Systematic Review on Noninvasive Nonpharmacological Treatment for Chronic Pain: Surveillance Report 1

Literature Update Period: August 2019 through September 2021

Background and Purpose

This is the first update for the 2020 report *Noninvasive Nonpharmacological Treatment for Chronic Pain*[1] (available at https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/research), covering the period August 2019 through September 2021. The 2020 report addressed benefits and harms of noninvasive nonpharmacological therapy for five common chronic pain conditions: low back pain (LBP); neck pain; knee, hip, or hand osteoarthritis (OA); fibromyalgia (FM); and tension headache. Given the clinical and public health importance of this topic, it is important to identify new evidence that could impact practice or policy. The purpose of this surveillance report is to identify new evidence published since the 2020 report and to determine how the new evidence impacts findings of the prior report. Subsequent surveillance reports are planned for January 2022 (based on evidence published from October to December 2021) and April 2022 (based on evidence published from January to March 2022).

Scope

The scope and eligibility criteria established at the time of the original report[1] were utilized for this surveillance report; no changes were made. That report included randomized controlled trials (RCTs) reporting outcomes at least 1 month following the completion of treatment and focused on the use of single, active, noninvasive nonpharmacological interventions (including exercise, mind-body practices, psychological therapies, mindfulness practices, manual therapies, physical modalities, acupuncture, and multidisciplinary rehabilitation) for adults with five common chronic pain conditions, LBP (Key Question 1), neck pain (Key Question 2), knee, hip, or hand OA (Key Question 3), FM (Key Question 4), and tension headache (Key Question 5). The report addressed:

- Whether the interventions work overall compared with sham, waitlist control, attention control, no treatment, or usual care;
- Whether the interventions work compared with pharmacological alternatives; and
- How outcomes for individual interventions (e.g., acupuncture) compare with a common comparator (exercise for LBP, neck pain, OA, and FM; biofeedback for headache).

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

The full protocol for the original report including detailed inclusion criteria using the PICOTS framework

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(https://www.ncbi.nlm.nih.gov/books/NBK556223/table/ch3.tab1/?report=objectonly) and full Key Questions (https://www.ncbi.nlm.nih.gov/books/n/cer227/ch2/#ch2.s2) is available on the Agency for Healthcare Research and Quality (AHRQ) website (https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/protocol) and on the PROSPERO systematic reviews registry (CRD42019132457).

Methods

Update searches were conducted to identify evidence published from August 2019 through September 2021. Search strategies from the original report were utilized,[1] and we searched the same databases as in the original report (Ovid® MEDLINE®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews). In addition, to capture articles not yet indexed in MEDLINE, we supplemented the original search strategies with a previously developed[2] optimized (text-word only) search in pre-MEDLINE to identify studies not yet indexed with Medical Subject Headings (MeSH). As in the original report, searches on electronic databases were supplemented by review of reference lists of relevant articles. Search strategies are available in Appendix A.

As in the original review, one investigator screened citations identified through searches for eligibility for full-text review. (Key Questions and inclusion criteria are available in Appendix B.) In addition, to increase efficiency of abstract review, we utilized a machine learning classifier in conjunction with a second investigator to assist in conducting dual reviews. The machine learning classifier was previously shown to have 100 percent recall for identifying eligible studies in update searches for this review.[2] The machine learning classifier screened all citations; the second investigator performed dual review on all studies except those classified by the machine learning classifier as very low probability. Any citation identified as potentially eligible by either investigator underwent full-text review to determine final eligibility.

We utilized the same methods for data abstraction and quality assessment as for the original report. As in the prior review, we assessed the risk of bias of RCTs using the approaches recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8.5, Risk of Bias Tool)[3] and the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Research*,[4] in conjunction with criteria and methods developed by the Cochrane Back and Neck Group.[5] The decision to update meta-analyses from the original report was based on the number and sample sizes of new studies eligible for meta-analysis (meta-analysis performed if new evidence was large relative to the studies in the original meta-analysis); consistency in findings between the new studies and the original meta-analysis (meta-analysis performed if findings from new evidence appear inconsistent and new studies were appropriate for pooling based on similarity in populations, interventions, and comparisons, in order to determine whether new studies impact conclusions); or whether new evidence could impact the strength of evidence (SOE) (meta-analysis performed if the SOE based on the original meta-analysis was low or insufficient and new evidence could increase the strength of evidence due to increased precision, quality, or other factors). The SOE was based on the totality of evidence (evidence in the original report plus new evidence) and determined using the methods described in the original report. We highlighted any changes in the SOE assessments.

A list of studies included in this surveillance report is provided in Appendix C. An evidence table providing data from included studies is available in Appendix D, and quality assessments for each study are shown in Appendix E. A list of articles excluded at full-text review, along

with reasons for exclusion, is available in Appendix F. Updated and new meta-analyses can be found in Appendix G.

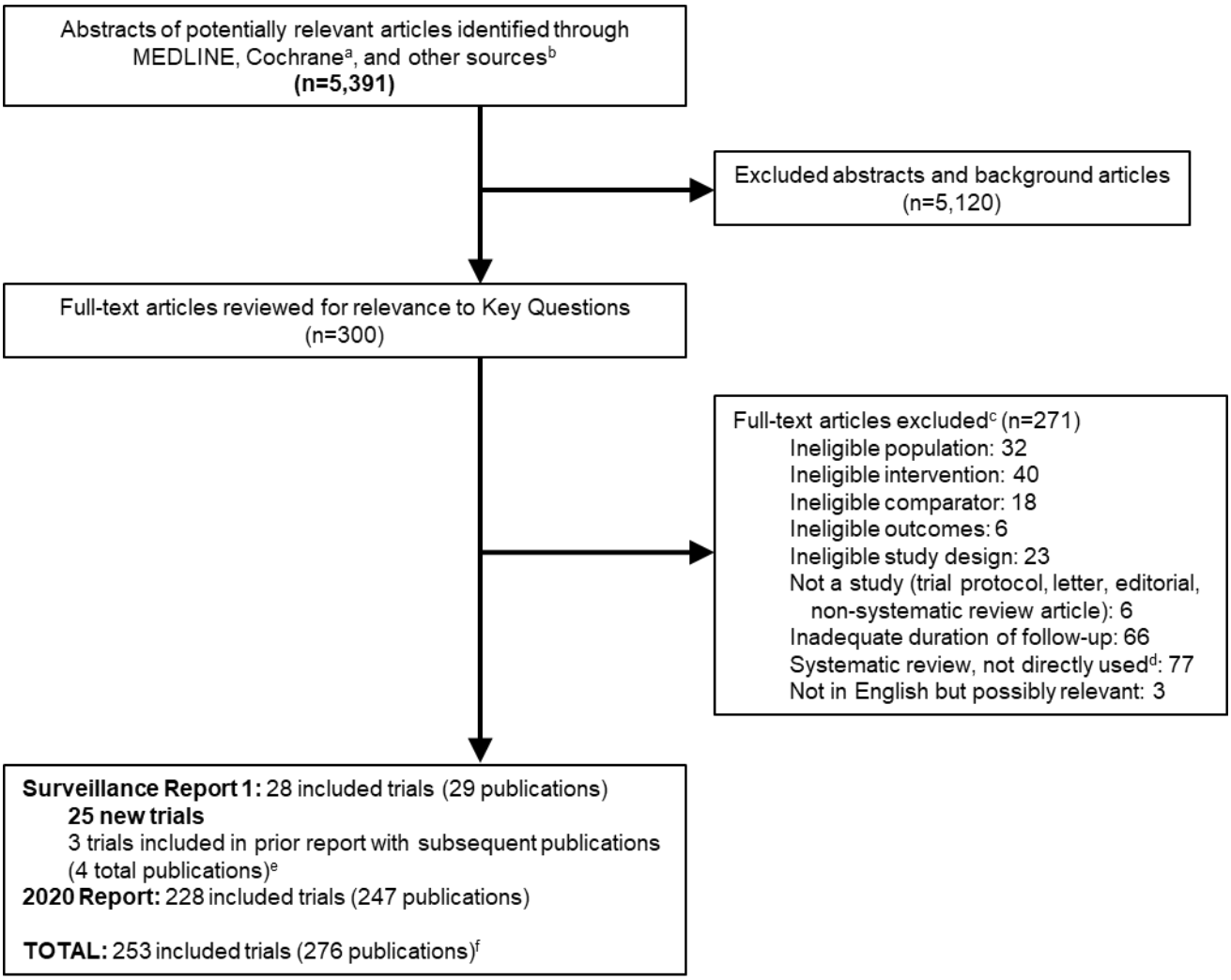
Results

The update search yielded 5,391 total citations and identified 29 new eligible citations (Figure 1). Of those, 25 were new RCTs[6-30] (3 good, 19 fair, and 7 poor quality) that reported on primary outcomes of interest, and 4 (3 LBP, 1 FM) were subsequent publications[31-34] for trials already included in the prior report and reported only secondary outcomes. This surveillance report focuses on the primary outcomes and changes in strength of evidence (SOE) based on new evidence. Secondary outcomes are not summarized in this update report but can be found in Appendix D of this report, and Appendix D of the original report.

For **chronic LBP**, a total of 10 new RCTs[7,14,15,17,18,20,22,27,28,30] (9 fair and 1 poor quality) were included that compared exercise versus usual care (2 RCTs),[17,27] psychological therapy versus usual care (2 RCTs)[7,27] and versus exercise (1 RCT),[27] low-level laser therapy (LLLT) versus sham (1 RCT),[14] transcutaneous electrical nerve stimulation versus sham (1 RCT),[30] spinal manipulation versus sham (1 RCT),[28] massage versus usual care (1 RCT),[15] yoga versus exercise (2 RCTs),[20,22] and acupuncture versus usual care (1 RCT).[18] Only one new fair-quality RCT was included for **chronic neck pain**; it compared manual therapy versus sham and versus exercise.[8] For **knee OA**, a total of 9 new RCTs[6,12,13,16,19,21,24,26,29] (3 good, 3 fair, and 3 poor quality) were included that compared exercise versus usual care or attention control (3 RCTs),[19,21,26] massage versus usual care (1 RCT),[24] ultrasound versus sham (1 RCT),[13] LLLT versus sham (1 RCT),[6] interferential current versus sham (1 RCT),[6] Tai Chi versus usual care (1 RCT),[12] Qigong versus exercise (1 RCT),[29] and acupuncture versus sham (1 RCT).[16] For **FM**, a total of 5 new RCTs[9-11,23,25] (2 fair and 3 poor quality) were included that compared exercise versus usual care (2 RCTs),[11,23] spinal manipulation versus sham (1 RCT),[10] mindfulness-based stress reduction versus usual care (1 RCT),[25] basic body awareness training versus usual care (1 RCT),[9] acupuncture versus usual care and versus exercise (1 RCT),[11] and multidisciplinary rehabilitation (MDR) versus usual care and versus exercise (1 RCT).[23] One LBP trial,[27] one knee OA trial,[6] and two FM trials[11,23] had more than two arms and provided data for multiple interventions and/or comparators; thus the numbers of RCTs cited above are not mutually exclusive.

No new trials were identified for hip or hand OA or chronic tension–type headache or that compared a nonpharmacological therapy with pharmacological therapy. There was no new evidence for the following interventions for LBP (mindfulness practices, MDR), neck pain (psychological therapies, physical modalities, mindfulness practices, mind-body practices, acupuncture, and MDR), knee OA (psychological therapies, mindfulness practices, MDR), and FM (psychological therapies, physical modalities). 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 (all Key Questions). No data were available to evaluate nociplasticity as a modifier to treatment effectiveness or safety (Key Question 6).

Figure 1. 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] Publications may be included or excluded for multiple interventions
[d] Used as source documents, studies checked for inclusion eligibility
[e] These 4 followup publications (to Groessl 2017, Saper 2017 [chronic low back pain], and McCrae 2019 [fibromyalgia] included in the 2020 report) reported only secondary outcomes of interest and are not summarized in this surveillance report, but details can be found in Appendix D.
[f] The 4 followup publications are not counted in the number of included trials but are counted under total publications.

Summary of Findings

- Twenty-five new RCTs that reported on primary outcomes of interest were identified for this update (10 in chronic LBP, 1 in chronic neck pain, 9 in knee OA, and 5 in FM). Nine of the new trials (2 in chronic LBP, 1 in chronic neck pain, 2 in knee OA, and 4 in FM; noted below) evaluated interventions, comparators, or timepoints not previously evaluated; otherwise, the trials evaluated comparisons with at least some prior evidence.

Chronic Low Back Pain

- **Exercise:** The addition of two new fair-quality trials comparing exercise with usual care did not change the previous report's conclusions of a small improvement in *function* short term (SOE: moderate), nor did it change the conclusion of no effect with the addition of one new fair-quality trial at intermediate term (SOE: low) based on updated meta-analyses. Similarly, data from these trials did not change the prior report's conclusion of a small improvement in *pain* with exercise short term (adding both new trials) or intermediate term (1 new trial) compared with usual care (SOE: low for both timepoints).
- **Psychological therapies:** The inclusion of one new fair-quality RCT of pain reprocessing therapy (PRT) to our previous meta-analysis resulted in a similar effect size and conclusion of a small improvement in *function* with psychological therapies short term, as found in the 2020 report. We downgraded the SOE from moderate to low based on increased inconsistency. The other new trial of relaxation therapy was excluded from the updated meta-analysis of function short term as an outlier. (The effect estimate was substantially larger than those in other included trials.) Addition of the PRT study to our previous meta-analysis did not change our previous conclusions of small improvements in *function* at intermediate term and long term (SOE: moderate). PRT was associated with small improvements in *pain* (0 to 10 scale) compared with usual care at short term, intermediate term, and long term (SOE: moderate), which is consistent with the conclusion of the 2020 report. Evidence was insufficient for one new small fair-quality trial comparing psychological therapy with exercise.
- **Physical modalities, low-level laser therapy:** The addition of one new small poor-quality trial of low-level laser therapy versus sham did not change the previous report's conclusions of a small improvement in *function* and moderate improvement in *pain* short term (SOE: low).
- **Physical modalities, transcutaneous electrical nerve stimulation:** The prior report did not contain studies of this modality. One new fair-quality RCT of transcutaneous electrical nerve stimulation (TENS) compared with sham TENS found no difference in function or pain short term (SOE: low).
- **Manual therapies, spinal manipulation:** Effect size based on updated meta-analysis including one new fair-quality RCT of manipulation and sham laser is consistent with the small improvement in *function* observed short term in the prior report. Similarly, the new trial's finding of no difference in *pain* short term was consistent with the 2020 report. SOE remained low.
- **Manual therapies, massage:** One new small fair-quality RCT of massage versus usual care found no difference between groups for function or pain short term. Its addition, it

did not change our previous conclusion of small improvements in *function and pain* short term (SOE: moderate).

