sham acupuncture (SOE: moderate). Small improvements in short-term pain were seen with exercise (SOE: moderate) and CBT (SOE: low) and moderate improvements with mind body practices (SOE: low), but not with acupuncture. No clear differences in function or pain outcomes were seen for mindfulness practices short term (SOE: moderate), but small improvements in both were noted at intermediate term (SOE: low). Intermediate term, small improvements in function continued for acupuncture and exercise (SOE: moderate). CBT was associated with moderate functional improvement (SOE: low) and small improvements were seen for mindfulness practices, myofascial release massage and MDR; there was no clear effect of magnetic mattress pads versus sham pad (SOE: low for all). Small improvements in pain intermediate term were seen for mindfulness practices and MDR (SOE: low) and for exercise (SOE: moderate), but not for CBT, acupuncture, or magnetic mattress pads (SOE: low). Long term, small improvements in function

continued for MDR but not for massage (SOE: low); while massage conferred a small improvement in pain long term, MDR did not (SOE: low). There was no clear long-term impact on function or pain for exercise (SOE: moderate). No clear differences were seen between MDR and exercise for the long term on function or pain (SOE: low). Tai chi was associated improved function compared with exercise at short and intermediate terms but this did not persist long term (SOE: low). CBT was associated with a small benefit for function but not for pain compared with pregabalin at intermediate term (SOE: low).

Chronic Tension Headache. Only nine trials of nonpharmacological treatments for chronic tension headache met the inclusion criteria and all but one was considered poor quality, resulting in a rating of insufficient evidence for comparisons of psychological therapies with waitlist or attention control, electrical stimulation versus sham, and acupuncture versus sham. One fair-quality trial of laser acupuncture versus sham suggested moderate improvement in pain short term (SOE: low), and another fair-quality trial of spinal manipulation versus usual care suggested a small effect on short-term function based on the Headache Impact Test (SOE: low). Approximately 25 percent of the patients in the trial had comorbid migraine headache.

Usual Care/Waitlist and Nonactive Comparators. For comparisons involving usual care/waitlist or nonactive comparators (placebo, sham, attention control), there were some differences depending on the specific comparator evaluated. For some interventions results different by control type. For example, in some analyses, acupuncture was associated with greater effects on pain in patients with chronic low back pain or OA when compared with usual care than when compared with sham acupuncture, suggesting that much of the benefit may be due to placebo or other nonspecific effect.

Harms. Harms were poorly reported across interventions. No serious intervention-related adverse events (e.g., death, disability or those requiring intensive medical attention were identified; reported adverse events were generally minor (e.g., muscle soreness 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 spinal manipulation versus exercise (LBP, 7 RCTs) or acupuncture versus sham, placebo, usual care (neck pain, 6 RCTs; knee OA, 9 RCTs; FM, 4 RCTs). Evidence across some conditions and interventions was insufficient to draw meaningful conclusions regarding harms and adverse events. Table 64 above provides an overview of treatment-related adverse events reported in included trials. Many trials stated that there were no adverse events. Adverse events were not always well-defined or described. Detailed information on reported events is contained in the data abstraction. Harms and adverse events, including SOE, are discussed by condition and intervention in the report; SOE is detailed in Appendix G.

Medication Use. Few trials compared opioid use pre- and postintervention, and medication use in general was not well reported across trials.

Subgroups. One fair-quality trial in people with knee OA formally examined factors that might modify the effect of exercise on disability; the effect of exercise on activities of daily living disability did not appear to be modified by age, sex, baseline disability, knee pain score, body mass index, or race.[57] The few trials that reported subgroup analyses either did not provide

sufficient data to assess modification by demographic or other factors or did not formally test for modification; trials were generally too small to effectively evaluate outcomes in subgroups.

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 OA, 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 OA 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 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.[28] Consistent with the prior review, we again found exercise, yoga, various psychological interventions (primarily CBT), acupuncture, spinal manipulation, and low-level laser therapy with small to moderate effects on function and/or pain. This report differs from the prior low back pain review by focusing on durability of treatment effects 1 month or longer after completion of a course of treatment and 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 (>1 year) outcomes were very sparse in previous reports and remain so.

A recent Institute for Clinical and Economic Review (ICER) review[285] on chronic low back pain and neck pain used relevant portions of our previous review for chronic low back pain and updated it with new publications so the findings are generally consistent with our review for this condition. For chronic neck pain, this report and the ICER report both suggest a small benefit for acupuncture. The ICER report focuses on evaluating comparative value for interventions and suggests that cognitive and mind-body therapies for treatment of chronic low back pain and chronic neck pain would be cost-effective, would meet value-based price benchmarks, and may result in only a small increase ($0.75) per member per month for a hypothetical payer plan covering 1 million members, compared with approximately $4.46 per member per month for pain medication.

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 recent reviews on exercise[286] acupuncture,[287] and complementary health approaches[288] for chronic pain management across various conditions, an AHRQ report on knee OA treatment,[289] and a review of chronic pain treatment guidelines on the use of manual and physical therapies.[290]

The protocol for a systematic review and network meta-analysis of interventions for fibromyalgia was identified;[291] no publication timeline for this review is currently available.

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 other chronic pain conditions not included in our specified populations. 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 people without such comorbidities who have moderate or severe intensity pain that has persisted for more than 12 months. 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 co-interventions may impact applicability. Substantial 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 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. In general, there were no clear differences in effects based on intervention factors or comparators (e.g., sham acupuncture, usual care); however analyses were quite limited by small numbers of trials. In clinical practice, most chronic pain patients likely use a combination of therapies and may continue to receive some types of therapies if benefit is perceived. We included only RCTs focused on a single intervention; it is unclear to what extent our findings represent the conditions under which the various interventions are currently delivered.

To facilitate interpretation of results across trials and interventions, we categorized the magnitude of effects for function and pain outcomes using the system described in our previous review.[28] Using this system, beneficial effects identified were generally in the small or moderate range. We recognize that effects that we classified as small (e.g., 5 to 10 points on a 0 to 100 scale for pain or function) may be below some proposed thresholds for minimum clinically important differences for some measures. However, our classification provides some consistent and objective benchmarks to assess magnitude of smaller effects across trials and interventions.

Interpretation of clinically important differences in mean change for continuous variables is challenging. If data were provided we also evaluated the proportion of patients who experienced a clinically important improvement in pain or function. This provides valuable insight regarding clinically important improvement.

Limitations of the Evidence Base

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. For example, one trial[104] of MBSR versus usual care in low back pain reported a small improvement in function on a modified Roland Morris Disability questionnaire (1.87, 95% confidence interval [CI] −3.14 to −0.60 on 0-23 scale); however, absolute difference between MBSR and usual care on the percentage of participants (20%) achieving a minimally clinically meaningful (≥30%) improvement from baseline (68.8% to 48.6%, risk ratio 1.56, 95% CI 1.14 to 2.14) suggests that the benefits may be more substantial. 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%). No trial of treatment for chronic tension headache was considered to be of good quality. For some interventions, it may not be possible to effectively blind participants and providers (e.g., CBT, MDR, exercise); thus, observed effects may be due in part to placebo, attention, or other nonspecific effects and results may have been susceptible to performance and other biases. Many included trials were small (<70 participants) and only few or single trials were available for some interventions (e.g., some physical modalities). The combination of these factors led to a determination that evidence was insufficient. There was no or little includable evidence for a number of interventions, including electromuscular simulation, traction, superficial heat or cold, bracing, use of magnets, interferential therapy, transcutaneous electrical nerve stimulation, and manual therapies (other than for low back pain). For most conditions, evidence was also sparse for mindfulness and mind-body practices. Evidence on interventions for hip and hand OA and chronic tension headache was very limited.

Heterogeneity in clinical diagnosis and presentation was present for most of the conditions, with the exception of fibromyalgia. It is likely that included patients may have additional conditions and/or psychological comorbidities that were not described in the trials. Details provided by trials were insufficient to conduct meaningful subanalyses.

Some of the limitations described for the review process reflect limitations of the evidence base, including those related to heterogeneity within and across interventions and heterogeneity within a given condition. Details of concurrent interventions and components of usual care were generally not reported or poorly reported. Additionally, it is assumed that most patients with chronic pain likely continued medications and other therapies or practices during the trials. These factors may have resulted in substantial mixing of effects of the intervention and cointerventions. These factors possibly attenuated observed effects.

Data on potential harms is sparse, although serious harms are not generally expected with the interventions included in this review. Serious treatment-related adverse events were not reported in any of the trials.

Implications for Clinical and Policy Decision Making

Our review provides updated evidence that an array of nonpharmacological treatments provide small to moderate benefits function and/or pain that are durable for more than 1 month for the five common 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 three months were highest for low back pain (28%), neck pain (15%), knee pain (19.5%) and severe headache or migraine (16%).[3,17]

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[15] from the Centers for Disease Control and Prevention (CDC) in the United States and the Canadian Guideline for Opioid Use in Chronic Non-Cancer Pain[290] recommend nonopioid treatment as the preferred treatment for chronic pain. Further, guidelines from the American College of Physicians recommend nonpharmacological therapies over medications for chronic back pain.[19] 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, CBT, MDR, mind-body interventions, 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. There was no evidence suggesting serious harms from these interventions, although harms data were limited.

Our report reviewed evidence that may also help inform decisions regarding prioritization of nonpharmacological therapies by clinicians selecting therapy and facilitate shared decision making between providers and patients. 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 MDR considered adjunctive or second line treatment for chronic low back pain[292] Our report provides indirect support for the adoption of integrated, multimodal management of chronic pain. While the CDC guidelines suggest use of a multi-modal 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.[292,293] Consistent with a biopsychosocial understanding of chronic pain,[3,9] 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, MDR, 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” vs. “passive” strategies.

Our review also has policy implications related to access to treatment and reimbursement. Given heterogeneity in chronic pain, variability in patient preferences for treatments,[3,9] and differential responses to specific therapies in patients with a given chronic pain condition,

policies that broaden access to a wider 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. Policymakers could prioritize access to interventions with evidence of persistent effectiveness across different pain conditions, such as exercise, MDR, 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 low back pain may not necessarily be extrapolated to OA). There is substantial variability in reimbursement and authorization procedures remain a potential barrier.[292-294] Although evidence supports the use of MDR 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 MDR may be similarly effective to high-intensity MDR, which could inform decisions about more efficient methods for delivering this intervention. Not all patients may require MDR.[295] Policy efforts that focus on use of MDR in individuals 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 Systematic Review Process

There were limitations in the systematic review process. Our analysis was restricted to trials that reported outcomes after at least 1 month following the end of therapy (except when therapy lasted at least 6 months; in these cases, we included assessments made immediately post-treatment). 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 nonpharamcological 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 interventions were grouped *a priori* to provide an organizational framework for the report. There is some overlap between categories and there a many other methods of grouping interventions. We performed separate or stratified analyses to the extent possible to evaluate specific techniques/methods within broader categories (e.g., we looked at different types of psychological therapies and mind-body practices). We also performed stratified analyses by comparator type where data were available. Sparse literature for many of the interventions precluded extensive examination specific types of intervention within a given category.

We excluded non-English-language articles; however, we did not identify large numbers of non-English-language articles in our review of bibliographies. We searched ClinicalTrials.gov and identified some potentially relevant studies, but none had results available. We did not search conference proceedings or other sources. We were unable to assess for publication bias using graphical or statistical methods to evaluate any potential impact of small samples, methodological limitations in trials, or heterogeneity in interventions, populations or outcomes. Based on hand searches of reference lists, searches of ClinicalTrials.gov, and suggestions from

technical experts, we did not find evidence indicating the presence of unpublished literature sufficient to impact conclusions.

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.[296] 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.[286,297-302]

Exhaustive listing, evaluation of explicit linkage to an intervention and appraisal of evidence quality for adverse events reported in the general medical literature are beyond the scope of this review. Examples of serious adverse events reported in the medical literature for acupuncture include vascular injuries, cardiac tamponade, subarachnoid hemorrhage and infective endocarditis as described in case reports or case series.[302-304]For spinal manipulation (including the neck), systematic reviews primarily report increases in nonserious AEs and that serious AEs are extremely rare and may include additional disc herniation, cauda equine syndrome, vertebral artery dissection, cerebral vascular accident or vertebrobasilar accident and death; reported frequencies ranged from < 1 per 10,000 patients to < 1 per millions of manipulations.[298] For interventions involving physical activity (including any form of exercise, yoga, tai chi, etc.), nonserious injuries (e.g., musculoskeletal strains and pains) are most common and resolve.[297,301] More serious events such as falls, fractures, fibrocartilaginous injuries, cardiovascular events and worsening of pre-existing conditions, peripheral neuropathy, stroke, transient headache, pneumothorax and rectus sheath hematoma, lumbar disc damage, have been reported in the medical literature. Risk for adverse events depends on factors such as type, intensity, and duration of activity, whether it is done under the supervision of a qualified individual versus being home-based or self-practice, underlying patient health and the presence of concomitant clinical morbidities (e.g., cardiovascular disease).

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[16] 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 that continue across the common conditions we included (Table 65). Four primary issues relate to (1) the need to understand the longer-term sustainability of intervention effects; (2) the need for standardization of interventions for future trials; (3) the standardization of research protocols for collection of and reporting of outcomes including harms; (4) the need 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,[305-310] the Analgesic, Anesthetic, and Addiction Clinical Trials

Translations, Innovations, Opportunities, and Networks,[311,312] the Report of the Task Force on Research Standards for Chronic Low Back Pain for the National Institutes of Health Pain Consortium[313] and the research priorities outlined in the recent Federal Pain Research Strategy.[314] 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.

To understand the sustainability of effects, methodologically rigorous traditional (explanatory) trials with longer followup are needed to better understand whether benefits are sustained over time under ideal conditions. In addition, well-designed pragmatic trial designs with long-term followup could facilitate understanding of how interventions are delivered and continued in real-world settings as well as effect sustainability. Methods for enhancing recruitment, adherence and retention need to be incorporated for all trials. Education of researchers examining nonpharmacological approaches to pain management on clinical trial design, execution, and analysis may also assist with improving the quality of the evidence base for many of the interventions.

Research to identify optimal techniques and their delivery would help define more standardized interventions to evaluate in future trials is needed. In addition, there is a need to understand what combinations of interventions may be most logical for a given condition and standardization of methods to study adjunct therapies. Pragmatic trials may help provide insight into these questions.

Standardization of research protocols for reporting and outcomes measures and use of a standard set of measures would facilitate comparison of results across trials. Outcome measures such as the Visual Analog Scale or Numeric Rating Scale may not fully capture the impact of pain or allow for accurate classification or evaluation of changes in chronic pain. Inclusion of recommendations for pain assessment[315] that incorporate understanding of pathophysiological mechanisms and address multiple domains of pain, including temporal dimensions, sensory and affective qualities of pain and the location and bodily distribution of pain in trial planning and execution may facilitate more accurate classification and longitudinal tracking of response to interventions. Reporting the proportions of patients achieving a clinically meaningful improvement in pain, function, or quality of life as measures of "success" may provide important additional clinical information to complement data on average changes in continuous measures of pain, function, and quality of life for which there is difficulty describing clinically important effects. Routine collection of common or known harms associated with interventions is needed in future trials.

There is heterogeneity with regard to research design, execution, and outcomes reporting in trials of interventions included in this review compared with well-funded trials of devices or pharmacological agents. Lack of funding to design methodologically sound studies with reasonable sample size of nonpharmacological interventions may have contributed to the general low quality of evidence.

Table 81. 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. Consider recommendations from IMMPACT, [305-310] ACTTION,[311,312] NIH Research Standards for Chronic Low Back Pain[313] and Federal Pain Research Strategy.[314]
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 breast feeding 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 a 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.
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 know 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, [305-310] ACTTION,[311,312] NIH Research Standards for Chronic Low Back Pain[313] and Federal Pain Research Strategy.[314]

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, MDR, acupuncture, CBT and 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 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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Acronyms and Abbreviations

Acronym/Abbreviation	Term
AC	Attention Control
ACT	acceptance and commitment therapy
ACTTION	Analgesic, Anesthetic, and Addiction Clinical Trials Translations, Innovations, Opportunities, and Networks
ADL	Activities of daily living
AE	Adverse event
AIMS	Arthritis Impact Measurement Scale
AQoL 6D	Assessment of Quality of Life version 6D
AUSCAN	Australia Canadian Osteoarthritis Hand Index
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body mass index
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CBT	Cognitive-behavioral therapy
CDC HRQOL-4	Centers for Disease Control and Prevention's Health-Related Quality of Life Questionnaire
CES-D	Center for Epidemiologic Studies Depression Scale
CGI-I	Clinical Global Impressions of Improvement Scale
CGI-S	Clinical Global Impressions of Severity Scale
CI	Confidence interval
CPAQ	Chronic Pain Acceptance Questionnaire
CSQ	Coping Strategies Questionnaire
CTTH	Chronic tension-type headache
DASS	Depression Anxiety Stress Scales
DPQ	Dallas Pain Questionnaire
DFI	Dreiser Functional Index
DRI	Disability Rating Index
EAET	emotional awareness and expression therapy
EEG	Electroencephalography
EMG	Electromyography
EQ-5D	EuroQoL-5D
FABQ	Fear Avoidance Beliefs Questionnaire
FIHOA	Functional Index for Hand Osteoarthritis
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
FMI	Freiburg Mindfulness Inventory
FRI	Functional Rating Index
FSI	Fatigue Symptom Inventory
FSS	Fatigue Severity Scale
GAR	Groningen Activity Restriction Scale
GCQ, GBB-24	Giessen Complaint Questionnaire
GDS	Geriatric Depression Scale
GPE	Global Perceived Effect Scale
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GSI	Global Severity Index (Symptom Checklist-90-Revised)
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depressions
HAM-A	Hamilton Anxiety Rating Scale (HAM-A)
HAM-D	Hamilton Depression Rating Scale (HAM-D)
HAQ	Health Assessment Questionnaire
HDI	Headache Disability Inventory
HHS	Harris Hip Score
HFAQ	Hannover Functional Ability
HIT-6	Headache Impact Test-6

Acronym/Abbreviation	Term
HRQoL	Health-related quality of life
HSCL-25	Hopkin's Symptom Checklist
HSS	Hospital for Special Surgery Knee Function
Hz	hertz
ICER	Institute for Clinical and Economic Review
IMMPACT	Initiative on Methods, Measurements, and Pain Assessment in Clinical Trials
IPAQ	International Physical Activity Questionnaire
IPQ(-R)	Illness Perception Questionnaire(-Revised)
IQR	Interquartile range
ITT	Intention-to-treat
J	joule
J/cm^2	Joules per square centimeter
kJ	kilojoules
KPS	Knee Pain Scale
JLEQ	Japan Low Back Pain Evaluation Questionnaire
JOA	Japanese Orthopedic Association
LBP	Low back pain
LBPOI	Low Back Pain Outcome Instrument
LBPRS	Low Back Pain Rating Scale
LI	Lequesne Index
LLFDI	Late Life Function and Disability Instrument
MACTAR	McMaster Toronto Arthritis patient preference questionnaire
MASQ	Mood and Anxiety Symptom Questionnaire
MASS	Mindful Attention Awareness Scale
MBSR	Mindfulness-based stress reduction
MCE	Motor control exercise
MCID	Minimal clinically important difference
MCS-12	Mental component score of the SF-12
MD	Mean difference
Mg	milligram
MHz	Mega Hertz
MIDAS	Migraine Disability Assessment questionnaire
MRDQ	Modified Roland-Morris Disability Questionnaire
MOS	Medical Outcome Study
MPI	Multidimensional Pain Inventory
MPQ(-SF)	McGill Pain Questionnaire(-Short Form)
mW	megawatt
NDI	Neck Disability Index
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NHP	Nottingham Health Profile
NHS	National Health Service
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH	National Institute of Health
Nm	nanometer
NPAD	Neck Pain and Disability Index
NPQ	Northwick Park Neck Pain Questionnaire
NR	Not reported
NRS	Numeric Rating Scale
NS	Not statistically significant
NSAID	Nonsteroidal anti-inflammatory drug
NT	No treatment
OA	Osteoarthritis
OARSI-OMERACT	Osteoarthritis Research Society International – Outcome Measures in Rheumatology
ODI	Oswestry Disability Index
OKS	Oxford Knee Score
PDI	Pain Disability Index
PHQ-8	Patient Health Questionnaire-8-item depression scale

