



Comparative Effectiveness Review Disposition of Comments Report

Research Review Title:

Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review

Draft review available for public comment from December 20, 2017 to February 10, 2018.

Research Review Citation: Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, Fu R, Brodt ED, Wasson N, Winter C, Ferguson AJR. Noninvasive Nonpharmacological Treatment for Chronic Pain: A Systematic Review. Comparative Effectiveness Review No. 209. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No 18-EHC013-EF. Rockville, MD: Agency for Healthcare Research and Quality; June 2018. Posted final reports are located on the Effective Health Care Program [search page](#). DOI: <https://doi.org/10.23970/AHRQEPCCER209>.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review 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.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. 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
TEP Reviewer #1	General	<p>The review is clinically meaningful as it provides a summary of evidence for the most commonly considered treatments for chronic musculoskeletal pain. The target audience is implicitly providers who treat patients with chronic pain conditions, potentially patients but this is not specifically written at a lay level. The key questions are appropriate and explicitly stated.</p> <p>Some comments on the structured abstract: I recommend removing or modifying the statement, “particularly as alternatives to opioids and other pharmacological treatments.” This may lead the reader to think that the review specifically involved studies with opioids as comparators, which it did not. The rationale in relation to promoting non-pharmacological alternatives is set up in other sections of the paper, but I don’t think that brief statement belongs here, at least as currently stated. Also in the structured abstract, the results section for chronic low back pain was a bit hard to follow. This is the condition for which there is the most information, with multiple comparators and lengths of follow-up, it was difficult to glean the key points here. I would recommend a review of how this results section is presented to see if it can be shortened or organized a bit differently for clarity.</p>	<p>Thank you for your comments. We have reviewed and modified statements related to opioids to emphasize this review focuses on noninvasive, nonpharmacological management options.</p> <p>We have revised the structured abstract to clarify the presentation of findings, particularly for low back pain.</p>
TEP Reviewer #1	Introduction	<p>The introduction is generally clear and well written. However, there are a few ways in which I think it could be strengthened. First, it is worth mentioning the rationale for the exercise comparator. This is described later in the document, but a brief mention earlier (either here or methods) would be helpful. Second, what was the rationale for including only single interventions? This also should be stated explicitly (but probably fine in a later section of the review). Third, there should be some rationale stated here (or elsewhere early in the document) for the treatments chosen to be included in the</p>	<p>Thank you for your feedback. We described the rationale for decisions on these points in the review protocol, and have added corresponding text in the Introduction and Methods sections to clarify our approach. Our rationale for the exercise comparator was that exercise is commonly recommended for a range of chronic pain conditions and for some conditions was likely to</p>

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		review. Another minor point is that there is a phrase, “particularly over the long term” on page 17; I’m not sure it’s true that long-term was a particular emphasis, though somewhat longer term outcomes are included.	be a frequent comparator. We examined single interventions, as given the numerous potential combinations of therapies (and few studies for any given comparison), it would be difficult to draw evidence-based conclusions across studies regarding individual, specific, noninvasive, nonpharmacological treatments. The list of interventions were felt to be those most commonly used and studied. Input from stakeholders (Key Informants at the topic refinement phase Technical Expert Panel at the protocol development phase) informed the final PICOTS, including the list of interventions to be included in the review.
TEP Reviewer #1	Methods	Methods are overall strong and clearly described. In terms of inclusion of studies, what was the latest publication date for which studies could be included? In the executive summary methods section, it would be useful to provide a bit more specificity regarding outcomes that were eligible – e.g., both self-report and objective measures of function? Which aspects of pain – severity, interference?	The latest publication date for studies to be included is November 2017, the date the search was updated for the final report (noted in the final report text). We have added to the evidence summary methods text that the primary focus was on validated measures for function and pain, including any related to pain interference if examined in included studies.
TEP Reviewer #1	Results	Overall I found the results section to be appropriate in the amount of detail and generally clearly written. The biggest challenge in the results is the large amount of information,	Thank you for your comments and questions. We are glad to know the evidence summary tables give a good

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		<p>given the different health conditions, different comparators and different follow up times. I think these distinctions are all appropriate, but there is a risk of readers getting “lost” among all of the different results, even within each health condition (and especially for the ones where there are more studies). However, Tables A-M in the executive summary help this a lot. There is still a huge amount of information, but these tables allow a reader / clinician to find information on a specific treatment. Some additional comments on the results, particularly in the executive summary (and some apply to the more detailed results section as well):</p> <ul style="list-style-type: none">• Statement that the “majority” of patients were female is vague• Should the “inability to effectively blind participants” really be considered a major limitation in clinical trials of behavioral interventions?• What is meant by “unacceptable” rates of attrition on p20?• On p22, for MBSR results, there are results presented for just high quality trials, but this is not done consistently. It seems that at least for the executive summary it would be useful to either report based on quality of trials or not, across conditions /treatments.• On pages 23 & 24, there are results presented for multidisciplinary rehab vs. exercise in both the multidisciplinary section & the comparative effectiveness section; should be just on one place.	<p>overview of the results. Female: % range has been added</p> <p>Acceptable attrition: percentage of withdrawals and drop outs does not exceed 20%; acceptable attrition between groups is <10% difference. This information has been added. For patient-reported outcomes, inability to blind subjects is a potential source of bias and was considered a major limitation.</p> <p>We have edited information on study quality for consistency in the evidence summary. (Complete data on study quality is in the full report results section and in the appendix.)</p> <p>Multidisciplinary rehabilitation vs. exercise: We have corrected/moved the information to the comparative effectiveness section.</p>
TEP Reviewer #1	Discussion	<p>Overall I found the discussion to be well written and useful, highlighting the key messages. Key findings and strength of evidence section is well done, particularly with the inclusion of the tables. I was not fully convinced by the evidence that this “blanket” statement is entirely true: “There tended to be more evidence for the effects of interventions on pain than for function and the</p>	<p>Thank you for your comments.</p> <p>We have made edits to the discussion to include additional conditions and have reviewed and revised our discussion of policy implications. We have noted that evidence on</p>

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		<p>effects on function were generally smaller or not clearly present.” Please consider whether this general of a statement is appropriate / accurate.</p> <p>The section on “findings in relation to what is already known” in the executive summary focuses almost entirely on low back pain; other conditions should be included more as well. If there is not as much ‘already known’ this should be explicitly stated, otherwise it just seems like an omission.</p> <p>In the “implications for policy and decision-making” section of the executive summary, I think this is a bit of an over-statement: “The evidence synthesized in this review may help inform guidelines and health care policy (including reimbursement policy) related to use of noninvasive, nonpharmacological treatments as alternatives to opioids for these conditions, and inform policy decisions regarding funding priorities for future research”</p> <p>In particular, it is a stretch to say this evidence may inform reimbursement policy, since very little is known about cost effectiveness. In the same paragraph there is a statement regarding evidence of “sustained effectiveness;” I think a caveat here should be that there is still relatively limited evidence for long-term outcomes. In the next paragraph, what are the “passive” treatments being referred to here?</p>	<p>sustained, long-term benefit is sparse and added clarification regarding passive outcomes.</p>
TEP Reviewer #1	Clarity and Usability	<p>Overall I found the report to be well structured. As noted above, there is a vast amount of information here. I think the tables in the executive summary are particularly important for presenting the findings in a pretty clear, summary form. I have commented above on a few specific points related to policy / practice decisions.</p>	<p>Thank you for your thoughtful comments.</p>
Peer Reviewer #1	General	<p>This is a thorough and well-written review that updates the previous AHRQ review on the topic. Overall the results should be informative for clinicians and policymakers. The key questions and messages are clear.</p>	<p>Thank you for your comments.</p> <p>Additional context regarding effect</p>