- **Mind-body practices, yoga:** Two new fair-quality RCTs found no differences between yoga and exercise for *function or pain* short term, which is consistent with findings of no effect from the 2020 report; the SOE remained low.
- **Acupuncture:** One new fair-quality RCT compared two different forms of acupuncture with usual care. Standard acupuncture was associated with moderate improvements in *function and pain,* while hand and ear acupuncture was associated with large improvements in *function and pain* versus usual care at short-term followup. Findings from this new RCT are consistent with our prior meta-analyses for the comparison with usual care; SOE remained low for function and moderate for pain.

Chronic Neck Pain

- **Exercise:** One new small fair-quality trial found exercise associated with moderate improvement in function and large improvement in pain versus a sham procedure short term; given the small sample size, it did not change our prior conclusions of no effect for *function or pain* (SOE: low).
- **Manual therapies (manipulation):** One new small fair-quality trial found that manipulation was associated with moderate improvement in *function* and large improvement in *pain* short term compared with a sham procedure (suboccipital inhibition). There was no difference in either *function or pain* short term between manual therapy and exercise. The prior report did not include comparisons of manipulation with sham treatment or with exercise. SOE was low for function and pain across both comparisons.

Knee OA

- **Exercise:** Addition of one poor-quality and two fair-quality RCTs comparing exercise with usual care or attention control in patients with knee OA did not change the 2020 report's conclusions or SOE for small improvement in *function and pain* short and long term, and moderate improvements in both at intermediate term (SOE moderate for both at short term and low at intermediate and long term).
- **Physical modalities, low-level laser therapy:** One new good-quality RCT compared LLLT versus sham. Its incorporation into a new meta-analysis for *function* revealed a small improvement at short and intermediate term. Its addition to a prior meta-analysis of two trials for *pain* did not change prior findings of no difference at short or intermediate term. With the addition of the new trial, the SOE was upgraded from insufficient to low for all.
- **Physical modalities, ultrasound:** One new good-quality RCT comparing ultrasound with sham reported no difference between groups in *function or pain* short term; this is consistent with the prior report and SOE remained low.
- **Physical modalities, inferential current:** No trials of this modality were identified for the prior report. The new good-quality RCT found no improvement in either *function or*

pain at short or intermediate term for interferential current compared with sham (SOE: low).

- **Manual therapies, massage:** One new small poor-quality RCT of massage versus usual care did not change our conclusion of insufficient evidence.
- **Mind-body therapies, Tai Chi and Qigong:** One new small poor-quality RCT comparing Tai Chi with usual care does not change conclusions of insufficient evidence from the prior report. Evidence for a new comparison of Qigong with exercise from one fair-quality trial was considered insufficient.
- **Acupuncture:** One new good quality RCT of acupuncture versus sham reported no difference between groups in *function or pain* short term; this is consistent with the prior report and SOE remained low.

Fibromyalgia

- **Exercise:** Two new poor-quality trials comparing exercise with usual care reported no difference between groups in short term function. Given the poor quality of these trials, our conclusions for a small improvement in *function* short term (SOE: low) did not change.
- **Manual therapy, spinal manipulation**. The prior report did not contain evidence for spinal manipulation versus sham manipulation. One new fair-quality RCT found no difference between groups in either *function or pain* at short or intermediate term (SOE: low).
- **Mindfulness practices, mindfulness-based stress reduction:** One new poor-quality trial reported a small improvement in *function* following mindfulness-based stress reduction compared with usual care. This is consistent with the original report and SOE remained low.
- **Mind-body therapies, basic body awareness therapy**: No trials of this modality were identified for the prior report. Evidence from one new small fair-quality trial of basic body awareness therapy was considered insufficient.
- **Acupuncture**: The prior report did not contain evidence for acupuncture versus usual care or versus exercise. Evidence from one new poor-quality RCT was considered insufficient.
- **Multidisciplinary rehabilitation:** One new poor-quality RCT compared MDR with usual care and with exercise, and found no difference between MDR and either comparator in function short term. The prior report found a small improvement in *function* short term compared with usual care (SOE: low); given the poor quality of the new RCT, the 2020 report's conclusions and SOE remain unchanged. For the comparison of MDR with exercise, we graded the evidence as insufficient; the prior report did not contain evidence for this comparison at short term.

Harms

- Consistent with the 2020 report, adverse events were not consistently reported in new studies and intervention-related serious life-threatening events requiring medical attention were not reported.

Summary of New Evidence

Table 1 provides the conclusions from the 2020 report and the new findings from studies identified in this surveillance report. Table 1 focuses on Key Questions and interventions with new evidence; the full SOE table is available in the prior report (https://www.ncbi.nlm.nih.gov/books/n/cer227/appg/).

Table 1. Summary of conclusions and assessments informed by new evidence

Condition: Intervention, Comparator	Outcome, Timing	Prior (2020) Update[a]	2021 Surveillance Report[a]	Change
LBP: Exercise vs. UC, AC or placebo	Function, short term	Small effect SOE: Moderate 10 RCTs (N=940) [Excluding an outlier trial]	2 fair-quality RCTs (N=147)[17,27] **MA updated** 12 RCTs (N=1,011)	No change in conclusions
	Function, intermediate term	No effect SOE: Low 5 RCTs (N=616)	1 fair-quality RCT (N=96)[17] **MA updated** 6 RCTs (N=712)	No change in conclusions
	Pain, short term	Moderate effect SOE: Low 11 RCTs (N=981)	1 fair-quality RCT (N=111)[17] No effect	No change in conclusions
	Pain, intermediate term	Small effect SOE: Low 5 RCTs (N=616)	1 fair-quality RCT (N=96)[17] No effect	No change in conclusions
LBP: Psychological therapies vs. UC	Function, short term	Small effect SOE: Moderate 3 RCTs (N=906)	2 fair-quality RCTs (N=146)[7,27] **MA updated** 4 RCTs (N=1,018)[b]	Small effect SOE: Low (downgraded one level)
	Function, intermediate term	Small effect SOE: Moderate 3 RCTs (N=1,026)	1 fair-quality RCT (N=116)[7] **MA updated** 4 RCTs (N=1,142)	No change in conclusions
	Function, long term	Small effect SOE: Moderate 3 RCTs (N=815)	1 fair-quality RCT (N=124)[7] **MA updated** 4 RCTs (N=939)	No change in conclusions
	Pain, short term	Small effect SOE: Moderate 3 RCTs (N=906)	1 fair-quality RCT (N=112)[7] Small effect	No change in conclusions
	Pain, intermediate term	Small effect SOE: Moderate 3 RCTs (N=1,026)	1 fair-quality RCT (N=116)[7] Small effect	No change in conclusions
	Pain, long term	Small effect SOE: Moderate 3 RCTs (N=815)	1 fair-quality RCT (N=124)[7] Small effect	No change in conclusions
LBP: Psychological therapies vs. exercise	Function, short term	No evidence at short term	1 fair-quality RCT (N=34)[27] No effect	Insufficient evidence
LBP: Physical modalities: LLLT vs. sham	Function, short term	Small effect SOE: Low 1 RCT (N=56)	1 poor-quality RCT (N=34)[14] Large effect	No change in conclusions
	Pain, short term	Moderate effect SOE: Low 1 RCT (N=56)	1 poor-quality RCT (N=34)[14] Large effect	No change in conclusions
LBP: Physical modalities: Burst	Function, short term	No evidence	1 fair-quality RCT (N=73)[30] No effect	New intervention No effect

Condition: Intervention, Comparator	Outcome, Timing	Prior (2020) Update[a]	2021 Surveillance Report[a]	Change
TENS vs. continuous TENS vs. sham				SOE: Low
	Pain, short term	No evidence	1 fair-quality RCT (N=73)[30] No effect	New intervention No effect SOE: Low
LBP: Manual therapy: Spinal manipulation vs. sham, UC, AC	Function, short term	Small effect SOE: Low 3 RCTs (N=704)	1 fair-quality RCT (N=155)[28] **MA updated** 4 RCTs (N=859)	No change in conclusions
	Pain, short term	No effect SOE: Low 3 RCTs (N=530)	1 fair-quality RCT (N=155)[28] No effect	No change in conclusions
LBP: Manual therapy: Massage vs. sham, UC, AC	Function, short term	Small effect SOE: Moderate 6 RCTs (N=694)	1 fair-quality RCT (N=59)[15] No effect	No change in conclusions
	Pain, short term	Small effect SOE: Moderate 5 RCTs (N=644)	1 fair-quality RCT (N=59)[15] No effect	No change in conclusions
LBP: Mind-body practices: Yoga vs. exercise	Function, short term	No effect SOE: Low 4 RCTs (N=559)	2 fair-quality RCTs (N=252)[20,22] No effect	No change in conclusions
	Pain, short term	No effect SOE: Low 5 RCTs (N=575)	2 fair-quality RCTs (N=252)[20,22] No effect	No change in conclusions
LBP: Acupuncture vs. sham, UC, or AC	Function, short term	Small effect SOE: Low 4 RCTs (N=2,066)	1 fair-quality RCT (N=152)[18] Large effect	No change in conclusions
	Pain, short term	Small effect SOE: Moderate 5 RCTs (N=2,109)	1 fair-quality RCT (N=152)[18] Moderate effect	No change in conclusions
Neck pain: Exercise vs. AC, WL, or NT	Function, short term	No effect [excluding outlier] SOE: Low 3 RCTs (N=444)	1 fair-quality RCT (N=43)[8] Moderate effect	No change in conclusions
	Pain, short term	No effect [excluding outlier] SOE: Low 3 RCTs (N=444)	1 fair-quality RCT (N=43)[8] Large effect	No change in conclusions
Neck pain: Manual therapy: Manipulation vs. sham	Function, short term	No evidence	1 fair-quality RCT (N=42)[8] Moderate effect	New intervention Moderate effect SOE: Low
	Pain, short term	No evidence	1 fair-quality RCT (N=42)[8] Large effect	New intervention Large effect SOE: Low
Neck pain: Manual therapy: Manipulation vs. exercise	Function, short term	No evidence	1 fair-quality RCT (N=43)[8] No effect	New intervention No effect SOE: Low
	Pain, short term	No evidence	1 fair-quality RCT (N=43)[8] No effect	New intervention No effect SOE: Low
Knee OA: Exercise vs. UC, AC, sham, or NT	Function, short term	Small effect SOE: Moderate 8 RCTs (N=748)	1 poor-quality RCT (N=84)[26] **MA updated** 9 RCTs (N=832)	No change in conclusions

Condition: Intervention, Comparator	Outcome, Timing	Prior (2020) Update[a]	2021 Surveillance Report[a]	Change
	Function, intermediate term	Moderate effect SOE: Low 11 RCTs (N=879)	1 fair-quality RCT (N=265)[19] **MA updated** 12 RCTs (N=1,144)	No change in conclusions
	Function, long term	Small effect SOE: Low 4 RCTs (N=1,199)	2 fair-quality RCTs (N=342)[19,21] **MA updated** 6 RCTs (N=1,541)	No change in conclusions
	Pain, short term	Small effect SOE: Moderate 8 RCTs (N=748)	1 poor-quality RCT (N=84)[26] **MA updated** 9 RCTs (N=832)	No change in conclusions
	Pain, intermediate term	Moderate effect SOE: Low 11 RCTs (N=879)	1 fair-quality RCT (N=261)[19] **MA updated** 12 RCTs (N=1,140)	No change in conclusions
	Pain, long term	Small effect SOE: Low 4 RCTs (N=1,199)	2 fair-quality RCTs (N=338)[19,21] **MA updated** 6 RCTs (N=1,537)	No change in conclusions
Knee OA: Physical modalities: LLLT vs. sham or UC	Function, short term	Insufficient evidence 1 RCT (N=49)	1 good-quality RCT (N=84)[6] **New MA** 2 RCTs (N=133)	Small effect SOE: Low (upgraded one level)
	Function, intermediate term	Insufficient evidence 2 RCTs (N=109)	1 good-quality RCT (N=84)[6] **New MA** 3 RCTs (N=193)	Small effect SOE: Low (upgraded one level)
	Pain, short term	Insufficient evidence 2 RCTs (N=76)	1 good-quality RCT (N=84)[6] **MA updated** 3 RCTs (N=160)	No effect SOE: Low (upgraded one level)
	Pain, intermediate term	Insufficient evidence 2 RCTs (N=109)	1 good-quality RCT (N=84)[6] **MA updated** 3 RCTs (N=193)	No effect SOE: Low (upgraded one level)
Knee OA: Physical modalities: Continuous and pulsed US vs. sham	Function and pain, short term	No effect SOE: Low 3 RCTs (N=249)	1 good-quality RCT (N=75)[13] No effect	No change in conclusions
Knee OA: Physical modalities: Interferential current vs. sham	Function, short and intermediate term	No evidence	1 good-quality RCT (N=84)[6] No effect	New intervention No effect SOE: Low
	Pain, short and intermediate term	No evidence	1 good-quality RCT (N=84)[6] No effect	New intervention No effect SOE: Low
Knee OA: Manual therapies: Massage vs. UC	Function, short term	Insufficient evidence 1 RCT (N=125)	1 poor-quality RCT (N=60)[24] No effect	No change in conclusions
	Pain, short term	Insufficient evidence 1 RCT (N=125)	1 poor-quality RCT (N=60)[24] Small effect	No change in conclusions

Condition: Intervention, Comparator	Outcome, Timing	Prior (2020) Update[a]	2021 Surveillance Report[a]	Change
Knee OA: Mind-body therapies: Tai Chi vs. AC or UC	Function and pain, intermediate term	Insufficient evidence 1 RCT (N=40)	1 poor-quality RCT (N=92)[12] Moderate effect	No change in conclusions
Knee OA: Mind-body therapies: Qigong vs. exercise	Function and pain, intermediate term	No evidence vs. exercise	1 fair-quality trial (N=68)[29] No effect	New comparator Insufficient evidence
Knee OA: Acupuncture vs. UC, NT, or sham	Function, short term	No effect SOE: Low 5 RCTs (N=944)	1 good-quality RCT (N=83)[16] No effect	No change in conclusions
	Pain, short term	No effect SOE: Low 6 RCTs (N=1065)	1 good-quality RCT (N=83)[16] No effect	No change in conclusions
FM: Exercise vs. UC, NT, sham, or AC	Function, short term	Small effect SOE: Low 7 RCTs (N=410)	2 poor-quality RCTs (N=135)[11,23] No effect	No change in conclusions
FM: Manual therapy: Spinal manipulation vs. sham	Function, short and intermediate term	No evidence	1 fair-quality RCT (N=101)[10] No effect	New intervention No effect SOE: Low
	Pain, short and intermediate term	No evidence	1 fair-quality RCT (N=101)[10] No effect	New intervention No effect SOE: Low
FM; Mindfulness practices: MBSR, MAT vs. AC or WL	Function, intermediate term	Small effect SOE: Low 1 RCT (N=148)	1 poor-quality RCT (N=98)[25] Small effect	No change in conclusions
FM: Mind-body therapies: BBAT vs. UC	Pain, short and intermediate term	No evidence	1 fair-quality RCT (N=39)[9] No effect	New intervention Insufficient evidence
FM: Acupuncture vs. UC	Function, short term	No evidence vs. usual care[c]	1 poor-quality RCT (N=67)[11] No effect	New comparator Insufficient evidence
FM: Acupuncture vs. exercise	Function, short term	No evidence vs. exercise	1 poor-quality RCT (N=67)[11] No effect	New comparator Insufficient evidence
FM: MDR vs. UC or WL	Function, short term	Small effect SOE: Low 3 RCTs (N=381)	1 poor-quality RCT (N=64)[23] No effect	No change in conclusions
FM: MDR vs. exercise	Function, short term	No evidence at short term	1 poor-quality RCT (N=64)[23] No effect	New timepoint (short term) Insufficient evidence

Abbreviations: AC = attention control; BBAT = basic body awareness training; FM = fibromyalgia; LBP = low back pain; LLLT = low-level laser therapy; MA = meta-analysis; MAT = meditation awareness training; MBSR = mindfulness-based stress reduction; MDR = multidisciplinary rehabilitation; NT = no treatment; RCT = randomized controlled trial; SOE = strength of evidence; TENS = transcutaneous electrical nerve stimulation; UC = usual care; US = ultrasound; vs. = versus; WL = waitlist.