Acronym/Abbreviation	Term
PICOTS	Populations, interventions, comparators, outcomes, timing, settings, study designs
PPS	Pain Perception Scale
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSEQ	Chronic Pain Self Efficacy Scale
PSFS	Patient-Specific Functional Scale
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
PT	Physical therapy
QBPDS	Quebec Back Pain Disability Scale
QHS	Each night at bedtime
QOL	Quality of life
RAND-36 QoL	Quality of Life RAND-36
QoL VAS	Quality of Life Visual Analog Scale
RCT	Randomized controlled trial
RDQ	Roland-Morris Disability Questionnaire
RR	Relative risk
SD	Standard Deviation
SA	Sham acupuncture
SCL-90	Symptom Checklist 90
SF-12, SF-12 MCS/PCS	Short Form-12, Physical Component Score/Mental Component Score
SF-36, SF-36 MCS/PCS	Short Form-36, Physical Component Score/Mental Component Score
SF-MPQ	McGill Pain Questionnaire Pain Rating Index-Short-Form
SHCI	Subjective Health Complaint Inventory
SIP	Sickness Impact Profile
SKFS	Saudi version of the Knee Function Scale
SMD	Standardized mean difference
SMT	Spinal manipulation therapy
SOE	Strength of evidence
SSDQ	Stanford Sleep Disorders Questionnaire
SSS	Swiss Spinal Stenosis Questionnaire
STAI	State-Trait Anxiety Inventory
TENS	Transcutaneous electrical nerve stimulation
UC	Usual Care
UK	United Kingdom
V	volt
VAS	Visual analog scale
VF	Von Korff functional disability
VKPS	Von Korff pain scale
W/cm^2	Watt per square centimeter
WHOQOL-BREF	World Health Organization Quality of Life-BREF instrument
WL	Waitlist
WMD	Weighted mean difference
WPAI	Work activity impairment subscale
WPSI	Wahler Physical Symptoms Inventory
ZPS	Zung Self-Rating Depression Scale

Appendix A. Search Strategies

Prior AHRQ Report, 2018

Database: Ovid MEDLINE(R) without Revisions 1996 to May Week 2 2017
Search Strategy:
1 exp Low Back Pain/
2 exp Chronic Pain/
3 2 and (back or spine or spinal or radicular).ti,ab.
4 or/1-3
5 Neck Pain/ or neck.ti,ab.
6 exp Osteoarthritis/ or osteoarthritis.ti,ab.
7 Headache/ or headache.ti,ab.
8 Fibromyalgia/ or fibromyalgia.ti,ab.
9 exp Exercise Therapy/
10 exp Physical Therapy Modalities/
11 exp Braces/
12 exp Mind-Body Therapies/
13 exp Acupuncture Therapy/
14 exp Rehabilitation/
15 exp Psychotherapy/
16 exp Musculoskeletal Manipulations/
17 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
18 (exercise or physical therapy or cognitive or behavioral or feedback or relaxation or acceptance or commitment or traction or ultrasound or stimulation or laser or magnet* or inferential or electromuscular or diathermy or heat or cold or manipulation or manual or craniosacral or mindfulness or meditation or mind-body or yoga or pilates or Qigong or acupuncture or “functional restoration” or multidisciplin* or interdisciplin*).ti,ab.
19 rh.fs.
20 or/9-19
21 (or/5-8) and pain.mp.
22 20 and 21
23 limit 22 to (meta analysis or systematic reviews)
24 limit 23 to (english language and humans)
25 limit 22 to randomized controlled trial
26 limit 25 to (english language and humans)
27 4 and 20
28 limit 27 to randomized controlled trial
29 limit 28 to yr="2016 - 2017"
30 limit 29 to (english language and humans)
31 24 or 26 or 30

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2017
1 exp Low Back Pain/
2 exp Chronic Pain/
3 2 and (back or spine or spinal or radicular).ti,ab.

4 or/1-3
5 Neck Pain/ or neck.ti,ab.
6 exp Osteoarthritis/ or osteoarthritis.ti,ab.
7 Headache/ or headache.ti,ab.
8 Fibromyalgia/ or fibromyalgia.ti,ab.
9 exp Exercise Therapy/
10 exp Physical Therapy Modalities/
11 exp Braces/
12 exp Mind-Body Therapies/
13 exp Acupuncture Therapy/
14 exp Rehabilitation/
15 exp Psychotherapy/
16 exp Musculoskeletal Manipulations/
17 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
18 (exercise or physical therapy or cognitive or behavioral or feedback or relaxation or acceptance or commitment or traction or ultrasound or stimulation or laser or magnet* or inferential or electromuscular or diathermy or heat or cold or manipulation or manual or craniosacral or mindfulness or meditation or mind-body or yoga or pilates or Qigong or acupuncture or functional restoration or multidisciplin* or interdisciplin*).ti,ab.
19 rh.fs.
20 or/9-19
21 (or/5-8) and pain.mp.
22 20 and 21
23 limit 22 to randomized controlled trial
24 4 and 20
25 limit 24 to randomized controlled trial
26 limit 25 to yr="2016 - 2017"
27 23 or 26
28 limit 27 to english language
29 limit 28 to medline records
30 28 not 29

Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to December 21, 2016
1 chronic.ti,ab.
2 (back or spine or spinal or radicular or neck or osteoarthritis or fibromyalgia or headache).ti,ab.
3 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
4 (exercise or psychosocial or "cognitive behavioral therapy" or CBT or biofeedback or relaxation or "physical modal*" or traction or ultrasound or "transcutaneous electrical nerve stimulation" or TENS or laser or heat or cold or cryotherapy or magnet* or manual* or manipulation or massage or mindfulness or meditation or "mind-body" or "yoga to tai chi" or qigong or acupuncture or "functional restoration" or "occupational therapy" or multidisciplinary).ti,ab.
5 1 and 2
6 3 or 4
7 5 and 6

AHRQ Report Update, 2019

(Slightly modified from prior search criteria as a result of peer review)

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R), September Week 1 2017 through December Week 2 2018

1 exp Low Back Pain/ or ((back or spine or spinal) adj2 pain).ti,ab.
2 exp Chronic Pain/
3 Neck Pain/ or neck.ti,ab.
4 exp Osteoarthritis/ or osteoarthritis.ti,ab.
5 Headache/ or headache.ti,ab.
6 Fibromyalgia/ or fibromyalgia.ti,ab.
7 exp Exercise Therapy/
8 exp Physical Therapy Modalities/
9 exp Braces/
10 exp Mind-Body Therapies/
11 exp Acupuncture Therapy/
12 exp Rehabilitation/
13 exp Psychotherapy/
14 exp Musculoskeletal Manipulations/
15 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
16 (exercise or physical therapy or cognitive or behavioral or feedback or relaxation or acceptance or commitment or traction or ultrasound or stimulation or laser or magnet* or inferential or electromuscular or diathermy or heat or cold or manipulation or manual or craniosacral or mindfulness or meditation or mind-body or yoga or pilates or Qigong or acupuncture or functional restoration or multidisciplin* or interdisciplin*).ti,ab.
17 rh.fs.
18 or/1-6
19 or/7-17
20 18 and 19
21 randomized controlled trial.pt.
22 controlled clinical trial.pt.
23 clinical trials as topic.sh.
24 (random* or trial or placebo).ti,ab.
25 clinical trials as topic.sh.
26 exp animals/ not humans.sh.
27 or/21-25
28 27 not 26
29 20 and 28
30 limit 29 to english language
31 limit 30 to humans
32 31 and (20171$ or 2018$).dt,ed,ep.
33 meta-analysis.pt.
34 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
35 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.

36 ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
37 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
38 (data synthes* or data extraction* or data abstraction*).ti,ab.
39 (handsearch* or hand search*).ti,ab.
40 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
41 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
42 (meta regression* or metaregression*).ti,ab.
43 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
44 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
45 (cochrane or (health adj2 technology assessment) or evidence report).jw.
46 (meta-analysis or systematic review).ti,ab.
47 (comparative adj3 (efficacy or effectiveness)).ti,ab.
48 (outcomes research or relative effectiveness).ti,ab.
49 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
50 or/33-49
51 20 and 50
52 limit 51 to english language
53 limit 52 to humans
54 53 and (20171$ or 2018$).dt,ed,ep.
55 32 or 54

Database: EBM Reviews - Cochrane Central Register of Controlled Trials, September Week 1 2017 through December Week 2 2018
1 exp Low Back Pain/ or ((back or spine or spinal) adj2 pain).ti,ab.
2 exp Chronic Pain/
3 Neck Pain/ or neck.ti,ab.
4 exp Osteoarthritis/ or osteoarthritis.ti,ab.
5 Headache/ or headache.ti,ab.
6 Fibromyalgia/ or fibromyalgia.ti,ab.
7 exp Exercise Therapy/
8 exp Physical Therapy Modalities/
9 exp Braces/
10 exp Mind-Body Therapies/
11 exp Acupuncture Therapy/
12 exp Rehabilitation/
13 exp Psychotherapy/
14 exp Musculoskeletal Manipulations/
15 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab.
16 (exercise or physical therapy or cognitive or behavioral or feedback or relaxation or acceptance or commitment or traction or ultrasound or stimulation or laser or magnet* or inferential or electromuscular or diathermy or heat or cold or manipulation or manual or

craniosacral or mindfulness or meditation or mind-body or yoga or pilates or Qigong or acupuncture or functional restoration or multidisciplin* or interdisciplin*).ti,ab.
17 rh.fs.
18 or/1-6
19 or/7-17
20 18 and 19
21 limit 20 to yr="2017 -Current"
22 limit 21 to medline records
23 21 not 22
24 limit 23 to english language

Database: EBM Reviews - Cochrane Database of Systematic Reviews, September Week 1 2017 through December Week 2 2018
1 ((back or spine or spinal) adj2 pain).ti.
2 (neck adj2 pain).ti.
3 osteoarthritis.ti.
4 headache.ti.
5 fibromyalgia.ti.
6 (noninvasive or non-invasive or nonpharmacologic* or non-pharmacologic*).ti,ab. (295)
7 (exercise or physical therapy or cognitive or behavioral or feedback or relaxation or acceptance or commitment or traction or ultrasound or stimulation or laser or magnet* or inferential or electromuscular or diathermy or heat or cold or manipulation or manual or craniosacral or mindfulness or meditation or mind-body or yoga or pilates or Qigong or acupuncture or functional restoration or multidisciplin* or interdisciplin*).ti,ab.
9 6 or 7
10 8 and 9
11 limit 10 to new reviews

Appendix B. Included Studies

1. Abbasi M, Dehghani M, Keefe FJ, et al. Spouse-assisted training in pain coping skills and the outcome of multidisciplinary pain management for chronic low back pain treatment: a 1-year randomized controlled trial. Eur J Pain. 2012 Aug;16(7):1033-43. doi: 10.1002/j.1532-2149.2011.00097.x. PMID: 22337646.
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* Trials/publications new to the 2019 update report

Appendix C. Excluded Studies

Exclusion Codes:

3 = Ineligible population
4 = Ineligible intervention
5 = Ineligible comparator
6 = Ineligible outcomes
7 = Ineligible study design for Key Question
8 = Not a study (letter, editorial, non-systematic review article, etc.)
9 = Inadequate duration of followup
10 = Systematic review not directly used, but studies checked for inclusion
11 = Not English language, but possibly relevant
12 = Not English language and not relevant

1. Aas RW, Tuntland H, Holte KA, et al. Workplace interventions for neck pain in workers. Cochrane Database of Systematic Reviews. 2011(4):CD008160. doi: http://dx.doi.org/10.1002/14651858.CD008160.pub2. PMID: 21491405. Exclusion: 10

2. Abasolo L, Carmona L, Hernandez-Garcia C, et al. Musculoskeletal work disability for clinicians: time course and effectiveness of a specialized intervention program by diagnosis. Arthritis & Rheumatism. 2007 Mar 15;57(2):335-42. doi: https://dx.doi.org/10.1002/art.22529. PMID: 17330282. Exclusion: 3

3. Abbott JH, Hobbs C, Gwynne-Jones D, et al. The ShortMAC: Minimum Important Change of a Reduced Version of the Western Ontario and McMaster Universities Osteoarthritis Index. Journal of Orthopaedic & Sports Physical Therapy. 2018 02;48(2):81-6. doi: https://dx.doi.org/10.2519/jospt.2018.7676. PMID: 29056072. Exclusion: 6*

4. Abbott JH, Robertson MC, McKenzie JE, et al. Exercise therapy, manual therapy, or both, for osteoarthritis of the hip or knee: a factorial randomised controlled trial protocol. Trials. 2009 Feb 08;10:11. doi: 10.1186/1745-6215-10-11. PMID: 19200399. Exclusion: 8

5. Abbott JH, Wilson R, Pinto D, et al. Long-term cost-effectiveness of exercise therapy and/or manual therapy for hip or knee osteoarthritis: randomized controlled trial and computer simulation modelling. Osteoarthritis Cartilage. 2019;27(Supp 1):S36. Exclusion: 3*

6. Abdelfattah A, Kattabei O, Nasef S. Strain counter strain technique versus kinesio tape in treating patients with myofascial neck pain syndrome. Physiotherapy. 2019 Jan;105(Supp 1):e70. doi: 10.1016/j.physio.2018.11.035. Exclusion: 7*

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9. Abeles M, Solitar BM, Pillinger MH, et al. Update on fibromyalgia therapy. American Journal of Medicine. 2008 Jul;121(7):555-61. doi: http://dx.doi.org/10.1016/j.amjmed.2008.02.036. PMID: 18589048. Exclusion: 10

10. Aboagye E, Karlsson ML, Hagberg J, et al. Cost-effectiveness of early interventions for non-specific low back pain: a randomized controlled study investigating medical yoga, exercise therapy and self-care advice. J Rehabil Med. 2015 Feb;47(2):167-73. doi: 10.2340/16501977-1910. PMID: 25403347. Exclusion: 5

11. Acedo AA, Luduvice Antunes AC, Barros dos Santos A, et al. Upper trapezius relaxation induced by TENS and interferential current in computer users with chronic nonspecific neck discomfort: An electromyographic analysis. Journal of Back & Musculoskeletal Rehabilitation. 2015;28(1):19-24. PMID: 24867904. Exclusion: 5

12. Adsuar JC, Del Pozo-Cruz B, Parraca JA, et al. Whole body vibration improves the single-leg stance static balance in women with fibromyalgia: a randomized controlled trial. J Sports Med Phys Fitness. 2012 Feb;52(1):85-91. PMID: 22327091. Exclusion: 4

13. Ahern M, Skyllas J, Wajon A, et al. The effectiveness of physical therapies for patients with base of thumb osteoarthritis: Systematic review and meta-analysis. Musculoskeletal Science & Practice. 2018 06;35:46-54. doi: https://dx.doi.org/10.1016/j.msksp.2018.02.005. PMID: 29510316. Exclusion: 10*

14. Ahmed MS, Shakoor MA, Khan AA. Evaluation of the effects of shortwave diathermy in patients with chronic low back pain. Bangladesh Med Res Counc Bull. 2009;35(1):18-20. PMID: 19637541. Exclusion: 9

15. Ahn H, Woods AJ, Kunik ME, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: An experimenter- and participant-blinded, randomized, sham-controlled pilot clinical study. Brain Stimulation. 2017 Sep - Oct;10(5):902-9. doi: https://dx.doi.org/10.1016/j.brs.2017.05.007. PMID: 28566193. Exclusion: 9

16. Ahsin S, Saleem S, Bhatti AM, et al. Clinical and endocrinological changes after electro-acupuncture treatment in patients with osteoarthritis of the knee. Pain. 2009 Dec 15;147(1-3):60-6. doi: http://dx.doi.org/10.1016/j.pain.2009.08.004. PMID: 19766392. Exclusion: 9

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18. Akhmadeeva L, Valeeva D, Kharisova E, et al. A double blind randomized placebo controlled trial for non-invasive dynamic trans-cutaneous electrical nerves stimulation in management of tension type headaches. J Headache Pain. 2014 START: 2015 May 14 CONFERENCE END: 2015 May 17, 17th Congress of the International Headache Society, IHC 2015 Valencia Spain;15(Suppl 1):J2. doi: 10.1186/1129-2377-15-S1-J2. Exclusion: 7

19. Alaranta H, Rytokoski U, Rissanen A, et al. Intensive physical and psychosocial training program for patients with chronic low back pain. A controlled clinical trial. Spine (Phila Pa 1976). 1994 Jun 15;19(12):1339-49. PMID: 8066514. Exclusion: 5

20. Alastair Gibson JN, Ahmed M. The effectiveness of flexible and rigid supports in patients with lumbar backache. Journal of Orthopaedic Medicine. 2002;24(3):86-9. Exclusion: 9

21. Alayat MSM, Alshehri MA, Shousha TM, et al. The effectiveness of high intensity laser therapy in the management of spinal disorders: A systematic review and meta-analysis. Journal of Back & Musculoskeletal Rehabilitation. 2019 Mar 21;21:21. doi: https://dx.doi.org/10.3233/BMR-181341. PMID: 30932879. Exclusion: 10*

22. Albers J, Jakel A, Wellmann K, et al. Effectiveness of 2 Osteopathic Treatment Approaches on Pain, Pressure-Pain Threshold, and Disease Severity in Patients with Fibromyalgia: A Randomized Controlled Trial. Complementary Medical Research. 2018;25(2):122-8. doi: https://dx.doi.org/10.1159/000464343. PMID: 28892807. Exclusion: 9*

23. Albornoz-Cabello M, Maya-Martin J, Dominguez-Maldonado G, et al. Effect of interferential current therapy on pain perception and disability level in subjects with chronic low back pain: a randomized controlled trial. Clinical Rehabilitation. 2017 Feb;31(2):242-9. doi: https://dx.doi.org/10.1177/0269215516639653. PMID: 26975312. Exclusion: 9

24. Albornoz-Cabello M, Perez-Marmol JM, Barrios Quinta CJ, et al. Effect of adding interferential current stimulation to exercise on outcomes in primary care patients with chronic neck pain: a randomized controlled trial. Clin Rehabil. 2019 Sep;33(9):1458-67. doi: 10.1177/0269215519844554. PMID: 31007047. Exclusion: 4*

25. Alexander A, Woolley SM, Bisesi M, et al. The effectiveness of back belts on occupational back injuries and worker perception. Professional Safety. 1995;40(9):22. Exclusion: 9

26. Alexandre NM, de Moraes MA, Correa Filho HR, et al. Evaluation of a program to reduce back pain in nursing personnel. Rev Saude Publica. 2001 Aug;35(4):356-61. PMID: 11600924. Exclusion: 9

27. Alghadir A, Omar MT, Al-Askar AB, et al. Effect of low-level laser therapy in patients with chronic knee osteoarthritis: a single-blinded randomized clinical study. Lasers in Medical Science. 2014 Mar;29(2):749-55. doi: https://dx.doi.org/10.1007/s10103-013-1393-3. PMID: 23912778. Exclusion: 9

28. Ali SS, Ahmed SI, Khan M, et al. Comparing the effects of manual therapy versus electrophysical agents in the management of knee osteoarthritis. Pakistan Journal of Pharmaceutical Sciences. 2014 Jul;27(4 Suppl):1103-6. PMID: 25016274. Exclusion: 9

29. Allen KD, Bongiorni D, Walker TA, et al. Group physical therapy for veterans with knee osteoarthritis: study design and methodology. Contemporary Clinical Trials. 2013 Mar;34(2):296-304. doi: http://dx.doi.org/10.1016/j.cct.2012.12.007. PMID: 23279750. Exclusion: 8

30. Allen KD, Somers TJ, Campbell LC, et al. Pain coping skills training for African Americans with osteoarthritis: results of a randomized controlled trial. Pain. 2019 Jun;160(6):1297-307. doi: 10.1097/j.pain.0000000000001525. PMID: 30913165. Exclusion: 3*

31. Allende S, Anandan A, Lauche R, et al. Effect of yoga on chronic non-specific neck pain: An unconditional growth model. Complement Ther Med. 2018 Oct;40(pagination):237-42. doi: 10.1016/j.ctim.2017.11.018. PMID: 30219458. Exclusion: 9*

32. Alnigenis MNY, Bradley JD, Wallick J, et al. Massage therapy in the management of fibromyalgia: a pilot study. J Musculoskelet Pain. 2001;9(2):55-67. Exclusion: 7

33. Alpayci M, Ilter S. Isometric Exercise for the Cervical Extensors Can Help Restore Physiological Lordosis and Reduce Neck Pain: a Randomized Controlled Trial. Am J Phys Med Rehabil. 2017 Sep;96(9):621-6. doi: 10.1097/PHM.0000000000000698. PMID: 28118272 Exclusion: 9

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35. Altinbilek T, Murat S, Yumusakhuylu Y, et al. Osteopathic manipulative treatment improves function and relieves pain in knee osteoarthritis: A single-blind, randomized-controlled trial. Turk J Phys Med Rehabil. 2018 Jun;64(2):114-20. doi: 10.5606/tftrd.2018.1384. PMID: 31453500. Exclusion: 4*

36. Altmaier EM, Lehmann TR, Russell DW, et al. The effectiveness of psychological interventions for the rehabilitation of low back pain: a randomized controlled trial evaluation. Pain. 1992 Jun;49(3):329-35. PMID: 1408299. Exclusion: 5

37. Alvarez-Gallardo IC, Bidonde J, Busch A, et al. Therapeutic validity of exercise interventions in the management of fibromyalgia. Journal of Sports Medicine & Physical Fitness. 2019 May;59(5):828-38. doi: https://dx.doi.org/10.23736/S0022-4707.18.08897-7. PMID: 30293405. Exclusion: 10*

38. Alvarez-Melcon AC, Valero-Alcaide R, Atin-Arratibel MA, et al. Effects of physical therapy and relaxation techniques on the parameters of pain in university students with tension-type headache: A randomised controlled clinical trial. Neurologia. 2018 May;33(4):233-43. doi: https://dx.doi.org/10.1016/j.nrl.2016.06.008. PMID: 27491303. Exclusion: 3*

39. Aman MM, Jason Yong R, Kaye AD, et al. Evidence-Based Non-Pharmacological Therapies for Fibromyalgia. Current Pain & Headache Reports. 2018 Apr 04;22(5):33. doi: https://dx.doi.org/10.1007/s11916-018-0688-2. PMID: 29619620. Exclusion: 10*

40. Amorim AB, Pappas E, Simic M, et al. Integrating Mobile health and Physical Activity to reduce the burden of Chronic low back pain Trial (IMPACT): a pilot trial protocol. BMC Musculoskelet Disord. 2016 Jan 19;17:36. doi: 10.1186/s12891-015-0852-3. PMID: 26787469. Exclusion: 8

41. Amris K, Luta G, Christensen R, et al. Predictors of improvement in observed functional ability in patients with fibromyalgia as an outcome of rehabilitation. Journal of Rehabilitation Medicine. 2016 Jan;48(1):65-71. doi: http://dx.doi.org/10.2340/16501977-2036. PMID: 26660148. Exclusion: 7

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* Trials/publications excluded from updated search.