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		The key messages could include a statement that effect sizes for effective treatments were generally modest.	sizes has been added to the key points.
Peer Reviewer #1	Introduction	<p>The introduction section lays out the rationale for the review quite effectively. The statements regarding consideration of the opioid epidemic in evaluating non-pharmacologic pain treatments are appropriate.</p> <p>On page E-4, is there any published validation of thresholds for judging effects on pain and function?</p> <p>On page E-5, can the authors provide a threshold for what was considered an "unacceptable rate of attrition" either overall or differential?</p>	<p>Thank you for your comments.</p> <p>Effect sizes: The magnitude of effects for pain and function were classified with the system used our previous AHRQ review on noninvasive treatment for low back pain. The methods in the full report and Appendix H provide additional information. Where a minimal clinically important difference (MCID) was known for a measure this was considered the basis for "moderate" effect size. Discussion on the interpretation of effect sizes is found in the Applicability section as well. While we acknowledge that small effects using this system may not meet standard thresholds for clinically meaningful effect, our method provided a consistent bench mark to compare results across trials. Interpretation of MCIDs in mean change for continuous variables is challenging. In some instances, a mean effect size may be small, but may related to a larger effect when the proportion of responders achieving that (or other) level is considered. There is variability across individual patients regarding what may</p>

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			constitute a clinically important effect, which is influenced by a number of factors (preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs). For some patients a small improvement in function or pain gained by using a treatment that has relatively low cost with no serious harms may be important. Attrition: less than 20% overall, less than 10% between groups. We added this definition.
Peer Reviewer #1	Methods	<p>In general standard methods for identifying and reviewing included studies were applied in this review. One concern however is the consideration of limitations inherent in studies involving non-pharmacologic therapies. The CONSORT extension for NPT acknowledges that blinding participants is frequently not possible with studies involving NPTs. This review however appears to make no distinction in evaluating SOE for treatments where participant blinding possible (e.g., acupuncture) or is not possible (multi-disciplinary rehab).</p> <p>A statement in the methods regarding definition of harms versus side effects or adverse events may be helpful for readers. Studies may document anticipated side effects (e.g., muscle soreness from spinal manipulation) but it is uncertain if this type of data would be considered to be information on "harms" in this review.</p>	<p>Thank you for your comments. Where patients could be blinded (e.g. sham acupuncture) this was noted in the risk of bias assessment; such trials were rated as "good" if there were no major study limitations. This was considered when determining the overall SOE across such trials for the individual outcomes. If the quality of trials summarized for a given outcome was "good", no downgrade for study limitations was made. If the trial had multiple arms (e.g. usual care as well as sham as controls), if patients were not/could not be blinded, the study quality was described as "fair" for outcomes related to that arm and factored into the final SOE determination.</p>

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			Harms, side effects, and adverse events were reported as defined by the authors of the included studies. For most interventions, many of these would likely be anticipated and were not considered serious effects requiring medical intervention.
Peer Reviewer #1	Results	It appears the review included appropriate studies and the results addressing the key questions are clearly displayed and presented in text.	Thank you.
Peer Reviewer #1	Evidence Summary	<p>The major findings are clearly stated. I find Tables A-M displaying the results to be very useful.</p> <p>On page E-24 I would recommend including a statement in the section addressing limitations of applicability noting the issue of heterogeneity with respect to the provider providing the treatments (e.g, psychologists versus other providers delivering CBT etc.).</p> <p>On page E-25 - the discussion of policy implications should be more explicit with respect to the need to take down financial barriers to effective opioid-alternative pain treatments. The financial issues of high deductibles, high patient co-pays and limitations in number of visits are barriers that can push patients and providers toward pharmacologic options. This is a crucial consideration, recognized by the CDC and other organizations promoting strategies to reduce the opioid epidemic.</p> <p>Also on page E-25, the advice regarding the incorporation of pragmatic research designs should be re-thought. The review states that pragmatic designs may improve participant recruitment and adherence but it seems more likely that pragmatic designs would exacerbate instead of remedy these concerns, particularly adherence. While incorporation of pragmatic designs may be useful advice for researchers, the</p>	<p>Thank you for your comments.</p> <p>We have added text to indicate there are a number of interventions employing different provider types, and the resulting heterogeneity may affect applicability of findings.</p> <p>We recognize the financial barriers and incentives that you point out, but it is beyond the scope of our review to do more than raise these issues as considerations for policymakers.</p> <p>We have reworded the discussion of pragmatic trials. Give the complexity of chronic pain populations and the range of interventions, pragmatic trials may offer important information on "real world" effectiveness, but should not be done to the exclusion of well done, traditional explanatory RCTs or well done prospective cohort studies.</p>

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		methods used in the review process will need to change to incorporate this research. These design will likely fail to meet a number of standards focused on internal validity (e.g. patient and clinician blinding) and is unlikely to evaluate uni-model interventions as the review does. Overall the advice to consider and encourage pragmatic designs is important, but not the reasons listed. Furthermore, the review methodology will need to evolve if these studies are not to be dismissed as merely poor quality research.	Categorization of trials based on the the pragmatic explanatory continuum indicator summary (PRECIS) tools and consideration of how the listed domains are addressed in such trials may facilitate decisions about how they may be best included into systematic reviews.
Peer Reviewer #1	Clarity and Usability	This report is organized well and sufficiently succinct considering the breadth of topics taken on. The main points in response to key questions are clearly presented. The review will benefit policy and practice although the utility for these groups may be enhanced through greater consideration of financial barriers to non-pharmacologic pain treatments and more nuanced consideration of the advice to researchers to incorporate pragmatic study designs.	Thank you for your perspective.
TEP Reviewer #2	General	I would make two general recommendations for the methodology and future research sections. First, the methods used involve summary statistics of pain and function based on questionnaire responses in RCTs. They tell us nothing about patient specific variables that might help understand why some treatments work for some patients and not for others. Second, the current public and personal health epidemic of disability from chronic pain (especially low back pain) is neglected, and future research should address this outcome.	Thank you for your perspective. We acknowledge that it would be valuable to have a better understanding of why some treatments work better than others for certain patients. However, little information was available in included trials to evaluate information on patient characteristics that may impact pain and function outcomes.
TEP Reviewer #2	Methods	It could be helpful, if not already done and I missed it, to mention the studies that changed the current assessment from the 2001 Cochrane Group's assessment that multidisciplinary treatment with functional restoration was better than less intensive physical therapy. The text does note that there are no new studies of functional restoration.	Thank you for your comments. We have made edits to the report to clarify that functional restoration is really more of an approach/goal of multidisciplinary rehabilitation and cannot really be evaluated as a standalone