[a] The sample size (N) reported is as analyzed.

[b] One new trial, Shariat 2019, was an outlier and conclusions are based on inclusion of the one new fair-quality RCT (Ashar 2021) which increased heterogeneity leading to downgrade from moderate to low SOE.

[c] In the previous report, 3 RCTs were included that compared acupuncture with sham acupuncture and found a small improvement in function short term (moderate SOE).

Evidence Details

Key Question 1: Chronic Low Back Pain

Exercise for Chronic Low Back Pain

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

Two new fair-quality trials of exercise (pedometer-based walking program [5 consecutive days per week for 12 weeks] and mobility/flexibility exercises [18 sessions over 6 weeks]) versus usual care were identified.[17,27] One moderate-sized RCT (n=96)[17] contributed data on function and pain short and intermediate term. The other, smaller RCT (n=36)[27] provided data for short-term function only.

In the short term, updated pooled estimates across 12 trials (n=1,011) did not change our previous conclusions of a small improvement in *function* (SOE moderate) with exercise versus usual care (pooled standardized mean difference [SMD] –0.36, 95% confidence interval [CI] –0.58 to –0.17, I^2=47.3% excluding the same outlier trial as the 2020 report). One of the new trials also reported results at intermediate term.[17] The conclusion of no difference in function between groups (6 RCTs, n=712; updated pooled SMD –0.18, 95% CI –0.42 to 0.03, I^2=31.3%) is consistent with the 2020 report and SOE remained low. (See Appendix G, Figure G-1 for updated function plot.) The same trial also found no difference in *pain* between exercise and usual care at short term (n=111; difference –0.6 on a 0 to 10 scale, 95% CI –1.26 to 0.06) or intermediate term (n=96; difference –0.8 on a 0 to 10 scale, 95% CI –1.60 to 0.01). The addition of these data did not change the prior report's conclusion of a small improvement in pain with exercise short term (11 RCTs) or intermediate term (5 RCTs) compared with usual care or SOE of low at either timepoint.

Of the two new trials, only one reported adverse events and it reported that no intervention-related adverse events occurred.[17]

Psychological Therapies for Chronic Low Back Pain

Psychological Therapies Compared With Usual Care or an Attention Control

Psychological therapies were associated with small functional improvements compared with usual care or attention control at short, intermediate, and long term (SOE: moderate for all) in the 2020 report. Cognitive behavioral therapy (CBT) was the most common psychological treatment reported and three trials reported for each time frame. We identified two new fair-quality trials comparing psychological therapies with usual care that reported on *function*. In one small RCT from Iran (N=34), patients received relaxation therapy for three 40–45-minute sessions per week for 6 weeks or continued usual care.[27] Patients in the other, U.S.-based trial (N=151 randomized)[7] received a proprietary pain reprocessing therapy (PRT) that aims to promote patients' reconceptualization of primary chronic pain as a brain-generated false alarm or usual care, which consisted of a chronic pain workbook or videos describing placebo treatments combined with an open-label subcutaneous saline injection at the site of greatest back pain. The PRT group received individual hourly sessions delivered twice weekly for 8 weeks.

An updated meta-analysis including the two new trials showed a moderate improvement in short-term *function* (5 RCTs, n=1,052, pooled SMD –0.58, 95% CI –1.27 to 0.01, I^2=90.7%) and

a substantial increase in heterogeneity compared with the original analyses' I^2 of 0 percent. The effect estimate from the new trial of relaxation therapy[27] was substantially larger (SMD –1.89) than those in other included trials (SMD range from –0.08 to 0.93). Exclusion of this outlier resulted in less heterogeneity and a smaller pooled effect size (4 RCTs, n=1,018, pooled SMD –0.34, 95% CI –0.74 to 0.02, I^2=70.5%), which was more consistent with, but larger than, the original report (prior report analysis, 3 RCTS, n=906, pooled SMD –0.24, 95% CI –0.38 to –0.04, I^2=0%); see Appendix G, Figure G-2 for updated plot. While the pooled estimate from the updated meta-analysis including the new PRT trial was similar to the prior report estimate, the heterogeneity was substantially higher. This may in part be due to differences in the therapeutic approach in the PRT trial compared with previously included trials. The bulk of the evidence for psychological therapies in the original report was from large trials focused on CBT. While PRT incorporates aspects of CBT, it also includes other psychological interventions used in pain management and emphasizes exposure-based interventions in conjunction with reappraising pain. Only the new trial of PRT[7] reported on intermediate- and long-term function. Updated meta-analyses to include this RCT resulted in a small increase in effect size for each time frame but did not change conclusions from the original report that psychological therapies were associated with small improvements in *function* at intermediate term (4 RCTs, n=1,142, pooled SMD –0.30, 95% CI –0.60 to –0.11, I^2=0%) and long term (4 RCTs, n=939, pooled SMD –0.31, 95% CI –0.47 to –0.18, I^2=0%). PRT was associated with small improvements in *pain* (0 to 10 scale) compared with usual care at short term (difference –0.95, 95% CI –1.43 to –0.46), intermediate term (difference –0.91, 95% CI –1.37 to –0.44), and long term (difference –0.89, 95% CI –1.34 to –0.42), which is consistent with the conclusion of the 2020 report. No adverse events were observed for PRT; the other trial did not report on adverse events.

Psychological Therapies Compared With Exercise

One new small fair-quality trial (n=36)[27] compared relaxation training versus mobility/flexibility exercises (modified from the McKenzie method) over 6 weeks (18 sessions total for both) and found no difference between groups in *function* at short-term followup (difference 0.00 on the 0 to 40 Functional Rating Index, 95% CI –1.09 to 1.09). This is the only trial identified to date evaluating short term outcomes for this comparison. Data were considered insufficient to draw conclusions. Harms were not reported.

Physical Modalities for Chronic Low Back Pain

Low-Level Laser Therapy Compared With Sham

One new poor-quality small (n=34) industry-funded trial from Iran compared LLLT with sham laser.[14] It was rated as poor quality primarily due to unclear concealment of treatment allocation, lack of patient and caregiver blinding, and differential loss to followup. The authors reported a large improvement in *function* (difference –5.70 on 0 to 24 Roland Morris Disability Questionnaire [RDQ], 95% CI –8.47 to –2.93) and large improvement in *pain* (difference –4.40 on a 0 to 10 scale, 95% CI –5.31 to –3.49) short term. The 2020 report found that LLLT was associated with a small improvement in *function* and moderate improvement in *pain* short term (SOE: low for both) compared with sham laser based on one small (n=56) fair-quality trial.[35] Given the small size and poor quality of the new trial, conclusions from the original report did not change. In the new trial, about 52 percent of the patients in the true laser group reported a temporary increase in pain following the first treatment session. Other adverse events were all

observed in the sham laser group; authors intimate that they were related to concomitant use of naproxen by participants.

Transcutaneous Electrical Nerve Stimulation Compared With Sham

There were no trials of TENS for chronic LBP in the prior report. One new fair-quality trial (n=73)[30] compared two applications of TENS, burst and conventional, versus sham TENS and found no differences between groups over the short term in *function* as measured by the modified Oswestry Disability Index (ODI) (burst vs. sham TENS: difference –2.90 on a 0 to 50 scale, 95% CI –7.97 to 2.17; conventional vs. sham TENS: difference –2.30 on a 0 to 50 scale, 95% CI –7.77 to 3.17) or in *pain* (burst vs. sham TENS: difference –0.80 on a 0 to 10 scale, 95% CI –2.24 to 0.64; conventional vs. sham TENS: difference –1.30 on a 0 to 10 scale, 95% CI –2.74 to 0.14). Results were similar across other measures of pain. SOE was low. No TENS-associated side effects occurred in any patient.

Manual Therapies for Chronic Low Back Pain

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

One new good-quality RCT (N=155)[28] compared groups receiving spinal manipulation, mobilization or sham laser treatment and reported on function and pain short term. Manipulation consisted of rapid thrust applied to the shoulder and pelvis; mobilization consisted of having the patient gently push the shoulder and pelvis into the clinician's hands. The sham laser treatment was done with the patient in the same position as the active interventions, and the machine appeared operational to patients and clinicians but delivered no energy. All sessions were twice weekly for 3 weeks. There were no differences in mean change scores for *function* (RDQ, 0 to 24 scale) between manipulation and sham treatment (−0.07, 95% CI −1.43 to 1.29) or mobilization and sham treatment (0.9, 95% CI −0.41 to 2.29). Given this, and the fact that studies in the 2020 report appear to have used a combination of manipulation and mobilization techniques, these active treatment groups were combined to update the meta-analysis. Inclusion of the new trial decreased the effect size estimate somewhat for *functional* improvement (4 RCTs, n=859, pooled SMD –0.24, 95% CI –0.61 to 0.09, I^2= 61.8%), and there was greater imprecision compared with the 2020 report (3 RCTs, n=704, pooled SMD –0.34, 95% CI –0.75 to –0.02, I^2= 44.6%); see Appendix G, Figure G-3 for updated plot. Our prior conclusion of a small improvement in *function* and low SOE did not change.

There were no differences in mean change scores for numerical rating scale (NRS) *pain* (0 to 10 scale) short term for either manipulation versus sham (difference −0.03, 95% CI −0.65 to 0.59) or mobilization versus sham (difference −0.26, 95% CI −0.38 to 0.85). In the 2020 report, there was no difference in pain short term between spinal manipulation and placebo/sham intervention or attention control across three studies. The addition of the new study did not change this conclusion and SOE remained low. Adverse events were not reported.

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

One new fair-quality trial (n=59)[15] compared Shiatsu massage (4 weekly 1-hour sessions) with usual care and found no differences between groups in *function* (difference in change scores –1.60 on the 0 to 24 RDQ, 95% CI –3.27 to 0.07) or *pain* (difference in change scores –0.80 on a 0 to 10 scale, 95% CI –1.92 to 0.32) at short-term followup. The addition of the new trial did not change the prior report's conclusion (small effect for *function and pain* short term) and SOE

remained moderate. Regarding harms, in the Shiatsu massage group, 10 percent of patients reported muscle pain and 3 percent reported headache; in the usual care group, 3 percent of patents reported each of the following events: dizziness, herpes zoster, and abdominal pain.

Mind-Body Practices for Chronic Low Back Pain

Yoga Compared With Exercise

Two new fair-quality trials (N=252)[20,22] comparing yoga with combination exercise (strengthening and stretching with or without stabilization) found no differences between groups in *function or pain* at short-term followup, consistent with the findings of the prior report (SOE remained low). Across trials, patients underwent weekly sessions of different duration (35 and 75 minutes) over 6 and 8 weeks. Both trials reported *function* according to the RDQ (0 to 24 scale); the difference in change scores from baseline was –0.06 (95% CI –1.55 to 1.43) in the larger trial (n=182),[20] and in the second trial (n=70) the median (interquartile range [IQR]) scores were 6 (3.5 to 12) versus 6 (1 to 11), p=0.26.[22] For *pain*, the difference in change scores was 0.04 on a 0 to 10 visual analog scale (VAS) (95% CI –0.50 to 0.58) in the larger trial,[20] and in the second trial the median (IQR) scores on the Defense and Veterans Pain Rating Scale (0 to 10 scale) were 4 (2.5 to 5) versus 4 (2 to 5), p=0.70.[22]

No serious adverse events occurred in either trial. The larger trial reported significantly fewer minor events in the yoga group compared with the exercise group, which included mild and self-limited exacerbating back pain (7% vs. 30%; risk ratio [RR] 0.23, 95% CI 0.10 to 0.50), general pain (4% vs. 18%; RR 0.33, 95% CI 0.11 to 1.00), and muscle pain (0% vs. 8%, p=0.001).[20] The second trial reported that three patients experienced a slight increase in pain; the authors did not indicate to which group the patients were randomized.[22]

Acupuncture for Chronic Low Back Pain

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

One new fair-quality trial (n=43)[18] compared two types of acupuncture, hand-ear acupuncture and standard acupuncture, with usual care for 7 weeks. At short-term followup, hand-ear acupuncture was associated with large improvements in both *function* (difference –7.34 on the 0-24 RDQ, 95% CI –9.50 to –5.18) and *pain* (difference –2.29 on a 0 to 10 scale, 95% CI –3.01 to –1.57), and standard acupuncture was associated with moderate improvements in both *function* (difference –4.89 on the 0-24 RDQ, 95% CI –7.47 to –52.31) and *pain* (difference –1.15 on a 0 to 10 scale, 95% CI –1.86 to –0.44) compared with usual care. The addition of the new trial did not change the prior report's conclusion (small effects short term), and SOE remained low for function and moderate for pain.

One patient (2%) who received hand-ear acupuncture complained of needling pain and two patients (4%) in the standard acupuncture group experienced anxiety. No other complications were reported.

