Comparative Effectiveness Review Disposition of Comments Report

Research ReviewTitle: Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update

Draft report available for public comment from October 8, 2019, to November 5, 2019.

Citation: Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, Fu R, Brodt ED, Wasson N, Kantner S, Ferguson AJR. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review Update. Comparative Effectiveness Review No. 227. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC009. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER227.

Comments to Draft Report

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Comments on draft reports and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final report is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Jacob Marzalik, American Psychological Association (APA)	Appendix	It would be helpful for guideline developers that may use your systematic reviews for clinical practice guideline development if you add evidence profiles to your appendixes. In particular, we would appreciate if you would add evidence profiles in the style of GRADE summarizing the data as these make the review much more user-friendly for guideline development.	Thank you for your suggestion. Our SOE summary was structured appropriately to meet the needs of this report and is consistent with the format used for our previous reports on this and related topics. The most detailed SOE tables are in Appendix G; these may most closely resemble GRADE profile tables. We realize that different organizational schemes may suit different audiences' needs. In addition, the evidence tables will be uploaded into SRDR and indeed be available to anyone who is interested.
Kara Gainer, American Physical Therapy Association	Background and Objectives	APTA appreciates that the Introduction concisely summarizes the population-health implications (i.e. overall chronic pain prevalence, opioid crisis, and need for viable non-pharmacological options). We believe the key questions are appropriate for this report, particularly given the scrutiny focused on non-pharmacological versus pharmacological treatment options. We note, however, that the interventions included in the review range from individual modalities (i.e. TENS or traction) to more complex, multimodal approaches like cognitive behavioral therapy or physical therapy (which are often comprised of individual approaches). A better approach may be to separate the approaches into single and multimodal approaches. This would be consistent with recent International Association for the Study of Pain recommendations.	Thank you for your comments. There is no standard method for categorizing many of the interventions. We realize that others may categorize interventions differently than we have and that there is heterogeneity within intervention categories. We believe that our strategy was structured appropriately to meet the needs of this report in consideration of the resources available to conduct the review and is consistent with strategies used for our previous reports on this and related topics.

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Kara Gainer, American Physical Therapy Association	Background and Objectives	As there are no standard definitions for what constitutes physical therapy and cognitive behavioral therapy, including them in the list of individual treatments could be confusing to readers. There also are similar issues with the term exercise – such term can be defined in several ways and describing it as only one intervention is a continuing problem that this report will perpetuate, if not resolved. Moreover, we encourage AHRQ to be more descriptive of what commonly utilized exercise approaches may be more successful and effective than others.	Thank you for your comments. As you point out, there is no standard method for categorizing many of the interventions or types of intervention within each category of intervention. We realize that others may categorize interventions differently than we have. We abstracted information on various techniques/methods, etc. and attempted to stratify results based on such information; unfortunately, in most instances, data were insufficient for stratification. In most instances, there was little evidence of difference depending on specific techniques. The categorization of exercise was based on input from the two physcial therapists and the physcical medicine/rehabiliation physician who were part of the EPC team and is provided in Appendix F. Where data were available, analyses by exercise type were done and are contained in the full report. We agree that it would be valuable to have an understanding of which type(s) of exercise/movement may confer the most benefit, however such comparisons were beyond the scope and resources available for this review. We used input from the clinical psychologist on the team together with those on the Technical Expert Panels for this update and the original report to obtain clarification on various psychological therapies.
Kara Gainer, American Physical Therapy Association	Background and Objectives	Additionally, we recommend that AHRQ include a statement within the Introduction that explains how there is less of an opportunity for large effect sizes when studying chronic pain, given the nature of the disease; this could provide readers better context when interpreting results.	Thank you for your comments. It is not necessarily true that there is less of an opportunity for large effect sizes. The effect size quantifies the differences in effect between two treatment groups (divided by the variability). If one treatment is substantially more effective than the other, the difference between the two groups could be large and if variability is low, the effect size may be moderate or large even if there may be smaller improvements in a given measure for the individual treatments.

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Kara Gainer, American Physical Therapy Association	Discussion	AHRQ can guide future work, especially as it relates to better treatment effect moderation opportunities. Moving forward, we recommend that AHRQ consider a discussion of stratification and treatment matching, and potential for the results to be affected by such. Further, while we appreciate that the report is assessing the effects at one month and beyond, the authors should acknowledge that immediate effects were not assessed, although those immediate effects might play an important role in the treatment process (certain pharmacological treatment, substitution maintenance therapy, etc.), particularly during an acute exacerbation. Moreover, APTA has concerns that very few studies demonstrate comparative effectiveness to something meaningful (i.e. another treatment); as such, we have concerns that the conclusions may be somewhat overstated.	Thank you for your comment. We believe that it is apparent that immediate post-treatment effects are not reported given that the inclusion criteria and methods state that we evaluated studies with a minimum of 1 month post-treatment follow-up. Given the chronic nature of the condition we felt that it was important to evaluate whether the effects of included interventions would persist for at least one month after treatment. This does not suggest that the immediate impact of such interventions may not be valuable. The paucity of comparative effectiveness studies is discussed in several places throughout the report including the section on research gaps. Throughout the report, we do qualify the results where appropriate to indicate that the data are sparse and that the overall strength of evidence is low.
Kara Gainer, American Physical Therapy Association	Evidence Summary	As recommended in our previous comments, APTA encourages AHRQ to include within the Executive Summary a summary of the effectiveness of the primary treatment categories for each diagnosis. The presentation of treatments by each diagnosis is difficult for the reader to understand. Additionally, we encourage AHRQ to provide additional clarification and justification for why the duration of follow-up post intervention was categorized as short-term, intermediate-term, and long-term, as this would help stakeholders, including clinical readers, policymakers, and researchers, to better understand and interpret the evidence. Finally, although effect sizes are moderate, we believe it is important to acknowledge that there were no adverse events associated with non-pharmacological interventions.	Thank you for your comments. There are many potential ways to categorize short, intermediate and long term, all of which are arbitrary. We defined them a priori as described in the report. We believe that our strategy was structured appropriately to meet the needs of this report and is consistent with strategies used for our previous reports on this and related topics. The report describes the harms and adverse events that were reported. Most were minor and time limited. This too is stated in the report.
Jacob Marzalik, American Psychological Association (APA)	Evidence Summary	On P. ES-1, does the statistic that 8% of adults report high-impact chronic pain mean that is 8% out of all adults or is it 8% within the 1 in 5 adults that the CDC estimated? The CDC estimated that 1 in 5 adults in the U.S. experienced chronic pain in 2016, with 8 percent reporting high-impact chronic pain that limited life or work activities daily or most days in the previous 6 months	This statistic is referring to 8% of all U.S. adults (19.6 million) [from: Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018 Sep 14;67(36):1001-6. doi: 10.15585/mmwr.mm6736a2. PMID: 30212442.] We have clarified this in the text.