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			intervention and have modified parts of the methods/interventions/etc. that refer to it as a separate intervention. We have noted that most multidisc rehab trials were based on a functional restoration approach, and that it was not really possible to identify multidisc rehab programs without a functional restoration approach.
TEP Reviewer #3	Evidence Summary	<p>My review is of the introductory materials (i-xv and ES-1 through ES-28), which is all the reader is likely to read. Comments for these introductory materials may be relevant to the rest of the report (pp 1-290+).</p> <p>The report is generally clear and well-written, but I offer comments/suggestions to make it clearer.</p> <p>ii,13: "function or pain outcomes 1 month to 1 year after the completion of therapy" has a problem. Many of the targeted interventions are ongoing and not "completed" (e.g., exercise, acupuncture), so "after the completion of therapy" doesn't really apply. As said later in the report, such a standard is not applied to pharmacological interventions. This issue needs to be stated/clarified here and in other relevant parts of the document.</p> <p>Because self-management education (SME) appears to have beneficial effects, some relatively long-term, a key message should be what categories were not addressed in the report that might have benefit as well.</p> <p>I suggest a statement addressing the evidence for the</p>	<p>Thank you for your comments. A number of edits have been made to the abstract and summary in response to your suggestions.</p> <p>As the report did not evaluate information on SME, we have not made statements regarding its benefits, but have noted that there are interventions that were beyond the scope of this review. It would not be possible to list and acknowledge all possible treatments that were excluded. We recognize that exclusion doesn't imply anything regarding the efficacy or safety of such treatments.</p> <p>Periodic assesement is done by AHRQ.</p>

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		<p>effectiveness of opioids, which my FDA colleague says have not been evaluated beyond 3 months, as a measure of how limited the research is in the pain management field in general.</p> <p>iii, 35: periodically be assessed (by whom?)...</p> <p>vii, 20: inclusions/exclusions need to be stated in general terms</p>	
TEP Reviewer #3	Evidence Summary	<p>vii, 32: This structured abstract may be all that some readers view. A good structure has been set up for the larger review itself (i.e., benefits on function and pain by ST, IT, and long-term; harms), and it would help the reader to present the results by those seven categories for each of the five conditions (e.g., function by ST, IT, and LT, pain by ST, IT, and LT, harms for chronic low back pain, then for chronic neck, pain, etc.). A bonus of this approach is that it makes clear where there is little evidence at all. As it reads now, there is a mix of these categories that makes it difficult to understand the findings clearly. [Having the SOE statement for these results is very good. I also suggest listing the number of studies for each of the five clinical categories.]</p> <p>viii, 35: There should also be a statement here addressing the targeted research question of differential efficacy (page ES-15).</p> <p>viii, 38: I think this is a bit too positive, and that greater emphasis should be placed on the fact that there is "insufficient or not evidence" for so many of these questions, and that more studies need to be done to address those gaps.</p>	Thank you for your comments. A number of edits have been made to the abstract and summary in response to your suggestions.
TEP Reviewer #3	Evidence Summary	Evidence Summary	Thank you for your comments. References 1 and 2 have been

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		<p>ES-1, 10: refs 1 and 2 relate to opioids, not chronic pain per se. There should be relevant references in the National Pain Strategy or the 2011 IOM report.</p> <p>ES-1, 43: need to be clear about what was not addressed by stating that other non pharm treatments, such as self-management education and others?, were not part of this review although there is evidence for their benefit. (See Brady ref in Discussion comments)</p> <p>ES-2, 16: KQ 6 should be listed here, and not buried in the paragraph below.</p> <p>ES-2, 28-41: burying such a long list of interventions in a paragraph makes it hard on the reader. I suggest a straightforward row list:</p> <ul style="list-style-type: none">a. exercise...b. mind-body...c. psychological......x. function restoration training.	<p>updated, citing IOM and NPS</p> <p>Line 43 is a general statement regarding what may be included; the protocol describes rationale for not including some interventions such as SME (scope, available resources).</p> <p>KQ 6 has been moved right after KQ 1-5.</p>
TEP Reviewer #3	Evidence Summary	<p>ES-3, 27: No criteria are listed here. At least a short list should be included, perhaps with a reference to Table 1.</p> <p>ES-3, 37: drop "longer term" because that phrase is used differently in this report (see next page).</p> <p>ES-3, 54: "synthesized qualitatively" needs elaboration or examples to help the reader.</p>	<p>Thank you for your comments; reference to table 1 of report is added. Edits related to "longer term"; qualitative assessment is defined there are including ranges and descriptive analyses.</p>
TEP Reviewer #3	Evidence Summary	<p>ES-5, 24: I'm not sure what "excluded at full text" means. Can this be stated more clearly?</p> <p>ES-5, 37-39: This important information should be in the</p>	<p>Thank you for your comments. "Excluded at full text" means that while a study appeared to meet inclusion criteria upon review of the</p>

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		<p>abstract.</p> <p>ES-5, 40-42: This important information should be in the abstract.</p> <p>ES-6, 4: I suggest including the number of individual pain management strategies (n=9), the number of RCTs (n=65), and referencing the relevant table (e.g., Table A on page ES-16) as a way to provide important information for the reader.for EACH of the 5 Key Questions</p> <p>ES-6, 6: I suggest ordering the 9 intervention categories as presented on page ES-2 and including those with no data to emphasize the lack of information/research. This should be done for all 5 Key Questions.</p> <p>ES-6, 37: The five physical modalities should be visually indented so that it is clear these are subgroups of physical modalities. Right now they look like separate, competing interventions. This same comment applies to the Mind-Body Practices section.</p> <p>ES-8, 30: This was labelled "interdisciplinary rehab" on page ES-2. You should use a single label throughout.</p> <p>ES-8, 52: This needs to be visually different from the preceding list of interventions so that the read knows you have moved on to a different topic. I suggest listing these in order from best/strongest evidence to poorest/weakest evidence so the reader doesn't have to do those calculations.</p> <p>ES-9, 30: The comments for the Low Back Pain section above apply to this and the remaining sections.</p>	<p>title and abstract, upon subsequent review of the full text of the publication, we found it did not meet our inclusion criteria and was excluded from the report.</p> <p>The length of the abstract and the evidence summary are limited, so we have had to be selective about the extent of data to present in these parts of the report.</p> <p>We have edited tables and text for clarity.</p> <p>We have assessed listing of interventions for consistency, based on how they are listed in the PICOTS table, to the extent possible, given that evidence for interventions varied by condition.</p>