Appendix D. Evidence Table

Located in associated Excel® file.

Appendix E. Quality Assessment

Table E-1. Quality assessment of randomized controlled trials

References are located in Appendix B.

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Abbassi, 2012	No	No	Yes	Yes	No	No	Unclear	Yes	Yes
Abbott, 2013	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes
Ajimsha, 2014	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Al Rashoud, 2014	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Unclear	No
Alda, 2011	Yes	Yes	Yes	Yes	No	No	Yes (CBO) No (PRO)	Unclear	Yes
Alfano, 2001	Yes	Unclear	No	Yes	Yes (magnetic field, sham); No (usual care)	Yes	Yes (outcome assessor); No (data analyst)	Unclear	Yes
Allen, 2018	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Altan, 2005	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Yes
Altan, 2009	Yes	Unclear	Yes	Yes	No	No	Yes (CBO) No (PRO)	Unclear	Yes
Amris, 2014	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Andersen, 2008	Unclear	Unclear	Yes	Unclear	No	No	No	No	No
Ang, 2010	Unclear	Unclear	Unclear	Unclear	No	No	No	Unclear	Yes
Areeudomwong, 2017	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Arguisuelas, 2017	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Aslan Telci, 2012	Unclear	Unclear	Unclear	No	No	No	No	Unclear	No
Assefi, 2005	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Banth, 2015	Unclear	Unclear	Yes	Unclear	No	No	Yes	Unclear	Yes
Baptista, 2012	Yes	Yes	Yes	No	No	No	No	Unclear	Yes
Baumueller, 2017	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Basford,1999	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Battisti 2004	Unclear	Unclear	Unclear	Unclear	No	No	No	Yes	No
Bendix,1995, 1997,1998	Yes (minimization)	Yes (minimization)	Yes	Yes	No	No	Yes	Unclear	Yes
Bendix, 2000	Yes (minimization)	Yes (minimization)	Yes	Yes	No	No	Yes	Unclear	Yes
Bendix,1996,1998	Yes (minimization)	Yes (minimization)	Yes	Yes	No	No	Yes	Unclear	Yes
Bennell, 2005	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Bennell, 2016	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Berman,1999	Yes	Yes	Yes	Yes	No	No	Unclear	Unclear	Yes
Berman, 2004	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Beurskens,1997	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Birch,1998	Unclear	Unclear	Unclear	No	Yes/No*	No	Yes/No*	Yes	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Abbassi, 2012	Yes	Yes	Yes	Unclear	Yes	Poor
Abbott, 2013	Yes	Yes	Yes	Yes	Yes	Fair
Ajimsha, 2014	Yes	Yes	Yes	Unclear	Yes	Fair
Al Rashoud, 2014	Unclear	Unclear	Yes	No	Yes	Fair
Alda, 2011	Yes	Yes	Yes	Yes	Unclear	Fair
Alfano, 2001	No	Yes	Yes	Unclear	Yes	Fair (all comparisons)
Allen, 2018	Yes	No	Yes	Yes	Yes	Fair
Altan, 2005	Yes	Yes	Yes	No	Yes	Fair
Altan, 2009	Yes	Yes	Yes	Unclear	Yes	Fair
Amris, 2014	Yes	Yes	Yes	Yes	Yes	Fair
Andersen, 2008	Unclear	Unclear	Yes	Yes	Yes	Poor
Ang, 2010	Yes	Yes	Yes	Yes	Unclear	Poor
Areeudomwong, 2017	Yes	Yes	Yes	Unclear	Yes	Fair
Arguisuelas, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Aslan Telci, 2012	Unclear	Unclear	Yes	No	Yes	Poor
Assefi, 2005	Yes	Yes	Yes	No	Yes	Good
Banth, 2015	No	Unclear	Yes	No	Unclear	Poor
Baptista, 2012	Yes	Yes	Yes	Yes	Unclear	Fair
Baumueller, 2017	Yes	Yes	Yes	No	Yes	Fair
Basford, 1999	Yes	Yes	Yes	Unclear	Yes	Fair
Battisti, 2004	Unclear	Unclear	Yes	No	Yes	Poor
Bendix, 1995, 1997, 1998	No (22% at 12 months)	Yes	Yes	Unclear	Yes	Fair
Bendix, 2000	No (22% at 12\0 months)	Yes	Yes	No	Unclear	Fair
Bendix,1996, 1998	Yes	No	Yes	No	Yes	Fair
Bennell, 2005	Yes	No	Yes	No	Yes	Fair
Bennell, 2016	Yes	Yes	Yes	Yes	Yes	Fair
Berman, 1999	Yes	Yes	Yes	No	Yes	Fair
Berman, 2004	No	Yes	Yes	No	Yes	Fair
Beurskens, 1997	No	Yes	Yes	Unclear	Yes	Fair
Birch, 1998	Yes	Yes	Yes	No	No	Poor

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to - Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Blanchard, 1990	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	No	Unclear	Yes
Blodt, 2015	Yes	Yes	Yes	No	No	No	Unclear	No (~70%)	Yes
Boline, 1995	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Bono, 2015	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No
Bourgault, 2015	Yes	Unclear	No	Yes	No	No	No	No	Yes
Bramberg, 2017	Unclear	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Brinkhaus, 2006a	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Brismee, 2007	Yes	Unclear	Yes	Yes	No	No	Yes/No (assessor blinded/ patient reported	Yes	Yes
Bronfort, 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Brosseau, 2005	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Brouwer, 2006	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Buckelew, 1998	Unclear	Unclear	Unclear	No	No	No	Yes (CBO) No (PRO)	Unclear	Yes
Cakir, 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Carlsson, 2001	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Unclear	Unclear
Cash, 2015/Sephton 2007	Yes	Unclear	Yes	Yes	No	No	Yes (CBO) No (PRO)	No	Yes
Castel, 2012	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Yes
Castel, 2013	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Castien, 2011	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Castro-Sanchez, 2011[a]	Yes	Unclear	Yes	Yes	No	No	No	Yes	Yes
Castro-Sanchez, 2011[b]	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Yes
Cedraschi, 2004	Yes	Yes	No	Yes	No	No	No	No	Yes
Chen, 2014	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	No
Cherkin, 2001	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Cherkin, 2009	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Cherkin, 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Cherkin, 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Chiu, 2011	Yes	Yes	Yes	No*	No	No	No	Unclear	Yes
Cho, 2013	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Yes
Cho, 2014	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Chow, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Blanchard, 1990	Yes	Yes - Relax only vs. AC/WL No - CBT/relax vs. AC/WL	Yes	No	Yes	Poor
Blodt, 2015	Yes	Yes	Yes	Yes	Yes	Fair
Boline, 1995	Yes	No	Yes	No	Yes	Poor
Bono, 2015	Unclear	Unclear	Yes	No	Yes	Poor
Bourgault, 2015	No	No	Yes	Yes	Yes	Poor
Bramberg, 2017	No	No	Yes	Yes	Yes	Fair
Brinkhaus, 2006a	Yes	Yes	Yes	Yes	Yes	Good
Brismee, 2007	No	No	Yes	No	Yes	Poor
Bronfort, 2011	Yes	Yes	Yes	Unclear	Yes	Fair
Brosseau, 2005	Yes	Yes	Yes	No	Yes	Good
Brouwer, 2006	No	No	Yes	No	Yes	Poor
Buckelew, 1998	Yes	Yes	Yes	Unclear	Yes	Poor (all comparisons)
Cakir, 2014	Yes	Yes	Yes	No	No	Fair
Carlsson, 2001	Unclear	Unclear	Unclear	Unclear	Yes	Poor
Cash, 2015/Sephton, 2007	No	No	Yes	Yes	No	Poor
Castel, 2012	No	Yes	Yes	Unclear	Unclear	Poor
Castel, 2013	No	No	Yes	No	Unclear	Poor
Castien, 2011	Yes	Yes	Yes	Yes	Yes	Fair
Castro-Sanchez, 2011[a]	Yes	Yes	Yes	No	Yes	Fair
Castro-Sanchez, 2011[b]	Yes	Yes	Yes	No	Yes	Poor
Cedraschi, 2004	No	No	Yes	No	Unclear	Poor
Chen, 2014	Unclear	Unclear	Yes	No	Yes	Poor
Cherkin, 2001	Yes	Yes	Yes	Unclear	Yes	Fair
Cherkin, 2009	Yes	Yes	Yes	Yes	Yes	Fair
Cherkin, 2011	Yes	Yes	Yes	Yes	Yes	Fair
Cherkin, 2016	No	Yes	Yes	Yes	Yes	Fair
Chiu, 2011	No**	No**	Yes	No	Yes	Poor
Cho, 2013	Yes	Yes	Yes	Yes	Yes	Fair
Cho, 2014	Yes	Yes	Yes	Yes	Yes	Poor
Chow, 2006	Yes	Yes	Yes	No	Yes	Good

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Clarke-Jenssen 2014	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Correa, 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Costa, 2009	Yes	Yes	Yes	Yes	No (not blinded to exercise)	No	Yes	Yes	Yes (figure 1)
Da Costa, 2005	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes
de Araujo Cazotti, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
de Rooij, 2017	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Dias, 2003	Yes	Unclear	Unclear	Yes	No	No	Yes	Unclear	Yes
Dilek, 2013	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Djavid, 2007	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ebadi, 2012	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Yes
Ebneshahidi, 2005	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes	Yes
Edinger, 2005	Unclear	Unclear	Unclear	Unclear	No	No	No	Yes	Yes
Ettinger, 1997	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Falcao, 2008	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Fary, 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Ferreira, 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Fontaine, 2010/2011	Yes	No	Yes	Yes	No	No	Unclear	No	Yes
Fukuda, 2011	Yes	Yes	Yes	Yes	Yes	No (control) Yes (placebo)	No	Yes	Yes
Garcia, 2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Giannotti, 2014	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Gibson, 1985	Unclear	Unclear	Yes	No	Yes	Yes	Yes	Unclear	Yes
Gilbert, 2018	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Giombini, 2011	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Goldby, 2006	Yes	Unclear	Yes	Yes	No	No	Yes	Unclear	Yes
Gowans, 2001	Unclear	Unclear	Yes	No	No	No	No	No	Yes
Groessl, 2017	Yes		Yes	Yes	No	No	No	No	Yes
Gudavalli, 2006	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Gur, 2004	Yes	Unclear	Unclear	Yes	Yes	No	Unclear	Yes	Yes
Gusi, 2006	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Yes
Haake, 2007	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	Yes
Haas, 2014	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Harkapaa, 1989	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Hegedus, 2009	Yes	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes
Helminen, 2015	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Clarke-Jenssen, 2014	Yes	Yes	Yes	No	Unclear	Fair
Correa, 2016	Yes	Yes	Yes	Yes	Yes	Fair
Costa, 2009	Yes	Yes	Yes	Yes	Yes	Fair
Da Costa, 2005	No	Yes	Yes	No	Yes	Fair
de Araujo Cazotti, 2017	Yes	Yes	Yes	Yes	Yes	Fair
de Rooij, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Dias, 2003	Yes	Yes	Yes	No	Unclear	Poor
Dilek, 2013	Yes	Yes	Yes	No	Yes	Fair
Djavid, 2007	Yes	Yes	Yes	Unclear	Yes	Fair
Ebadi, 2012	Yes	No	Yes	Yes	Yes	Fair
Ebneshahidi, 2005	Yes	Yes	Yes	No	Yes	Fair
Edinger, 2005	No	No	Yes	No	Unclear	Poor
Ettinger, 1997	Yes	Yes	Yes	No	Yes	Fair
Falcao, 2008	Yes	Yes	Yes	No	Unclear	Fair
Fary, 2011	Yes	Yes	Yes	Yes	Yes	Good
Ferreira, 2007	Yes	Yes	Yes	Yes	Yes	Fair
Fontaine, 2010/2011	No	Yes	Yes	No	Unclear	Fair
Fukuda, 2011	No	Yes	No	No	Yes	Poor
Garcia, 2018	Yes	Yes	Yes	Yes	Yes	Good
Giannotti, 2014	No	No	Yes	Yes	Unclear	Poor
Gibson, 1985	No	No (21% vs. 6%)	Yes	Unclear	Yes	Poor
Gilbert, 2018	No	Yes	Yes	Yes	Yes	Fair
Giombini, 2011	Yes	Yes	Yes	No	Yes	Fair
Goldby, 2006	Yes (>80% at 12 months)	No	Yes	Unclear	Yes	Fair
Gowans, 2001	Yes	Yes	Yes	No	Unclear	Poor
Groessl, 2017	No	Yes	Yes	Yes	Yes	Fair
Gudavalli, 2006	Yes	No	Yes	Unclear	Yes	Fair
Gur, 2004	Yes	Yes	Yes	No	Yes	Fair
Gusi, 2006	Yes	Yes	Yes	No	Unclear	Poor
Haake, 2007	Yes	Yes	Yes	Yes	Yes	Fair
Haas, 2014	Yes	Yes	Yes	Yes	Yes	Fair
Harkapaa, 1989	Yes	Yes	Yes	No	Yes	Poor
Hegedus, 2009	No	No	Yes	No	Yes	Poor
Helminen, 2015	Yes	Yes	Yes	Yes	Yes	Fair

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Highland, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Hinman, 2014	Yes	Yes	Yes	Yes	Yes (vs. sham) No (vs. NT)	Yes (vs. sham) No (vs. NT)	Yes	Yes	Yes
Ho, 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Hoeksma, 2004	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Holroyd, 1991	Unclear	Unclear	Unclear	Yes	No	No	Unclear	Yes	Yes
Holroyd, 2001	Yes	Yes	Yes	Yes	Yes-medication, No-stress	Yes	Yes	Yes	Yes
Holsgaard-Larsen, 2017, 2018	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Hondras, 2009	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Huang, 2003	Yes	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes
Huang, 2005a Arth & Rheum	Yes	Yes	Yes	Yes	Unclear	No	Yes	Unclear	Yes
Huang, 2005b, Archives PM&R	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes
Jensen, 2012/Wicksell 2013	Unclear	Yes	Unclear	Yes	No	No	No	Unclear	Yes
Jia, 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Johnson, 2007	Yes	Yes (minimization	Yes	Yes	No	No	No	No	Yes
Jousset, 2004	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Jubb, 2008	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Juhakoski, 2011	Yes	Yes	Yes	Yes	No	No	No (PRO)/Yes (CRO)	Yes/No (1st year 86%, 2nd year 58%)	Yes
Kankaanpaa, 1999	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Karatay, 2018	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes
Karlsson, 2015	Yes	Yes	Unclear	Yes	No	No	Unclear	Yes	Yes
Karst, 2000	Unclear	Unclear	Unclear	No*	Yes	No	Yes	Yes	No
Kayiran, 2010	Unclear	Unclear	Unclear	No	No	No	Yes (CBO) No	Unclear	Yes
Kayo, 2012	Yes	Yes	Yes	No	No	No	No	Unclear	Yes
Kerr, 2003	Yes	Unclear	Yes	Yes	Unclear	No	Yes	No	Yes
King, 2002	Yes	unclear	No	Unclear	No	No	No	No	Yes
Lamb, 2010/2012	Yes	Yes	Yes	Yes	No	No	Unclear	No	Yes
Lambeek, 2010a	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Lami, 2017	Yes	Yes	No	No	No	No	No	No	Yes
Lansdown, 2009	Yes	Yes	Yes	Yes	No	No	Unclear	Yes	Yes

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Highland, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Hinman, 2014	Yes	Yes	Yes	Yes	Yes	Good - vs. sham Fair - vs. no treatment
Ho, 2017	Yes	Yes	No	Yes	Yes	Fair
Hoeksma, 2004	Yes	Yes	Yes	Unclear	Yes	Fair
Holroyd, 1991	Yes	No	Yes	No	Yes	Poor
Holroyd, 2001	No	No	Yes	No	Yes	Poor
Holsgaard-Larsen, 2017, 2018	Yes	Yes	Yes	Yes	Yes	Fair
Hondras, 2009	Yes	No	Yes	Unclear	Yes	Fair
Huang, 2003	Yes	No	Yes	No	Yes	Poor
Huang, 2005a Arth & Rheum	Yes	Yes	Yes	No	Yes	Fair
Huang, 2005b, Archives PM&R	Yes	Yes	Yes	No	Yes	Fair
Jensen, 2012/Wicksell, 2013	No	Yes	Yes	No	Unclear	Fair
Jia, 2016	Yes	Yes	Yes	Yes	Yes	Good
Johnson, 2007	Yes	Yes	Yes	Yes	Yes	Fair
Jousset, 2004	Yes	Yes	Yes	No	Yes	Poor
Jubb, 2008	Yes	Yes	Yes	No	Yes	Fair
Juhakoski, 2011	Yes	Yes	Yes	Yes	Yes	Fair
Kankaanpaa, 1999	Yes	Yes	Yes	Unclear	Yes	Fair
Karatay, 2018	Yes	Yes	Yes	No	Yes	Fair
Karlsson, 2015	Yes	Yes	Yes	No	Yes	Fair
Karst 2000	Unclear	Unclear	Yes	No	Yes	Poor
Kayiran, 2010	Yes	Yes	Yes	Yes	Yes	Poor
Kayo, 2012	No	Yes	Yes	Yes	Unclear	Fair
Kerr, 2003	No	No	Yes	Unclear	Yes	Poor
King, 2002	No	Unclear	Yes	No	Unclear	Poor
Lamb, 2010/2012	Yes	Yes	Yes	Yes	Yes	Fair
Lambeek, 2010a	Yes	Yes	Yes	Yes	Yes	Fair
Lami, 2017	No	Yes	Yes	No	Yes	Poor
Lansdown, 2009	No	No	Yes	No	Yes	Poor