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Kara Gainer, American Physical Therapy Association	General	1. APTA recommends that the “key messages” include a reference to physical therapy or care delivered by a physical therapist. Additionally, while we agree with the statement that “The evidence synthesized in this review may help inform guidelines and health care policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments, and inform policy decisions regarding funding priorities for future research,” there was no mention of physical therapy or physical therapist services, which appears to be a largely missed opportunity to touch on access barriers. Beneficiaries across the health spectrum encounter access barriers due to copay and cost-sharing requirements. Copays create a significant financial burden for patients requiring multiple encounters over an extended period. Patients are usually presented with a single copay for a month’s supply of opioids versus a copay for each physical therapy visit, not to mention the fact that prescription copays often are lower than visits with a physical therapist. Unless appropriate management of the cause of pain is incentivized, patients will avoid treatment, either allowing their pain to worsen or seeking immediate albeit short-term relief via an opioid prescription. Eliminating or reducing financial barriers such as copays will promote access to physical therapist services that often are the safer, more effective option.	Thank you for your comments. This review focuses on specific treatment modalities and interventions not specific professions/professional provider types given that some treatments, such as various ty pes of manipulation may be done by various provider types.
Kara Gainer, American Physical Therapy Association	General	2. Draft report statement: “Compared with exercise, multidisciplinary rehabilitation improved both function and pain at short and intermediate terms (small effects, SOE: moderate.” APTA recommends that AHRQ define multidisciplinary rehabilitation and discuss how it differentiated therapeutic exercise from exercise.	As stated in the report, 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. Exercise was categorized as reported in Appendix F

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Kara Gainer, American Physical Therapy Association	General	3. Draft report statement: “Studies of combination or adjunctive interventions were excluded. We categorized interventions a priori to provide a framework for the report, realizing that there is some overlap and that other methods for such categorization are possible.” APTA has significant concerns with this statement, as most care delivered by physical therapists for these conditions would be a combination of interventions. It appears that this statement eliminates physical therapy.	We recoginize that in practice, individuals would not receive a single therapy. An important first step to evaluating the efficacy of a therapy is to evaluate it as an isolated therapy. In addition, given the multitude of combinations of therapies and the likelihood that few studies would study the same combination/adjunctive therapies, it would be difficult to draw meaningful conclusions across studies for any given combination/adjunctive therapy. Individual components of a physcial therapy program were included (e.g. forms of exercise as part of PT, use of ultrasound, use of low level laser, etc.) if they were the focus of a given study.
Kara Gainer, American Physical Therapy Association	General	4. Draft report statement: “We focused on randomized controlled trials (RCTs) reporting outcomes at least 1 month following the completion of a course of treatment.” In most cases, physical therapists do not have data on a patient’s status 1 month following completion of treatment. APTA encourages AHRQ to clarify how this data is captured.	Data were abstracted as reported in the studies. For example, if a study intervention lasted 8 weeks and measurements were taken at 8 and 16 weeks. The 8 week measurement was considered to be immediately post intervention and was not included in the analysis andthe 16 week measurements were we classified as 8 weeks following completion of the intervention (short term).
Kara Gainer, American Physical Therapy Association	General	5. Draft report statement: “To evaluate comparative effectiveness, exercise was chosen as a common active comparator for all conditions except headache for which biofeedback was considered the common comparator, and we sought trials of intervention compared with pharmacological treatment.” Exercise is a highly variable term. We request that AHRQ clarify how exercise was defined for the purpose of this review.	Thank you for your comments. We agree that excerices may be variably defined. For inclusion, studies needed to describe components of a formal exercise program. This information was included in the evidence tables in the report and in the data abstraction (Appendix D). Exercises was categorized as described in Appendix F.
Kara Gainer, American Physical Therapy Association	General	6. Draft report statement: “We classified effects for measures with a 0 to 10 scale for pain or function as small (0.5 to 1 point), moderate (>1 to 2 points), or large (>2 points).” We request that AHRQ clarify if a numeric pain scale is the only pain measure.	Thank you for your comments. VAS or NRS on 0-10 scale (or 0-100) was most commonly reported. We did report other pain (and function) measures as they were reported in included studies; these included measures other than VAS 0-10 pain scale such Norwick Park Neck Pain Questionnaire and WOMAC Pain score among others. Where studies reported on the % of responders this was reported.The methods described in the full report and Appendix H provide additional information on pain and function outcomes and effect sizes.

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Kara Gainer, American Physical Therapy Association	General	7. Draft report statement: “The majority of trials (60%) were rated fair quality, with only 6 percent considered good quality. Attrition was greater than 20 percent in 28 percent of trials. For a number of interventions, providers and patients could not be effectively blinded. Other methodological shortcomings were unclear reporting of randomization or allocation concealment methods. Adherence to interventions was poorly reported.” These shortcomings lead to limited results. This should be considered when conducting studies in the future.	Yes, we agree.
Richard Lawhern, Alliance for the Treatment of Intractable Pain (ATIP)	General	This draft report suffers from the same major failings as the June 2018 publication which it is intended to augment. AHRQ appears to be trying to "make a silk purse out of a sow's ear" by dressing up findings with the most optimistic interpretations, based on extremely weak data. Moreover you state explicitly that "Our review is intended to address some of the needs described in the NPS3 and IOM2 reports and others for evidence to inform guidelines and health care policy (including reimbursement policy) related to use of noninvasive nonpharmacological treatments as possible alternatives to opioids and other pharmacological treatments". However, none of the trials you have identified attempted this comparison.	Thank you for your comments. Where data were available, RCTs comparing nonpharmacologic treatments with pharmacologic treatments were included. No RCTs that compared such interventions to opioids were identified.
Richard Lawhern, Alliance for the Treatment of Intractable Pain (ATIP)	General	You have also buried the most important findings of this two year long process on page 392. ("Limitations of the Evidence Base"). I must wonder if you have not deliberately chosen this approach in hopes that the weakness of this literature will not be widely recognized and publicly debated as it needs to be. This report appears to be a blatantly self-interested attempt to support wide use of highly experimental and unproven "alternative medicine" as a substitute for better known, reliable and safe pharmacological treatments (opioids, NSAIDS, off-label use of Tricyclic Antidepressant drugs). Such an agenda is disqualifying.	Thank you for your perspective.