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TEP Reviewer #3	Evidence Summary	<p>ES-16, 16: "for each chronic pain condition in THE RESULTS and in Tables A_M"</p> <p>ES-16, 17: It is too easy for the main findings to get lost in this long paragraph. I suggest starting a new paragraph for each main finding or using a bulleted list, such as</p> <p>"The strength of evidence was low..."</p> <p>"We focused on evaluating..."</p> <p>"The majority of trials..."</p> <p>"No trials directly compared...opioids..."</p> <p>"Information on adherence..."</p> <p>"Harms were poorly reported..."</p> <p>ES-16, 41: For this and the following tables, I again suggest adding the number of trials; ordering the list of interventions in some standard way (e.g., best to worst? by RMD? by SOE?)</p> <p>ES-17, 29: Footnotes: I suggest three row titles with details for this and subsequent tables:</p> <p>Effect size: +, ++, ...</p> <p>SOE: Low...Moderate...</p> <p>Acronyms: MBSR, SOE.</p> <p>ES-17, 36: Rather than Table B, I suggest that all tables related to a single KQ be given a single letter and relevant number (e.g., Table A-1, A-2...). I also suggest that an empty table or at least a statement be made for advertised comparisons (compared with usual care compared with exercise; compared with pharma) that had no data to make clear that you looked and didn't find anything meeting your standards.</p> <p>ES-23, 28: What about a statement for the other three target conditions?</p> <p>ES-23, 50-52: without saying this in the methods or abstract, this statement about <90% caught me by surprise. Another</p>	<p>Thank you for your comments.</p> <p>Labeling and formatting of tables needs to be consistent with AHRQ and 508 accessibility guidelines.</p> <p>ES-23-28; this section (Findings in relation to what is known) has been edited based on the range of comments received).</p> <p>Exclusion criteria are detailed in the protocol and full report (Table 1).</p> <p>Edits to the discussion (including limitation section) have been made. The full text of the report contains a more detailed version of the discussion.</p> <p>The citation provided describes findings related to the delivery and impact of a specific type of chronic disease self-management program (Stanford) with a search focused on arthritis in general. Since such programs were not part of the scope of this review, we cannot comment regarding the strength of evidence for benefits of such programs. We have</p>

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		<p>reason to add this exclusion to the methods.</p> <p>ES-24, 32: Seems like the CDC and ACP sentence warrants a new paragraph.</p> <p>ES-24, 38: New paragraph for this summary statement is needed. It shouldn't be buried in a big paragraph.</p>	<p>added information to the discussion that there are a number of interventions that were not included.</p> <p>Detail regarding the number of trials for each condition and for various interventions, including those for which there is insufficient evidence, is in the full text of the report in order to keep the evidence summary as streamlined as possible.</p>
TEP Reviewer #3	Evidence Summary	<p>ES-25, 46: For the Limitations paragraph, I think you need to add more limitations, for example:</p> <ol style="list-style-type: none">1. we could not review all promising non-pharm interventions, such as self-management education (SME) that have evidence supporting positive effects.[[e.g., Brady TJ et al. A Meta-analysis of health status, health behaviors, and health care utilization outcomes of the Chronic Disease Self-Management Program. Preventing Chronic Disease 2013;10:120112 DOI: http://dx.doi.org/10.5888/pcd10.120112. This article touches on pain benefits.]. Also, mention how you handled "ongoing" (e.g. acupuncture) rather than "completed" interventions.2. we restricted our analysis to RCTs, and did not examine other types of studies.3. Erika Brodt sent me these limitations in July:<ol style="list-style-type: none">1. Interventions: In order to keep things as pure as possible, only single interventions (as opposed to combinations of interventions) were included; interventions that were additive in nature or assessed for incremental value relative to another intervention were excluded.	<p>Thank you for your comments.</p> <p>Edits to the discussion (including limitation section in the) have been made. The full text of the report contains a more detailed version of the discussion.</p> <p>The citation provided describes findings related to the delivery and impact of a specific type of chronic disease self-managment program (Stanford) with a search focused on arthritis in general. Since such programs were not part of the scope of this review, we cannot comment regarding the strenght of evidence for benefits of such programs. We have added information to the discussion that there are a number of interventions that were not included.</p>

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Commentator & Affiliation	Section	Comment	Response
		<p>2. Comparators: In order to limit the scope and to make the report more meaningful/useable, we agreed upon a common comparator intervention for each Key Question/Condition (subquestion c); thus, any studies that compared one intervention to another intervention (as opposed to the standard comparator) were excluded.</p> <p>3. Timing: Trials were required to have a minimum of 4 weeks of follow-up after the end of the treatment period; any studies that reported outcomes immediately post-treatment only were excluded.</p> <p>ES-25, 50: Need to lead with some powerful summary statement like "The gaps in/lack of evidence are striking, and we examined relatively common conditions with the best research history. A review of less common conditions would likely find even less evidence. Filling these gaps is essential in developing a rational, more evidence-based approach to reducing pain and improving function for those with chronic pain....."</p> <p>ES-26, 38: "But the bigger picture is the lack of evidence and the need for additional research on pain management as well as comparative research on the sustainability..."</p>	
TEP Reviewer #3	Clarity and Usability	<p>The authors have done a good job in providing the content relevant to this review, which is an important piece of understanding what we know about non-pharma interventions that are crucial to a more rational, evidence-based approach to pain management.</p> <p>As a fresh reader I've made many suggestions that I think will help more clearly communicate what was done and the main conclusions to be drawn--especially for the abstract and the</p>	Thank you for your comments.



Commentator & Affiliation	Section	Comment	Response
		Executive summary (also called Evidence Summary), which a likely the only parts to be viewed and used by most readers.	
TEP Reviewer #4	General	The report is limited by inclusion of only studies with longer term follow up, however, the data presented are clear and the forrest plots are very helpful	Thank you for your comments. We have noted that this reviewer's comments are confined to the sections related to fibromyalgia
TEP Reviewer #4	Introduction	Clearly described	Thank you.
TEP Reviewer #4	Methods	Clearly described	Thank you.
TEP Reviewer #4	Results	Clearly described	Thank you.
TEP Reviewer #4	Discussion/ Conclusion	Clearly described	Thank you.
TEP Reviewer #4	Clarity and Usability	The report was clearly presented and easy to follow. Researchers will benefit greatly from the evidence tables.	Thank you.
Peer Reviewer #2	General	<p>The report will have limited clinical utility for several reasons. Although the target population and audience are explicitly defined and key questions are appropriate and explicitly stated, the following concerns undermine confidence in the results and conclusions.</p> <p>Only a minority of patients with chronic pain have one specific site of pain or painful condition. The decision to examine the effectiveness of these approaches for the treatment of specific sites of pain without consideration of the broader context of sociodemographic and clinical characteristics especially pain duration and presence of other painful conditions and sites of pain, not to mention medical and mental health comorbidities is a serious limitation. In particular, the failure to examine studies of patients with "chronic pain" as opposed to more</p>	<p>Thank you for your comments.</p> <p>We are aware that a proportion of patients may have more than one specific source of pain and that chronic pain is complex for the reasons stated by the reviewer. Our report is a start on identifying types of nonpharmacologic interventions that may work for the various conditions, potentially laying the ground work for understanding what may be helpful for patients with a more specific etiology for pain, and where the gaps in the research are. This in turn may lay some</p>