Key Question 2: Chronic Neck Pain

Exercise for Chronic Neck Pain

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

One new small fair-quality trial (n=43),[8] compared therapeutic muscle performance exercise (21 total sessions) with sham suboccipital inhibition for 3 weeks in patients with nonspecific chronic neck pain.[8] Exercise was associated with a moderate improvement in *function* (difference –16.81 on the 0 to 100 Neck Disability Index [NDI], 95% CI –25.00 to –8.62) and a large improvement in *pain* (difference –2.43 on a 0 to 10 scale, 95% CI –2.69 to –2.17) over the short term. Given the small size of the new trial, its addition did not change the prior report's conclusion (no effect for pain and function) and SOE remained low.

Manual Therapies for Chronic Neck Pain

Spinal Manipulation Compared With Sham Manipulation and With Exercise

There were no trials of spinal manipulation for chronic nonspecific neck pain in the prior report. One new small fair-quality trial (n=42)[8] compared spinal manipulation versus sham suboccipital inhibition and versus therapeutic exercise (n=45) for 3 weeks. Spinal manipulation was associated with a moderate improvement in *function* (difference –18.67 on the 0 to 100 NDI, 95% CI –26.04 to –11.30) and a large improvement in *pain* (difference –3.05 on a 0 to 10 scale, 95% CI –3.30 to –2.80) over the short term compared with sham manipulation but when compared with exercise therapy, there were no differences between groups for either outcome. The SOE was low. Harms were not reported.

Key Question 3: Osteoarthritis Knee Pain

Exercise for Osteoarthritis Knee Pain

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

Three new trials comparing group muscle performance exercises with usual care or attention control in patients with knee OA were identified.[19,21,26] Aquatic exercise was compared with usual care in two trials: cycling 45 minutes twice weekly for 12 weeks (24 sessions) was done in one poor-quality trial (N=102 randomized)[26] and one-hour sessions of lower limb resistance training three times per week for 4 months (total of 48 sessions) was done in a fair-quality trial in post-menopausal women (N=87 randomized).[21] In the third, fair-quality, trial (N= 377 randomized),[19] 60-minute high-intensity or low-intensity strength training sessions three times per week for 18 months were compared with an attention control consisting of 24, 60-minute group workshops over 18 months. To update meta-analyses the high and low intensity groups were combined.

Across time frames, the addition of these new trials did not change the 2020 report's conclusions or strength of evidence regarding *function*.

At short term, the new poor-quality RCT reported no difference in *function* between exercise and usual care.[26] Its addition to the previous meta-analysis did not change effect estimates substantially or change conclusions that exercise was associated with a small improvement in

function compared with usual care (9 RCTs, n=832, pooled SMD –0.29, 95% CI –0.44 to –0.12, I^2=4.2%, SOE remained moderate). Similarly, one new fair-quality trial reporting function at intermediate term found no difference between groups;[19] its addition to the prior meta-analysis did not change the 2020 report's conclusions of moderate functional improvement with exercise (12 RCTs, n=1,144, pooled SMD –0.57, 95% CI –1.07 to –0.08, I^2=92%, excluding the same outlier as the 2020 report, SOE remained low). Neither of the two new fair-quality trials[19,21] found a difference in function between exercise and usual care or attention control at long term. Their addition to the prior meta-analysis did not alter our 2020 report's conclusions of small functional improvement with exercise or low SOE (6 RCTs, n=1,541, pooled SMD –0.18, 95% CI –0.38 to –0.03, I^2= 0%). See Appendix G, Figure G-4 for updated function plot.

For *pain*, across the new trials, no differences between exercise and usual care or attention control were seen, and their contributions to updated meta-analyses did not alter the 2020 report's conclusions. At short term, there continued to be small improvement in pain with exercise compared with usual care, attention control, or sham intervention (9 RCTs, n=832, pooled difference 0.50, 95% CI –0.84 to –0.16, I^2=37.5%) with the inclusion of the one new poor-quality trial[26] (SOE remained moderate). As seen in the 2020 report, moderate improvement in pain (0 to 10 scale) was seen at intermediate term with the addition of one new fair-quality trial (12 RCTs, n=1,140, pooled difference –1.21, 95% CI –1.96 to –0.44, I^2=92.1%, SOE: low), and there were small improvements in pain that persisted long term with the addition of the two new fair-quality trials (6 RCTs, pooled difference –0.26, 95% CI –0.43 to 0.01, I^2=0%, SOE remained low).[19,21] See Appendix G, Figure G-5 for updated pain plot.

Regarding harms, one new poor-quality trial reported that one patient in the exercise group with a history of cardiovascular disease hyperventilated and was hospitalized overnight, and continued with training after 2 weeks of rest.[26] Twenty patients experienced body pain in the trial of strength training, 19 experienced falls, and 10 experienced muscle strain.[19] The third trial did not report on adverse events.[21]

Manual Therapies for Osteoarthritis Knee Pain

Massage Compared With Usual Care

One new poor-quality trial (n=60)[24] compared six sessions (over 3 weeks) of massage therapy with usual care in elderly patients (mean age 77 years) with knee pain due to OA. There was no difference between groups in short-term *function* according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function (difference –1.63 on a 0 to 68 scale, 95% CI –6.72 to 3.46), but massage was associated with a small improvement in short-term *pain* according to WOMAC pain (difference –1.65 on a 0 to 20 scale, 95% CI –2.93 to –0.37). The trial included in the prior report found no difference between massage and usual care for any outcome short term. The addition of the new poor-quality trial did not change the prior report's conclusion; the evidence remained insufficient to draw conclusions. Harms were not reported.

Physical Modalities for Osteoarthritis Knee Pain

Ultrasound Compared With Sham

One new good-quality trial (n=75)[13] compared 24 sessions of pulsed ultrasound (US) compared with sham US over 8 weeks and found no difference between groups in *function* according to WOMAC physical function (difference –2.47 on a 0 to 68 scale, 95% CI –8.07 to

3.13) or in *pain* either at rest (difference –0.03 on a 0 to 10 scale, 95% CI –1.13 to 1.07) or with activities of daily living (difference –0.69 on a 0 to 10 scale, 95% CI –1.95 to 0.57) at short-term followup. The addition of the new trial did not change the prior report's conclusion (no effect for function and pain short term) and SOE remained low. Harms were not reported but two (4%) patients in the sham US group withdrew due to severe knee pain.

Low-Level Laser Therapy Compared With Sham

One new good-quality trial (n=84)[6] comparing LLLT to sham laser reported on pain and function at short and intermediate term. Evidence in the 2020 report for LLLT versus sham laser, which included one fair-quality trial (n=49)[36] and two poor-quality trials (n=27 and n=60),[37,38] was judged to be insufficient for function and pain. There was a small improvement in *function* at short term between LLLT and sham laser in pooled analysis including the new good-quality and the previously included fair-quality trial (2 RCTs, n=133, pooled SMD –0.39, 95% CI –0.80 to 0.00, I^2=0%) and a small improvement at intermediate term when the new trial was added to two previously included trials (3 RCTs, n=193, pooled SMD –0.54, 95% CI –1.19 to 0.05, I^2=46.5%); see Appendix G, Figure G-6 for new plot. Inclusion of the new trial in meta-analysis resulted in no clear difference in *pain* (0 to 10 scale) between LLLT and sham short term (3 RCTs, n=160, difference –1.50, 95% CI –3.18 to 0.16, I^2=76.5%) or intermediate term (3 RCTs, n=193, difference –1.24, 95% CI –2.22 to 0.12, I^2=6.5%); see Appendix G, Figure G-7 for updated plot. Based on the addition of the new good-quality trial, the SOE for short- and intermediate-term followup for both *function and pain* was upgraded from insufficient to low. No trial reported long-term outcomes. Adverse events were not reported in the new trial.

Interferential Current Compared With Sham

There were no trials of interferential current for OA knee pain in the prior report. One new, good-quality trial (n=84)[6] compared 12 50-minute sessions of interferential current with sham intervention (sham interferential current and sham photobiomodulation) over 4 weeks and found no differences between groups on any measure of function or pain at short- and intermediate-term followup (SOE: low). *Function* was measured using the WOMAC total score (0 to 96 scale) (short term: difference 0.55, 95% CI −24.31 to 7.05; intermediate term: difference 1.42, 95% CI −6.73 to 9.58) and the Lequesne Functional Index (0 to 24 scale) (short term: difference –1.10, 95% CI −3.11 to 0.89; intermediate term: difference –0.16, 95% CI −2.15 to 1.81). *Pain* was measured on the NRS (0 to 10 scale) both at rest (short term: difference –0.87, 95% CI −2.01 to 0.26; intermediate term: difference –0.32, 95% CI −1.34 to 0.70) and during activity (short term: difference –0.42, 95% CI −1.65 to 0.80; intermediate term: difference 0.49, 95% CI −1.63 to 0.64). Harms were not reported.

Mind-Body Therapies for Osteoarthritis Knee Pain

Tai Chi Compared With Attention Control

One new poor-quality trial (n=92)[12] compared Tai Chi (72 sessions total) versus an attention control (health education lectures and discussion) over a treatment period of 6 months. Tai Chi was associated with moderate improvements in both *function* (difference –17.47 on a 0 to 68 WOMAC physical function scale, 95% CI –22.10 to –12.84) and *pain* (difference –1.07 on a 0 to 10 scale, 95% CI –1.74 to –0.40) at intermediate-term followup. The addition of the new trial does not change the prior report's conclusion; the evidence remained insufficient to draw conclusions. Harms were not reported.

Qigong Compared With Exercise

There were no trials of Qigong compared with exercise for OA knee pain in the prior report. One new fair-quality trial (n=68)[29] compared Qigong with combination exercise (strength and aerobic training) in older participants (mean age 70 years); both groups received treatment 4 days a week for 6 months (96 sessions total). At intermediate-term followup, there were no between-group differences on measures of *function* (difference –2.20 on the 0 to 68 WOMAC physical function scale, 95% CI –6.24 to 1.84) or *pain* (difference –1.20 on the 0 to 20 WOMAC pain scale, 95% CI –3.04 to 0.64). The SOE was considered insufficient to draw conclusions. Attrition in this study was over 30 percent. The authors also note that adherence to Qigong was high while adherence in the exercise group was very low, possibly due to differences in the comfort level of older patients for performing the exercise types. This may have impacted the findings. Harms were not reported.

Acupuncture for Osteoarthritis Knee Pain

Acupuncture Compared With Usual Care, Waitlist, or Sham

One new good-quality trial (n=83)[16] compared superficial needling acupuncture with sham acupuncture (10 sessions total over 4 weeks) and found no differences between groups in *function* (difference –45.3 on a 0 to 1700 WOMAC physical function scale, 95% CI –183.8 to 93.3) or *pain* (difference –0.22 on a 0 to 10 scale, 95% CI –1.31 to 0.88) at short-term followup. No differences were seen in the proportion of patients with 30 percent or more (59% vs. 56%) or 50 percent or more (39% vs. 36%) improvement on VAS pain. Similar results were seen across other measures of function and pain. These results are consistent with the prior report; the addition of the new trial did not change the prior report's conclusion (no effect for function and pain short term) and SOE remained low.

Adverse events occurred with greater frequency in the true acupuncture (4.4%) versus the sham acupuncture (0.8%) group; (RR 5.86, 95% CI 1.87 to 18.39), due primarily to pain during needle insertion or needle adjustment. Pain during needle removal, bleeding, bruising, and numbness were also reported by patients randomized to true acupuncture (range of frequencies, 0.2% to 0.7%).

Key Question 4: Fibromyalgia

Exercise for Fibromyalgia

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

Two new small poor-quality trials compared exercise therapies with usual care for fibromyalgia and reported only short-term *function*.[11,23] One trial (n=69)[11] evaluated core stability-based physiotherapy and found no difference between groups on the Fibromyalgia Impact Questionnaire (FIQ) physical function item (difference –0.15 on a 0 to 10 scale, 95% CI –1.05 to 0.75). The second trial (n=66)[23] reported that combination exercise (aerobics, balance, postural, stretching, and Pilates) was associated with improved function compared with usual care but that the difference did not reach statistical significance (mean [standard deviation]: 52.8 [17.9] vs. 68.9 [17.5] on the 0-100 FIQ). The addition of the two new poor-quality trials did not change the prior report's conclusion (small effect for function short term) and SOE remained low.

Only one of the trials reported harms. One patient in the exercise group experienced knee pain exacerbation and had to rest during the last three sessions; no other events were reported.[11]

Manual Therapies for Fibromyalgia

Spinal Manipulation Compared With Sham Manipulation

There were no trials of spinal manipulation for fibromyalgia in the prior report. One new fair-quality trial (n=101)[10] comparing six sessions (over 6 weeks) of spinal manipulation versus sham manipulation reported no differences between groups in *function* on the 0 to 100 FIQ at short term (adjusted difference 1.2, 95% CI −4.9 to 7.3) and intermediate term (adjusted difference −1.1, 95% CI −7.9 to 5.6) or in *pain* on a 0 to 10 VAS scale at short term (adjusted difference −0.56, 95% CI −2.21 to 1.08) and intermediate term (adjusted difference −0.50, 95% CI −2.48 to 1.47). Similarly, there were no differences between groups in estimated odds ratios (ORs) for global improvement in pain at either timepoint (short term: OR 1.44, 95% CI 0.60 to 3.43; intermediate term: OR 1.51, 95% CI 0.65 to 3.51). Attrition in this trial was high (48% at both timepoints). The strength of evidence was considered low.

Mindfulness Practices for Fibromyalgia

Mindfulness-Based Stress Reduction or Meditation Awareness Training Compared With Usual Care, Waitlist, or Attention Control

One new poor-quality trial (n=98)[25] found that mindfulness-based stress reduction (MBSR) (8 weekly sessions) was associated with a small improvement in *function* versus usual care over intermediate-term followup (difference –9.77 on the 0-100 FIQ, 95% CI –17.99 to –1.55). The addition of the new trial does not change the prior report's conclusion (small effect for function intermediate term) and SOE remained low.

Eight (16%) patients randomized to MBSR reported adverse events that occurred during and/or after the intervention. These events occurred at a very low intensity and frequency in five patients (no other information provided) and with "significant frequency" in three patients (mild fatigue, intense palpitations, and a variety of moderate adverse effects such as fatigue, tension, headaches, dizziness, somnolence, gain of weight, and loss of sexual desire).

Mind-Body Therapies for Fibromyalgia

Basic Body Awareness Therapy Compared With Usual Care

There were no trials of basic body awareness therapy (BBAT) for fibromyalgia in the prior report. One new small fair-quality trial (n=39)[9] found no difference in *pain* (on a 0 to 10 scale) at short term (mean 6.9 vs. 7.4, p>0.05) and intermediate term (mean 7.1 vs. 7.5, p>0.05) between BBAT (10 sessions over 5 weeks) and usual care. Means were estimated from author figures; no information on variability (e.g., standard deviation) was provided, precluding estimation of effect size with corresponding confidence intervals. The data were judged to be insufficient to draw conclusions. Harms were not reported.