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Richard Lawhern, Alliance for the Treatment of Intractable Pain (ATIP)	General	As I have written with Stephen E Nadeau, MD, in the journal "Practical Pain Management", the state of the medical literature for non-invasive non-pharmacological therapies for chronic pain is simply abysmal. Even in the small number of trials that supposedly passed your quality review, protocols did not identify the specifics of what comprises "usual therapy". AHRQ contracted investigators were forced to "assume" that usual therapy was in many cases continued in parallel with introduction of alternative therapies. Such trial designs cannot with confidence assess the actual contribution of the non-pharmacological therapy, and run a significant risk of introducing placebo or nocebo effects from the added attention and interaction that patients experienced when introduced to the added therapy. Likewise, neither the June 2018 edition nor this draft re-release have identified large-scale / multi-center Phase II or Phase III trials; direct comparisons of these alternative therapies to medication are described as "rare" (in a brief reading, I saw no specific tabulation of trials where this actually occurred) References: – Richard A Lawhern, PhD, “The CDC’s Fictitious Opioid Epidemic, Part 1” The Journal of Medicine, US National College of Physicians, January 2017, https://www.ncnp.org/journal-of-medicine/1929-doctors-fleeing-pain-management-dumping-patients.html; – Richard A Lawhern, Ph.D. "The CDC's Fictitious Opioid Epidemic, Part 2" The Journal of Medicine, US National College of Physicians, April 15, 2017, https://www.ncnp.org/journal-of-medicine/1980-the-cdcs-fictitious-opioid-epidemic-part-2.html; – Richard A Lawhern and Michael E Schatman, “Do Alternatives to Opioids Really Exist?” The Morning Consult, February 16, 2018, https://morningconsult.com/opinions/do-alternatives-to-opioids-really-exist/; – Richard A Lawhern, PhD, and Stephen E Nadeau, MD, “Understanding the Limitations of Non-Opioid Therapies in Chronic Pain”, invited editorial for the October 2017 print edition, in Practical Pain Management https://www.practicalpainmanagement.com/resources/practice-management/behind-ahrq-report	Thank you for your comments. We have evaluated the refererences provided; none meet the stated inclusion criteria for this report.

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Richard Lawhern, Alliance for the Treatment of Intractable Pain (ATIP)	General	I strongly recommend that this report and your online summary of its outcomes be restructured to identify the major weaknesses of this trials literature up front, in the introduction, rather than burying such qualifications deeply behind masses of otherwise unpromising data. In layman's terms, it may not be going too far to suggest that this entire literature be burned to the ground and started over under rigorous protocols. At the present state of medical knowledge, AHRQ is at substantial risk of comprising its professional and public reputation, by sponsoring an apologia for therapies that border on outright quackery.	Thank you for your perspective. Information on and discussion of the limitations of the literature and the review process are described in both the executive summary and the full report in multiple locations. Formal critical appraisal of included studies is in Appendix E.
Richard Lawhern, Alliance for the Treatment of Intractable Pain (ATIP)	General	I also strongly suggest that the public review period for this document be extended to at least 90 days, announced through the Federal Register, and supported in a publicly transparent process at the Federal Regulations site.	Thank you for your suggestion. A Federal Register notice was posted during posting of the study protocol and a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal was available as stated in the report Methods.
Sage Rosenthal, Policy and Advocacy Associate, Coalition to Transform Advanced Care (C-TAC)	General	Overall, we support the Agency's efforts to promote evidence-based nonpharmacological treatments to reduce chronic pain and feel this review will be helpful to direct care for chronic pain. This is an issue that affects the quality of life for some with advanced illness. We are hopeful that the review's identification of the evidence gaps will prompt research funding to add to this body of evidence. Perhaps support of additional research could be a recommendation in the review. Our only concern is that the review could inadvertently diminish the importance of pharmacological treatments for chronic pain in those individuals who need such treatment. Ideally, pharmacological and nonpharmacological approaches should both be considered and implemented on a patient by patient basis based on that person's goals and the joint decision with their health care provider. Although the review's focus is on nonpharmacological treatment, perhaps the final version could address this concern.	Thank you for your comments. We agree that treatment decisions should be implemented on a patient by patient basis as part of a shared decision-making process between provider and patient. We have made minor edits to clarify this point. The discussion acknowledges that persons with chronic pain likely make use of a combination of pharmacological and nonpharmacological treatments. We do not believe that this report diminishes the importance of pharmacologic agents. The "Implications for Clinical and Policy Decision Making" indicates that the report supports a multimodal approach for pain managment that includes the nonpharmacologic inteventions. There are two concurrent reviews, one on opioids and the other on non-opioid pharmacologic treatments that accompany this review and speak to the benefits and harms of the pharmacologic treatments.

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Frances Southwick, CommuniCare	General	You could consider adding OMT (Osteopathic Manipulative Treatment) as a helpful modality. There is data to support this. Please see links below. https://www.ncbi.nlm.nih.gov/pubmed/29037623 https://www.ncbi.nlm.nih.gov/pubmed/30534176 https://www.ncbi.nlm.nih.gov/pubmed/31658037 https://www.ncbi.nlm.nih.gov/pubmed/31462989 - MET (muscle energy) is a form of OMT https://www.ncbi.nlm.nih.gov/pubmed/31404469 https://www.ncbi.nlm.nih.gov/pubmed/31277529 https://www.ncbi.nlm.nih.gov/pubmed/31005246 https://www.ncbi.nlm.nih.gov/pubmed/31659663	Thank you for your comments. OMT is classified as "manual therapies" in our report. Our literature search included terms for "musculoskeletal manipulation" which is an umbrella term/MeSH heading that includes osteopathic manipulation. Thus, relevant studies of osteopathic manipulative treatment should have been captured. We did review the citations provided; none met the inclusion criteria as noted below. 1. Franke H, Franke JD, Belz S, et al. Osteopathic manipulative treatment for low back and pelvic girdle pain during and after pregnancy: A systematic review and meta-analysis. J Bodyw Mov Ther. 2017 Oct;21(4):752-62. doi: 10.1016/j.jbmt.2017.05.014. PMID: 29037623. **[EXCLUDED: SR; included trials reviewed for eligibility - none met inclusion criteria]** 2. Silva ACO, Biasotto-Gonzalez DA, Oliveira FHM, et al. Effect of Osteopathic Visceral Manipulation on Pain, Cervical Range of Motion, and Upper Trapezius Muscle Activity in Patients with Chronic Nonspecific Neck Pain and Functional Dyspepsia: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Evid Based Complement Alternat Med. 2018;2018:4929271. doi: 10.1155/2018/4929271. PMID: 30534176. **[EXCLUDED: <15 patients per treatment arm]** 3. de Oliveira Meirelles F, de Oliveira Muniz Cunha JC, da Silva EB. Osteopathic manipulation treatment versus therapeutic exercises in patients with chronic nonspecific low back pain: A randomized, controlled and double-blind study. J Back Musculoskelet Rehabil. 2019 Oct 14doi: 10.3233/BMR-181355. PMID: 31658037.[**EXCLUDED-inadequate follow-up time]** 4. Thomas E, Cavallaro AR, Mani D, et al. The efficacy of muscle energy techniques in symptomatic and asymptomatic subjects: a systematic review. Chiropr Man Therap. 2019;27:35. doi: 10.1186/s12998-019-0258-7. PMID: 31462989. **[EXCLUDED: SR; included trials reviewed for eligibility - none met inclusion criteria]**