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Lansinger, 2007	Yes	Yes	Yes	Yes	No	No	No	Unclear*	Yes
Larsson, 2015	Yes	Yes	Yes	Yes	No	No	Yes (CBO) No (PRO)	No	Yes
Lauche, 2016	Yes	Yes	Yes	Yes	No	No	No	Yes/No*	Yes
Laufer, 2005	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Li, 2017	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes
Liang, 2011	Yes	Yes	Unclear	Yes	Yes	No	Unclear	Yes	Yes
Licciardone, 2013	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes
Little, 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Luciano, 2014, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Lumley, 2017	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Lund, 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Lynch, 2012	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes
MacPherson, 2015/Essex, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Mannerkorpi, 2009	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Martin, 2006	Unclear	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Martin, 2012	Yes	Unclear	Yes	Yes	No	No	No	No	Yes
Mat, 2017	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Mazloum, 2017	Unclear	Unclear	No	Yes	No	No	Yes	Unclear	Yes
Mazzuca, 2004	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
McCrae, 2019	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Messier, 2004	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Mist, 2018	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Miyamoto, 2013	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Miyamoto, 2018	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Monticone, 2013	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Monticone, 2014	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Morone, 2009	Yes	Yes	Unclear	Yes	No	No	Yes	Unclear	Yes
Morone, 2016	Yes	Yes	Unclear	Yes	No	No	Yes	Unclear	Yes
Movahedi, 2017	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	Unclear	Yes
Nambi, 2014	Yes	Unclear	Yes	Yes	No	No	Unclear	Yes	Yes
Nassif, 2011	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Natour, 2015	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Nicholas, 1991 Behav	Unclear	Unclear	Yes	Yes	No	No	Unclear	Unclear	Yes
Nicholas, 1992 Pain 1992;48:339–47	Unclear	Unclear	Yes	Yes	No	No	Unclear	Unclear	Yes
O'Moore, 2018	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes
Osteras, 2014	Yes	Yes	Yes	No	No	No	Yes	No	Yes
Pach, 2018	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Paolucci, 2015	Yes	Unclear	Yes	Yes	No	No	No	Yes	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Lansinger, 2007	No	No	No	Unclear	No	Poor
Larsson, 2015	No	Yes	Unclear	Unclear	Yes	Poor
Lauche, 2016	Yes/No**	Yes/No**	Yes	Yes	Yes	Fair Tai chi vs. WL; Poor Tai chi vs. Ex., Ex. vs. WL
Laufer, 2005	Yes	No	Yes	No	Yes	Poor
Li, 2017	Yes	Yes	Yes	Unclear	Yes	Fair
Liang, 2011	Yes	Yes	Yes	Yes	Yes	Fair
Licciardone, 2013	Yes	Yes	Yes	Yes	Yes	Good
Little, 2008	Yes	Yes	Yes	Yes	Yes	Fair
Luciano, 2014, 2017	Yes	Yes	Yes	No	Yes	Fair
Lumley, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Lund, 2008	Yes	Yes	Yes	No	Yes	Fair
Lynch 2012	Yes	No	Yes	Yes	Yes	Fair
MacPherson, 2015	Yes	Yes	Yes	Yes	Yes	Fair
Mannerkorpi, 2009	No	Yes	Yes	No	Yes	Fair
Martin, 2006	Yes	Yes	Yes	Unclear	Yes	Good
Martin, 2012	No	Yes	Yes	No	Yes	Poor
Mat, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Mazloum, 2017	Unclear	Yes	Yes	No	Yes	Poor
Mazzuca, 2004	Yes	Yes	Yes	No	Yes	Fair
McCrae, 2019	No	No	Yes	Yes	Yes	Fair
Messier, 2004	Yes	Yes	Yes	No	Yes	Fair
Mist, 2018	Yes	Yes	Yes	Yes	Yes	Fair
Miyamoto, 2013	Yes	Yes	Yes	Yes	Yes	Fair
Miyamoto, 2018	Yes	Yes	Yes	Yes	Yes	Good
Monticone, 2013	Yes	Yes	Yes	Unclear	Yes	Fair
Monticone, 2014	Yes	Yes	Yes	Unclear	Yes	Fair
Morone, 2009	Yes	Yes	Yes	Unclear	Yes	Fair
Morone, 2016	Yes	Yes	Yes	Yes	Yes	Fair
Movahedi, 2017	Yes	Yes	Yes	Unclear	Unclear	Poor
Nambi, 2014	Yes	Yes	Yes	Unclear	Unclear	Fair
Nassif, 2011	No	No	Yes	Unclear	Unclear	Poor
Natour, 2015	Yes	Yes	Yes	Unclear	Yes	Fair
Nicholas, 1991 Behav	No	Unclear	Yes	No	Yes	Poor
Nicholas, 1992 Pain;48:339–47	Yes	Yes	Yes	No	Yes	Fair
O'Moore, 2018	Yes	Yes	Yes	No	Yes	Fair
Osteras, 2014	No	No	Yes	Yes	Yes	Poor
Pach, 2018	Yes	Yes	Yes	Yes	Yes	Fair
Paolucci, 2015	Yes	Yes	Yes	No	Unclear	Fair

Author, Year	Randomization	Concealed Treatment Allocation	Intention-To-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Pennix, 2001 (FAST)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Pennix, 2002 (FAST)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Pennix, 2002 (FAST)	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Perlman, 2012	Yes	Yes	Yes	Unclear	No	No	No	Yes	Yes
Poole, 2007	Yes (minimization)	Yes (minimization)	Yes	Yes	No	No	No	Unclear	Yes
Quilty, 2003	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Quinn, 2008	Yes	Unclear	Yes	Yes	Yes	No	Unclear	Yes	Yes
Redondo, 2004	Yes	Unclear	Yes	Yes	No	No	No	Yes	Yes
Rejeski, 2002	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Rejeski, 2002	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Roche, 2007/2011	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes
Rosedale, 2014	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes
Rudolfsson, 2014	Yes	Unclear	Unclear	Yes	No	No	Yes/No*	Unclear	Yes
Sahin, 2010	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Sanudo, 2010	Yes	Unclear	Yes	Yes	No	No	No	Yes	Yes
Sanudo, 2012	Unclear	Unclear	No	Yes	No	No	No	No	Yes
Sanudo, 2015	Unclear	Unclear	Yes	Unclear	No	No	No	Unclear	Yes
Saper, 2017	Yes	Unclear	Yes	Yes	No	No	Yes	No	Yes
Saral, 2016	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Schimmel, 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Schmidt, 2011	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Seferiadis, 2015	Yes	Yes	Yes	Yes	No	No	Yes/No*	No	Yes
Segal, 2015	Yes	Yes	Yes	Unclear	No	No	No	Yes	Yes
Sencan, 2004	Unclear	Unclear	Unclear	Yes	No	No	No	Unclear	Yes
Senna, 2011	Unclear	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Sherman, 2005	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Sherman, 2009	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Sherman, 2011	Yes	Yes	Yes	Yes	No	No	Yes	Ye	Yes
Somers, 2012	Yes	Yes	Yes	Yes	No	No	Yes/No (data	No	Yes
Soriano, 1998	Unclear	Unclear	No	Yes	Yes	Yes	Unclear	No	Yes
Stewart, 2007	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Strand, 2001	Unclear	Unclear	Yes	Yes	No	No	Yes	Unclear	Yes
Stukstette, 2013	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Suarez-Almazo, 2010	Yes	Yes	Yes	Yes	Yes - sham No - waitlist	Yes - sham	Yes	Unclear	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Pennix, 2001 (FAST)	Yes	Yes	Yes	No	Yes	Fair
Pennix, 2002 (FAST)	Yes	Yes	Yes	No	Yes	Fair
Pennix, 2002 (FAST)	Yes	Yes	Yes	No	Yes	Fair
Perlman, 2012	Yes	Yes	Yes	Yes	Yes	Fair
Poole, 2007	No	No	Yes	No	Yes	Poor
Quilty, 2003	Yes	Yes	Yes	No	Yes	Fair
Quinn, 2008	Yes	Yes	Yes	Unclear	Yes	Fair
Redondo, 2004	No	Yes	Yes	No	Yes	Poor
Rejeski, 2002	Yes	Yes	Yes	No	Yes	Fair
Rejeski, 2002	Yes	Yes	Yes	No	Yes	Fair
Roche, 2007/2011	Yes	No	Yes	Unclear	Yes	Fair
Rosedale, 2014	No	Yes	Yes	Yes	Yes	Fair
Rudolfsson, 2014	No	Yes	Yes	Yes	Unclear	Fair
Sahin, 2010	Yes	No	Yes	No	No	Fair
Sanudo, 2010	Yes	Yes	Yes	Yes	Yes	Fair
Sanudo, 2012	No	Yes	Yes	No	Unclear	Poor
Sanudo, 2015	Yes	No	Yes	No	Yes	Poor
Saper, 2017	Yes	Yes	Yes	Yes	Yes	Fair
Saral, 2016	Yes	Yes	Yes	Yes	Yes	Fair
Schimmel, 2009	Yes	Yes	Yes	Unclear	Yes	Fair
Schmidt, 2011	Yes	Yes (vs. attention control)	Yes	No	Yes	Fair
Seferiadis, 2015	Yes	Yes	Yes	Yes	No	Fair
Segal, 2015	No	Yes (3 months); No (9 months)	Yes	Yes	Yes	Fair (3 months); Poor (9 months)
Sencan, 2004	Unclear (vs. placebo); Yes (vs. paroxetine)	Unclear (vs. placebo); No (vs. paroxetine)	Yes	No	Yes	Poor
Senna, 2011	No	No	Yes	Unclear	Yes	Poor
Sherman, 2005	Yes	Yes	Yes	Yes	Yes	Fair
Sherman, 2009	Yes	Yes	Yes	No	Yes	Fair
Sherman, 2011	Yes	Yes	Yes	Yes	Yes	Fair
Somers, 2012	No	No	Yes	No	Yes	Poor
Soriano, 1998	No	No	Unclear	Unclear	Unclear	Poor
Stewart, 2007	Yes	Yes	Yes	Yes	Yes	Fair
Strand, 2001	Yes	Yes	Yes	No	Yes	Poor
Stukstette, 2013	Yes	Yes	Yes	Yes	Yes	Fair
Suarez-Almazo, 2010	Yes	Yes	Yes	No	Yes	Good (sham); Fair (waitlist)

Author, Year	Randomization	Concealed Treatment Allocation	Intention-to-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Sullivan, 1998	Unclear	Unclear	Unclear	No	No	No	Yes	Unclear	Yes
Tak, 2005	Yes	Unclear	Yes	Yes	No	No	No/Yes (primary outcomes were patient reported and patient's	No	Yes
Tascioglu, 2004	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	Unclear	No
Tavafian, 2008	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Tavola, 1992	Unclear	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes
Teirlinck, 2016	Yes	Yes	Yes	Yes	No	No	No	Yes (3 month treatment period); No (booster sessions)	Yes
Thamsborg, 2005	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Thieme, 2006	No	Unclear	Yes	Unclear	No	No	No	No	Yes
Thomas, 2006	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Thomas, 2002	Unclear	Unclear	Yes	Yes	Unclear	No	Yes	No	Yes
Thorstensson, 2005	Yes	Unclear	Unclear	Yes	No	No	Unclear	Yes	Yes
Tilbrook, 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Tomas-Carus, 2008, 2009	Unclear	Unclear	No	Unclear	No	No	No	Yes	Yes
Trock, 1994	Yes	Yes	Unclear	No	Yes	No	Yes	Unclear	No
Turner, 1990	Unclear	Unclear	Yes	Yes	No	No	No	Unclear	Yes
UK BEAM Trial Team, 2004	Yes	Yes	Yes	Yes	No	No	No	No	Yes
van der Roer, 2008	Yes	Yes	Yes	Yes	No	No	No	Unclear	Yes
van Eijk-Hustings, 2013	Yes	Yes	Yes	Yes	No	No	No	No	Yes
van Gordon, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
van Santen, 2002	Unclear	Unclear	Yes	No	No	No	Yes (CBO), No (PRO)	Unclear	Yes
Vas, 2006	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Vas, 2016	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Sullivan, 1998	No	No	Yes	No	Yes	Poor
Tak, 2005	No	Yes	Yes	Unclear	Yes	Poor
Tascioglu, 2004	Unclear	Unclear	Yes	No	Yes	Poor
Tavafian, 2008	No	Yes	Yes	Unclear	Yes	Poor
Tavola, 1992	Yes	Yes	Yes	No	Yes	Poor
Teirlinck, 2016	Yes	Yes	Yes	Yes	Yes	Fair
Thamsborg, 2005	Yes	Yes	Yes	Yes	Yes	Fair
Thieme, 2006	Yes	No	Unclear	No	Yes	Poor
Thomas, 2006	Yes	Yes	Yes	Yes	Yes	Fair
Thomas, 2002	No	Yes	Yes	No	Unclear	Poor
Thorstensson, 2005	Yes	Yes	Yes	Yes	Yes	Fair
Tilbrook, 2011	Yes	Yes	Yes	Yes (see note at end of text)	Yes	Fair
Tomas-Carus, 2008/Tomas-Carus, 2009	Yes	Yes	Yes	No	Unclear	Poor
Trock, 1994	Unclear	Unclear	Yes	No	Yes	Poor
Turner, 1990	No	No	Yes	No	Yes	Poor
UK BEAM Trial Team, 2004	Yes	Yes	Yes	Yes	Yes	Fair
Van der Roer, 2008	Yes	Yes	Yes	Yes	Yes	Fair
van Eijk-Hustings, 2013	Yes	Yes	Yes	Yes	Unclear	Fair
van Gordon, 2017	No	Yes	Yes	Yes	Yes	Fair
van Santen, 2002	Yes	No	Yes	Unclear	Yes	Poor (all comparisons)
Vas, 2006	No	Yes	Yes	No	Unclear	Fair
Vas, 2016	Yes	Yes	Yes	Yes	Yes	Good

Author, Year	Randomization	Concealed Treatment Allocation	Intention-To-Treat Analysis	Baseline Group Similarity	Patient Blinded	Care Provider Blinded	Outcome Assessor/ Data Analyst Blinded	Compliance Acceptable in All Groups	Attrition Reported
Verkaik, 2014	Yes	Unclear	Yes	Yes	No	No	No	Yes	Yes
Viljanen, 2003	Yes	Yes	Yes	No*	No	No	No	No**	Yes
Villafaina, 2019	Unclear	Unclear	Yes	Yes	No	No	Yes	Unclear	Yes
Von Korff, 2005	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Waling, 2002	Unclear	Unclear	Yes	No	No	No	No	Unclear	Yes
Waller, 2017	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes
Wang, 2009	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Wang, 2010	Yes	Yes	Yes	No	No	No	Yes (CBO) No (PRO)	No	Yes
Wang, 2018	Yes	Yes	Yes	Yes	No	No	No	No	Yes
Weng, 2009	Yes	Yes	Yes	Unclear	Unclear	No	Yes	Yes	Yes
White, 2004	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Wigers, 1996	Yes	Unclear	Yes	Yes	No	No	No	Unclear	Yes
Williams, 2002	Unclear	Unclear	Unclear	Unclear	No	No	No	Unclear	Yes
Williams, 2005	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Williams, 2009	Unclear	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Williamson, 2007	Yes	Yes	Yes	Yes	No	No	Yes	Unclear	Yes
Witt, 2005	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Yes
Yegin, 2017	Unclear	Unclear	Yes	Yes	Yes	No	Yes	Unclear	Yes
Yildiz, 2015	Yes	Unclear	Unclear	No	Yes	Yes	Unclear	Unclear	Yes
Yurtkuran, 2007	Yes	Unclear	Yes	Yes	Yes	No	Yes	Unclear	Yes
Zgierska, 2016	Yes	Yes	Yes	No	No	No	Unclear	No	Yes
Zhang, 2013	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes

Author, Year	Attrition Acceptable	Attrition Between Groups Acceptable	Timing of Outcome Assessment in All Groups Similar	Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Quality Rating
Verkaik, 2014	No	Yes	Yes	Yes	Yes	Poor
Viljanen, 2003	Yes	Yes	Yes	No	Yes	Fair
Villafaina, 2019	Yes	Yes	Yes	Yes	Yes	Fair
Von Korff, 2005	Yes	Yes	Yes	Unclear	Yes	Fair
Waling, 2002	No	Yes	Yes	No	Yes	Poor
Waller, 2017	Yes	No	Yes	Yes	Yes	Fair
Wang, 2009	Yes	Yes	Yes	Yes	Yes	Fair
Wang, 2010	Yes	Yes	Yes	Yes	Yes	Fair
Wang, 2018	No	Yes	Yes	Yes	Yes	Fair
Weng, 2009	Yes	No	Yes	No	Yes	Poor
White, 2004	No	Yes	Yes	No	Yes	Fair
Wigers, 1996	No	No (stress management vs. usual care and vs. exercise) Yes (exercise vs. usual care)	Yes	Unclear	Yes	Poor (stress management vs. usual care and vs. exercise) Fair (exercise vs. usual care)
Williams, 2002	Yes	Yes	Yes	No	Unclear	Poor
Williams, 2005	No	No	Yes	Unclear	Yes	Fair
Williams, 2009	Yes	No	Yes	Unclear	Yes	Fair
Williamson, 2007	No	No	Yes	No	Yes	Poor
Witt, 2005	Yes	Yes	Yes	Yes	Yes	Fair
Yegin, 2017	Yes	Yes	Yes	No	Yes	Poor
Yildiz, 2015	Yes	Yes	Yes	No	Yes	Fair
Yurtkuran, 2007	Yes	Yes	Yes	No	Yes	Fair
Zgierska, 2016	Yes	Yes	Yes	Yes	Yes	Poor
Zhang, 2013	No	Yes	Yes	No	Yes	Fair

Table E-2. Quality assessment of crossover trial

Author, Year	Randomization	Concealed Treatment Allocation	Intention-To-Treat Analysis	Independent or Blind Assessment	Appropriate Washout Period for Condition	Attrition Reported	Attrition Acceptable	Number Completing Period Reported; Attrition b/w Periods Acceptable (<10%)
Paolucci, 2016	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes - first period; No - second period	Yes

Author, Year	Results From First Phase Reported Separately	Accounting for Missing Data	Use of Methods for Within-Subject Variation, Correlated Data	Analysis of Carryover Effect	Is There a Registered or Published Protocol	Avoidance of Selective Outcomes Reporting	Risk of Bias (Cochrane Back Group)
Paolucci, 2016	Yes	No	Yes	No	Yes	Yes	Poor

Appendix F. Exercise Categories

Table F-1. Exercise and related intervention categories

General Category	Types Included
Muscle Performance	• Resistance training (strength, power or endurance exercises) • Sling exercise • Aquatic therapy/exercise • Musculoskeletal rehabilitation • Pilates
Neuromuscular Re-Education	• Motor control exercises (MCE) • Trunk coordination/trunk strengthening • Stabilization exercises • Posture training
Mobility, Flexibility	• McKenzie/directional preference • Stretching • Lumbar flexion exercises • Other mobility or flexibility exercises
Cardiovascular/Aerobic	• Cardiovascular training • Aerobic training • Walking • Aquatic therapy/exercise if aerobic focused
Combined Exercise	• Intervention combining exercises from two or more of the above categories

Appendix G. Strength of Evidence

All outcomes were considered direct; therefore, the Directness domain is not shown on the strength of evidence tables.

References are located in Appendix B.