Acupuncture for Fibromyalgia

Acupuncture Compared With Usual Care and With Exercise

There were no trials of acupuncture compared with usual care (there were 3 trials vs. sham acupuncture) or with exercise in the prior report. One new small, poor-quality trial (n=69)[11] compared 10 sessions (over 5 weeks) of Traditional Chinese Medicine needle acupuncture versus usual care and versus core stability exercise, and found no differences between groups in short-term *function* according to the FIQ physical function item (versus usual care: difference –0.62 on a 0 to 10 scale, 95% CI –1.62 to 0.38; versus exercise: difference –0.47 on a 0 to 10 scale, 95% CI –1.44 to 0.50). The evidence was considered insufficient to draw conclusions. Intermediate- and long-term data and *pain* outcomes were not reported. No harms were reported in either group.

Multidisciplinary Rehabilitation for Fibromyalgia

Multidisciplinary Rehabilitation Compared With Usual Care or Waitlist and With Exercise

One new poor-quality trial (n=66)[23] compared 12 sessions (over 12 weeks) of MDR (i.e., CBT and occupational therapy) versus usual care and versus combination exercise (aerobics, balance, postural, stretching, and Pilates) and reported only short-term *function*. There was no difference between MDR and usual care (difference –0.30 on the 0 to 100 FIQ, 95% CI –8.61 to 8.00); MDR was associated with less improvement in function compared with exercise, but the difference did not reach statistical significance (mean [standard deviation]: 68.6 [15.7] vs. 52.8 [17.9]). The addition of the new trial does not change the prior report's conclusion for MDR versus usual care or waitlist (small effect for function short term, SOE remained low). There was no evidence for function at short-term followup for MDR versus exercise in the prior report; the evidence from this new trial was considered insufficient to draw conclusions.

Conclusions

The original report evaluated noninvasive nonpharmacological treatments for five common chronic pain conditions (LBP, neck pain, OA, FM, and tension headache). Across trials in the prior report, exercise, MDR, acupuncture, CBT, mindfulness practices, 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. There was very little evidence for chronic tension headache specifically. The majority of trials compared interventions with usual care, with very few trials employing pharmacological treatments or exercise as comparators. Harms were poorly reported across interventions. No serious intervention-related adverse events (e.g., leading to death or disability. or requiring intensive medical attention) were identified; reported adverse events were generally minor and time limited.

New evidence for noninvasive nonpharmacological treatments for chronic LBP, chronic neck pain, knee OA, and FM for this surveillance report was generally consistent with the prior report and did not alter its conclusions. For chronic LBP, new trials for psychological interventions versus usual care resulted in downgrading of SOE from moderate to low for short-term function. For knee OA, a new trial of low-level laser therapy with sham allowed us to pool data with previously included trials, upgrading SOE from insufficient to low for small improvements in

function but no effect on pain at short or intermediate term. New interventions or comparators for which there was at least low strength of evidence of no effect for function and/or pain were: TENS versus sham TENS in chronic LBP, spinal manipulation versus exercise for chronic neck pain, inferential current versus sham for knee OA, and spinal manipulation versus sham manipulation for FM. Spinal manipulation was associated with improvements in function and pain short term compared with sham laser for chronic neck pain. SOE for all these findings was low. Consistent with the original report, no trials in pregnant or breastfeeding women with pre-existing chronic pain or trials comparing interventions with opioids, topical agents, medical cannabis, or muscle relaxants were identified for this update, and no new data were available to evaluate nociplasticity as a modifier to treatment effectiveness or safety.

The next surveillance report is scheduled for February 2022.

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Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: research associate and librarian Tracy Dana, M.L.S., and research associate Christina Bougatsos, M.P.H., both from Oregon Health & Science University; Task Order Officer Suchitra Iyer, Ph.D., at the Agency for Healthcare Research and Quality.

Disclaimers

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 75Q80120D00006). 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 health care 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.

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AHRQ appreciates appropriate acknowledgment and citation of its work. Suggested language for acknowledgment: This work is a quarterly update report of a living systematic evidence report based on Noninvasive Nonpharmacological Treatments for Chronic Pain, by the Evidence-based Practice Center Program at the Agency for Healthcare Research and Quality (AHRQ).

Suggested citation: Skelly AC, Brodt ED, Kantner S, Diulio-Nakamura A, Mauer K, Shetty KD. Systematic Review on Noninvasive Nonpharmacological Treatments for Chronic Pain: Surveillance Report 1. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 75Q80120D00006.) AHRQ Publication No. 22-EHC008. Rockville, MD: Agency for Healthcare Research and Quality; February 2022.
DOI: https://doi.org/10.23970/AHRQEPCSURVEILLANCENONINVASIVENONPHARMA. Posted final reports are located on the Effective Health Care Program search page.

Afterword

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

This and future quarterly progress reports will provide up-to-date information about the evidence base to inform health plans, providers, purchasers, government programs, and the healthcare system as a whole on the state of the science. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this 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. They will be considered in the next update of this report.

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Appendix Contents

Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R), All 2020 through September 30, 2021

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, All 2020 through September 30, 2021
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, All 2020 through September 30, 2021
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. Key Questions and Inclusion and Exclusion Criteria

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

Key Question 4: Adults with fibromyalgia

Key Question 5: Adults with chronic tension headache

Key Questions 1–5 incorporate 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, 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?

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.

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?

Inclusion and Exclusion Criteria

Table B-1. 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). ○ 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 (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 • Health care utilization	**All KQs:** • Intermediate outcomes (e.g., biomarkers for inflammation) • Other nonclinical outcomes

PICOTS	Inclusion	Exclusion
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
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; 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.

Appendix C. Included Studies List

1. Alqualo-Costa R, Rampazo EP, Thome GR, et al. Interferential current and photobiomodulation in knee osteoarthritis: A randomized, placebo-controlled, double-blind clinical trial. Clinical Rehabilitation. 2021 Apr 26:2692155211012004. doi: https://dx.doi.org/10.1177/02692155211012004. PMID: 33896234.
2. Ashar YK, Gordon A, Schubiner H, et al. Effect of Pain Reprocessing Therapy vs Placebo and Usual Care for Patients With Chronic Back Pain: A Randomized Clinical Trial. JAMA Psychiatry. 2021 Sep 29doi: 10.1001/jamapsychiatry.2021.2669. PMID: 34586357.
3. Bernal-Utrera C, Gonzalez-Gerez JJ, Anarte-Lazo E, et al. Manual therapy versus therapeutic exercise in non-specific chronic neck pain: a randomized controlled trial. Trials [Electronic Resource]. 2020 Jul 28;21(1):682. doi: https://dx.doi.org/10.1186/s13063-020-04610-w. PMID: 32723399.
4. Bravo C, Skjaerven LH, Espart A, et al. Basic Body Awareness Therapy in patients suffering from fibromyalgia: a randomized clinical trial. Physiotherapy theory and practice. 2019;35(10):919-29. PMID: CN-01980930.
5. Coste J, Medkour T, Maigne JY, et al. Osteopathic medicine for fibromyalgia: a sham-controlled randomized clinical trial. Therapeutic Advances in Musculoskeletal Disease. 2021;13:1759720X211009017. doi: https://dx.doi.org/10.1177/1759720X211009017. PMID: 33948127.
6. Garrido-Ardila EM, Gonzalez-Lopez-Arza MV, Jimenez-Palomares M, et al. Effectiveness of acupuncture vs. core stability training in balance and functional capacity of women with fibromyalgia: a randomized controlled trial. Clinical Rehabilitation. 2020 May;34(5):630-45. doi: https://dx.doi.org/10.1177/0269215520911992. PMID: 32204612.
7. Groessl EJ, Liu L, Schmalzl L, et al. Secondary Outcomes from a Randomized Controlled Trial of Yoga for Veterans with Chronic Low-Back Pain. Int J Yoga Therap. 2020 Jan 1;30(1):69-76. doi: 10.17761/2020-D-19-00036. PMID: 31509451.
8. Hu X, Lai Z, Wang L. Effects of Taichi exercise on knee and ankle proprioception among individuals with knee osteoarthritis. Research in Sports Medicine. 2020 Apr-Jun;28(2):268-78. doi: https://dx.doi.org/10.1080/15438627.2019.1663520. PMID: 31524502.
9. Joyce C, Roseen EJ, Keysor JJ, et al. Can Yoga or Physical Therapy for Chronic Low Back Pain Improve Depression and Anxiety Among Adults From a Racially Diverse, Low-Income Community? A Secondary Analysis of a Randomized Controlled Trial. Archives of Physical Medicine & Rehabilitation. 2021 Jun;102(6):1049-58. doi: https://dx.doi.org/10.1016/j.apmr.2021.01.072. PMID: 33556352.
10. Karakas A, Dilek B, Sahin MA, et al. The effectiveness of pulsed ultrasound treatment on pain, function, synovial sac thickness and femoral cartilage thickness in patients with knee osteoarthritis: a randomized, double-blind clinical, controlled study. Clinical Rehabilitation. 2020 Dec;34(12):1474-84. doi: https://dx.doi.org/10.1177/0269215520942953. PMID: 32715744.
11. Kholoosy L, Elyaspour D, Akhgari MR, et al. Evaluation of the Therapeutic Effect of Low Level Laser in Controlling Low Back Pain: A Randomized Controlled Trial. Journal of Lasers in Medical Sciences. 2020;11(2):120-5. doi: https://dx.doi.org/10.34172/jlms.2020.21. PMID: 32273951.
12. Kobayashi D, Shimbo T, Hayashi H, et al. Shiatsu for chronic lower back pain: Randomized controlled study. Complementary Therapies in Medicine. 2019 Aug;45:33-7. doi: https://dx.doi.org/10.1016/j.ctim.2019.05.019. PMID: 31331579.

13. Lam WC, Au KY, Qin Z, et al. Superficial needling acupuncture versus sham acupuncture for knee osteoarthritis: a randomized controlled trial. American Journal of Medicine. 2021 Jun 11;11:11. doi: https://dx.doi.org/10.1016/j.amjmed.2021.05.002. PMID: 34126097.

14. Lang AE, Hendrick PA, Clay L, et al. A randomized controlled trial investigating effects of an individualized pedometer driven walking program on chronic low back pain. BMC Musculoskeletal Disorders. 2021 Feb 19;22(1):206. doi: https://dx.doi.org/10.1186/s12891-021-04060-8. PMID: 33607979.

15. Luo Y, Yang M, Liu T, et al. Effect of hand-ear acupuncture on chronic low-back pain: a randomized controlled trial. Journal of traditional chinese medicine = chung i tsa chih ying wen pan. 2019;39(4):587-98. PMID: CN-02144857.

16. McCrae CS, Curtis AF, Miller MB, et al. Effect of cognitive behavioural therapy on sleep and opioid medication use in adults with fibromyalgia and insomnia. Journal of Sleep Research. 2020 12;29(6):e13020. doi: https://dx.doi.org/10.1111/jsr.13020. PMID: 32126156.

17. Messier SP, Mihalko SL, Beavers DP, et al. Effect of High-Intensity Strength Training on Knee Pain and Knee Joint Compressive Forces Among Adults With Knee Osteoarthritis: The START Randomized Clinical Trial. JAMA. 2021 02 16;325(7):646-57. doi: https://dx.doi.org/10.1001/jama.2021.0411. PMID: 33591346.

18. Michalsen A, Jeitler M, Kessler CS, et al. Yoga, Eurythmy Therapy and Standard Physiotherapy (YES-Trial) for Patients With Chronic Non-specific Low Back Pain: A Three-Armed Randomized Controlled Trial. Journal of Pain. 2021 Apr 20;20:20. doi: https://dx.doi.org/10.1016/j.jpain.2021.03.154. PMID: 33892154.

19. Munukka M, Waller B, Hakkinen A, et al. Effects of progressive aquatic resistance training on symptoms and quality of life in women with knee osteoarthritis: A secondary analysis. Scandinavian Journal of Medicine & Science in Sports. 2020 Jun;30(6):1064-72. doi: https://dx.doi.org/10.1111/sms.13630. PMID: 31999876.

20. Neyaz O, Sumila L, Nanda S, et al. Effectiveness of Hatha Yoga Versus Conventional Therapeutic Exercises for Chronic Nonspecific Low-Back Pain. Journal of Alternative & Complementary Medicine. 2019 Sep;25(9):938-45. doi: https://dx.doi.org/10.1089/acm.2019.0140. PMID: 31347920.

21. Patru S, Padureanu R, Dumitrescu F, et al. Influence of multidisciplinary therapeutic approach on fibromyalgia patients. Experimental & Therapeutic Medicine. 2021 May;21(5):528. doi: https://dx.doi.org/10.3892/etm.2021.9960. PMID: 33815601.

22. Pehlivan S, Karadakovan A. Effects of aromatherapy massage on pain, functional state, and quality of life in an elderly individual with knee osteoarthritis. Japan journal of nursing science. 2019;16(4):450-8. PMID: CN-02078086 NEW.

23. Perez-Aranda A, Feliu-Soler A, Montero-Marin J, et al. A randomized controlled efficacy trial of mindfulness-based stress reduction compared with an active control group and usual care for fibromyalgia: the EUDAIMON study. Pain. 2019 11;160(11):2508-23. doi: https://dx.doi.org/10.1097/j.pain.0000000000001655. PMID: 31356450.

24. Rewald S, Lenssen AFT, Emans PJ, et al. Aquatic Cycling Improves Knee Pain and Physical Functioning in Patients With Knee Osteoarthritis: A Randomized Controlled Trial. Archives of Physical Medicine & Rehabilitation. 2020 08;101(8):1288-95. doi: https://dx.doi.org/10.1016/j.apmr.2019.12.023. PMID: 32169459.

25. Roseen EJ, Gerlovin H, Femia A, et al. Yoga, Physical Therapy, and Back Pain Education for Sleep Quality in Low-Income Racially Diverse Adults with Chronic Low Back Pain: a Secondary Analysis of a Randomized Controlled Trial. Journal of General Internal Medicine. 2020 01;35(1):167-76. doi: https://dx.doi.org/10.1007/s11606-019-05329-4. PMID: 31667747.

26. Shariat A, Alizadeh R, Moradi V, et al. The impact of modified exercise and relaxation therapy on chronic lower back pain in office workers: a randomized clinical trial. Journal of Exercise Rehabilitation. 2019 Oct;15(5):703-8. doi: https://dx.doi.org/10.12965/jer.1938490.245. PMID: 31723560.