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Frances Southwick, CommuniCare	General	You could consider adding OMT (Osteopathic Manipulative Treatment) as a helpful modality. There is data to support this. Please see links below. https://www.ncbi.nlm.nih.gov/pubmed/29037623 https://www.ncbi.nlm.nih.gov/pubmed/30534176 https://www.ncbi.nlm.nih.gov/pubmed/31658037 https://www.ncbi.nlm.nih.gov/pubmed/31462989 - MET (muscle energy) is a form of OMT https://www.ncbi.nlm.nih.gov/pubmed/31404469 https://www.ncbi.nlm.nih.gov/pubmed/31277529 https://www.ncbi.nlm.nih.gov/pubmed/31005246 https://www.ncbi.nlm.nih.gov/pubmed/31659663	Response continued from above: We did review the citations provided; none met the inclusion criteria as noted below. 5. Deodato M, Guolo F, Monticco A, et al. Osteopathic Manipulative Therapy in Patients With Chronic Tension-Type Headache: A Pilot Study. J Am Osteopath Assoc. 2019 Aug 12doi: 10.7556/jaoa.2019.093. PMID: 31404469. **[EXCLUDED: <15 patients per arm; f/u immediately post-tx]** 6. Qu XD, Zhou JJ, Zhai HW, et al. [Therapeutic effect of exercise acupuncture and osteopathy on traumatic knee arthritis]. Zhongguo Gu Shang. 2019 Jun 25;32(6):493-7. doi: 10.3969/j.issn.1003-0034.2019.06.002. PMID: 31277529. **[EXCLUDED: article in Chinese; interventions groups are likely combination treatments based on description in abstract and would be excluded]** 7. Chvetzoff G, Berthier A, Blanc E, et al. [Osteopathy for chronic pain after breast cancer surgery: A monocentric randomised study]. Bull Cancer. 2019 May;106(5):436-46. doi: 10.1016/j.bulcan.2019.03.005. PMID: 31005246. **[EXCLUDED: ineligible population (chronic pain post-cancer); <15 per arm; article in French]** 8. Meerwijk EL, Larson MJ, Schmidt EM, et al. Nonpharmacological Treatment of Army Service Members with Chronic Pain Is Associated with Fewer Adverse Outcomes After Transition to the Veterans Health Administration. J Gen Intern Med. 2019 Oct 28doi: 10.1007/s11606-019-05450-4. PMID: 31659663. **[EXCLUDED: wrong study design - longitudinal, observational cohort study]**

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Dave Schechter	General	Just wanted to expose you to the EAET treatment approach, which is both similar to and different from CBT and has been recently published extensively by schubiner, lumley, et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5680092/ https://psycnet.apa.org/record/2018-50121-010	Thank you. The cited article by Lumley, et al. is already included in the report. [Lumley MA, Schubiner H, Lockhart NA. et al. Emotional awareness and expression therapy, cognitive behavioral therapy, and education for fibromyalgia: a cluster-randomized controlled trial. Pain. 2017 Dec;158(12):2354-2363. doi: 10.1097/j.pain.0000000000001036. PMID: 28796118.]
Dave Schechter	General	References (1-7) [1] Lumley, M.A., Cohen, J.L., Borszcz, G.S., Cano, A., Radcliffe, A., Porter, L., Schubiner, H., & Keefe, F.J. (2011). Pain and emotion: A biopsychosocial review of recent research. Journal of Clinical Psychology, 67, 942 – 968. [2] Abbass, A., Kisely, S., & Kroenke, K. (2009). Short-term psychodynamic psychotherapy for somatic disorders. Psychotherapy and Psychosomatics, 78, 265-274. [3] Larson, D. G., Chastain, R. L., Hoyt, W. T., & Ayzenberg, R. (2015). Self-concealment: Integrative review and working model. Journal of Social and Clinical Psychology, 34, 705-e774. [4] Wenzlaff, R. M., & Wegner, D. M. (2000). Thought suppression. Annual Review of Psychology, 51, 59-91. [5] Burns, J. W., Quartana, P., Gilliam, W., Gray, E., Matsuura, J., Nappi, C., . . . Lofland, K. (2008). Effects of anger suppression on pain severity and pain behaviors among chronic pain patients: evaluation of an ironic process model. Health Psychology, 27, 645-652. [6] van Middendorp, H., Lumley, M. A., Jacobs, J. W., van Doornen, L. J., Bijlsma, J. W., Geenen, R., . . . Geenen, R. (2008). Emotions and emotional approach and avoidance strategies in fibromyalgia. Journal of Psychosomatic Research, 64, 159-167. [7] Bernardy, K., Klose, P., Busch, A. J., Choy, E. H. S., & Hauser, W. (2013). Cognitive behavioural therapies for fibromyalgia. Cochrane Database of Systematic Reviews(9). doi:10.1002/14651858.CD009796.pub2	Thank you for your comments. We did review the citations provided; none met the inclusion criteria as noted below. [1] Ineligible study design (narrative review article) [2] Ineligible population (somatic disorders) [3] Ineligible study design (narrative review article) [4] Ineligible study design (book chapter/narrative review) [5] Ineligible study design (observational cohort) [6] Ineligible study design (observational cohort) [7] SR of children, adolescents and adults; references checked for includable trials in adults (children and adolsecents were excluded)