Table G-1. Low back pain (KQ 1) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Exercise	*Exercise vs. usual care, attention control, or a placebo intervention*	Function *Short-term*	10 (N=940) Bramberg 2017[a] Costa 2009 Garcia 2018[a] Goldby 2006 Kankaanpaa 1999 Mazloum 2017[a] Miyamoto 2013 Miyamoto 2018[a] Nassif 2011 Natour 2014	Moderate	Consistent	Precise	Undetected	Moderate (upgraded 1 level from prior report)	Pooled SMD –0.31 (95% CI –0.50 to –0.13); I^2=32% (excluding an outlier trial)[b]
		Function Intermediate-term	5 (N=616) Costa 2009 Garcia 2018[a] Goldby 2006 Kankaanpaa 1999 Miyamoto 2018[a]	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD –0.17 (95% CI –0.39 to 0.02); I^2=0%
		Function Long-term	1 (N=124) Goldby 2006	Moderate	Unknown	Imprecise	Undetected	Low	Difference 0.0 (95% CI –11.4 to 11.4) on the 0 to 100 ODI

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Short-term*	11 (N=981) Areeudomwong, 2017[a] Bramberg 2017[a] Costa 2009 Garcia 2018[a] Goldby 2006 Kankaanpaa 1999 Mazloum 2017[a] Miyamoto 2013 Nassif 2011 Natour 2014 Miyamoto, 2018[a]	Moderate	Inconsistent	Precise	Undetected	Low (downgraded 1 level from prior report)	Pooled difference –1.21 (95% CI –1.77 to –0.65) on a 0 to 10 scale; I^2=64%
		Pain *Intermediate-term*	5 (N=616) Costa 2009 Garcia 2018[a] Goldby 2006 Kankaanpaa 1999 Miyamoto 2018 [a]	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference –0.85 (95% CI –1.67 to –0.07) on a 0 to 10 scale; I^2=50%
		Pain *Long-term*	1 (N=124) Goldby 2006	Moderate	Unknown	Imprecise	Undetected	Low	Difference –1.55 on a 0 to 10 scale (95% CI –2.76 to –0.34)
		Harms	2 (N=240) Costa 2009 Miyamoto 2013	Moderate	Consistent	Imprecise	Undetected	Low	No evidence of increased risk of serious harms
Psychological Therapy	*Psychological therapy vs. usual care or attention control*	Function *Short-term*	3 (N=906) Cherkin 2016 Lamb 2010/2012 Poole 2007	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.24 (95% CI –0.38 to –0.04); I^2=0%
		Function *Intermediate-term*	3 (N=1,026) Cherkin 2016/2017 Johnson 2007 Lamb 2010/2012	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.24 (95% CI –0.38 to –0.10); I^2=0%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Function *Long-term*	3 (N=815) Cherkin 2017 Johnson 2007 Lamb 2010/2012	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.28 (95% CI –0.43 to –0.13); I^2=0%
		Pain *Short-term*	3 (N=906) Cherkin 2016 Lamb 2010/2012 Poole 2007	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.75 (95% CI –1.01 to –0.41) on a 0 to 10 scale; I^2=0%
		Pain *Intermediate-term*	3 (N=1,026) Cherkin 2016 Johnson 2007 Lamb 2010/2012	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.71 (95% CI –0.97 to –0.46); I^2=0%
		Pain *Long-term*	3 (N=816) Cherkin 2016/2017 Johnson 2007 Lamb 2010/2012	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.55 (95% CI –0.92 to –0.23); I^2=0%
	Psychological therapy vs. exercise	Function *Intermediate- and long-term*	1 (N=49) Turner 1990	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from 1 poor-quality trial
		Pain *Intermediate- and long-term*	1 (N=49) Turner 1990	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from 1 poor-quality trial
		Harms	1 (N=701) Lamb 2010/2012	Moderate	Unknown	Imprecise	Undetected	Low	One trial reported no serious adverse events and withdrawal due to adverse events in <1% of patients randomized to psychological therapy
Physical Modalities	*Short-wave diathermy vs. sham diathermy*	Pain, function, harms	1 (N=68) Gibson, 1985	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial
	Ultrasound vs. sham ultrasound	Function *Short-term*	2 (N=505) Ebadi 2012 Licciardone 2013	Moderate	Inconsistent	Precise	Undetected	Insufficient	Inconsistent effects on function in two trials

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Short-term*	2 (N=505) Ebadi 2012 Licciardone 2013	Moderate	Consistent	Precise	Undetected	Low	No effects on pain in two trials
		Harms	1 (N=455) Licciardone 2013	Moderate	Consistent	Imprecise	Undetected	Low	Any adverse event: RR 1.03 (95% CI 0.49 to 2.13) Serious adverse event: RR 0.48 (95% CI 0.12 to 1.88)
	Interferential therapy vs. placebo interferential therapy	Function *Short-term*	1 (N=150) Correa 2016[c]	Moderate	Unknown	Unknown	Undetected	Low[d]	Difference 0.2 to 0.3 points (CI unclear)
		Pain *Short-term*	1 (N=150) Correa 2016[c]	Moderate	Unknown	Unknown	Undetected	Low[d]	Difference 0.2 to 0.4 points (CI unclear)
		Harms	1 (N=150) Correa 2016[c]	Moderate	Unknown		Undetected		Withdrawals due to adverse events: RR 1.0 (95% CI 0.14 to 6.8)
	Low-level laser therapy vs. sham laser	Function *Short-term*	1 (N=56) Basford 1999	Moderate	Unknown	Precise	Undetected	Low	Difference –8.2 (95% CI –13.6 to –2.8) on the 0 to 100 ODI
		Pain *Short-term*	1 (N=56) Basford 1999	Moderate	Unknown	Imprecise	Undetected	Low	Difference –16.0 (95% CI –28.3 to –3.7) on a 0 to 100 scale
	Low-level laser therapy vs. exercise therapy	Function *Intermediate-term*	1 (N=35) Djavid 2007	Moderate	Unknown	Imprecise	Undetected	Low	Difference –4.4 (95% CI –11.4 to 2.5) on the ODI (0 to 100 scale)
		Pain *Intermediate-term*	1 (N=35) Djavid 2007	High	Unknown	Imprecise	Undetected	Low	Difference –0.9 (95% CI –2.5 to 0.7) on a 0 to 10 scale
		Harms	3 (N=162) Djavid 2007 Basford 1999 Soriano 1998	Moderate	Consistent	Imprecise	Undetected	Low	No adverse events were reported

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
Manual Therapies	*Massage vs. sham massage, usual care, or attention control*	Function *Short-term*	6 (N=694) Ajimsha 2014 Arguisuelas 2017[e] Cherkin 2011 Movahedi 2017[e] Poole 2007 Quinn 2008	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.38 (95% CI –0.63 to –0.20); I^2=0%
		Function *Intermediate-term*	3 (N=676) Cherkin 2001 Cherkin 2011 Little 2008	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD –0.09 (95% CI –0.26 to 0.12); I^2=0%
		Pain *Short-term*	5 (N=644) Ajimsha 2014 Arguisuelas 2017[e] Cherkin 2011 Poole 2007 Quinn 2008	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.55 (95% CI –0.88 to –0.23) on a 0 to 10 scale; I^2=0%
		Pain *Intermediate-term*	3 (N=680) Cherkin 2001 Cherkin 2011 Little 2008	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference –0.02 (95% CI –0.56 to 0.44); I^2=0%
	Massage vs. exercise	Function Intermediate-term	1 (N=144) Little 2008	Moderate	Unknown	Imprecise	Undetected	Low	Difference 1.2 (95% CI –1.47 to 3.87) on the 0 to 24 Roland Disability Questionnaire
		Pain *Intermediate-term*	1 (N=144) Little 2008	Moderate	Unknown	Imprecise	Undetected	Low	Difference 0.60 (95% CI –0.67 to 1.87) on the 0 to 10 Von Korff pain scale
	Massage vs. sham, usual care, attention control, or exercise	Harms	7 (N=906) Ajimsha 2014 Arguisuelas 2017[e] Cherkin 2001 Cherkin 2011 Little 2008 Movahedi 2017[e] Quinn 2008	Moderate	Consistent	Imprecise	Undetected	Low	Four trials reported no serious adverse events and one trial reported no adverse events; in four trials the proportion of massage patients with increased pain ranged from <1% to 26%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Traction vs. sham traction	Function *Short-term*	2 (N=211) Beurskens 1997 Schimmel 2009	Moderate	Consistent	Imprecise	Undetected	Low	Differences 2 points on the ODI and 0.7 points on the Roland Disability Questionnaire, p>0.05 in both trials
		Pain *Short-term*	2 (N=211) Beurskens 1997 Schimmel 2009	Moderate	Consistent	Imprecise	Undetected	Low	Differences –4 points in one trial and 4 points in one trial, p>0.05 in both trials
		Harms	No studies	--	--	--	--	--	No evidence
	Spinal manipulation vs. sham manipulation, usual care, attention control, or placebo intervention	Function *Short-term*	3 (N=704) Haas 2014 Hondras 2009 Senna 2011	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.34 (95% CI –0.75 to –0.02); I^2=45%
		Function *Intermediate-term*	3 (N=1,000) Haas 2014 Senna 2011 UK BEAM 2004	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.40 (95% CI –0.85 to –0.05); I^2=65%
		Pain *Short-term*	3 (N=530) Gibson 1985 Haas 2014 Senna 2011	High	Inconsistent	Imprecise	Undetected	Low	Pooled difference –0.36 (95% CI –0.62 to 0.25) on a 0 to 10 scale; I^2=0%
		Pain *Intermediate-term*	3 (N=978) Haas 2014 Senna 2011 UK BEAM 2004	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.64 (95% CI –0.93 to –0.35); I^2=0%
	Spinal manipulation vs. exercise	Function *Short-term*	3 (N=640) Bronfort 2011 Ferreira 2007 Gudavalli 2006	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled SMD 0.02 (95% CI –0.28 to 0.30); I^2=37%
		Function *Intermediate-term*	4 (N=1,117) Bronfort 2011 Ferreira 2007 Gudavalli 2006 UK BEAM 2004	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled SMD 0.01 (95% CI –0.15 to 0.21); I^2=19%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Short-term*	3 (N=636) Bronfort 2011 Ferreira 2007 Gudavalli 2006	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled difference 0.31 (95% CI –0.42 to 1.06) on a 0 to 10 scale; I^2=34%
		Pain *Intermediate-term*	4 (N=1,093) Bronfort 2011 Ferreira 2007 Gudavalli 2006 UK BEAM 2004	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference 0.23 (95% CI –0.14 to 0.59); I^2=0%
		Harms	7 (N=2,201) Bronfort 2011 Ferreira 2007 Gudavalli 2006 Haas 2014 Hondras 2009 Senna 2011 UK BEAM 2004	Moderate	Consistent	Precise	Undetected	Moderate	No serious adverse events or withdrawals due to adverse events in 7 trials. Nonserious adverse events (primarily increased pain) reported in 3 trials
Mindfulness Practices	*Mindfulness-based stress reduction vs. usual care or attention control*	Function *Short-term*	4 (N=581) Cherkin 2016 Morone 2009 Morone 2016 Zgierska 2017	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled SMD –0.14 (95% CI –0.51 to 0.02); I^2=0%
		Function *Intermediate-term*	1 (N=229) Cherkin 2016	Moderate	Unknown	Imprecise	Undetected	Low	SMD –0.20 (95% CI –0.46 to 0.06)
		Function *Long-term*	1 (N=229) Cherkin 2016/2017	Moderate	Unknown	Imprecise	Undetected	Low	SMD –0.09 (95% CI –0.35 to 0.16)
		Pain *Short-term*	3 (N=546) Cherkin 2016 Morone 2009 Morone 2016	Moderate	Consistent[f]	Precise	Undetected	Moderate	Pooled difference –0.68 (95% CI –1.29 to –0.28) on a 0 to 10 scale; I^2=45% (excluding 2 outlier trials)[f]

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Intermediate-term*	1 (N=229) Cherkin 2016	Moderate	Unknown	Precise	Undetected	Low	Difference –0.75 (95% CI –1.16 to –0.34)
		Pain *Long-term*	1 (N=229) Cherkin 2017	Moderate	Unknown	Precise	Undetected	Low	Difference –0.22 (95% CI –0.63 to 0.19)
		Harms	4 (N=577) Cherkin 2016 Morone 2009 Morone 2016 Zgierska 2017	Moderate	Consistent	Imprecise	Undetected	Low	One trial reported temporarily increased pain in 29% of patients undergoing MBSR and three trials reported no adverse events
Mind-Body Practices	*Yoga vs. attention control or wait list*	Function *Short-term*	8 (N=982) Bramberg 2017[g] Groessl 2017 Highland, 2017[g] Saper 2017 Sherman 2005 Sherman 2011 Tilbrook 2011 Williams 2009	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.45 (95% CI –0.69 to –0.28); I^2=31%
		Function *Intermediate-term*	3 (N=540) Saper 2017 Tilbrook 2011 Williams 2009	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD –0.29 (95% CI –0.47 to –0.11); I^2=0%
		Pain *Short-term*	7 (N=710) Bramberg 2017[g] Groessl 2017 Highland 2017[g] Saper 2017 Sherman 2005 Sherman 2011 Williams 2005	Moderate	Inconsistent	Precise	Undetected	Low	Pooled difference –0.87 (95% CI –1.49 to –0.24) on a 0 to 10 scale; I^2=64%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Intermediate-term*	2 (N=268) Saper 2017 Williams 2009	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –1.16 (95% CI –2.16 to –0.27); I^2=0%
	Yoga vs. exercise	Function *Short-term*	4 (N=559) Bramberg 2017[g] Saper 2017 Sherman 2005 Sherman 2011	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD –0.04 (95% CI –0.27 to 0.16); I^2=0%
		Function *Intermediate-term*	1 (N=246) Saper 2017	Moderate	Unknown	Imprecise	Undetected	Low	SMD –0.01 (95% CI –0.26 to 0.24)
		Pain *Short-term*	5 (N=575) Bramberg, 2017[g] Nambi 2014 Saper 2017 Sherman 2005 Sherman 2011	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled difference –0.63 (95% CI –1.68 to 0.245) on a 0 to 10 scale; I^2=88%
		Pain *Intermediate-term*	1 (N=246) Saper 2017	Moderate	Unknown	Imprecise	Undetected	Low	Difference 0.30 (95% CI –0.39 to 0.99)
		Harms	3 (N=616) Saper 2017 Sherman 2011 Tilbrook 2011	Moderate	Consistent	Imprecise	Undetected	Low	No difference in risk of any adverse event (primarily mild back or joint pain); three serious adverse events in yoga patients were reported by one trial each: worsening back pain related to yoga, herniated disc, and cellulitis (≤1% of patients in each trial)
	Qi Gong vs. exercise therapy	Function *Short-term*	1 (N=125) Blodt 2015	Moderate	Unknown	Imprecise	Undetected	Low	Difference 0.9 (95% CI –0.1 to 2.0) on the 0 to 24 Roland Disability Questionnaire
		Function *Intermediate-term*	1 (N=125) Blodt 2015	Moderate	Unknown	Precise	Undetected	Low	Difference 1.2 (95% CI 0.1 to 2.3) on the Roland Disability Questionnaire

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Pain *Short-term*	1 (N=125) Blodt 2015	Moderate	Unknown	Precise	Undetected	Low	Difference 7.7 (95% CI 0.7 to 14.7) on a 0 to 100 scale
		Pain *Intermediate-term*	1 (N=125) Blodt 2015	Moderate	Unknown	Imprecise	Undetected	Low	Difference 7.1 (95% CI –1.0 to 15.2) on a 0 to 100 scale
		Harms	1 (N=125) Blodt 2015	Moderate	Unknown	Imprecise	Undetected	Low	No difference in risk of adverse events
Acupuncture	*Acupuncture vs. sham acupuncture, usual care, attention control, or a placebo intervention*	Function *Short-term*	4 (N=2,066) Brinkhaus 2006a Cherkin 2009 Cho 2013 Haake 2007	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.23 (95% CI –0.35 to –0.04); I^2=25%
		Function *Intermediate-term*	3 (N=997) Brinkhaus 2006a Cherkin 2001 Cherkin 2009	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled SMD –0.08 (95% CI –0.42 to 0.28); I^2=64%
		Function *Long-term*	1 (N=218) Thomas 2006	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference –3.4 (95% CI –7.8 to 1.0) on the 0 to 100 ODI
		Pain *Short-term*	5 (N=2,109) Brinkhaus 2006a Carlsson 2001 Cherkin 2009 Cho 2013 Haake 2007	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.54 (95% CI –0.91 to –0.16) on a 0 to 10 scale; I^2=25%
		Pain *Intermediate-term*	5 (N=1,264) Brinkhaus 2006a Carlsson 2001 Cherkin 2001 Cherkin 2009 Thomas 2006	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference –0.22 (95% CI –0.67 to 0.21) on a 0 to 10 scale; I^2=0%
		Pain *Long-term*	1 (N=218) Thomas 2006	Moderate	Unknown	Precise	Undetected	Low	Difference –0.83 (95% CI –1.53 to –0.13) on a 0 to 10 scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Harms	6 (N=2,525) Brinkhaus 2006a Cherkin 2001 Cherkin 2009 Cho 2013 Haake 2007 Thomas 2006	Moderate	Consistent	Imprecise	Undetected	Low	No evidence of increased risk of serious harms
Multi-disciplinary Rehabilitation	*Multi-disciplinary rehabilitation vs. usual care*	Function *Short-term*	4 (N=907) Bendix 1996 Harkapaa 1989 Lambeek 2010 von Korff 2005	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.30 (95% CI –0.63 to 0.00); I^2=58%
		Function *Intermediate-term*	4 (N=481) Abbassi 2012 Lambeek 2010 Strand 2001 von Korff 2005	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.37 (95% CI –0.69 to –0.08); I^2=34%
		Function *Long-term*	2 (N=286) Bendix 1996 von Korff 2005	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD –0.04 (95% CI –0.36 to 0.35); I^2=0%
		Pain *Short-term*	4 (N=907) Bendix 1996 Harkapaa 1989 Lambeek 2010 von Korff 2005	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.53 (95% CI –0.86 to –0.11) on a 0 to 10 scale; I^2=0%
		Pain *Intermediate-term*	4 (N=481) Abbassi 2012 Lambeek 2010 Strand 2001 von Korff 2005	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.62 (95% CI –1.06 to –0.18); I^2=0%
		Pain *Long-term*	2 (N=286) Bendix 1996, von Korff 2005	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference –0.35 (95% CI –1.10 to 0.34); I^2=0%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
	Multi-disciplinary rehabilitation vs. exercise	Function *Short-term*	6 (N=379) Bendix 1995 Jousset 2004 Monticone 2014 Nicholas 1991 Nicholas 1992 van der Roer 2008	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD –0.21 (95% CI –0.54 to 0.01); I^2=32%
		Function *Intermediate-term*	5 (N=415) Bendix 2000 Nicholas 1991 Roche 2007/2011 Turner 1990 van der Roer 2008	Moderate	Consistent[h]	Precise	Undetected	Moderate	Pooled SMD –0.20 (95% CI –0.40 to –0.00); I^2=0% (excluding an outlier trial)[h]
		Function *Long-term*	2 (N=136) Bendix, 1995 Turner 1990	Moderate	Consistent[h]	Imprecise	Undetected	Low	Pooled SMD –0.07 (95% CI –0.50 to 0.39); I^2=0% (excluding an outlier trial)[h]
		Pain *Short-term*	6 (N=377) Bendix 1995 Jousset 2004 Monticone 2014 Nicholas 1991 Nicholas 1992 van der Roer 2008	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.69 (95% CI –1.15 to –0.22) on a 0 to 10 scale; I^2=0%
		Pain *Intermediate-term*	5 (N=409) Bendix 2000 Nicholas 1991 Roche 2007/2011 Turner 1990 van der Roer	Moderate	Consistent[h]	Precise	Undetected	Moderate	Pooled difference –0.55 (95% CI –1.00 to –0.11); I^2=0% (excluding an outlier trial)[h]
		Pain *Long-term*	2 (N=136) Bendix, 1995 Turner 1990	Moderate	Consistent[h]	Imprecise	Undetected	Low	Pooled difference 0.00 (95% CI –1.31 to 1.17); I^2=0% (excluding an outlier trial)[h]

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction, and Magnitude of Effect
		Harms	2 (N=94) Monticone 2014 Tavafian 2008	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient data on harms from 2 trials, though no serious harms were reported

a New Exercise trial
b Outlier trial exclude, Areeudomwong, 2017
c New Physical Modalities trial, Interferential therapy,
d There were no Interferential therapy trials in the prior report.
e New Manual therapies – massage trial
f Outlier trial excluded, Banth 2015
g New Mind Body Practice – yoga trial
h Outlier trial excluded, Monticone 2013