27. Thomas JS, Clark BC, Russ DW, et al. Effect of Spinal Manipulative and Mobilization Therapies in Young Adults With Mild to Moderate Chronic Low Back Pain: A Randomized Clinical Trial. JAMA Network Open. 2020 08 03;3(8):e2012589. doi: https://dx.doi.org/10.1001/jamanetworkopen.2020.12589. PMID: 32756930.

28. Xiao CM, Li JJ, Kang Y, et al. Follow-up of a Wuqinxi exercise at home programme to reduce pain and improve function for knee osteoarthritis in older people: a randomised controlled trial. Age & Ageing. 2021 02 26;50(2):570-5. doi: https://dx.doi.org/10.1093/ageing/afaa179. PMID: 32931545.

29. Yaksi E, Ketenci A, Baslo MB, et al. Does transcutaneous electrical nerve stimulation affect pain, neuropathic pain, and sympathetic skin responses in the treatment of chronic low back pain? A randomized, placebo-controlled study. The Korean journal of pain. 2021 Apr 01;34(2):217-28. doi: https://dx.doi.org/10.3344/kjp.2021.34.2.217. PMID: 33785674.

Appendix D. Evidence Tables

Shown in associated Excel files for Surveillance Report 1 at https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/research.

Appendix E. Quality Assessment

Shown in associated Excel files for Surveillance Report 1 at https://effectivehealthcare.ahrq.gov/products/noninvasive-nonpharm-pain-update/research.

Appendix F. Excluded Studies List

1. Abdel-Aal NM, Elsayyad MM, Megahed AA. Short-term effect of adding graston technique to exercise program in treatment of patients with cervicogenic headache: a single-blinded, randomized controlled trial. European journal of physical & rehabilitation medicine. 2021 May 05;05:05. doi: https://dx.doi.org/10.23736/S1973-9087.21.06595-3. PMID: 33947825. **Exclusion:** Ineligible population

2. Abdelbasset WK, Nambi G, Alsubaie SF, et al. A Randomized Comparative Study between High-Intensity and Low-Level Laser Therapy in the Treatment of Chronic Nonspecific Low Back Pain. Evidence-Based Complementary & Alternative Medicine: eCAM. 2020;2020:1350281. doi: https://dx.doi.org/10.1155/2020/1350281. PMID: 33178306. **Exclusion:** Inadequate duration of followup

3. Ahmadnezhad L, Yalfani A, Gholami Borujeni B. Inspiratory Muscle Training in Rehabilitation of Low Back Pain: A Randomized Controlled Trial. Journal of Sport Rehabilitation. 2020 11 01;29(8):1151-8. doi: https://dx.doi.org/10.1123/jsr.2019-0231. PMID: 31910393. **Exclusion:** Inadequate duration of followup

4. Akaltun MS, Altindag O, Turan N, et al. Efficacy of high intensity laser therapy in knee osteoarthritis: a double-blind controlled randomized study. Clinical Rheumatology. 2021 May;40(5):1989-95. doi: https://dx.doi.org/10.1007/s10067-020-05469-7. PMID: 33074393. **Exclusion:** Ineligible intervention

5. Alayat MSM, Aly THA, Elsayed AEM, et al. Correction to: Efficacy of pulsed Nd:YAG laser in the treatment of patients with knee osteoarthritis: a randomized controlled trial. Lasers in Medical Science. 2020 Oct;35(8):1875. doi: https://dx.doi.org/10.1007/s10103-020-03088-x. PMID: 32647935. **Exclusion:** Not a study

6. Alayat MSM, Atya AM, Ali MME, et al. Correction to: Long-term effect of high-intensity laser therapy in the treatment of patients with chronic low back pain: a randomized blinded placebo-controlled trial. Lasers in Medical Science. 2020 Feb;35(1):297. doi: https://dx.doi.org/10.1007/s10103-019-02926-x. PMID: 31788745. **Exclusion:** Not a study

7. Albuquerque NF, Lopes BS. Musculoskeletal applications of infrared thermography on back and neck syndromes: a systematic review. European journal of physical & rehabilitation medicine. 2021 Jun;57(3):386-96. doi: https://dx.doi.org/10.23736/S1973-9087.20.06287-5. PMID: 33111511. **Exclusion:** Systematic review used as source document

8. Allen KD, Woolson S, Hoenig HM, et al. Stepped Exercise Program for Patients With Knee Osteoarthritis : A Randomized Controlled Trial. Annals of Internal Medicine. 2021 03;174(3):298-307. doi: https://dx.doi.org/10.7326/M20-4447. PMID: 33370174. **Exclusion:** Ineligible intervention

9. Alrwaily M, Schneider M, Sowa G, et al. Stabilization exercises combined with neuromuscular electrical stimulation for patients with chronic low back pain: a randomized controlled trial. Brazilian Journal of Physical Therapy. 2019 Nov - Dec;23(6):506-15. doi: https://dx.doi.org/10.1016/j.bjpt.2018.10.003. PMID: 30482602. **Exclusion:** Ineligible intervention

10. Alzayed KA, Alsaadi SM. Efficacy of Pulsed Low-Frequency Magnetic Field Therapy on Patients with Chronic Low Back Pain: A Randomized Double-Blind Placebo-Controlled Trial. Asian Spine Journal. 2020 Feb;14(1):33-42. doi: https://dx.doi.org/10.31616/asj.2019.0043. PMID: 31575112. **Exclusion:** Ineligible intervention

11. Amaral DDV, Miyamoto GC, Franco KFM, et al. Examination of a Subgroup of Patients With Chronic Low Back Pain Likely to Benefit More From Pilates-Based Exercises Compared to an Educational Booklet. Journal of Orthopaedic & Sports Physical Therapy. 2020 Apr;50(4):189-97. doi: https://dx.doi.org/10.2519/jospt.2019.8839. PMID: 31443627. **Exclusion:** Ineligible study design

12. Amaral LKB, Souza MB, Campos MGM, et al. Efficacy of conservative therapy in older people with nonspecific low back pain: A systematic review with meta-analysis and GRADE recommendations. Archives of Gerontology & Geriatrics. 2020 Sep - Oct;90:104177. doi: https://dx.doi.org/10.1016/j.archger.2020.104177. PMID: 32682168. **Exclusion:** Systematic review used as source document

13. An J, Ryu HK, Lyu SJ, et al. Effects of Preoperative Telerehabilitation on Muscle Strength, Range of Motion, and Functional Outcomes in Candidates for Total Knee Arthroplasty: A Single-Blind Randomized Controlled Trial. International Journal of Environmental Research & Public Health [Electronic Resource]. 2021 06 04;18(11):04. doi: https://dx.doi.org/10.3390/ijerph18116071. PMID: 34199913. **Exclusion:** Ineligible population

14. Andersen TE, Ravn SL, Armfield N, et al. Trauma-focused cognitive behavioural therapy and exercise for chronic whiplash with comorbid posttraumatic stress disorder: a randomised controlled trial. Pain. 2021 04 01;162(4):1221-32. doi: https://dx.doi.org/10.1097/j.pain.0000000000002117. PMID: 33086286. **Exclusion:** Ineligible comparator

15. Anheyer D, Klose P, Lauche R, et al. Yoga for Treating Headaches: a Systematic Review and Meta-analysis. Journal of General Internal Medicine. 2020 03;35(3):846-54. doi: https://dx.doi.org/10.1007/s11606-019-05413-9. PMID: 31667736. **Exclusion:** Systematic review used as source document

16. Annaswamy TM, Cunniff KJ, Kroll M, et al. Lumbar Bracing for Chronic Low Back Pain: A Randomized Controlled Trial. American Journal of Physical Medicine & Rehabilitation. 2021 08 01;100(8):742-9. doi: https://dx.doi.org/10.1097/PHM.0000000000001743. PMID: 33789322. **Exclusion:** Ineligible intervention

17. Areeudomwong P, Buttagat V. Proprioceptive neuromuscular facilitation training improves pain-related and balance outcomes in working-age patients with chronic low back pain: a randomized controlled trial. Brazilian Journal of Physical Therapy. 2019 Sep - Oct;23(5):428-36. doi: https://dx.doi.org/10.1016/j.bjpt.2018.10.005. PMID: 30361077. **Exclusion:** Inadequate duration of followup

18. Arguisuelas MD, Lison JF, Domenech-Fernandez J, et al. Effects of myofascial release in erector spinae myoelectric activity and lumbar spine kinematics in non-specific chronic low back pain: randomized controlled trial. Clinical biomechanics. 2019;63:27-33. PMID: CN-01707030. **Exclusion:** Inadequate duration of followup

19. Atalay SG, Durmus A, Gezginaslan O. The Effect of Acupuncture and Physiotherapy on Patients with Knee Osteoarthritis: A Randomized Controlled Study. Pain Physician. 2021 May;24(3):E269-E78. PMID: 33988943. **Exclusion:** Ineligible comparator

20. Avendano-Coy J, Comino-Suarez N, Grande-Munoz J, et al. Extracorporeal shockwave therapy improves pain and function in subjects with knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. International Journal Of Surgery. 2020 Oct;82:64-75. doi: https://dx.doi.org/10.1016/j.ijsu.2020.07.055. PMID: 32798759. **Exclusion:** Systematic review used as source document

21. Barassi G, Supplizi M, Prosperi L, et al. Dual-wavelength high-power laser therapy and neuromuscular manual therapy in chronic neck pain: a randomized clinical trial. Journal of Biological Regulators & Homeostatic Agents. 2021 Mar-Apr;35(2):767-73. doi: https://dx.doi.org/10.23812/21-37-L. PMID: 33902272. **Exclusion:**Ineligible study design

22. Batistella CE, Bidin F, Giacomelli I, et al. Effects of the Russian current in the treatment of low back pain in women: A randomized clinical trial. Journal of Bodywork & Movement Therapies. 2020 Apr;24(2):118-22. doi: https://dx.doi.org/10.1016/j.jbmt.2019.10.009. PMID: 32507136. **Exclusion:**: Ineligible study design

23. Bauer CM, Kankaanpaa MJ, Meichtry A, et al. Efficacy of six months neuromuscular exercise on lumbar movement variability - A randomized controlled trial. Journal of Electromyography & Kinesiology. 2019 Oct;48:84-93. doi: https://dx.doi.org/10.1016/j.jelekin.2019.06.008. PMID: 31252284. **Exclusion:** Ineligible outcomes

24. Baumeister H, Paganini S, Sander LB, et al. Effectiveness of a Guided Internet- and Mobile-Based Intervention for Patients with Chronic Back Pain and Depression (WARD-BP): A Multicenter, Pragmatic Randomized Controlled Trial. Psychotherapy & Psychosomatics. 2021;90(4):255-68. doi: https://dx.doi.org/10.1159/000511881. PMID: 33321501. **Exclusion:** Ineligible intervention

25. Bellomo TR, Schrepf A, Kruger GH, et al. Pressure Pain Tolerance Predicts the Success of Emotional Awareness and Expression Therapy in Patients With Fibromyalgia. Clin J Pain. 2020 Jul;36(7):562-6. doi: 10.1097/AJP.0000000000000829. PMID: 32271184. **Exclusion:** Inadequate duration of followup

26. Beltrame R, Ronconi G, Ferrara PE, et al. Capacitive and resistive electric transfer therapy in rehabilitation: a systematic review. International Journal of Rehabilitation Research. 2020 Dec;43(4):291-8. doi: https://dx.doi.org/10.1097/MRR.0000000000000435. PMID: 32909988. **Exclusion:** Systematic review used as source document

27. Bendrik R, Kallings LV, Broms K, et al. Physical activity on prescription in patients with hip or knee osteoarthritis: A randomized controlled trial. Clinical Rehabilitation. 2021 Apr 11:2692155211008807. doi: https://dx.doi.org/10.1177/02692155211008807. PMID: 33843297. **Exclusion:** Ineligible population

28. Bernard S, Gentilcore-Saulnier E, Masse-Alarie H, et al. Is adding pelvic floor muscle training to an exercise intervention more effective at improving pain in patients with non-specific low back pain? A systematic review of randomized controlled trials. Physiotherapy. 2021 03;110:15-25. doi: https://dx.doi.org/10.1016/j.physio.2020.02.005. PMID: 32349867. **Exclusion:** Systematic review used as source document

29. Bidonde J, Busch AJ, Schachter CL, et al. Mixed exercise training for adults with fibromyalgia. Cochrane Database of Systematic Reviews. 2019(5) PMID: 00075320-100000000-11748. **Exclusion:** Systematic review used as source document

30. Bokaeian HR, Esfandiarpour F, Zahednejad S, et al. Effects of an Exercise Therapy Targeting Knee Kinetics on Pain, Function, and Gait Kinetics in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. Adapted Physical Activity Quarterly. 2021 Mar 30;38(3):377-95. doi: https://dx.doi.org/10.1123/apaq.2020-0144. PMID: 33785660. **Exclusion:**Ineligible comparator

31. Bronfort G, Haas M, Evans RL, et al. Non-invasive physical treatments for chronic/recurrent headache. Cochrane Database of Systematic Reviews. 2019(8) PMID: 00075320-100000000-01345. **Exclusion:** Systematic review used as source document

32. Burgess DJ, Evans R, Allen KD, et al. Learning to Apply Mindfulness to Pain (LAMP): Design for a Pragmatic Clinical Trial of Two Mindfulness-Based Interventions for Chronic Pain. Pain Medicine. 2020 12 12;21(Suppl 2):S29-S36. doi: https://dx.doi.org/10.1093/pm/pnaa337. PMID: 33313730. **Exclusion:** Not a study

33. Buttagat V, Muenpan K, Wiriyasakunphan W, et al. A comparative study of Thai massage and muscle energy technique for chronic neck pain: A single-blinded randomized clinical trial. J Bodyw Mov Ther. 2021 Jul;27:647-53. doi: 10.1016/j.jbmt.2021.05.007. PMID: 34391301. **Exclusion:** Inadequate duration of followup

34. Calatayud J, Guzman-Gonzalez B, Andersen LL, et al. Effectiveness of a Group-Based Progressive Strength Training in Primary Care to Improve the Recurrence of Low Back Pain Exacerbations and Function: A Randomised Trial. International Journal of Environmental Research & Public Health [Electronic Resource]. 2020 11 11;17(22):11. doi: https://dx.doi.org/10.3390/ijerph17228326. PMID: 33187076. **Exclusion:** Ineligible comparator

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264. You Y, Liu J, Tang M, et al. Effects of Tai Chi exercise on improving walking function and posture control in elderly patients with knee osteoarthritis: A systematic review and meta-analysis. Medicine. 2021 Apr 23;100(16):e25655. doi: https://dx.doi.org/10.1097/MD.0000000000025655. PMID: 33879749. **Exclusion:** Systematic review used as source document