Commentator & Affiliation	Section	Comment	Response
Dave Schechter	General	References (8-14) [8] Glombiewski, J. A., Sawyer, A. T., Gutermann, J., Koenig, K., Rief, W., & Hofmann, S. G. (2010). Psychological treatments for fibromyalgia: A meta-analysis. Pain, 151(2), 280-295. [9] Lumley, M.A., Schubiner, H., Lockhart, N.A., Kidwell, K.M., Harte, S., Clauw, D.J., & Williams, D.A. (2017). Emotional awareness and expression therapy, cognitive-behavioral therapy, and education for fibromyalgia: A cluster-randomized controlled trial. PAIN, 158, 2354-2363. [10] Thakur, E.R., Holmes, H.J., Lockhart, N.A., Carty, J.N., Ziadni, M.S., Doherty, H.K., Lackner, J.M., Schubiner, H., & Lumley, M.A. (2017). Emotional awareness and expression training improves irritable bowel syndrome: A randomized controlled trial. Neurogastroenterology and Motility, 29:e13143 [11] Slavin-Spenny, O., Lumley, M.A., Thakur, E.R., Nevedal, D.C., & Hijazi, A.M. (2013). Effects of anger awareness and expression training and relaxation training on chronic headaches: a randomized trial. Annals of Behavioral Medicine, 46, 181-192. [12] Ziadni, M.S., Carty, J.N., Doherty, H.K., Porcerelli, J.H., Rapport, L.J., Schubiner, H., & Lumley, M.A. (2018). A life-stress, emotional awareness and expression interview for primary care patients with medically unexplained symptoms: A randomized controlled trial. Health Psychology, 37(3):282-290 [13] Carty, J., Ziadni, M., Holmes, H., Lumley, M., Tomakowsky, J., Schubiner, H., Dove-Medows, E., & Peters, K. (2016). The effects of a stress and emotion interview for women with urogenital pain: A randomized trial (Abstract). The Journal of Pain, 17, S103. [14] Burger, A.J., Lumley, M.A., Carty, J.N., Latsch, D.V., Thakur, E.R., Hyde-Nolan, M.E., Hijazi, A.M., & Schubiner, H. (2016). The effects of a novel psychological attribution and emotional awareness and expression therapy for chronic musculoskeletal pain: A preliminary, uncontrolled trial. Journal of Psychosomatic Research, 81, 1-8.	Thank for your comments. We reviewed the citations provided; none met the inclusion criteria as noted below. [8] SR; references checked for includable trials [9] Already included in the report [10] Ineligible population (irritable bowel syndrome) [11] Excluded previously (ineligible population; mixed headache types); see Appendix C for complete list of trials excluded after full text review [12] Ineligible population [13] Ineligible population (urogenital pain); abstract only [14] Ineligible study design (case series, pre-post)

Commentator & Affiliation	Section	Comment	Response
Jacob Marzalik, American Psychological Association (APA)	General	These comments were developed by members and staff of the American Psychological Association (APA) who have expertise on the topic, but they are not an official statement of the APA. Thank you for the opportunity to comment on AHRQ's draft report Noninvasive Nonpharmacological Treatments for Chronic Pain: A Systematic Review Update. The overall report provided a nice comprehensive summary of the current state of the literature in noninvasive, nonpharmacological treatments for chronic pain. We appreciated the emphasis on improving research reporting on harms in treatments and in your attempt in reviewing the limited literature in this area. We have several comments and requests for clarification that we would like for you to consider.	Thank you for your review.
Jacob Marzalik, American Psychological Association (APA)	General	We agree that there needs to be a standardized approach to measuring pain and pain outcomes, as the Visual Analog Scale does not adequately assess the patients' overall health and quality of life through chronic pain. Notably, the provider's nonverbal behaviors and intonations toward patients with chronic pain can play a significant role in the level of pain the patient reports (Daniali & Flaten, 2019). Daniali, H., & Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. Frontiers in Psychiatry, 10(242). https://doi.org/10.3389/fpsyt.2019.00242	Thank you for your comments.
Jacob Marzalik, American Psychological Association (APA)	General	Please note that "relaxation training" and "biofeedback" are techniques used in psychotherapy but are not of themselves psychotherapy. These strategies are regularly used by psychologists and other professionals in delivering care for chronic pain. For convenience, it may make sense to group these strategies in the category of psychotherapy, but we recommend distinguishing- perhaps via footnote- that these are strategies as opposed to complete psychotherapies. Or, perhaps the category would be better termed psychological interventions.	Thank you for your comments. The intent of the report was to include psychological techniques not only interventions that might be classified as "psychotherapy". As currently written, we use the umbrella term "psychological therapies" to encompass both. In the SOE tables and the report we attempt to specify the specific techniques (e.g. relaxation training) or types of psychotherapy (e.g. CBT) are used as reported in the included studies. We have made additional clarifications throughout the report.
Jacob Marzalik, American Psychological Association (APA)	General	We appreciate the call for more research on long-term outcomes in patients' functioning and pain. More research is needed on the quality of life in patients with chronic pain.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Jacob Marzalik, American Psychological Association (APA)	General	It is disappointing that there is a paucity of high quality trials examining treatment effectiveness for pregnant and/or breastfeeding women with chronic pain and agree more research is needed.	Thank you for your comments.
Jacob Marzalik, American Psychological Association (APA)	General	We are also surprised that in this recent update there continues to be a paucity of research comparing nonpharmacological and noninvasive interventions with pharmacological therapies and agree more comparative effectiveness research is needed.	Thank you for your comments.
Ashley Walton, American Society of Anesthesiologists (ASA)	General	The American Society of Anesthesiologists (ASA) finds the systematic review to be thorough; the methodology and conclusions made are appropriate. However, we recommend some additions/changes to this document.	Thank you for your comments.
Ashley Walton, American Society of Anesthesiologists (ASA)	General	ASA questions the title of the document as solely "noninvasive." One of the treatments highlighted includes traditional needle acupuncture, which is percutaneous and therefore, invasive. ASA recommends that the document would be more appropriately titled "minimally invasive and noninvasive nonpharmacological treatments for chronic pain."	Thank you for your perspective. From the perspective that acupuncture does not involve injection of any substances (e.g. steroids) it is non-invasive for our purposes.
Ashley Walton, American Society of Anesthesiologists (ASA)	General	ASA also recommends that TENS be included in the text on key messages; it is reviewed in the body of the document but not as part of the summarized key messages.	Thank you for your comments. The key messages summarize interventions for which there was at least low SOE of at least a small effect on pain and/or function at one or more time periods. TENS does not appear in the key messages as there was no difference in function or pain between it and sham TENS based on pooled estimates of effect across included studies in knee OA patients at intermediate term. For other conditions and time frames either there was no evidence or it was considered to be insuficient.
Ashley Walton, American Society of Anesthesiologists (ASA)	General	The document is lacking any reference to interventional procedures. The North American Spine Society (NASS) is in the process of developing clinical guidelines on low-back pain and though not complete yet, ASA advises that AHRQ should consult this evidence-based document with multi-society involvement to ensure other minimally invasive treatments are included in the review. For example, literature on epidural steroid injections (ESI) should be considered.	Thank you for your comments. We acknowledge that the report doesn't include interventional procedures such as epidural steroid injections in the discussion of the report. Inclusion of such interventions was not within the already large scope of this report. In addition previous AHRQ reviews have addressed some of these interventions (e.g. the "Pain Management Injection Therapies for Low Back Pain" https://www.cms.gov/Medicare/Coverage/DeterminationProcess/Downloads/id98TA.pdf).

Commentator & Affiliation	Section	Comment	Response
Ashley Walton, American Society of Anesthesiologists (ASA)	General	Recognizing that it is difficult to conduct trials of nonpharmacologic therapies because the trial sizes tend to be small, blinding is difficult and the response/change in pain and function over time can be hard to quantify—ASA is pleased the evidence for efficacy for many of the techniques is quite good. The document could emphasize the encouragement of these therapies better, rather than discourage their use due to lack of evidence, especially given the absence of harm noted in virtually all of the trials. This is especially important for the information that is given to providers and the public to avoid any misinterpretation of the existing literature on chronic pain treatments.	Thank your for your comments. Our purpose is to provide a balanced, objective report that includes context regarding the overall quality/strenght of evidence. We believe that the results and discussion appropriately describes the strenghts and limitations of the evidence for effectiveness and safety of the interventions studied; the data are available for individuals to arrive at their own conclusions.