Table G-2. Neck pain (KQ 2) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Exercise	*Exercise vs. attention control, no treatment or waitlist*	Function *Short-term*	3 (N=444) Stewart 2007 Lauche 2016 Viljanen 2003	Moderate	Inconsistent[a]	Imprecise	Undetected	Low	Pooled SMD –0.22, 95% CI –0.66 to 0.17, I^2=72.6% [excluding outlier trial][a] Combination exercise only (2 trials), pooled SMD –0.44, 95% CI –0.76 to –0.09
		Function *Intermediate-term*	1 (N=230) Viljanen 2003	Moderate	Unknown	Precise	Undetected	Low	SMD 0.14, 95% CI –0.12 to 0.40)
		Function *Long-term*	1 (N=125) Stewart 2007	Moderate	Unknown	Imprecise	Undetected	Low	SMD –0.39, 95% CI –0.74 to –0.03
		Pain *Short-term*	3 (N=444) Stewart 2007 Lauche 2016 Viljanen 2003	Moderate	Inconsistent[a]	Imprecise	Undetected	Low	Pooled difference –0.70, 95% CI –1.62 to 0.15, I^2=63.7% [excluding outlier trial][a] Combination exercise only (2 two trials), pooled difference –1.12, 95% CI –1.82 to –0.43
		Pain *Intermediate-term*	2 (N=353) Andersen 2008 Viljanen 2003	Moderate	Consistent	Precise	Undetected	Low	Pooled difference –0.25, 95% CI –0.81 to 0.31, I^2=0.0%
		Pain *Long-term*	3 (N=349) Stewart 2007 Andersen 2008 Waling 2002	Moderate	Inconsistent	Precise	Undetected	Low	Pooled difference 0.07, 95% CI –0.51 to 0.88, I^2=0%
		Harms	2 (N=201) Stewart 2007 Lauche 2016	High	Consistent	Imprecise	Undetected	Low	No evidence of increased risk of serious harms

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
	Exercise vs. pharmaco-logical therapy	Function *Short-term*	1 (N=40) Aslan Telci 2012 (vs. NSAIDs + muscle relaxants)	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient data from 1 poor quality trial
		Function *Short-term*	1 (N=64) de Araujo Cazotti 2018[b] (vs. acetaminophen)	Moderate	Unknown	Imprecise	Undetected	Low	Difference –5.6 (95% CI –8.36 to –2.83) on the 0 to 50 NDI scale
		Pain *Short-term*	1 (N=40) Aslan Telci 2012 (vs. NSAIDs + muscle relaxants)	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient data from 1 poor quality trial
		Pain *Short-term*	1 (N=64) de Araujo Cazotti 2018[b] (vs. acetaminophen)	Moderate	Unknown	Imprecise	Undetected	Low	Difference –3.11 (95% CI –4.17 to –2.05) on the 0 to 10 NPS
		Pain, Function, *Intermediate-term*	1 (N=40) Aslan Telci 2012 (vs. NSAIDs + muscle relaxants)	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient data from 1 poor quality trial
		Harms	1 (N=64) de Araujo Cazotti 2018[b] (vs. acetaminophen)	Moderate	Unknown	Imprecise	Undetected	Low[c]	One trial reported no adverse events
Psychological Therapies	*Relaxation training vs. no intervention*	Function *Short-term*	1 (N=258) Viljanen 2003	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference 0.1 (95% CI –2.9 to 3.2) on 0-80 scale
		Function *Intermediate-term*	1 (N=258) Viljanen 2003	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference 0.2 (95% CI –2.8 to 3.1) on 0-80 scale
		Pain *Short-term*	1 (N=258) Viljanen 2003	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference 0.2 (95% CI –0.4 to 0.8) on 0-10 scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Intermediate-term*	1 (N=258) Viljanen 2003	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference 0.2 (95% CI –0.3 to 0.8) on 0-10 scale
	Relaxation training vs. exercise	Function *Short-term*	1 (N=263) Viljanen 2003	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference 0.2 (95% CI –2.8 to 3.2) on 0-80 scale
		Function *Intermediate-term*	1 (N=263) Viljanen 2003	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference 0.2 (95% CI –2.7 to 3.2) on 0-80 scale
		Pain *Short-term*	1 (N=263) Viljanen 2003	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference –0.2 (95% CI –0.8 to 0.4) on 0-10 scale
		Pain *Intermediate-term*	1 (N=263) Viljanen 2003	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference –0.2 (95% CI –0.8 to 0.3) on 0-10 scale
	Relaxation training vs. no intervention or exercise	Harms	None	–	–	–	–	–	No evidence
Physical Modalities	*Traction vs. attention control*	Function, Pain, Harms *Short-term*	1 (N=79) Chiu 2011	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial.
	Laser vs. sham intervention	Function *Short-term*	2 (N=144) Chow 2006 Gur 2004	Low	Consistent	Imprecise	Undetected	Moderate	Pooled difference –13.60 (95% CI –26.30 to –6.30) on a 0-100 scale: I^2=0%
		Pain *Short-term*	3 (N=192) Chow 2006 Gur 2004 Altan 2005	Low	Consistent	Imprecise	Undetected	Moderate	Pooled difference –1.89, (95% CI –3.34 to –0.06) on a 0-10 scale: I^2=61%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	1 (N=90) Chow 2006	Low	Unknown	Imprecise	Undetected	Low	Adverse effects occurred with similar frequency in both groups. The most frequently reported adverse effects in the intervention group included mild (78%) or moderate (60%) increased neck pain, increased pain elsewhere (78%), mild headache (60%) and tiredness (24%).
	Electro-magnetic fields vs. sham intervention	Function, Pain, Harms *Short-term*	1 (N=81) Trock 1994	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial.
Manual Therapies	*Massage vs. attention or waitlist control*	Function *Short-term*	2 (N=148) Sherman 2009 Pach 2018[c]	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference –3.66, (95% CI –6.58 to –0.56) on a 0-50 NDI scale: I^2=10% 1 trial (Sherman): Success (≥5 points), 39% vs. 17%; RR 2.7 (95% CI 0.99 to 7.5)
		Function *Intermediate-term*	1 (N=58) Sherman 2009	Moderate	Unknown	Imprecise	Undetected	Low	Success (≥5 points): 57% vs. 31%, RR 1.8 (95% CI 0.97 to 3.5)
		Pain *Short-term*	1 (N=92) Pach 2018[c]	Moderate	Unknown	Imprecise	Undetected	Low	Difference –1.8 (95% CI –2.7 to –0.9) on a 0-10 scale
	Massage vs. exercise	Pain *Intermediate-term*	1 (N=85) Rudolfsson 2014	Moderate	Unknown	Imprecise	Undetected	Low	Difference 0.2 (95% CI –0.82 to 1.22) on the 0-10 NRS
	Massage vs. attention control or vs. exercise	Harms	2 (N=143) Sherman 2009 Rudolfsson 2014	Moderate	Unknown	Imprecise	Undetected	Low	No evidence of increased risk of serious harms
Mind-body Practices	*Alexander Technique plus usual*	Function *Short-term*	1 (N=344) MacPherson 2015	Moderate	Unknown	Precise	Undetected	Low	Difference –5.56 (95% CI –8.33 to –2.78) on 0-100% scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
	care vs. usual care alone	Function *Intermediate-term*	1 (N=344) MacPherson 2015	Moderate	Unknown	Precise	Undetected	Low	Difference –3.92 (95% CI –6.87 to –0.97) on 0-100% scale
		Harms	1 (N=344) MacPherson 2015	Moderate	Unknown	Imprecise	Undetected	Low	No clear difference in the risk of any non-serious adverse event (e.g., pain and incapacity, knee injury, muscle spasm, and complications after surgery): RR 2.25 (95% CI 1.00 to 5.04) No serious treatment-related adverse events reported.
	Basic body awareness therapy vs. exercise	Function *Short-term*	1 (N=113) Seferiadis 2016	Moderate	Unknown	Imprecise	Undetected	Low	Difference between groups in mean change from baseline –1, p>0.05
		Function *Intermediate- and long-term*	1 (N=139) Lansinger 2007	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial
		Pain *Intermediate- and long-term*	1 (N=139) Lansinger 2007	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial
		Harms	1 (N=113) Seferiadis 2016	Moderate	Unknown	Imprecise	Undetected	Low	No serious adverse effects Any non-serious adverse effects: RR 0.65 (95% CI 0.37 to 1.14)
Acupuncture	Acupuncture vs. sham, placebo or usual care	Function *Short-term*	5 (N=919) White 2004 Liang 2011 Zhang 2013 MacPherson 2015 Ho 2017	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.40 (95% CI –0.67 to –0.14); I^2=61%
		Function *Intermediate-term*	3 (N=563) White 2004 Zhang 2013 MacPherson 2015	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD –0.19 (95% CI –0.37 to 0.05); I^2=0%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Long- term*	1 (N=107) White 2004	Moderate	Unknown	Imprecise	Undetected	Low	Difference –1.8 (95% CI –4.84 to 1.24) on a 0-50 scale
		Pain *Short-term*	4 (N=490) Sahin 2010 White 2004 Liang 2011 Zhang 2013	Moderate	Inconsistent[d]	Precise	Undetected	Low	Pooled difference –0.27 (95% CI –0.59 to 0.05) on a 0-10 scale; I^2=2% [excluding outlier trial][d]
		Pain *Intermediate-term*	3 (N=354) White 2004 Vas 2006 Zhang 2013	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled difference 0.40 (95% CI –0.45 to 1.44) on a 0-10 scale; I^2=19%
		Pain *Long- term*	1 (N=107) White 2004	Moderate	Unknown	Imprecise	Undetected	Low	Pooled difference –0.35 (95% CI –1.34 to 0.64) on a 0-10 scale
	Acupuncture vs. pharmaco-logical care	Function *Short-term*	1 (N=30) Cho 2014	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence due to study limitations, unknown consistency and imprecision from one poor-quality study
		Pain *Short-term*	2 (N=53) Birch 1998 Cho 2014	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence due to study limitations and imprecision from 2 poor quality studies
	Acupuncture vs. sham, placebo, usual care or pharmaco-logical care	Harms	6 (N=937) Cho 2014 MacPherson 2015 Vas 2006 White 2004 Liang 2011 Zhang 2013	Moderate	Consistent	Precise	Undetected	Moderate	No serious treatment-related adverse events reported. Most common non-serious adverse effects included numbness/ discomfort, fainting and bruising.

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference.

a Outlier trial excluded, Li 2017b. Heterogeneity is explained in part by the contribution of the good quality study; the others are fair quality.

b New Exercise trial.

c New Manual therapies – massage – trial.

d Outlier trial excluded, Ho 2017.

Table G-3. Knee osteoarthritis pain (KQ 3) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Exercise	*Exercise vs. usual care, attention control, or no intervention*	Function *Short-term*	8 (N=748) Bennell 2005 de Rooij 2017[a] Lund 2008 Quilty 2003 Rosedale 2014 Segal 2015 Thorstensson 2005 Williamson 2007	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD −0.29, 95% CI −0.46 to −0.11, I^2=9.9%
		Function *Intermediate-term*	11 (N=879) Allen 2018[a] Chen 2014 Huang 2005a Huang 2005b Huang 2003 Mat 2017[a] Messier 2004 Quilty 2003 Segal 2015 Sullivan 1998 Weng 2009	Moderate	Inconsistent[b]	Imprecise	Undetected	Low	Pooled SMD −0.63, 95% CI −1.17 to −0.10, I^2=90.8% [excluding outlier trial][b]

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Long-term*	4 (N=1,199) Allen 2018[a] Messier 2004 Thomas 2002 Waller 2017[a]	High	Consistent	Precise	Undetected	Low	Pooled SMD −0.22, 95% CI −0.34 to −0.08, I^2=0%
		Pain *Short-term*	8 (N=748) Bennell 2005 de Rooij 2017[a] Lund 2008 Quilty 2003 Rosedale 2014 Segal 2015 Thorstensson 2005 Williamson 2007	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference on 0-10 scale: −0.47, 95% CI −0.86 to −0.10, I^2=41.7% One fair-quality trial (Bennell 2005) found no statistical difference between exercise and sham in proportion with clinically relevant reductions (≥1.75 points) in: VAS pain on movement: 58% (34/59) vs. 42% (27/65); RR 1.4, 95% CI 1.0 to 2.0; VAS global improvement in pain: 59% (35/59) vs. 50% (33/65); RR 1.2, 95% CI 0.8 to 1.6
		Pain *Intermediate-term*	11 (N=880) Allen 2018[a] Chen 2014 Huang 2005a Huang 2005b Huang 2003 Mat 2017[a]	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled difference on a 0-10 scale: −1.34, 95% CI −2.12 to −0.54, I^2=90%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
			Messier 2004 Quilty 2003 Segal 2015 Sullivan 1998 Weng 2009						
		Pain *Long-term*	4 (N=1,200) Allen 2018[a] Messier 2004 Thomas 2002 Waller 2017[a]	High	Consistent	Precise	Undetected	Low	Pooled difference on a 0-10 scale: −0.30, 95% CI −0.49 to −0.00, I^2=0%
	Exercise vs. pharmacologic therapy (acetaminophen and NSAIDs)	Function, *Intermediate-term*	1 (N=93) Holsgaard-Larsen 2018 and 2017[a]	Moderate	Unknown	Imprecise	Undetected	Low[c]	No differences between groups on any measure. Proportion achieving a clinically meaningful improvement (>10 points on KOOS ADL): 47% (22/47) versus 28% (13/46); RR 1.7, 95% CI 1.0 to 2.9 KOOS ADL (0-100): difference −3.6, 95% CI −9.2 to 2.1 KOOS Sport and Recreation (0-100): difference −2.9, 95% CI −11.4 to 5.5
		Pain *Intermediate-term*	1 (N=93) Holsgaard-Larsen 2018 and 2017[a]	Moderate	Unknown	Precise	Undetected	Low[c]	KOOS Pain (0-100): difference 4.2, 95% CI −10.0 to 1.6
	Exercise vs. usual care, attention control, no intervention, or pharmacologic therapy	Harms	8 (N=1097) Abbott 2013 Bennell 2005 Chen 2014 Ettinger 1997 Huang 2003 Holsgaard-Larsen 2018 and 2017[a] Thorstensson 2005 Weng 2009	Moderate	Consistent	Precise	Undetected	Moderate	One RCT in older patients reported six serious adverse events, with no significant difference between groups: five in the exercise group [four falls (1 resulting in distal radius fracture), one foot fracture from dropping a dumbbell] vs. one instance of sudden death in a control participant; 1.7% (5/290) vs.

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
									0.7% (1/149), RR 2.57 (95% CI 0.30 to 21.79) One trial reported greater temporary, minor increases in pain in the exercise group versus a sham group; however, four trials found no difference in worsening of pain symptoms with exercise vs. comparators. No difference in adverse events was reported on the one new trial of exercise compared to standard analgesics and anti-inflammatory therapy.
Psychological Therapies	*CBT/MI/pain coping skills training vs. usual care*	Function, Pain *Short-term to long-term*	2 (N=222) Helminen 2015 Somers 2012	Moderate	Consistent	Imprecise	Undetected	Low	No differences in one fair quality trial of CBT and one poor quality trial of pain coping skills training averaged over 6 to 12 months (intermediate to long term) and 1.5 to 10.5 months (short to intermediate term).
		Function, *Short-term*	2 (N=210) Gilbert 2018[d] O'Moore 2018[d]	Moderate	Consistent	Imprecise	Undetected	Low	Pooled SMD on a 0-68 scale −2.09, 95% CI −8.70 to 1.61, I^2=63.3%
		Pain *Short-term*	2 (N=210) Gilbert 2018[d] O'Moore 2018[d]	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference on a 0-20 scale: −0.60, 95% CI −1.48 to −0.08, I^2 = 0.0%
		Harms	4 (N=371) Gilbert 2018[d] Helminen 2015 O'Moore 2018[d] Somers 2012	Moderate	Consistent	Imprecise	Undetected	Low	No adverse events observed across four trials (3 fair quality and 1 poor quality).
	Pain coping skills training vs. exercise	Function *Short-term and*	1 (N=149) Bennell 2016	Moderate	Unknown	Imprecise	Undetected	Low	No difference in WOMAC physical 0-68

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		intermediate term							Short-term: difference 2.0 (95% CI −2.4 to 6.4), p=0.37 Intermediate-term: MD 3.2 (95% CI −0.6 to 7.0), p=0.10
		Pain *Short-term and intermediate term*	1 (N=149) Bennell 2016	Moderate	Unknown	Imprecise	Undetected	Low	No difference in WOMAC pain 0-20) Short-term: difference −0.1 (95% CI −1.2 to 1.0) Intermediate-term: difference 0.4 (95% CI −0.8 to 1.6), p=0.49)
		Harms	1 (N=149) Bennell 2016	Moderate	Unknown	Imprecise	Undetected	Low	Knee pain was more common in the exercise group during treatment (31% versus 3%) and during short and intermediate term followup (10% versus 7%) as was overall body pain (15% versus 2%)
Physical Modalities	*Ultrasound vs. sham*	Function, *Short-term*	3 (N=249) Jia 2016[e] Yegin 2017[e] Yildiz 2015	Moderate	Unknown	Imprecise	Undetected	Low	Continuous and pulsed ultrasound vs. sham, difference −2.50, 95% CI −6.37 to 1.22, I^2=94.0%
		Function *Intermediate-term*	1 (N=60) Cakir 2014	Moderate	Unknown	Imprecise	Undetected	Low	Continuous and pulsed ultrasound vs. sham, 0-68 scale, differences: −2.9 (95% CI −9.19 to 3.39) and 1.6 (95% CI −3.01 to 6.22)
		Pain *Short-term*	3 (N=249) Jia 2016[e] Yegin 2017[e] Yildiz 2015	Moderate	Unknown	Imprecise	Undetected	Low	Continuous and pulsed ultrasound vs. sham, 0-10 scale, pooled difference −1.20, 95% CI −3.71 to 1.31, I^2=91.1%
		Pain *Intermediate-term*	1 (N=60) Cakir 2014	Moderate	Unknown	Imprecise	Undetected	Low	Continuous and pulsed ultrasound vs. sham, 0-20 scale, differences: −1.6 (95% CI −3.26 to 0.06) vs. 0.2 (95% CI −1.34 to 1.74); also no