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266. Zhang C, Li Y, Zhong Y, et al. Effectiveness of motor control exercise on non-specific chronic low back pain, disability and core muscle morphological characteristics: A meta-analysis of randomized controlled trials. European journal of physical & rehabilitation medicine. 2021 May 07;07:07. doi: https://dx.doi.org/10.23736/S1973-9087.21.06555-2. PMID: 33960180. **Exclusion:** Systematic review used as source document

267. Zhang L, Yuan H, Zhang L, et al. Effect of acupuncture therapies combined with usual medical care on knee osteoarthritis. Journal of traditional chinese medicine = chung i tsa chih ying wen pan. 2019;39(1):103-10. PMID: CN-02133212 NEW.Exclusion: Inadequate duration of followup

268. Zhang Q, Fang J, Chen L, et al. Different kinds of acupuncture treatments for knee osteoarthritis: a multicentre, randomized controlled trial. Trials [Electronic Resource]. 2020 Mar 14;21(1):264. doi: https://dx.doi.org/10.1186/s13063-019-4034-8. PMID: 32171318. **Exclusion:** Not a study

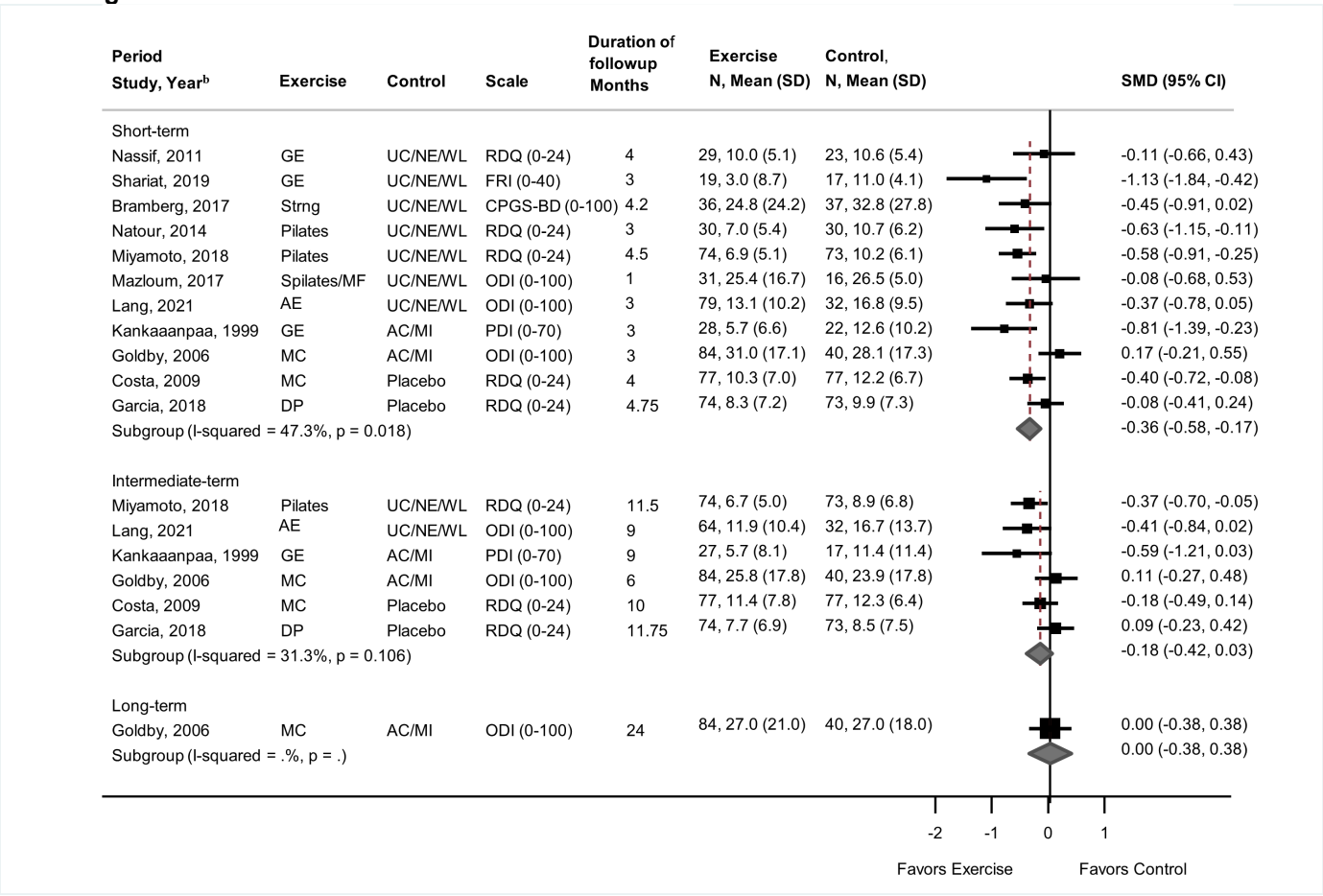
269. Zhao L, Cheng K, Wu F, et al. Effect of Laser Moxibustion for Knee Osteoarthritis: A Multisite, Double-blind Randomized Controlled Trial. Journal of Rheumatology. 2021 Jun;48(6):924-32. doi: https://dx.doi.org/10.3899/jrheum.200217. PMID: 32611673. **Exclusion:** Ineligible intervention

270. Zheng Z, Gibson S, Helme RD, et al. Effects of Electroacupuncture on Opioid Consumption in Patients with Chronic Musculoskeletal Pain: a Multicenter Randomized Controlled Trial. Pain medicine (Malden, Mass.). 2019;20(2):397-410. PMID: CN-01943577. **Exclusion:** Ineligible population

271. Zhu F, Zhang M, Wang D, et al. Yoga compared to non-exercise or physical therapy exercise on pain, disability, and quality of life for patients with chronic low back pain: A systematic review and meta-analysis of randomized controlled trials. PLoS ONE [Electronic Resource]. 2020;15(9):e0238544. doi: https://dx.doi.org/10.1371/journal.pone.0238544. PMID: 32870936. **Exclusion:** Systematic review used as source document

Appendix G. Updated or New Meta-Analyses

Figure G-1. Exercise versus usual care, an attention control, or a placebo intervention for chronic low back pain: effects on function, excluding outlier trial[a]

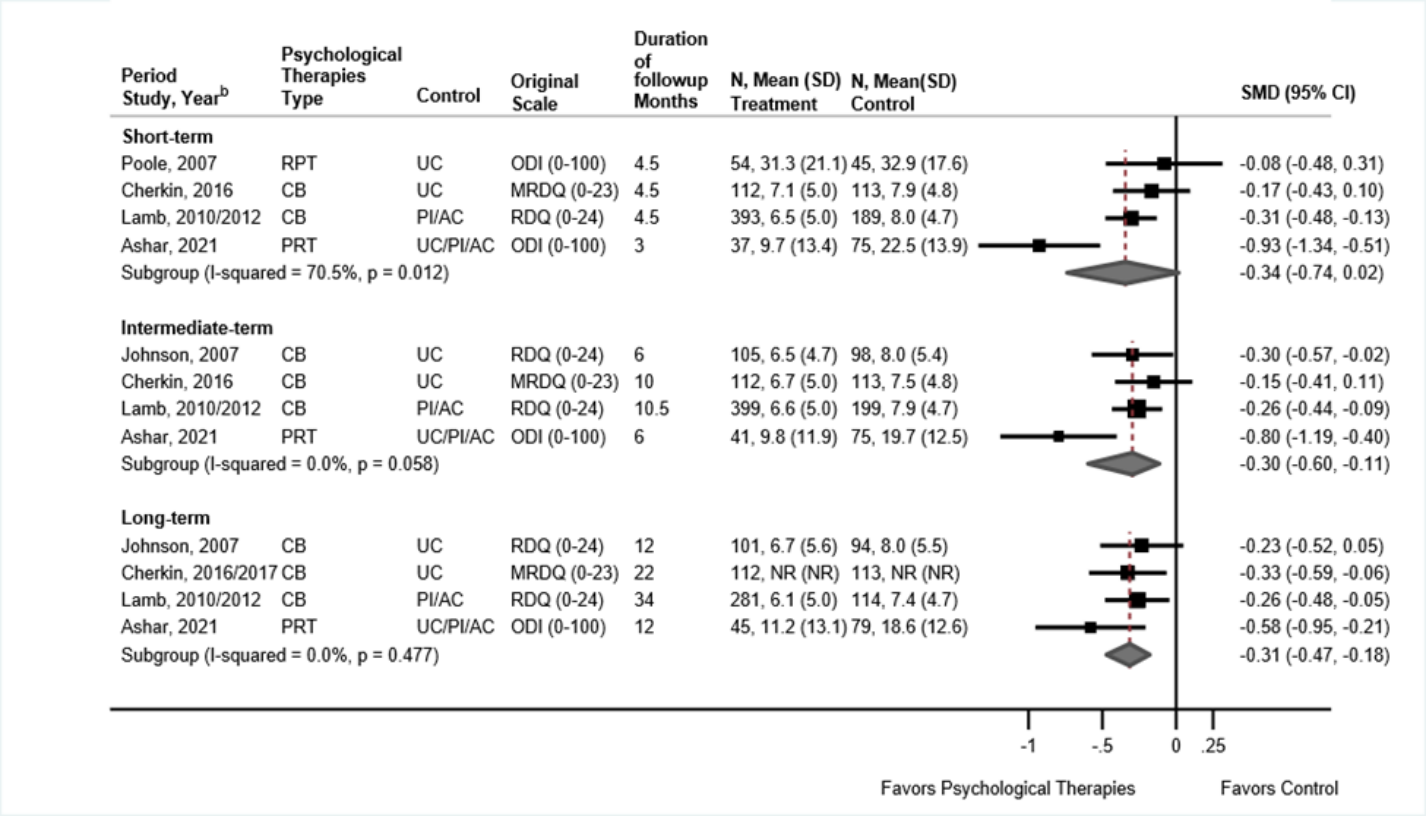


AC = attention control; AE = aerobic exercise (walking); CI = confidence interval; CPGS –BD =Von Korff Chronic Pain Grade Score Back Disability; DP = directional preference; GE= general exercise; MC = motor control; MF = mobility/flexibility; MI = minimal intervention; N = number; NE = no exercise; NM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

[a] Areeudomwong 2017, included in prior report.

[b] New trials: Shariat 2019, Lang 2021

Figure G-2. Psychological therapy versus usual care or an attention control for chronic low back pain: effects on function, excluding outlier trial[a]

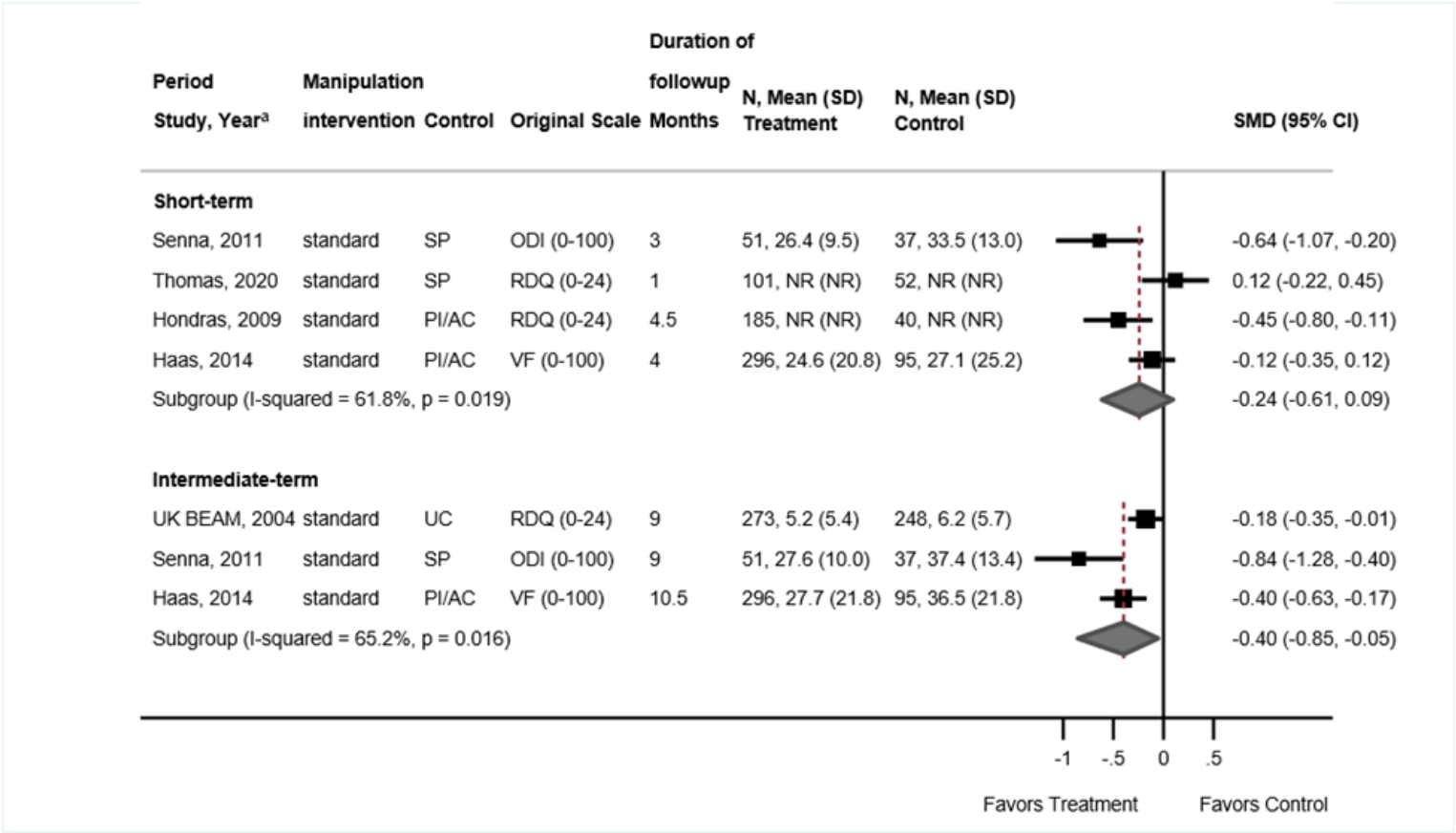


AC = attention control; CB = cognitive-behavioral therapy; CI = confidence interval; MRDQ = Modified Roland-Morris Disability Questionnaire; N = number; ODI = Oswestry Disability Index; PI = placebo intervention; PRT = pain reprocessing therapy; RDQ = Roland-Morris Disability Questionnaire; RPT = respondent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

[a] Shariat 2019, new trial.