Commentator & Affiliation	Section	Comment	Response
Ashley Walton, American Society of Anesthesiologists (ASA)	General	The Department of Health and Human Services (HHS) Pain Management Best Practices Inter-agency Task Force also highlights chronic pain treatments, such as restorative therapies and interventional procedures that might be considered for the review. Even where evidence is lacking, the treatments included in the report as safe and effective for some patients should be appropriately cited. A multidisciplinary panel of health experts thoughtfully considered all of the options and evidence available to make the final recommendations included in the report and ASA is supportive. Restorative therapies evaluated in the HHS Task Force include: • Therapeutic Exercise. • Transcutaneous Electric Nerve Stimulation • Massage Therapy • Traction • Cold and Heat • Therapeutic Ultrasound • Bracing Interventional procedures evaluated in the HHS Task Force include: • Epidural Steroid Injections • Facet Joint Nerve Block and Denervation Injection. • Cryoneuroablation • Radiofrequency Ablation • Peripheral Nerve Injections • Sympathetic Nerve Blocks • Neuromodulation • Intrathecal Medication Pumps • Vertebral Augmentation • Trigger Points • Joint Injections • Interspinous Process Spacer Devices • Regenerative/Adult Autologous Stem Cell Therapy	Thank you for your comments. We focused on commonly used interventions that were widely available. We believe that the results and discussion appropriately describes the strenghts and limitations of the evidence for effectiveness and safety of the interventions studied. In the discussion,w e acknowledge that the inclusion of some interventions would have expanded the report scope beyond available resources. Organizations such as yours can certainly nominate topics for AHRQ's consideration for future reviews via the AHRQ website.

Commentator & Affiliation	Section	Comment	Response
Ashley Walton, American Society of Anesthesiologists (ASA)	General	Notably, it's also important to emphasize that the decrease of change in pain for these minimally invasive therapies is about the same as those reported for opioids. The systematic review on opioids did not conclude long-term benefits whereas some of the nonpharmacological techniques do. It is important to emphasize these points with the information circulated to providers and the public to ensure that nonpharmacological treatments are weighed with appropriate confidence against opioids. This can also encourage appropriate coverage by payors for these nonpharmacological therapies.	Thank you for your comments. The discussion does acknowlege that our previous reviews found that opioids were associated with small to moderated effects on pain and that there was little evidence of long-term benefit. Given that studies did not directly compare the nonpharmacologic interventios to opioids, extensive comparison of the effects of nonpharmacologic interventions to opioids (or other pharmacologic agents) is not appropriate as the comparison is indirect.
Ashley Walton, American Society of Anesthesiologists (ASA)	General	Last, ASA recommends that any conclusions made from the systematic review that are incorporated into the CDC Guideline update/expansion include the appropriate background information. For example, it should be noted that the treatments reviewed are not an exhaustive list of nonpharmacologic therapies and that the decision for any course of pain treatment should be based upon the individual patient and the decision made between that patient and their health care provider. The literature should not be misinterpreted as a mandate for certain treatment options either.	Thank you for your comments. The discussion does acknowlege that the included interventions are not an exhaustive list of nonpharmacologic interventions. It is not the role of the EPC or its review to make explicit recommendations to the CDC regarding the use of the review or evidicenc for their guidelines.
Sunny Linnebur, PharmD, FCCP, BCPS, BCGP, President; Nancy E. Lundebjerg, Chief Executive Officer; The American Geriatrics Society (AGS)	General	AGS is a not-for-profit organization of over 6,000 health professionals devoted to improving the health, independence and quality of life of all older people. We very much appreciate this opportunity to provide feedback on a topic that is particularly important to our members. We shared your call for comments with member experts on the topic as well as our Executive Committee. Our comments are outlined below.	Thank you for your comments on this review.
Sunny Linnebur, PharmD, FCCP, BCPS, BCGP, President; Nancy E. Lundebjerg, Chief Executive Officer; The American Geriatrics Society (AGS)	General	We are appreciative of the draft report continuing to include new studies and an update of metaanalyses from prior reports. We would suggest that studies from 2019 be included but recognize that this may not be feasible. If the reports are frequently updated, this would capture newer studies on a regular basis. We found the methods in the report strong and appropriate for the review and analyses.	Thank you for your comments. The update report does include all studies from both the 2018 report as well as new studies identified for the 2019 update.

Commentator & Affiliation	Section	Comment	Response
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	Together, the NCCAOM and the ASA represent over 20,000 professional acupuncturists across the United States. As a facilitator for evidence-based research, AHRQ is uniquely situated to influence access to pain-management treatments. Now, more than ever, this influence is critical to identifying and facilitating viable pathways to non-opioid and nonpharmacological pain-management treatments. AHRQ continues to make significant progress in establishing these pathways—and the NCAAOM and the ASA commend AHRQ for investigating, and subsequently acknowledging, acupuncture as an effective nonpharmacologic treatment for pain. While current research indicates acupuncture as an effective treatment option, much of the current literature is limited in scope, expertise, and overall thoroughness.	Thank you for your comments.
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The NCCAOM and the ASA encourage AHRQ to delve further into acupuncture research to discover a stronger evidence base for acupuncture's effects on chronic pain by initiating more specific and thorough acupuncture studies that include—and are led by—nationally certified and licensed acupuncturists. Both groups also recommend that AHRQ and its associated research bodies further explore the dangers and costs of opioids compared to acupuncture treatments, as well as comparative effectiveness research, and other trending research nuances. Acupuncture is an established method to stem opioid abuse, as well as a reasonable and effective treatment method for chronic pain. The NCCAOM and the ASA stand by as resources to AHRQ, both with regard to consulting on, and assessing, study designs, and identifying research gaps.	Thank you for your comments. Studies of acupuncture that met our inclusion criteria (regardless of provider certification or licensure) were included and summarized. Studies were identified from a broad literatures search encompassing multiple bibliographic databases and by evaluating references cited in systematic reviews, included studies, suggested during peer review, public review and stakeholder engagement. There was limited information on certification and licensure in the included studies and extensive exploration of the impact of such is beyond the scope of this review. There were no studies meeting our inclusion criteria that compared acupuncture to opioid use. Lack of comparison of the nonpharmacologic treatments overall to pharmacologic alternatives is acknowleged in the report as an important evidence gap. Our concurrent reviews on opioids and nonopioid pharmacologic treatments address the effectiveness and safety of these for specific chronic pain conditions. Evaluation of costs or cost-effectiveness of the included intervention was not within the scope of this review.