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
									difference between groups for other pain measures.
		Harms	4 (N=318) Cakir 2014 Jia 2016[e] Yegin 2017[e] Yildiz 2015	Moderate	Unknown	Imprecise	Undetected	Low	No adverse events reported during the four trials (1 good, 2 fair, and 1 poor quality)
	TENS vs. sham	Function *Intermediate-term*	1 (N=70) Fary 2011	Low	Unknown	Imprecise	Undetected	Low	Proportion of patients who achieved MCID (≥9.1) in WOMAC function: 38% vs 39%, RR 1.2 (95% CI 0.6 to 2.2); Difference in mean change −1.9 (95% CI −9.7 to 5.9) on a 0-100 scale
		Pain *Intermediate-term*	1 (N=70) Fary 2011	Low	Unknown	Imprecise	Undetected	Low	Proportion of patients who achieved MCID (≥20) in pain VAS: 56% vs 44%, RR 1.3 (95% CI 0.8 to 2.0) Difference in mean change 0.9 (95% CI −11.7 to 13.4) on 0-100 VAS and −5.6 (95% CI −14.9 to 3.6) on 0-100 WOMAC pain scale.
		Harms	1 (N=70) Fary 2011	Low	Unknown	Imprecise	Undetected	Low	No evidence of increased risk of serious harms; no differences between treatments for harms (RR 1.06, 95% CI 0.38 to 2.97)
	Low-level laser therapy vs. sham laser	Function *Short-term*	1 (N=49) Al Rashoud 2014	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one small fair quality trial
		Function *Intermediate-term*	2 (N=109) Al Rashoud 2014 Tascioglu 2004	High	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient evidence from one small fair trial and one poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Short-term*	2 (N=76) Al Rashoud, 2014 Hegedus 2009	High	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two small trials, one fair trial and one poor quality
		Pain *Intermediate-term*	2 (N=109) Al Rashoud, 2014 Tascioglu, 2004	High	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient evidence from one small fair trial and one poor quality trial
		Harms	2 (N=109) Al Rashoud, 2014 Tascioglu, 2004	High	Consistent	Imprecise	Undetected	Insufficient	Data for harms was insufficient. No adverse events were reported.
	Microwave diathermy vs. sham	Function *Short-term*	1 (N=63) Giombini 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	There was insufficient evidence to determine short-term effects or harms from one small trial microwave diathermy
		Pain *Short-term*	1 (N=63) Giombini 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	There was insufficient evidence to determine short-term effects or harms from one small trial microwave diathermy; substantial imprecision noted
		Harms	1 (N=63) Giombini 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	Data for harms were insufficient. However, no serious adverse events occurred in either group. Two patients in the diathermy group reported transient aggravation of symptoms.
	Pulsed Short-wave Diathermy vs. Sham	Function *Short-term*	1 (N=115) Laufer 2005	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial
		Function *Long-term*	1 (N=86) Fukuda 2011	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Short-term*	1 (N=115) Laufer 2005	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial
		Pain *Long-term*	1 (N=86) Fukuda 2011	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial
		Harms	2 (N=201) Laufer 2005 Fukuda 2011	High	Unknown	Imprecise	Undetected	Insufficient	Data were insufficient for harms. No adverse events were reported by either trial.
	Electro-magnetic fields vs. sham	Function *Short-term*	2 (N=180) Battisti 2004 Thamsborg 2005	Moderate	Consistent	Imprecise	Undetected	Low	The fair quality trial: (WOMAC) activities of daily living subscale (0-85) mean difference −3.48 (95% CI −4.44 to −2.51)
		Pain *Short-term*	2 (N=180) Battisti 2004 Thamsborg 2005	Moderate	Consistent	Imprecise	Undetected	Low	The fair quality trial: WOMAC-pain subscale (0-25) versus sham, −0.84 (95% CI −1.10 to −0.58).
		Harms	1 (N=90) Thamsborg 2005	Moderate	Unknown	Imprecise	Undetected	Low	More patients who received real versus sham electromagnetic field therapy reported throbbing or warming sensations or aggravation of pain; however the difference was not significant (RR 1.95, 95% CI 0.81 to 4.71)
	Superficial heat vs. placebo	Pain *Short-term*	1 (N=52) Mazzuca 2004	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one small, fair-quality trial
		Harms	1 (N=52) Mazzuca 2004	Moderate	Unknown	Imprecise	Undetected	Insufficient	Data was insufficient for harms; no adverse events were reported
	Brace vs. usual care	Function, Pain, Harms *Intermediate- and long-term*	1 (N=118) Brouwer 2006	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Manual Therapies	*Manipulation vs. usual care*	Function, Harms *Intermediate-term*	1 (N=58 knee OA) Abbott 2013	Moderate	Unknown	Unknown	Undetected	Insufficient	Insufficient evidence from one fair-quality trial; inadequate data to determine effect sizes or statistical significance
	Manipulation vs. exercise	Function, Harms *Intermediate-term*	1 (N=59 knee OA) Abbott 2013	Moderate	Unknown	Unknown	Undetected	Insufficient	Insufficient evidence from one fair-quality trial; inadequate data to determine effect sizes or statistical significance
	Massage vs. usual care	Function, Pain, Harms *Short-term*	1 (N=125) Perlman 2012	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one fair-quality trial.
Mind-body Practices	*Tai Chi vs. attention control*	Function *Short-term*	2 (N=81) Brismee 2007 Wang 2009	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, unblinded trials; (one fair, one poor quality)
		Function *Intermediate-term*	1 (N=40) Wang 2009	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, unblinded trials (one fair, one poor quality)
		Pain *Short-term*	2 (N=81) Brismee 2007 Wang 2009	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, unblinded trials (one fair, one poor quality)
		Pain *Intermediate term*	1 (N=40) Wang 2009	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, unblinded trials (one fair, one poor quality)
		Harms	2 (N=81) Brismee 2007 Wang 2009	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, unblinded trials(one fair, one poor quality)
Acupuncture	*Acupuncture vs. usual care, no treatment, waitlist, or sham*	Function *Short-term*	4 (N=871) Jubb 2008 Suarez-Almazo 2010 Yurturan 2007 Witt 2005	Moderate	Inconsistent[f]	Precise	Undetected	Low	Pooled SMD −0.05, 95% CI −0.32 to 0.38) [Excluding outlier][f]
		Function	4 (N=767)	Moderate	Consistent	Precise	Undetected	Moderate	

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Intermediate-term	Berman 2004 Hinman 2014 Lansdown 2009 Witt 2005						Pooled SMD[g] −0.15, 95% CI −0.31 to 0.02, I^2=0%
		Pain *Short-term*	6 (N=1065) Berman 1999 Jubb 2008 Suarez-Almazo 2010 Williamson 2007 Witt 2005 Yurturan 2007	Moderate	Inconsistent	Precise	Undetected	Low	Pooled SMD −0.27, 95% CI −0.67 to 0.12, I^2=79.3%
		Pain *Intermediate term*	4 (N=767) Berman 2004 Hinman 2014 Lansdown 2009 Witt 2005	Moderate	Consistent	Precise	Undetected	Moderate	Pooled SMD −0.16, 95% CI −0.32 to −0.01, I^2=0%); Individually no trial reached statistical significance.
		Harms	9 (N=1796) Berman 2004 Berman 1999 Hinman 2014 Jubb 2008 Lansdown 2009 Suarez-Almazo 2010 Williamson 2007 Witt 2005 Yurtkuran 2007	Moderate	Consistent	Imprecise	Undetected	Moderate	There is no apparent difference in risk of serious adverse events between any form of acupuncture and the control group. Worsening of symptoms (7%-14%), mild bruising, swelling or pain at the acupuncture site (1%-18%) were most common; One case of infection at an electroacupuncture site was reported.
	Acupuncture vs. exercise	Function, Pain, Harms *Short-term*	1 (N =120) Williamson 2007	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor-quality trial.

CI = confidence interval; OA: osteoarthritis; MCID = minimal clinically important difference; MI = motivation interveiewing; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference; TENS = transcutaneous electrical stimulation; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a New Exercise trial.

b Outlier excluded, Dias 2003.

c There were no trials comparing exercise with pharmacologic therapy in the prior report.

d New Psychological Therapy trial.
e New Physical Modality (ultrasound) trial.
f Outlier excluded, Berman 1999.
g Results for all trials individually were not statistically significant.

Table G-4. Hip osteoarthritis pain (KQ 3) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Exercise	*Exercise vs. usual care*	Function *Short-term*	3 (N=377) Juhakoski 2011 Teirlinck 2016 Tak 2005	Moderate	Consistent	Precise	Undetected	Low	Pooled SMD −0.33, 95% CI −0.58 to −0.11, I^2=0%
		Function *Intermediate-term*	2 (N=307) Juhakoski 2011 Teirlinck 2016	Moderate	Consistent	Precise	Undetected	Low	Pooled SMD −0.28, 95% CI −0.55 to 0.02, I^2=0%
		Function *Long-term*	1 (N=118) Juhakoski 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	SMD −0.37, 95% CI −0.74 to −0.01
		Pain *Short-term*	3 (N=371) Juhakoski 2011 Teirlinck 2016 Tak 2005	Moderate	Inconsistent	Imprecise	Undetected	Low	Pooled SMD −0.30, 95% CI −0.70 to −0.02, I^2=0%
		Pain *Intermediate-term*	2 (N=307) Juhakoski 2011 Teirlinck 2016	Low	Consistent	Imprecise	Undetected	Low	Pooled SMD −0.14, 95% CI −0.40 to 0.12, I^2=0%
		Pain *Long-term*	1 (N=118) Juhakoski 2011	Moderate	Unknown	Imprecise	Undetected	Insufficient	SMD −0.25, 95% CI −0.62 to 0.11
		Harms	2 (N=170) Tak 2005 Abbott 2013[a]	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient data from two trials although no serious harms were reported in two trials.
Manual Therapies	*Manipulation vs. usual care*	Function *Intermediate-term*	1 (N=47) Abbott 2013[a]	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one fair quality trial. No effect size could be calculated.
		Harms	1 (N=47) Abbott 2013[a]	Moderate	Unknown	Imprecise	Undetected	Insufficient	No treatment-related serious adverse events were detected
	Manipulation vs. exercise	Function *Short-term*	1 (N=109) Hoeksma 2004	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted difference 11.1 (95% CI 4.0 to 18.6) on 0-100 scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Intermediate-term*	2 (N=155) Abbott 2013[a] Hoeksma 2004	Moderate	Consistent	Imprecise	Undetected	Low	Adjusted difference 9.7, 95% CI, 1.5 to 17.9 on 0-100 scale; no effect size could be calculated in the other trial but direction of effect was similar
		Pain *Short-term*	1 (N=109) Hoeksma	Moderate	Unknown	Imprecise	Undetected	Low	Adjusted differences −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 on 0-10 scale
		Pain *Intermediate-term*	1 (N=109) Hoeksma	Moderate	Unknown	Imprecise	Undetected	Insufficient	Adjusted differences −0.70 (95% CI −2.03 to 0.59) for pain at rest and −1.27 (95% CI −2.40 to −0.19) for pain walking on 0-10 scale; impact on pain is unclear from different measures
		Harms	2 (N=155) Abbott 2013[a] Hoeksma 2004	Moderate	Consistent	Imprecise	Undetected	Low	No treatment-related serious adverse events were detected in one trial; similar rates of study withdrawal due to symptom aggravation were seen in the second trial (5% vs. 4%; RR 1.42, 95% CI 0.25 to 8.16)

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference.

[a]Authors did not provide data on the number of hip osteoarthritis patients for each intervention, only gave hip osteoarthritis population as a whole

Table G-5. Hand osteoarthritis pain (KQ 3) strength of evidence

Intervention	Comparator	Outcome	N RCTs (patients)	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Exercise	*Exercise vs. usual care*	Function, Pain, Harms *Short-term*	1 (N=130) Osteras	High	Unknown	Imprecise	Undetected	Insufficient	Poor quality trial of exercise vs waitlist; high attrition rate in exercise arm (29%). No serious adverse events; increased pain (hand or neck/shoulders) in eight patients (6%), not reported by group.
Physical Modalities	*Low level laser therapy vs. sham intervention*	Function *Short-term*	1 (N=88) Brosseau	Low	Unknown	Imprecise	Undetected	Low	No differences observed in one good quality trial (difference 0.2, 95% CI −0.2 to 0.6).
		Pain *Short-term*	1 (N=88) Brosseau	Low	Unknown	Imprecise	Undetected	Low	No differences observed in one good quality trial (difference 0.1, 95% CI −0.3 to 0.5).
		Harms	1 (N=88) Brosseau	Low	Unknown	Imprecise	Undetected	Low	No serious adverse events identified in one good quality trial.
	Superficial heat (paraffin) vs. no treatment	Function, Pain, Harms *Short-term*	1 (N=56) Dilek	Moderate	Unknown	Imprecise	Possible	Insufficient	Insufficient evidence from one small trial
Multidisci-plinary Rehabilitation	*Multidisci-plinary rehabilitation vs. waitlist*	Function *Short-term*	1 (N=151) Stukstette	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference 0.49 (95% CI −0.09 to 0.37); OASRI-OMERACT Responder: OR 0.82 (95% CI 0.42 to 1.61)
		Pain *Short-term*	1 (N=151) Stukstette	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference 0.40 (95% CI −0.5 to 1.3)
		Harms	1 (N=151) Stukstette	Moderate	Unknown	Imprecise	Undetected	Insufficient	No serious adverse events identified.

CI = confidence interval; OASRI-OMERACT = Osteoarthritis Research Society International-Outcome Measures in Rheumatology; OR = odds ratio; RCT = randomized controlled trial.

Table G-6. Fibromyalgia (KQ 4) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Exercise	*Exercise vs. usual care, attention control, or a placebo intervention*	Function *Short-term*	7 (N=410) Altan 2009 Baptista 2012 Da Costa 2005 Giannotti 2014 Kayo 2012 King 2002 Paolucci 2015	Moderate	Inconsistent	Precise	Undetected	Low	Pooled difference, −7.68 on a 0 to 100 scale, 95% CI, −13.04 to −1.84, I^2=59.9%
		Function *Intermediate-term*	8 (N=461) Da Costa 2005 Fontaine 2011 Giannotti 2014 Gowans 2001 Mannerkorpi 2009 Sanudo 2010 Saunudo 2012 Tomas-Carus 2008	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference on 0-100 scale, −6.04 95% CI −9.25 to −3.01, I^2=0%
		Function *Long-term*	3 (N=178) Fontaine 2011 Sanudo 2012 Van Eijk-Hustings 2013	Moderate	Consistent	Imprecise	Undetected	Low	Pooled difference, on 0-100 scale, −4.33, 95% CI −10.46 to 1.97, I^2=0%)
		Pain *Short-term*	6 (N=337) Altan 2009 Buckelew 1998 Da Costa 2005 Giannotti 2014 Gusi 2006 Kayo 2012	Moderate	Consistent[a]	Imprecise	Undetected	Moderate	Pooled difference −0.88, 95% CI −1.33 to −0.27, I^2=1.5%; (Excluding outlier)[a]

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Intermediate-term*	8 (N=382) Da Costa 2005 Fontaine 2011 Giannotti 2014 Tomas-Carus 2008 Sanudo 2015 Sencan 2004 van Santen 2002 Villafaina 2019[b]	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference −0.51, 95% CI −0.92 to −0.06, I^2=0%
		Pain *Long-term*	4 (N=241) Buckelew 1998 Fontaine 2011 van Eijk-Hustings 2013 Wiggers 1996	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference –0.18, 95% CI −0.77 to 0.42, I^2=0%
		Harms	3 (N=132) Gusi 2006 Kayo 2012 Paolucci 2015	Moderate	Unknown	Imprecise	Undetected	Insufficient	Insufficient data on harms. Most trials of exercise did not report on adverse events at all. One trial reported one non-study-related adverse event. Two trials reported no adverse events.
	Exercise vs. pharma-cologial therapy	Pain *Intermediate-term*	1 (N=32) Sencan 2004	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small, poor-quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Psychological Therapies	*Psycho-logical therapy vs. usual care, waitlist, or attention control*	Function *Short-term*	Any therapy: 5 (N=258) Pooled Baumueller 2017[c] Castel 2012 Jensen 2012 Lami 2018[c] Verkaik 2014[c] 2 CBT (N=96) for RR Ang 2010 Castel 2012 CBT/ACT (N=169) Castel 2012 Jensen 2012 Lami 2018[c] EMG Biofeedback: 1 (N=59) Baumueller 2017[c] Buckelew 1998 Imagery: 1 (N=70) Verkaik 2014	Moderate	Inconsistent	Imprecise	Undetected	Low (CBT) Insufficient (biofeed-back, imagery)	FIQ total score 0-100 scale **Any therapy** Pooled mean difference −2.82 (95% CI −9.79 to 2.81, I^2=70.6% **CBT only:** More CBT recipients with clinically important improvement, 2 trials, RR 2.2 (0.5 to 9.3) and RR 2.8 (1.3 to 6.1) Pooled mean difference (3 trials [1 new] −6.14, 95% CI −16.86 to 3.74 **Other therapies**: No clear difference for guided imagery (1 poor quality trial) or EMG biofeedback (1 poor quality trial, 1 small fair quality trial)

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Intermediate-term*	CBT: 3 (N=280 Pooled) Alda 2011 Castel 2012 Luciano 2014[c] Not pooled Karlsson 2015 (N=48)[c] McCrae 2019 (N=113)[c] Thieme 2006 (N=82) EMG Biofeedback: 1 (N=85) van Santen 2002	Moderate	Inconsistent	Imprecise	Undetected	Low (CBT) Insufficient (biofeed-back)	CBT: Pooled difference on FIQ Total (0-100): −12.81, 95%CI −24.07 to −2.33, I^2 = 94.2%) Difference on FIQ Physical Function Scale (0-10) (1 trial, Thieme): −1.8, 95% CI −2.9 to −0.70 More CBT recipients with a clinically important improvement RR 2.9 (95% CI 1.4 to 6.3) in one trial (Castel) New trials: No difference between CBT and waitlist on Pain Disability Index (McCrae) or West Haven - Yale Multidimensional Pain Inventory (MPI) pain interference subscale (Karlsson) Trial of biofeedback vs. usual care: unclear difference, mean changes −1.6 (95% CI −3.4 to 0.2) versus −0.6 (95% CI −2.9 to 1.7)
		Function *Long-term*	CBT: 2 (N=227) Thieme 2006 Williams 2002 EMG Biofeedback: 1 (N=59) Buckelew 1998	High	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient data from three poor quality trials

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Short-term*	CBT: 4 (N=197) Ang 2010 Castel 2012 Jensen 2012 Lami 2018[c] EMG Biofeedback: 1 (N=53) Buckelew 1998	High	Consistent	Precise	Undetected	Low (CBT) Insufficient (biofeed-back)	CBT: Pooled mean difference −0.62, 95% CI −1.08 to −0.14, 0-10 scale No clear difference for EMG biofeedback (1 poor quality trial)
		Pain *Intermediate-term*	CBT/ACT: 6 (N=551) Alda 2011 Castel 2012 Karlsson 2015[c] Luciano 2014[c] Lumley 2017[c] McCrae 2017[c] EMG Biofeedback: 1 (N=65) Van Santen 2002	Moderate	Consistent	Imprecise	Undetected	Moderate (CBT) Insufficient (biofeed-back)	CBT: Pooled mean difference −0.55, 95% CI −1.13 to −0.06,, 0-10 scale Mean difference −1.11, 95% CI −2.06 to −0.16 for EMG biofeedback (1 poor quality trial)
		Pain *Long-term*	CBT: 1 (N=40) Wiggers 1996 EMG Biofeedback: 1 (N=53) Buckelew 1998	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient data from two poor quality trials

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	5 (N=482) Alda 2011 Ang 2010 Luciano 2014[c] Lumley 2017[c] Thieme 2006	High	Unknown	Imprecise	Undetected	Insufficient	Data were insufficient; withdrawals due to adverse events were reported by three trials: 0% vs. 3.6% (2 cases) and 7% vs. 8% (1 in each group for pain during testing) for CBT vs. usual care, respectively, in two trials (1 fair, poor quality), and in 5% (2 cases of depression) vs. 50% (worsening of symptoms in 20 patients) for CBT vs. attention control in one poor quality trial. Two (1 new) fair quality trials reported no adverse events for CBT.
	Psychological therapy vs. pharma-cological therapy	Function *Short-term*	CBT plus amitriptyline vs. amitriptyline 1 (N=51) Falcao 2008 EEG Biofeedback vs. escitalopram, 1 (N=36) Kayiran 2010	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient data from onefair and one poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Intermediate-term*	2 (N=212) Alda 2011 (CBT) Luciano 2014[c] (ACT) vs. pregabalin (plus duloxetine for depressed patients)	Moderate	Inconsistent	Imprecise	Undetected	Low	FIQ 0-100 scale Pooled difference −9.81, 95%CI −21.2 to 1.58, I^2=96% Improvement in function reported for both trials of CBT versus pregabalin (plus duloxetine as needed) (small improvement in one trial, difference −4.0, 95% CI −7.4 to −0.56; moderate improvement in the second trial, difference −15.6, 95% CI −19.0 to −12.2). Different magntitude of effects resulted in substantial heterogeneity.
		Pain *Short-term*	CBT: 1 (N=51) Falcao 2008 EEG Biofeedback 1 (N=36) Kayiran 2010	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient data from one fair and one poor quality trial
		Pain *Intermediate-term*	2 (N=212) Alda 2011 (CBT) Luciano 2014[c] (ACT) vs. pregabalin (plus duloxetine for depressed patients)	Moderate	Inconsistent	Precise	Undetected	Low	VAS 0-10 scale, pooled difference, −0.31, 95% CI −1.15 to 0.51, I^2= 63.5%)

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	2 (N=216) Alda 2011 (CBT) Luciano 2014[c] (ACT)	Moderate	Unknown	Imprecise	Undetected	Low	Withdrawals due to adverse events, CBT vs. pregabalin: 0% vs. 5.5%; events included two digestive problems, and one dizziness in one trial. In the second (new) trial, for ACT vs. pregabalin, withdrawals due to lack of efficacy (5.9% vs. 1.9, respectively) or patients decision (3.9% vs. 0%, respectively); adverse events reported in the pregabalin group only included nausea (25%), dry mouth (23%), drowsiness, headache and fatigue (21% each) and constipation (19%).
	Psychological therapy vs. exercise	Function *Short-term*	1 (N=51) Buckelew 1998 (EMG Biofeedback)	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one small, poor quality trial
		Function *Intermediate-term*	CBT: 1 (N=40) Redondo 2004 EMG Biofeedback: 1 (N=114) Van Santen 2002	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two poor quality trials