[b] New trial: Ashar 2021

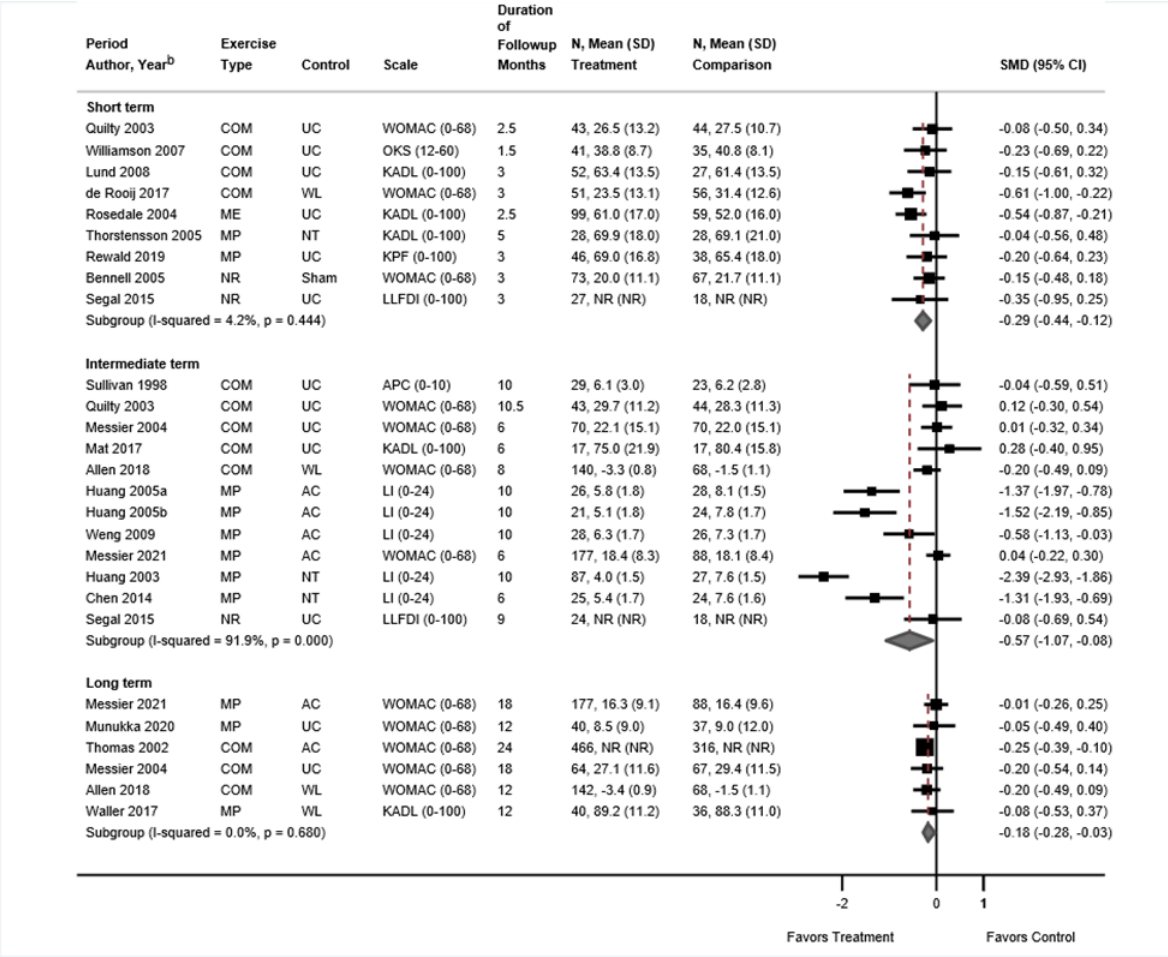
Figure G-3. Spinal manipulation versus sham manipulation, usual care, an attention control, or a placebo intervention for chronic low back pain: effects on function



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

[b] New trial: Thomas 2020

Figure G-4. Exercise versus usual care, no treatment, sham, or an attention control for osteoarthritis knee pain: effects on function, excluding outlier trial[a]

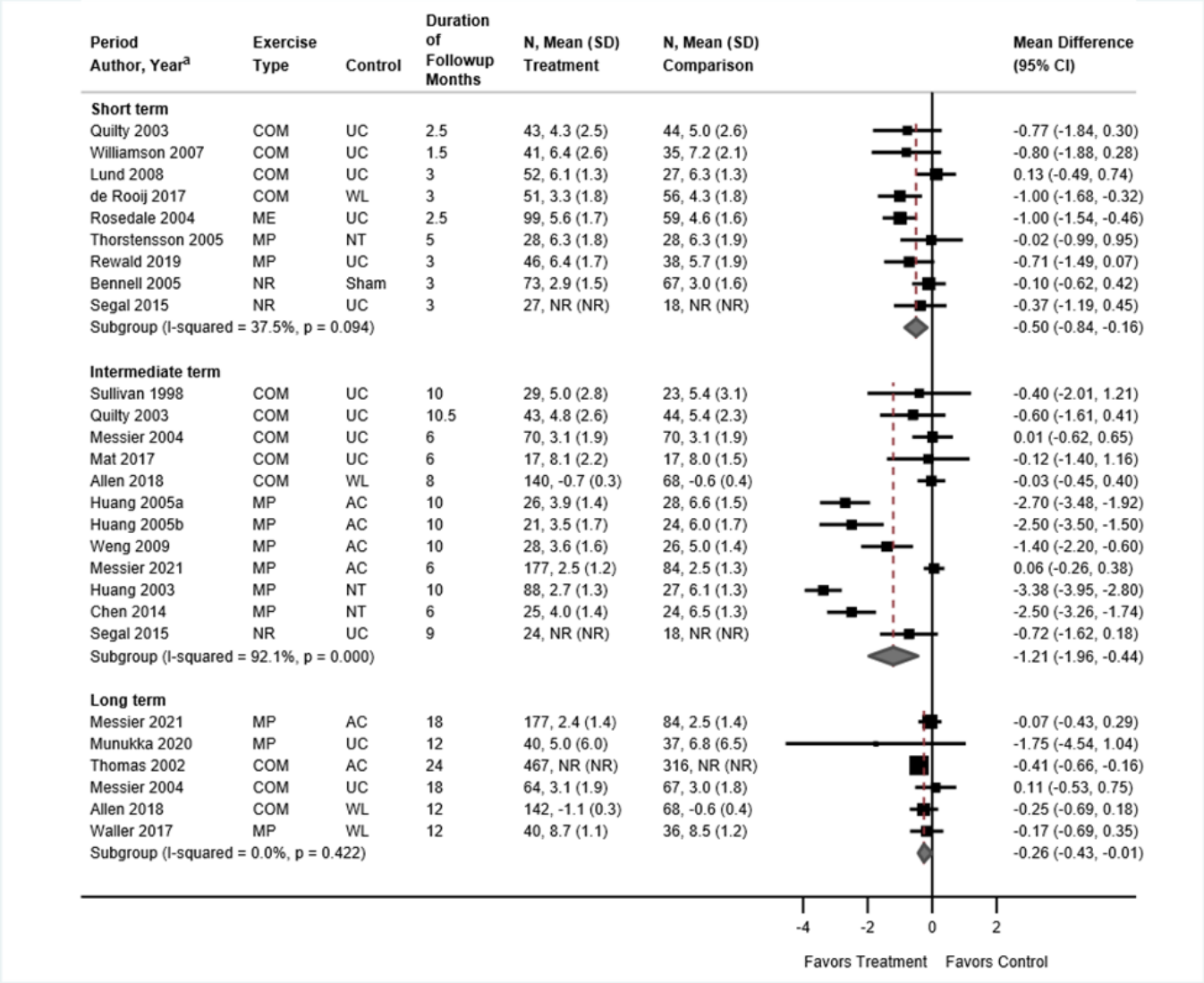


AC = attention control; APC = Arthritis Impact Measurement Scale (AIMS) physical activity component; CI = confidence interval; COM = combination exercise therapy; KADL = Knee Injury and Osteoarthritis Outcome Score (KOOS) ADL subscore; LI = Lequesne Index; LLFDI = Late Life Function and Disability Index 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

[a] Dias 2003, included in prior report.

[b] New trials: Messier 2021, Munukka 2020 and Rewald 2019.

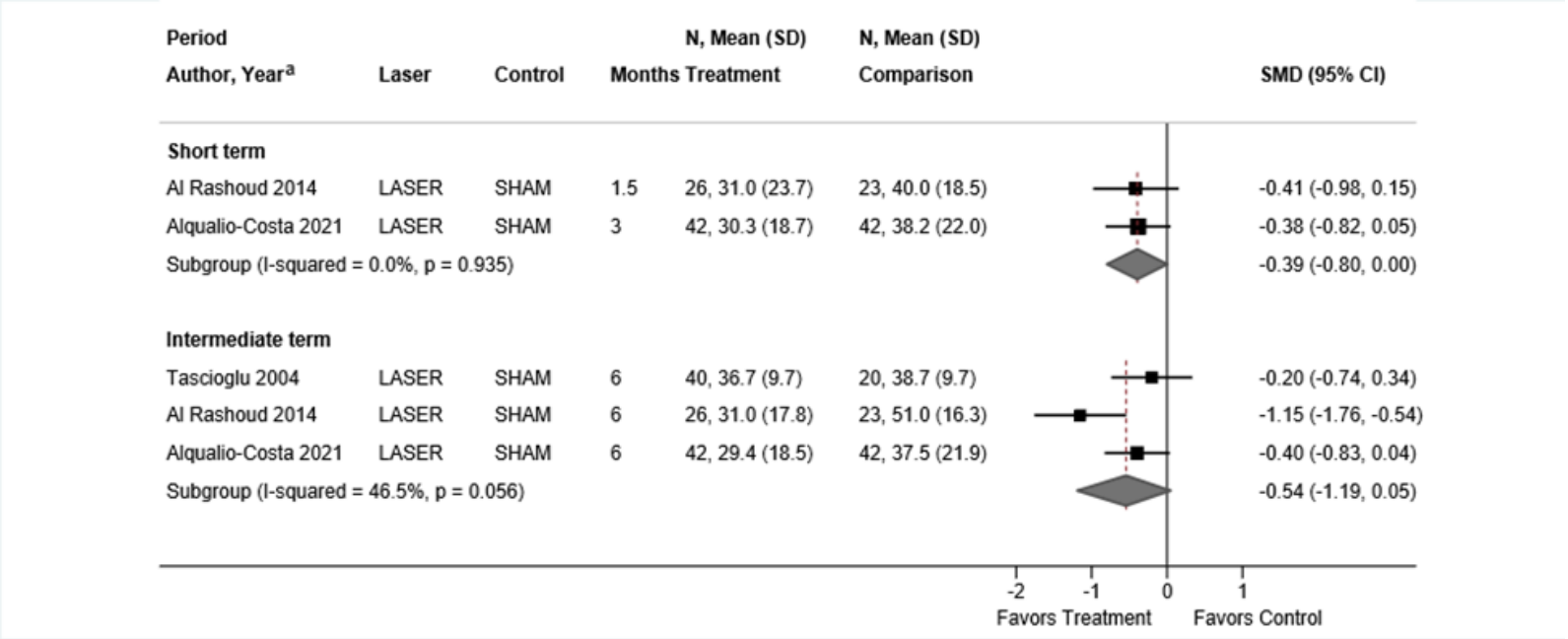
Figure G-5. Exercise versus usual care, no treatment, sham, or an attention control for osteoarthritis knee pain: effects on pain



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

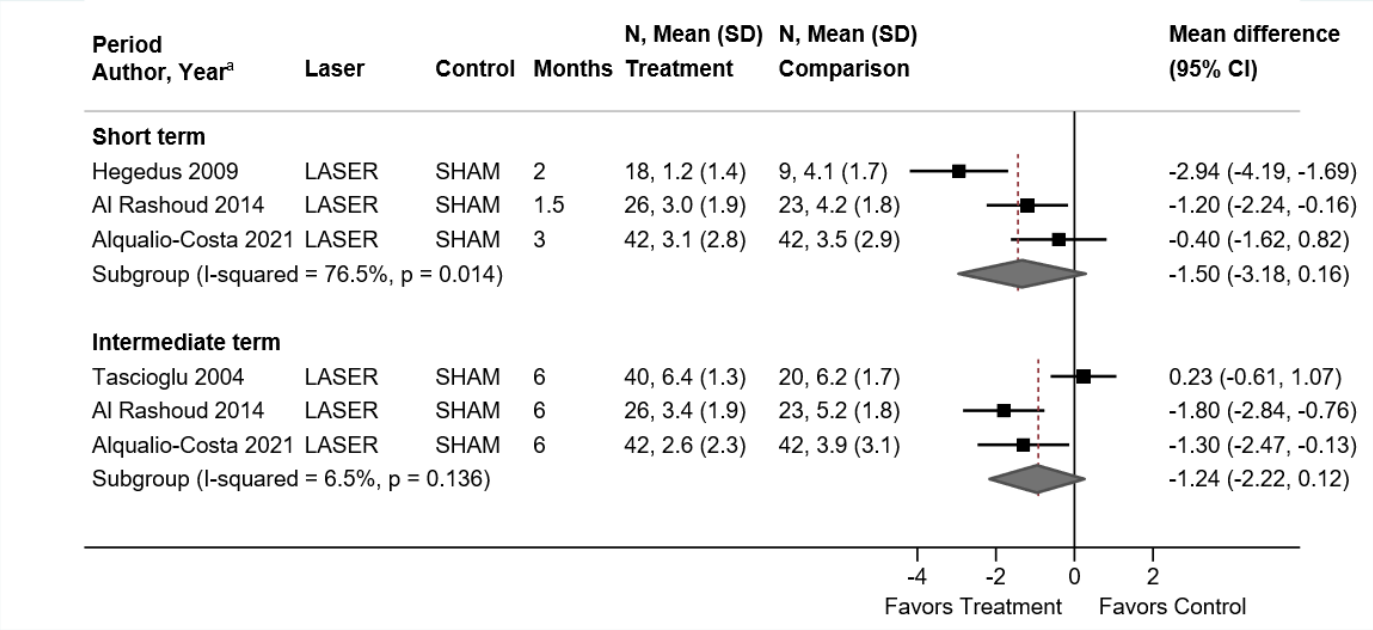
[a] New trials: Messier 2021, Munukka 2020 and Rewald 2019.

Figure G-6. Low-level laser therapy versus usual care or sham for osteoarthritis knee pain: effects on function (new meta-analysis)



CI = confidence interval; SD = standard deviation; UC = usual care
[a] New trial: Alqualio-Costa 2021

Figure G-7. 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
[a] New trial: Alqualio-Costa 2021