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		<p>homogeneous groups is a serious limitation since several published high quality trials of these interventions targeted more heterogeneous samples of persons with chronic pain.</p> <p>There is an inconsistency in the level of specificity of therapeutic approaches examined that undermines utility, Why are "psychological therapies" examined as a category whereas other very specific approaches are examined (e.g., low level laser therapy, pulsed short-wave diathermy).</p> <p>The serious methodological concerns raised below undermine confidence in the reliability of the findings and conclusions.</p>	<p>ground work for further evaluation of a broader scope of "chronic pain" in general. As noted in our report, various interventions were more common for some conditions, less common for others, and there is variation in the volume of evidence for some interventions for the various conditions. Our findings also suggest that there may be evidence of efficacy for some interventions for a given condition, but not for another condition. This may be important for clinicians and patients when considering what interventions to use.</p> <p>We have edited aspects of the report for consistency regarding detail of interventions within various category for the ES. Detail of all intervention subcategories is contained in the full report.</p> <p>The scope and limitations discussed with key informants an the technical expert panel.</p>
Peer Reviewer #2	Introduction	<p>Important to define scope of interventions by what they are, not just what they aren't.</p> <p>How was "chronic pain" defined?</p> <p>A rationale for the limited nature of the search should be provided. Why weren't other important databases searched,</p>	<p>Thank you for your comments.</p> <p>Chronic pain is defined in the evidence summary and full report as pain lasting 12 weeks (3 months) or longer or persisting past the normal time for tissue healing for purposes of this</p>

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		<p>especially given the focus of this review (e.g., PsychInfo, EMBASE, CINAHL, CENTRAL)?</p> <p>Justification for selected conditions is weak.</p> <p>Justification for comparison conditions is weak (e.g., pharmacological treatment or exercise?). Why would one expect these comparators to have been used in the relevant clinical trials?</p> <p>Does this reflect bias on the part of the reviewers suggesting that meds or exercise are gold standards for comparison?</p> <p>Why was “multidisciplinary rehabilitation” examined as a “treatment?” This term is better conceptualized as a “model of care rather than a specific approach.</p> <p>What is the rationale for examining “psychological therapy” as a unit? This level of analysis is entirely inconsistent with an approach for other therapies that is much more specific (e.g., low level laser therapy, pulsed short-wave diathermy).</p>	<p>report.</p> <p>Databases: We searched those felt to be most relevant to this review and those which were most likely to yield appropriate citations without substantial overlap in citations. Data bases such as Embase provide a low yield of relevant citations for nonpharmacological interventions in particular. It is reassuring to note that citations suggested by reviewers and public commentators were captured by our searches and/or did not meet our inclusion criteria.</p> <p>Edits for clarity have been made as appropriate.</p> <p>Justifications for conditions and comparisons: The conditions chosen were considered to be among the most common seen in primary care and additional reference to this is provided. Regarding comparisons, the protocol contains additional justification which was discussed with Key Informants and Technical Experts.</p> <p>We recognize that multidisciplinary rehabilitation involves a system/model of care and it has also been studied as a specific intervention in our previous</p>

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			<p>reports and many other reports. We used the definition of MDR that was used for our low back pain report as a coordinated program with both physical and biopsychosocial treatment components (e.g., exercise therapy and cognitive behavioral therapy) provided by professionals from at least two different specialties.</p> <p>Detail regarding therapies: We have clarified specific therapies represented in the executive summary; they are detailed in the full report in plots and tables.</p> <p>Outcomes are described in the full report (and in the posted protocol). We focused on results from validated measures for physical function and pain that were common across studies. Self-reported Visual Analog Scale (VAS) assessments for pain were most commonly reported across studies, and available results related to pain interference, etc. were described. Measures related to health-related quality of life (HRQOL) are described in the full report to the extent that data were available; this was considered a secondary outcome.</p>
Peer Reviewer #2	Abstract	With regard to the Structured Abstract: What is meant by “most of the trials were small?”	Thank you for your perspective. We have made edits for clarity and

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		<p>Why were “psychological therapies” lumped together? Terms such as “inactive control” or “attention control” require definitions.</p> <p>Define terms characterizing outcomes such as “function” and “pain.” Note that this is a major problem throughout the document. These terms must be defined and consistently applied throughout the document. The use of the word “pain” as an outcome is unhelpful; presumably this refers to self-reported pain severity or pain intensity. Function can refer to pain interference, disability, social role functioning, ADLs and IADLs, and other constructs. The lack of precision in the use of these terms is likely to encourage misunderstanding or confusion on the part of many readers.</p> <p>The organization of presentation of results is confusing. What is the rationale for separately considering and reporting on some sites of OA?</p> <p>The inconsistent level of detail (e.g., psychological therapies vs CBT; Alexander Technique, mind body practices) is problematic.</p> <p>As mentioned above, the failure to examine the domain of “chronic pain” trials is a serious limitation.</p> <p>The Conclusion seems inconsistent with the Results. Results are organized around specific conditions with varying level of specificity in labeling interventions, outcomes, and characterizing findings. The Conclusions section reverts to the use of the term “chronic pain” without this specificity and inaccurately summarizes the findings from the previous section (e.g., why isn’t “psychological therapies” listed as an approach with evidence across conditions?</p>	<p>consistency.</p> <p>Detail of specific psychological therapies has been added to the Evidence Summary as appropriate; there is detail in the full report.</p> <p>Pain and function were assessed using validated measures and are briefly described in the PICOTS.</p> <p>Most trials had fewer than 70 participants.</p> <p>Measures and definitions for function varied across included trials. Most studies reported VAS pain; Information from validated pain and function measures is reported with a focus on measures used across trials.</p> <p>Detail of interventions is found in the full report. We've added some detail to the Evidence Summary.</p> <p>We've reviewed and edited the discussion and conclusions based on the aggregate of comments received.</p>
Peer Reviewer #2	Evidence Summary	<p>With regard to the section headed "Evidence Summary":</p> <p>The definition of chronic pain should acknowledge the lack of consensus (3 vs 6 mos duration; not usually defined by weeks).</p>	<p>Thank you for your perspective.</p> <p>References 1 and 2 in the executive summary have been corrected. We</p>

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		<p>Highlighting the opioid crisis in two paragraphs relative to emphasizing the public health crisis of under-treatment of chronic pain is inappropriate.</p> <p>More attention should be placed on acknowledging the scientific knowledge and clinical practice gaps related to chronic pain management as a framework. Frankly, I find the focus on the opioid issue a distraction and largely irrelevant unless there is an explicit attempt to examine or even highlight opioid sparing effects of these interventions or to examine subsets of the population of persons with chronic pain who are in receipt of opioid therapy. The fact that the first several references relate to opioids rather than pain suggests an outrageous bias.</p> <p>Although only recently published, the Federal Pain Research Strategy should be integrated into this report.</p> <p>Some acknowledgement of other invasive non-pharmacological treatments (e.g., surgery, neuromodulation) and invasive pharmacological interventions (e.g., injections) should be included. The specific issues of limited evidence of benefit, apparent risk of harms, and costs often associated with these approaches should be specifically cited as background and context for this review.</p>	<p>have made edits to the referencing of the opioid crisis.</p> <p>The review scope, framework, Key Questions, and PICOTS inclusion/exclusion criteria were developed by the review team, after consideration of input from a group of Key Informants and a Technical Expert Panel to obtain broad perspective and expertise (as described in the front matter of the report), in addition to input from the review sponsors and AHRQ.</p> <p>We have referenced the Federal Pain Research Strategy.</p> <p>The discussion includes a brief statment that there are a number of interventions that were not part of the scope of this report. We have clarified that the list of possible nonpharmacological approaches in the introduction refers to those that are the subject of the report.</p>
Peer Reviewer #2	Evidence Summary	<p>Why are these specific nonpharmacological approaches cited in the last paragraph of the Introduction? This betrays some bias of the authors. What about copper bracelets or other complementary and integrative health approaches such as energy approaches or herbals and supplements? Acupuncture is listed twice!</p>	<p>Thank you for your perspective.</p> <p>The review scope, framework, Key Questions, and PICOTS inclusion/exclusion criteria were developed by the review team, after consideration of input from a group of</p>