Commentator & Affiliation	Section	Comment	Response
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The NCCAOM seeks to ensure the safety and well-being of the public and to advance the professional practice of acupuncture by establishing and promoting national, evidence-supported competence and credentialing standards. Since its inception in 1982, the NCCAOM has issued more than 21,000 certificates in acupuncture, Oriental medicine, Chinese herbology, and Asian Bodywork Therapy. The NCCAOM currently certifies 1,200-1,500 acupuncturists each year and represents almost 18,000 nationally certified practitioners.	Thank you for your comments.
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The NCCAOM continues to work with federal agencies to establish its certification programs and its Diplomates in the federal arena. This includes its work with the ASA to create a distinct classification code with the Bureau of Labor Statistics (BLS) for the profession “Acupuncturist,” and developing a qualification standard within the Veterans Health Administration for acupuncture practitioners. The ASA represents the largest voluntary professional membership body of practitioners under the BLS professional designation “Acupuncturists.” Its mission is to promote the highest standards of professional practice for acupuncture and East Asian medicine in the United States to benefit the public health. The ASA strives to strengthen the profession at the state level while collaborating nationally and internationally, in addition to providing resources to its members, the public, and policymakers. The ASA federation consists of 46 participating professional acupuncture state associations.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The NCCAOM and the ASA recognize that the current literature pertaining to acupuncture is limited because many studies do not meet standard criteria for systematic, evidence-based research. This creates glaring evidence and knowledge gaps. The report's cited studies around acupuncture do however show that acupuncture is a safe, effective, and reliable. As such, more research is necessary to continue to develop this evidence base to increase access to acupuncture, and enable acupuncture to take a bigger, yet appropriate, role in reducing opioid and pharmacological overreliance. The draft report's findings are significant, particularly with regard to the challenges and limitations associated with acupuncture research. These challenge include consistency in research design and protocol, methodology, low sample size, and qualitative short- and long-term effects.	Thank you for your comments.
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	There is much discussion concerning the legitimacy of "sham acupuncture" within the acupuncture research field than this report acknowledges. The NCCAOM and the ASA recommend that AHRQ and other research bodies devote more funding toward clinical acupuncture research that more fully reflects actual treatment with nationally board certified and licensed acupuncturists as principal investigators or co-leads on these studies.	Thank you for your comments. The EPC does not make decisions regarding research funding.

Commentator & Affiliation	Section	Comment	Response
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The NCCAOM and the ASA agree with the report's intention to include more research on specific populations (e.g. pregnant and breast-feeding women) as well as specific concentrations on older populations. Future designs should include these populations. All acupuncture research trials also need to better document adverse reactions, as well as the methodology for reporting adverse reactions. Given the significant differences in training (e.g. length of time and depth of training), studies should explicitly note the credentials of those who deliver acupuncture treatment for the sake of consumer safety and for research study integrity. The NCCAOM and the ASA applaud the AHRQ for extensively assessing nonpharmacological interventions and hope that this report helps enable a positive turning point for the future of acupuncture research.	Thank you for your comments.
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	When qualified healthcare professionals deliver acupuncture, the treatment is a safe, cost-effective, and evidence-based option for mitigating chronic pain and reducing opioid use. The NCCAOM, the ASA, the Council of Colleges of Acupuncture and Oriental Medicine, and the Accreditation Commission of Acupuncture and Oriental Medicine collaborate to provide a well-developed system to educate, train, certify, and regulate acupuncturists. This infrastructure can train many more interested applicants than currently enter the system. Increasing acupuncture-specific research to strengthen its evidence base would enable more to enter the workforce. Medicare program, and there is a growing, reliable workforce able to provide the service.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Afua Bromley, MSOM, Dipl. Ac. (NCCAOM), L.Ac. Chair, NCCAOM Board of Commissioners; The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM)® and the American Society of Acupuncturists (ASA)	General	The existing evidence shows that acupuncture is a valuable component to the universal efforts to reduce opioid reliance and overuse. It also offers promising secondary benefits that may further boost the health of seniors, as well as potentially increasing satisfaction with the Medicare program. The NCCAOM and the ASA are grateful for AHRQ's continued attention to, and acknowledgement of, acupuncture chronic-pain management option and look forward to opportunities to enhance the current research protocol for acupuncture.	Thank you for your comments
Jacob Marzalik, American Psychological Association (APA)	Key Questions	In your key questions, "usual care" was used as one of the comparators to the interventions examined. It would be helpful if you would provide additional information on what defines "usual care" as we know there can be variation in the operational definition of this term.	Thank you for your question. "Usual care" was poorly and variably defined across studies; most did not specify the components. We included studies for which "usual care" would likely be that provided by a primary care provider. Where information was available on components of usual care it is included in the data abstraction (see appendices) and general evidence tables in the report. The discussion acknowledges the heterogeneity of what was described as usual care across studies.

Commentator & Affiliation	Section	Comment	Response
Kara Gainer, American Physical Therapy Association	Methods	APTA agrees with AHRQ's statement that one of the limitations of the study/review was the lack of longevity of studies and standardization of research protocols. This type of research design is not the best way to analyze a multifactorial health issue as pain (individual intervention randomized controlled trials (RCTs)). Accordingly, we recommend that AHRQ conduct its systematic reviews by adding literature searches in comparative effectiveness research (studies with multifactorial designs) and health services research; and using larger health care outcomes databases. This will better allow AHRQ to examine the effect sizes of various interventions and combination of interventions (or those health professionals who provide them).	Thank you for your suggestion. Our literature search was broad and the MEDLINE and CCRCT searches were likely to identify relevant trials (there is some published literature out there that confirms this assumption). We feel that it is unlikely that any major relevant publications meeting our inclusion criteria were missed, including those evaluating comparative effectiveness or multifactorial designs. No specific citations were identified by the current or previous TEP or peer reviewers. We believe that our strategy was appropriate given the scope and Key Questions. Over 8100 citations were reviewed for inclusion in this report. The focus on RCT data generally provides the least biased estimates of effects. Evaluation of combination treatments was beyond the scope of this report as described in the protocol for the original report. Inclusion of such studies would have precluded meaningful summary of evidence across studies as there are a large number of possible combinations of treatments and likely only one or two trials evaluating any given combination.
Kara Gainer, American Physical Therapy Association	Results	While we believe that Key Question 6: Differential Efficacy touches on the important issue of moderation of treatment effect, it requires further development. We recommend that AHRQ provide additional clarification on why the factors of age, sex, and presence of comorbidities were selected a priori for consideration. Moreover, regarding Key Question 6, AHRQ indicates that there is insufficient evidence for osteoarthritis of the knee and hip, as well as fibromyalgia. APTA recognizes that there may not be sufficient evidence to make strong recommendations, but the statement that there is insufficient evidence should be expanded upon in some manner. For example, what are the main barriers to addressing this question and what are the key research priorities in this area?	Thank you for your comments. The factors chosen were considered to be the most important initial modifers to examine to stay within the report scope and were confirmed by discussions during the Key Informant and Technical Expert Panel calls held for the original report. Differential efficacy refers to the determination of effect modification or interaction (which is different than effect moderation). The evidence is insufficient because included studies did not stratify or provide sufficient data for testing of effect modification (i.e. interaction) and/or there wasn't sufficient high quality evidence with a large enough sample size to evaluate this. The key research priority is listed in Table P in the Executive Summary (vis a vis, "Documentation of coexisting conditions and factors in trials with sufficient sample-size to evaluate the differential impact of conditions and factors is needed.....")