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function Long-term	CBT: 2 (N=40) Larsson 2015 Redondo 2004 Relaxation 1 (n=130) Larsson 2015 EMG Biofeedback 1 (N=51) Buckelew 1998	High	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient evidence from three poor quality trials; inconsistency in findings noted.
		Pain *Short-term*	1 (N=51) Buckelew (EMG Biofeedback)	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one small, poor quality trial
		Pain *Intermediate-term*	CBT: 12 (N=40) Redondo 2004 van Santen 2002 EMG Biofeedback: 1 (N=114) van Santen 2002	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence two poor quality trials
		Pain *Long-term*	CBT: 2 (N=80) Redondo 2004 Wiggers 1996 Relaxation 1 (n=130) Larsson 2015 EMG Biofeedback 1 (N=51) Buckelew 1998	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from four poor quality trials

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	2 (N=170) Larsson 2015 Wiggers 1996	High	Consistent	Imprecise	Undetected	Insufficient	Data were insufficient for harms. In one trial no patient had an adverse event in relaxation group compared to five (7.5%) in the strengthening exercise group (increased pain, three of which withdrew). In the other trial, withdrawals due to adverse events were similar between groups and none of the events were related to treatment.
Physical Modalities	*Magnetic fields vs. usual care or sham*	Function and Pain *Short-term*	(N=33) Paolucci 2016 (cross-over trial)	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one poor quality trial
		Function *Intermediate-term*	(N=119) Alfano 2001 (parallel trial)	Moderate	Unknown	Imprecise	Undetected	Low	Difference −5.0 (95% CI −14.1 to 4.1) vs. sham and −5.5 (95% CI −14.4 to 3.4) vs. usual care on the 0-80 scale FIQ
		Pain *Intermediate-term*	(N=119) Alfano 2001 (parallel trial)	Moderate	Unknown	Imprecise	Undetected	Low	Difference −0.6 (95% CI −1.9 to 0.7) vs. sham and −1.0 (95% CI −2.2 to 0.2) vs. usual care on a 0-10 NRS
		Harms	(N=119) Alfano 2001 (parallel trial)	Moderate	Unknown	Imprecise	Undetected	Low	No differences in adverse events between the functional and sham magnetic groups (data not reported); none of the events were deemed to be related to the treatments
Manual Therapies	*Massage/ myofascial release vs. sham*	Function *Intermediate-term*	1 (N=94) Castro-Sanchez 2011[a]	Moderate	Unknown	Imprecise	Undetected	Low	Mean 58.6 (SD 16.3) vs. 64.1 (SD 18.1) on the FIQ (0-100 scale), p=0.048

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Long-term*	1 (N=94) Castro-Sanchez 2011[a]	Moderate	Unknown	Imprecise	Undetected	Low	Mean 62.8 (SD 20.1) vs. 65.0 (19.8) on the FIQ (0-100 scale), p=0.329
		Pain *Short-term*	1 (N=64) Castro-Sanchez 2011[b]	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one poor quality trial
		Pain *Intermediate-term*	2 (N=158) Castro-Sanchez 2011[a] Castro-Sanchez 2011[b]	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Insufficient evidence from one fair and one poor quality trial due to inconsistency in the estimates
		Pain *Long-term*	1 (N=94) Castro-Sanchez 2011[a]	Moderate	Unknown	Imprecise	Undetected	Low	MPQ sensory domain, mean 18.2 (SD 8.3) vs. 21.2 (7.9) on a 0-33 scale, p=0.038; MPQ evaluative domain, mean 23.2 (SD 7.6) vs. 26.7 (SD 6.9) on a 0-42 scale, p=0.036
		Harms	1 (N=94) Castro-Sanchez 2011[a]	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Data for harms were insufficient; however, no adverse effect occurred in one fair quality trial
Mindfulness Practices	*Mindfulness-based stress reduction or "Meditation*	Function *Short-term*	2 (N=1258) Cash 2015 Schmidt 2011	Moderate	Consistent	Precise	Undetected	Moderate	No clear effect: difference 0 to 0.06 on a 0-10 scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
	Awareness Training: vs. waitlist or attention control	Pain *Short-term*	2 (N=1258) Cash 2015 Schmidt 2011	Moderate	Consistent	Precise	Undetected	Moderate	No clear effect: difference 0.1 on a 0-100 VAS pain scale in one poor quality trial; 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 fair-quality trial; Clinically meaningful improvement in function (≥14% on the FIQ total, 0-100 scale) was not different for MBSR versus either comparator in that trial; vs. AC%, RR 1.21 (95% CI 0.79 to 1.82; vs. WL, RR 1.37 (95% CI 0.83 to 1.94)
		Function *Intermediate term*	1 (N=148) Van Gordon 2017[d]	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference −7.9, 95% CI −8.2 to −4.3 on 0-100 FIQ-R
		Pain *Intermediate term*	1 (N=148) Van Gordon 2017[d]	Moderate	Unknown	Precise	Undetected	Low	Adjusted difference −3.0, 95% CI −4.1 to −1.9 on 0-45 SF-MPQ
		Harms	No studies	--	--	--	--	--	No evidence
Mind-Body Therapies	*Tai Chi, Qigong vs. waitlist or attention control*	Function *Short-term*	(N=154) Lynch 2012 Wang 2010	Moderate	Consistent[e]	Imprecise	Undetected	Low	FIQ total score (0-100): Qigong, mean difference −7.5 (95% CI −13.3 to −1.68); Tai chi, mean difference −23.5 (95% CI −30 to −17) Heterogeneity may be explained by duration and intensity of intervention and control group

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Short-term*	(N=154) Lynch 2012 Wang 2010	Moderate	Consistent[e]	Imprecise	Undetected	Low	Pooled difference −1.44, 95% CI −2.96 to −0.23; I^2=46%, scale 0-10
		Harms	(N=154) Lynch 2012 Wang 2010	Moderate	Inconsistent	Imprecise	Undetected	Insufficient	Data for harms were insufficient. One trial reported two adverse events judged to be possibly related to Qigong practice: an increase in shoulder pain and plantar fasciitis; neither participant withdrew from the study. In the trial of Tai chi, no adverse events were reported.
	Tai Chi vs. aerobic exercise	Function *Short to intermediate term*	1 (N=181) Wang 2018[f]	Moderate	Unknown	Precise	Undetected	Low[g]	FIQ (Revised) 0-100 scale Short to intermediate term : Any tai chi (12 or 24 weeks of sessions) (N= 181) Difference in change scores −5.5, 95% CI −0.6 to −10.4
		Function *Intermediate term*	1 (N=89) Wang 2018[f]	Moderate	Unknown	Imprecise	Undetected	Low[g]	FIQ (Revised) 0-100 scale 2 sixty-minute tai chisessions/week for 24 weeks vs aerobic exercise 2 sixty-minute sessions/week for 24 weeks (N= 89): difference in change scores −16.2, 95% CI −8.7 to −23.6
		Function *Intermediate to long term*	1 (N=158) Wang 2018[f]	Moderate	Unknown	Precise	Undetected	Low[g]	Intermediate to long term : Any tai chi (12 or 24 weeks of sessions) (N=158) Difference in change scores: −2.7 (95% CI −2.3 to 7.7); p=0.29

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Function *Long term*	1 (N=78) Wang 2018[f]	Moderate	Unknown	Imprecise	Undetected	Low[g]	FIQ (Revised) 0-100 scale 2 sixty-minute sessions/week for 24 weeks. vs aerobic exercise 2 sixty-minute sessions/week for 24 weeks (N=78): Difference in change scores −11.1, 95% CI −2.7 to −19.6)
		Harms	1 (N=226) Wang 2018[f]	Moderate	Unknown	Imprecise	Undetected	Low[g]	No severe adverse events were reported for either treatment. Mild/moderate adverse events were reported for 5.3% of the tai chi participants and 5.3% of the aerobic exercise participants.
Acupuncture	*Acupuncture vs. sham*	Function *Short-term*	3 (N=283) Karatay 2018[h] Martin 2006 Vas 2016	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference −9.21, 95% CI −13.65 to −5.78, I^2=0%, 0-100 scale
		Function *Intermediate-term*	2 (N=211) Martin 2006 Vas 2016	Moderate	Consistent	Precise	Undetected	Moderate	Pooled difference −9.82, 95% CI −14.35 to −3.01, I^2=27.4%, 0-100 scale

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Short-term*	Sham or attention control 5 (N= 399) Assefi 2005 Karatay 2018[h] Martin 2006 Mist 2018[g] Vas 2016 Sham control 4 (N=369) Assefi 2005 Karatay 2018[h] Martin 2006 Vas 2016	Moderate	Inconsistent	Precise	Undetected	Low	Pooled difference, all control conditions (5 trials): −1.14, 95% CI −2.56 to 0.33, I^2=91.6%, 0-10 scale. Pooled difference, sham only (4 trials): −0.86, 95% CI −2.73 to 0.92, I^2=88.9%,
		Pain *Intermediate-term*	3 (N=297) Assefi 2005 Martin 2006 Vas 2016	Moderate	Inconsistent	Precise	Undetected	Low	Pooled difference −0.65, 95% CI −1.15 to 0.17, I^2=45.5%, 0-10 scale
		Harms	4 (N=369) Assefi 2005 Karatay 2018[h] Martin 2006 Vas 2016	Moderate	Consistent	Precise	Undetected	Moderate	Discomfort and bruising were the most common reported adverse events and were more common in the true acupuncture groups. Discomfort was substantially more common for acupuncture or sham needling (61%to 70%) compared with simulated acupuncture (29%). Vasovagal symptoms and aggravation of fibromyalgia symptoms were less common (4% of sessions)

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Multidisciplinary Rehabilitation	*Multi-disciplinary rehabilitation vs. usual care or waitlist*	Function *Short-term*	3 (N=381) Amris 2014 Castel 2013 Saral 2016 ("long-term" intervention arm)[i]	Moderate	Consistent[j]	Imprecise	Undetected	Low	Pooled mean difference −6.08, 95% CI −14.17 to 0.16, I^2=48.9%, on 0-100 FIQ Proportion with clinically meaningful improvement in FIQ total score compared with usual care at short (OR 3.1, 95% CI 1.6 to 6.2)
		Function *Intermediate-term*	3 (N=394) Castel 2013 Cedraschi 2004 Martin 2012	High	Consistent	Precise	Undetected	Low	Pooled difference −7.77, 95% CI −12.22 to −3.83, I^2=0% Proportion with clinically meaningful improvement in FIQ total score compared with usual care at short (OR 3.1, 95% CI 1.5 to 6.4)
		Function *Long-term*	2 (N=311) Castel 2013 van Ejik-Hustings 2013	Moderate	Consistent	Precise	Undetected	Low	Pooled difference −8.54, 95% CI −15.00 to −1.30, I^2=0% Proportion with clinically meaningful improvement in FIQ total score compared with usual care at short (OR 8.8, 95% CI 2.5 to 30.9)
		Pain *Short-term*	2 (N=341) Amris 2014 Castel 2013	Moderate	Consistent[j]	Precise	Undetected	Low	Pooled difference on 0-10 scale −0.24, 95%CI −0.63 to 0.15, I^2=0% (Excluding outlier)[k]
		Pain *Intermediate-term*	3 (N=394) Castel 2013 Cedraschi 2004 Martin 2012	High	Consistent	Precise	Undetected	Low	Pooled difference −0.68, 95% CI −1.10 to −0.27, I^2=0%

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Pain *Long-term*	2 (N=311) Castel 2013 van Ejik-Hustings 2013	Moderate	Consistent	Precise	Undetected	Low	Pooled difference −0.25, 95% CI −0.79 to 0.36, I^2=0%
		Harms	1 (N=164) Cedraschi 2004	High	Unknown	Imprecise	Undetected	Insufficient	Data were insufficient for harms; however, one poor quality trial reported that 19% (16/84) in the multidisciplinary group withdrew (versus 0% for waiting list), two gave increased pain as the reason. Reasons for other withdrawals were not given and there was not systematic reporting of adverse events
	Multi-disciplinary rehabilitation vs. exercise	Function *Long-term*	1 (N=155) van Eijk-Hustings 2013	Moderate	Unknown	Precise	Undetected	Low	Difference −1.10, 95% CI −8.40 to 6.20, on a 0-100 scale
		Pain *Long-term*	1 (N=155) van Eijk-Hustings 2013	Moderate	Unknown	Precise	Undetected	Low	Difference 0.10, 95% CI −0.67 to 0.87, on a 0-10 scale
		Harms	1 (N=155) van Eijk-Hustings 2013	Moderate	Unknown	Imprecise	Undetected	Insufficient	Data were insufficient. Harms not reported

CBT = cognitive behavioral therapy; CI = confidence interval; EMG = electromyography; FIQ = Fibromyalgia Impact Questionnaire; MD = mean difference; MPQ = McGill Pain Questionnaire; NDI = Neck Disability Index; PSFS = Patient Specific Functional Scale; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; VAS = visual analog scale.

[a] Outlier excluded, Baptista 2012.

[b] New Exercise Therapy trial (combination exercise via exergame)

[c] New Psychological Therapy trial, with the exeption of Verkaik. Verkaik was included in the prior AHRQ report but was not included in the pooled estimate; for this update report it was determined that Verkaik could be pooled.

[d] New Mindfulness Practices trial.

[e] Effect estimates go in the same direction even though magnitude of effect may differ

[f] New Mind-body Therapies trial (Tai Chi).
[g] There were no trials in the prior report that compared a Mind-body Therapy with Exercise.
[h] New Acupuncture trial.
[i] The "long-term" multidisciplinary arm (2 days of education and exercise followed by 10 weeks of CBT) was determined to be most consistent with interventions employed by the other trials and was included in the pooled estimates; results for the "short-term" group (2 days of education, exercise and CBT programs) were similar to those of the "long-term" group and are detailed in Table 42 of the full report.
[j] I^2 >40% but not downgraded for inconsistency because direction of effect consistent across >75% of trials or heterogeneity explainable in subgroup/stratified/sensitivity analyses.
[k] Outlier excluded, Saral 2016.

Table G-7. Chronic tension headache (KQ 5) strength of evidence

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
Psychological Therapies	*CBT vs. waitlist, attention control, or placebo*	Function *Short- and intermediate term*	1 (N=60) Holroyd 2001	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial
		Pain *Short-term*	2 (N=105) Holroyd 2001 Blanchard 1990	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from two small poor quality trials
		Pain *Intermediate-term*	1 (N=60) Holroyd 2001	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial
		Harms	1 (N=60) Holroyd 2001	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial. The risk of withdrawal due to adverse events did not differ between CBT plus placebo and placebo alone (2% vs. 6%).
	Relaxation vs. waitlist of attention control	Pain, Harms *Short-term*	1 (N=55) Blanchard 1990	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial
	CBT vs. amitriptyline	Function *Short- and intermediate term*	1 (N=60) Holroyd 2001	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial
		Pain *Short-term*	2 (N=96) Holroyd 2001 Holroyd 1991	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from two small poor quality trials
		Pain *Intermediate-term*	1 (N=60) Holroyd 2001	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	2 (N=96) Holroyd 2001 Holroyd 1991	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from two small poor quality trial. Lower risk of "at least mild" adverse events in the CBT group (0% vs. 59%) in one poor quality trial; similar risk of withdrawal due to adverse events (2% in each group).
Physical Modalities	Occipital transcutaneous electrical stimulation vs. sham	Function, Pain, *Short-term*	1 (N=83) Bono 2015	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one small poor quality trial
		Harms	1 (N=83) Bono 2015	High	Unknown	Precise	Undetected	Insufficient	Data for harms were insufficient; however, no adverse events occurred in either the real or the sham OTES group
Manual Therapies	Spinal manipulation vs. usual care	Function *Short-term*	1 (N=75) Castien 2011	Moderate	Unknown	Precise	Undetected	Low	Difference −5.0, 95% CI −9.02 to −1.16, on the Headache Impact Test, scale 36-78; Difference −10.1, 95% CI −19.5 to −0.64, on the Headache Disability Inventory, scale 0-100
		Pain *Short-term*	1 (N=75) Castien 2011	Moderate	Unknown	Precise	Undetected	Low	Difference −1.4 on a 0-10 NRS scale, 95% CI −2.69 to −0.16
		Harms	1 (N=75) Castien 2011	Moderate	Unknown	Precise	Undetected	Low	No adverse events occurred in either group.
	Spinal manipulation vs. amitriptyline	Pain *Short-term*	1 (N=126) Boline 1995	High	Unknown	Precise	Undetected	Insufficient	Insufficient evidence from one poor quality trial

Intervention	Comparator	Outcome	Number of RCTs (patients) Author Year	Study Limitations	Consistency	Precision	Reporting Bias	Strength of Evidence	Findings, Direction and Magnitude of Effect
		Harms	1 (N=126) Boline 1995	High	Unknown	Precise	Undetected	Low	Fewer adverse events with manipulation versus amitriptyline (RR 0.05, 95% CI 0.02 to 0.16), though the risk of withdrawal due to adverse events was not significantly different (RR 0.16, 95% CI 0.02 to 1.33). Common complaints were neck stiffness in the manipulation group and dry mouth, dizziness, and weight gain in the medication group
Acupuncture	Traditional Chinese needle acupuncture vs. sham	Pain *Short-term*	2 (N=69) Karst 2000 Tavola 1992	High	Consistent	Imprecise	Undetected	Insufficient	Insufficient evidence from two small, poor quality trials
		Pain *Intermediate- and long-term*	1 (N=30) Tavola 1992	High	Unknown	Imprecise	Undetected	Insufficient	Insufficient evidence from one small, poor quality trial
		Harms	No studies	--	--	--	--	--	No evidence
	Laser acupuncture vs. sham laser	Pain *Short-term*	1 (N=50) Ebneshahidi 2005	Moderate	Unknown	Precise	Undetected	Low	Median difference −2, IQR 6.3, on a 0-10 VAS scale for pain intensity median difference −8, IQR 21.5, for number of headache days per month
		Harms	1 (N=50) Ebneshahidi 2005	Moderate	Unknown	Precise	Undetected	Low	No adverse events occurred in either group.

CBT = cognitive behavioral therapy; CI = confidence interval; IQR = interquartile range; NRS = numerical rating scale; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

Appendix H. Definitions for Magnitude of Effects

Table H-1. Definitions for magnitude of effects, based on mean between-group differences

Outcome	Slight/Small Magnitude of Effect	Moderate Magnitude of Effect	Large/Substantial Magnitude of Effect
Pain	5–10 points on a 0-to 100-point VAS or the equivalent	>10–20 points on a 0-to 100-point VAS or the equivalent	>20 points on a 0-to 100-point VAS or the equivalent
	0.5–1.0 points on a 0-to 10-point numerical rating scale or the equivalent	>1–2 points on a 0-to 10-point numerical rating scale or the equivalent	>2 points on a 0-to 10-point numerical rating scale or the equivalent
Function	5–10 points on the ODI	>10–20 points on the ODI	>20 points on the ODI
	1–2 points on the RDQ	>2–5 points on the RDQ	>5 points on the RDQ
	1-2 points on the Lequesne Index	>2-5 points on the Lequesne Index	5 points on the Lequesne Index
	1-5 points on the SF-MPQ	>5-10 points on the SF-MPQ	>10 points on the SF-MPQ
	5–10 points on the WOMAC	>10–20 points on the WOMAC	>20 points on the WOMAC
	5–10 points on the KOOS	>10–20 points on the KOOS	>20 points on the KOOS
	5-10 points on the NPQ	>10–20 points on the NPQ	>20 points on the NPQ
	5-10 points on the FIQ Total Score	>10–20 points on the FIQ Total Score	>20 points on the FIQ Total Score
	7.5-10 points on the NDI	>10-20 on the NDI	>20 points on the NDI
	1.3 – 2.2 on the PSFS	23.3 -2.6 on the PSFS	>2.6 on the PSFS
Pain or Function	0.2–0.5 SMD	>0.5–0.8 SMD	>0.8 SMD

FIQ = Fibromyalgia Impact Questionnaire; KOOS=Knee Injury and Osteoarthritis Outcome Score; NDI = neck disability index; NPQ = Northwick Park Questionnaire; ODI = Oswestry Disability Index; PSFS = Patient-Specific Functional Scale; RDQ = Roland Morris Disability Questionnaire; SF-MPQ = Short-Form McGill Pain Questionnaire; SMD = standardized mean difference; VAS = visual analogue scale; WOMAC = Western Ontario and Mc Master Universities Osteoarthritis index.