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		<p>Terms should be defined when first used to promote clarity and precision. (e.g., biopsychosocial nature of the disease, noninvasive, nonpharmacological, benefits, harms, pain score)</p> <p>Why is the list of pain medications preceded by “e.g.?” Medications are either used for pain or not?</p> <p>Again, why exercise and biofeedback as comparators?</p> <p>What is the source for the list of approaches listed in categories on page 17? What about hypnosis, as just one missing example, and what about other categories of CIH, as already mentioned?</p>	<p>Key Informants and a Technical Expert Panel to obtain broad perspective and expertise (as described in the front matter of the report), in addition to input from the review sponsors and AHRQ.</p> <p>The discussion includes a brief statement that there are a number of interventions that were not part of the scope of this report. We have clarified that the list of possible nonpharmacological approaches in the introduction refers to those that are the subject of the report.</p>
Peer Reviewer #2	Methods	<p>Inconsistent use of terms such as “investigator” vs “researcher” vs “senior investigator” is distracting and encourages confusion unless these terms were specifically indicative of some important differences in characteristics or status of those being referenced.</p> <p>What is meant by the phrase “All outcomes were considered direct?” (page 19)</p> <p>Why were only those involved in primary care or management invited for public comment? Does this introduce unintended bias?</p> <p>Page 19 “publication” should be “publications.”</p> <p>Be consistent in use of terminology (low back pain vs chronic low back pain; neck pain vs chronic neck pain; this is a major issue beginning when presenting the Results on page 21.</p>	<p>Thank you.</p> <p>Directness of an outcome generally reflects whether the outcome is directly or indirectly related to health outcomes of interest (described in the report and protocol).</p> <p>Peer reviewers from a broad range of disciplines were invited to provide comments. AHRQ ensured that a broad range of stakeholders were made aware of the posting of the draft report (as well as the Key Questions) and offered the opportunity to respond as part of the public comment process.</p>

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		<p>When noting that blinding is a high frequency limitation, the obvious challenge of conducting blind trials of nonpharmacological approaches should be acknowledged. In fact, it has been recommended by some that this standard not be applied to such trials.</p> <p>Key issues such as treatment “dose” and adherence are generally not considered. There is a reference to unreported adherence on page 31, but the basis for this statement is not supported. It is likely that attendance at psychotherapy sessions is reported in these trials, for example.</p>	<p>We have made edits through the report for consistency.</p>
Peer Reviewer #2	Discussion	<p>In the Applicability section, it is hard to imagine that any of the factors discussed as caveats to conclusions are any different from discussions of the evidence for any health care intervention for any indication. After all, even the delivery of chemotherapy occurs in persons with a complex array of individual differences including all of the factors cited in this section. I think that it is important either to delete this section or note this obvious fact that at least some of the literature relevant to this review does include attention to comorbid medical and mental health conditions and concurrent treatment among other factors. In other words, care should be taken not to suggest a higher standard than reviews of other “traditional” approaches and/or for other medical and mental health conditions.</p>	<p>Thank you. We have reviewed the wording in the Applicability section; edits have been made based on the aggregate of comments received.</p>
Peer Reviewer #2	Discussion	<p>The section on Clinical and Policy Implications and Decisionmaking is particularly strong. The integration of the findings is well justified and well stated. The paragraph about “active” vs “passive” interventions is particularly interesting and potentially quite important and could be elaborated, perhaps even in the Abstract and certainly in the earlier</p>	<p>Thank you for your comments. We have added brief definitions.</p>

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		summary. In this context, greater definitional clarity about this distinction could be important	
Peer Reviewer #2	Discussion	<p>Page 40 introduces the outdated acronym “CAM” and should be replaced and defined.</p> <p>The discussion about multi or inter-disciplinary rehabilitation should be reconsidered. It is unclear why this is included in a review that otherwise focuses on specific approaches. The last section about who might benefit most from this model of care is unfounded and should be deleted, at least.</p> <p>The limitations section could be expanded to include the concerns already raised about the scope of the search, in particular, and the likelihood that a significant number of published reports of relevance to this review may have been missed by not specifically searching databases such as PsychInfo and CINAHL. Additional sensitivity analyses to reassure readers that this is not a serious limitation could be considered. The failure to consider the presumably large number of trials that examined treatment for heterogenous samples of persons defined as having “chronic pain” without reference to specific conditions is a related concern. After all, it is understood that a large majority of persons with one of the conditions examined in these trials likely concurrently experienced other sites of pain and painful medical conditions. And, unless clearly specified in the published reports, outcomes such as changes in pain intensity or functioning may reflect a global experience of chronic pain that is not specific to the site that is the focus of the intervention. This, of course, is most likely to be true for “active” interventions such as many psychological and exercise/movement approaches.</p>	CAM has been corrected to CIM and is spelled out where it appears in the report.

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Peer Reviewer #2	Discussion	The research section is pretty good and could be expanded to include a more comprehensive, perhaps even enumerated, list of recommendations. Citations to other groups' recommendations such as those articulated in the Federal Pain Research Strategy and from IMMPACT and ACTION could be cited, in particular. In the last paragraph on research recommendations, it could be helpful to call out journal editors for their role in encouraging more complete information that could address some of the quality gaps.	Thank you for your comments. We have added citations for the FPRS, IMMPACT, and ACTION as resources to inform future research.
Peer Reviewer #2	Methods	<p>Page 44. I don't think that the IOM report stated that chronic pain was a disease in all cases. I think it proposed that chronic pain may be a disease in some cases.</p> <p>Again, define or elaborate use of terms such as biopsychosocial. This is important because of its relevance for several aspects of this review, not just the focus on noninvasive nonpharmacological approaches. The focus on multiple outcome domains is another important implication of this model and its use as a framework, among other implications.</p> <p>I'm not sure that I appreciate the framing of this as a comparative effectiveness review. The results are largely framed as reporting on effects over time rather than effects relative to other efficacious interventions, which is usually how CER is framed.</p> <p>The use of overarching labels for some interventions and not others is confusing. Why cluster some interventions as "psychological?" Why use the term "mind-body" practices and labeling some, but not other, approaches that incorporate attention to psychological and behavioral factors such as cognitive-behavioral therapy or even structured exercise</p>	<p>Thank you for your comments. We have made additional edits for clarity. The review scope, framework, Key Questions, and PICOTS inclusion/exclusion criteria were developed by the review team, after consideration of input from a group of Key Informants and a Technical Expert Panel. The posted protocol provides additional rationale for the approaches taken.</p> <p>The labels we used were an attempt to provide some level of categorization for the many included interventions. There is no standard method for categorizing many of the interventions. We realize that others may categorize interventions differently. We acknowledge that there is overlap between our categories. Specific interventions within categories that were assessed separately (e.g. Yoga, Tai Chi, MBSR).</p>