Commentator & Affiliation	Section	Comment	Response
Jacob Marzalik, American Psychological Association (APA)	Results	The paucity of population subgroup information and analyses is very glaring in the report, and we appreciate your note of this and the call for more research. In particular, we strongly recommend adding more information on the race and ethnicity of study participants, including noting when a study did not report this information. While this information is included about some studies, many do not have any information. We also recommend examining any sub-group effects for race and ethnicity if possible with the data available. Information on race and ethnicity is particularly important given the role providers' cognitive biases may play in the amount and quality of care received by patients with chronic pain who are racial and ethnic minorities. Recent research suggests that providers have little awareness that the decisions made for the patient's care was influenced by the patients' race and/or socioeconomic status (Grant et al., 2019).	Thank you for your comments.We understand that these are important factors. As you point out, included studies rarely reported on these. Data that were available are in the report evidence tables and the data abstraction in Appendix D. There were insufficient data to formally evaluate the impact of any of the factors.
Jacob Marzalik, American Psychological Association (APA)	Results	Similarly, we recommend adding any additional information available on sex and gender of study participants (some already reported) and examining any sub-group effects possible with the data available. This is important given that gender biases in treating patients with chronic pain are also prevalent across medical settings (Oliva et al., 2015). We also want to emphasize the important role psychologists play within the healthcare system in treating diverse patient populations who have chronic pain (Frohm & Beehler, 2010). Frohm, K. D., & Beehler, G. P. (2010). Psychologists as change agents in chronic pain management practice: Cultural competence in the health care system. Psychological Services, 7(3), 115-125. https://psycnet.apa.org/fulltext/2010-17074-001.pdf Oliva, E. M., Midboe, A. M., Lewis, E. T., Henderson, P. T., Dalton, A. L., Im, J. J., Seal, K., Paik, M. C., & Trafton, J. A. (2015). Sex differences in chronic pain management practices for patients receiving opioids from the Veterans Health Administration. Pain Medicine, 16(1), 112-118. https://doi.org/10.1111/pme.12501	Thank you for your comments.We understand that these are important factors. As you point out, included studies rarely reported on these. Data that were available are in the report evidence tables and the data abstraction, Appendix D. There were insufficient data to formally evaluate the impact of any of the factors.

Commentator & Affiliation	Section	Comment	Response
Sunny Linnebur, PharmD, FCCP, BCPS, BCGP, President; Nancy E. Lundebjerg, Chief Executive Officer; The American Geriatrics Society (AGS)	Results	Subpopulations: We noticed in our review of the report that the data syntheses do not examine differences or evidence by subpopulations, specifically older adults and/or frail older adults. It appears that the evidence for osteoarthritis is based on samples from older adults, but the summary reports and interpretation of level of evidence for older persons across the problems examined are challenging. We recognize that in this type of review it is difficult to address the many different subpopulations that are of interest, but we wish to underscore the importance of understanding the evidence related to older adults and suggest this be addressed in future reports.	Thank your for your comments. There were insufficient data to examine the extent to which age might modify the effect of interventions. Included studies did not stratify by age or did not do subanalyses based on age. Studies of OA were primarily in patients >62 years old. Across the other conditions only 4 RCTs were in patients >60 years of age.
Sunny Linnebur, PharmD, FCCP, BCPS, BCGP, President; Nancy E. Lundebjerg, Chief Executive Officer; The American Geriatrics Society (AGS)	Results	Analgesics: Upon review of the report, we had questions about the control of co-management with analgesics. There appear to be some comparators to analgesic treatment, such as acetaminophen or topical analgesics, but no information on whether not use of analgesics was controlled as exclusion criteria. Many patients would use nonpharmacological interventions along with analgesics, and this is an area that we recommend needs further examination.	There was substantial variability across studies regarding how (or if) use of analgesics in addition to nonpharmacological interventions which precluded any detailed evaluation of this. Individual studies may or may not have reported use of such interventions or exclusion based on their use. Where data were available, they are included in the data abstraction (please see appendices).

Commentator & Affiliation	Section	Comment	Response
Leonard A. Wisneski, MD, FACP: Chairman of the Board; Integrative Health Policy Consortium (IHPC)	General	The Integrative Health Policy Consortium (IHPC) is grateful to the Agency for Healthcare Research and Quality (AHRQ) for its work in producing these three evidence reviews. Although we do not have any substantive comments to make regarding the process of developing these reports, or about the contents of the reports, we believe them to be very important in helping healthcare providers and people with pain find the safest and most effective treatments available. We are struck by the fact that all three of these reports find much the same thing: low-to-moderate quality evidence of a modest effect on pain over the short term. Where things diverge, however, is with respect to evidence of potential harms, which varies from essentially no evidence of harms from noninvasive nonpharmacological treatments, to modest harms associated with nonopioid pharmacologic treatments, to the potential for serious harms from opioid therapy if safe prescribing practices are not followed. Taken together, these three reports support the recommendations recently issued by the HHS Inter-Agency Pain Management Best Practices Task Force, which focus on an integrative, multimodal, interdisciplinary approach to treating chronic pain. Such an approach allows for additive or synergistic benefits derived from combining treatments, while minimizing risks by minimizing doses and durations of opioid and nonopioid pharmacologic treatments. In this context, the report on noninvasive nonpharmacological treatments is especially important, due to the limited understanding of these treatments by many healthcare payers. Having a continuously updated compendium of the evidence is extraordinarily valuable as both an educational tool for providers and an advocacy tool for organizations such as IHPC. We are especially gratified by AHRQ's undertaking an update of this report so soon after issuing its previous version, and we encourage AHRQ to continue updating it periodically. Your efforts are leading the way as we seek to carry out the recommendations found in essentially every recent guideline for treating chronic pain, which call for maximizing use of these treatments, using an interdisciplinary approach, and using them as first-line approaches to chronic pain. Thank you for your excellent and substantial work on these reports, and we look forward to the publication of their final versions.	Thank you for your comments.