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		<p>which certainly is known to have effects on cognition and affect?</p> <p>Under Scope and Key Questions, there is a suggestion of a focus on single active interventions. However, the inclusion of a focus on multidisciplinary pain rehabilitation belies this assertion. And, the use of the term “active” interventions to refer to those approaches that involve active patient participation in using skills taught during treatment is problematic. Overall, the frequent imprecise and inconsistent use of language throughout the document is problematic and requires careful editing.</p>	<p>We realize that there is heterogeneity within specific interventions (e.g. psychological therapies, Yoga, etc.) which we have addressed via stratified analyses where possible. In general, there was no clear difference between techniques.</p>
Peer Reviewer #2	Methods	<p>The issue about the limitations of the databases that were searched is a specific and potentially serious limitation.</p> <p>On page 47, why aren’t efforts to obtain unpublished reports from investigators in the field detailed in this section?</p> <p>In applying the PICOTs criteria, and particularly with efforts to specify exclusion criteria, was there an unintended risk of over-exclusion of otherwise relevant studies? For example, the exclusion of papers that excluded patients with chronic low back who had evidence of radiculopathy may be problematic, or the exclusion of studies of patients with only tension headache seems unnecessarily restrictive and problematic. In the end, these limitations on the sampling approaches of the studies included in the analyses is stated as a limitation of the overall review in terms of encouraging generalization. Very few people with chronic pain have only one specific pain condition let alone other important multimorbidities. At least some mention of the studies that were excluded from consideration because of these “tight” exclusion criteria could be helpful in interpreting the results.</p>	<p>Databases: We searched those felt to be most relevant to this review with the least amount of duplication. Databases such as Embase provide a low yield of relevant citations for nonpharmacological interventions in particular. It is reassuring to note that citations suggested by reviewers and public commenters were captured by our search and/or did not meet our inclusion criteria.</p> <p>Effect sizes: The magnitude of effects for pain and function were classified with the system used in our previous AHRQ review on noninvasive treatment for low back pain. The methods described in the full report and Appendix H provide additional information. Where a minimal clinically important difference (MCID) was known for a measure this was</p>

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		<p>Page 54 – Why isn't the operational definition of moderate effect sizes more complete with regarding to specific measures of pain and function?</p> <p>Lack of specific information regarding efforts to identify unpublished articles is a serious limitation. Use of a statistic such as Fail Safe N would have been useful to determine whether missing articles could have significantly reduced the observed effects.</p>	<p>considered the basis for "moderate" effect size. Discussion on the interpretation of effect sizes is found in the Applicability section as well. We acknowledge that small effects using this system may not meet standard thresholds for clinically meaningful effect. Our method provided a consistent bench mark to compare results across trials. Interpretation of clinically important differences in mean change for continuous variables is challenging. In some instances, a mean effect size may be small, but may related to a larger effect when the proportion of responders achieving that (or other) level is considered. There is variability across individual patients (and clinicians) regarding what may constitute a clinically important effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in function or pain gained by using a treatment that has relatively low cost with no serious harms may be important.</p> <p>Unpublished literature:Based on hand searches of reference lists, searches of ClinicalTrials.gov, and suggestions</p>

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			from technical experts, we did not find evidence indicating the presence of unpublished literature sufficient to impact conclusions. All citations and suggested reports (published or unpublished) that were brought to our attention during the peer review and public comment processes were evaluated against our inclusion criteria. Given the breadth and complexity of the conditions and interventions in the report, contacting individual investigators would not be feasible. A notice was placed in the Federal Register calling for supplemental evidence, but no responses were received. Statistical evaluation of publication bias was not feasible.
Peer Reviewer #2	Results	<p>I have no problems with the presentation of Results other than those already articulated (e.g., inconsistent clustering of approaches, inconsistent labeling of conditions or sites).</p> <p>Yes, I am seriously concerned that many relevant studies were not included. This concern is based on the limitations already cited.</p>	<p>Thank you for your comments. We do not believe that there is substantial evidence that was missed based on our methods and given the focus and objectives for this review. It is reassuring to note that overall, citations suggested by reviewers and public commenters were captured by our search and/or did not meet our inclusion criteria.</p>
Peer Reviewer #2	Discussion/ Conclusion	<p>The discussion of the major findings is appropriate given the review that was conducted. As noted, other serious limitations of the review methods should be acknowledged. The future research section is limited relative to existing</p>	<p>Thank you for your comments.</p>

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		published reports. The recently published Federal Pain Research Strategy should serve as a framework for this section.	
Peer Reviewer #2	Clarity and Usability	The report is generally well structured and organized, although in reading the Structured Abstract and Evidence Summary, I kept expecting more details in the complete report about the justification and rationale for several decisions such as the decision not to examine studies of heterogeneous samples of chronic pain, decisions regarding lumping versus splitting of types of interventions, databases searched, and strategies for identifying unpublished results, among other key decisions, as well as details about the proportion of results that were obtained from different sources and statistical estimates of the reliability of the findings. Although there is reason to be confident that the review was conducted with integrity, the limitations of the method undermine the value of the report and confidence that it can be appropriately used to inform policy and practice decisions. On the whole, I doubt that it adds useful information or understanding.	Thank you for your perspective. The published protocol provides additional information about the methods used (https://effectivehealthcare.ahrq.gov/topics/nonpharma-treatment-pain/research-protocol). The EPC used methodology prescribed in the AHRQ Methods Guide to provide a methodologically sound report, including quantitative analyses, and methods to mitigate the potential for bias.
Peer Reviewer #3	General	<p>I would like to congratulate the authors for putting together such a comprehensive and thoughtful report! The scope of the systematic review is extremely broad and the authors did an excellent job in focusing on the most important issues. The methodology used for the systematic review and meta-analysis is appropriate. The presentation is clear and easy to follow. And most importantly, the evidence is summarized at a level appropriate for the intended users.</p> <p>I have the following major comments for the authors to consider:</p> <p>(1) Searching: Is there any reason EMBASE is not searched? When relevant systematic reviews were identified, did you use</p>	<p>Thank you for your comments. We have made a number of edits for clarification of the items noted.</p> <p>Databases: We searched those felt to be most relevant to this review and those which were most likely to yield appropriate citations without substantial overlap in citations. Databases such as Embase provide a low yield of relevant citations for nonpharmacological interventions in particular.</p>

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		<p>trials from those reviews or relied on the data and findings from the systematic reviews without conducting additional data extraction and analysis? Please clarify.</p> <p>(2) Outcomes for the review: It would be useful to specify all five elements of the outcomes following the framework described in Zarin NEJM 2011;364:852-60 and Saldanha PlosOne 2014;9(10):e109400. The outcome definition should include the domain (name of the outcome), specific measurement, metric, method of aggregation, and time point. If any measurements, metric, and methods of aggregation are considered/analyzed in the review, please say so explicitly.</p> <p>(3) Please label the x-axis of all forest plots to indicate which is the favored treatment (on each side of the null).</p> <p>(4) It seems that you conducted meta-analyses regardless of the amount of statistical heterogeneity. Some meta-analyses have I-squared value as high as 90%. Could you justify that? When there is substantial amount of heterogeneity, it may not be sensible to pool data, especially when the estimates are not even on the same side of the null. In such cases, please check the data and you may want to refrain from meta-analysis. When continuous outcome is analyzed in its original scale, please change ‘pooled difference’ to ‘pooled mean difference’. Please do a global change for this.</p> <p>(5) Policy implications –Given the limitations of the evidence based, I would be very careful of suggesting broadened access and reimbursement for these interventions. You may consider tuning down the wording.</p>	<p>Primary data from trials included in relevant systematic reviews were abstracted from the primary publication, assessed for risk of bias, and combined with data from other trials as appropriate.</p> <p>Forest plots will be labeled.</p> <p>Despite the variability of measures used for function in particular, we were able to use data in meta-analyses that used standardized mean differences (SMD). We will add a statement to the methods indicating use of SMDs. The full report reports on additional outcomes.</p>

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		<p>(6) Could you comment on the variability in outcome definition and measurement in the included trials? It seems a lot of data are ‘wasted’ because they did not contribute to the meta-analysis. Would you recommend a core outcome set should be developed for these conditions? Patient-centered and patient-reported outcomes should be considered in future trials too.</p> <p>(I downloaded the draft from the peer review website. It’s a PDF with 334 pages in total. The page numbers before refer to the PDF page number on topic right corner of the document, instead of the page number inserted by the authors.)</p> <p>Data Analysis and Synthesis section of the Evidence Summary did not mention the use of SMD. Please add it so that the methods are consistent with the results (presented in the Evidence Summary). SMD - abbreviation not defined in the Evidence Summary (page 21).</p> <p>Page 19 of 334, line 17: Meta-analysis may or may not provide a more precise effect estimates – it depends on the level of heterogeneity. Please re-word this sentence.</p> <p>Page 19 of 334, line 25: Suggest change “control group” “controls” to “comparison group” – make sure the same terminology is used throughout (I noticed that this is a problem with the executive summary, but not the main text.)</p> <p>Page 21 of 334, line 7: change to “slightly greater”</p> <p>Page 21 of 334, line 9: change “no effects on” to “no evidence of effects on” – please do a global change.</p>	

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		<p>Page 21 of 334, lines 38 & 49: change “no differences” to “no evidence of difference” – please do a global change.</p> <p>Pages 39 & 40 of 334, Policy implications –Given the limitations of the evidence based, I would be very careful of suggesting broadened access and reimbursement for these interventions. You may consider tuning down the wording.</p> <p>Page 41 of 334, Research recommendations – Re-order the paragraphs so that each paragraph focuses on one issue; insert topic sentences for all paragraphs.</p> <p>Page 55 of 334, line 23: Add that “CI does not include 1 for binary data”.</p>	
TEP Reviewer #5	General	<p>This systematic review involving Noninvasive, Nonpharmacological Treatment for Chronic Pain aims to consider the broad swath of interventions aimed towards reducing the pain and/or improving the function of patients with various chronic pain conditions. Given the physical, emotional, psychological, and behavioral challenges associated with chronic pain, there has been ever-increasing acknowledgement that optimal treatment for patients with chronic pain will involve interdisciplinary treatment rather than reliance on single monotherapies. The Center for Disease Control’s (2016) assessment that nonpharmacologic therapy is a preferred treatment modality for chronic pain is a formal endorsement of this perspective. Although this appreciation of and desire to integrate non-invasive, non-pharmacological interventions into chronic pain care is laudable, the National Pain Strategy (2015) report highlights the need for understanding the efficacy and value of these modalities. This review addresses that issue directly by providing a systematic</p>	<p>Thank you for your comments. We have made edits to help clarify our approach.</p> <p>Rationale for conditions: Musculoskeletal pain, particularly related to joints and the back, is the most common single type of chronic pain. The report focuses on five of the most common conditions that are primarily related to musculoskeletal pain for which opioid might be prescribed.</p> <p>Interventions: We focused on commonly used interventions that were widely available. We acknowledge that the inclusion of</p>

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		<p>review regarding the evidence of these modalities for sustaining improvements post-intervention for short-term, intermediate-term, and long-term outcomes among patients with a host of chronic pain conditions.</p> <p>Providing a compendium of non-invasive, non-pharmacological interventions containing post-intervention outcomes would alone render this review valuable; however, by adding meta-analytic analyses to provide insight regarding the strength of evidence for these interventions, the authors have provided a guide for clinicians, patients, and decision-makers to the current evidence base.</p> <p>In creating this review, the authors appear to have been challenged with a host of issues that impact the parameters of this review, its methods, results, and its clinical utility. Having engaged key informants and technical experts to inform the study design gives one confidence regarding the methods; however, the rationale and context surrounding these decisions is not always clear and as such, uninformed consumers of this review could make erroneous assumptions that could influence clinical and policy decisions. For example, decisions about which chronic pain populations to include/exclude may have unintentionally left some chronic pain populations out of the report whose inclusion could have expanded the impact and value of the report. Similarly, by not providing insight into the rationale that behind the taxonomy of interventions could lead to assumptions that the categories represent disparate approaches to treating the patient with chronic pain. A different challenge emanated from the reviewers being forced, in most situations (with the exception of the few multidisciplinary treatments available for evaluation), to consider these interventions as monotherapies.</p>	<p>some interventions would have expanded the report scope beyond available resources.</p> <p>We recognize 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.</p> <p>We have reviewed and modified statements related to opioids, given the focus of this review is on noninvasive, nonpharmacological management options.</p>

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		<p>In practice, it is the exception that a care provider would prescribe, or a patient participate, in a noninvasive, nonpharmacologic treatment alone as opposed to being integrated into an interdisciplinary treatment plan. Together, these issues must be included when considering the value of this review.</p> <p>This review, although challenged by certain limitations, is clinically meaningful in many ways. For example, the decision to consider function as a primary outcome is reflective of the actual clinical considerations providers make each day when considering the efficacy of an intervention for chronic pain. Although pain is a vital measure to assess and consider, it is not alone a marker of an intervention's degree of efficacy in chronic pain. Moreover, the inclusion of a vast array of treatment modalities is reflective of the varied proposed nonpharmacologic interventions that patients often query their providers (and/or their mobile device search engines or apps) regarding potential value. The desire to analyze, where possible, the potential influence of age, sex, and psychological co-morbidities reveals an appreciation of how the patient's own physical, psychological, and social history and current situation influences the likelihood that a chronic pain treatment plan will be effective. The authors also demonstrated adherence to methodologic best practice by clearly stating their inclusion and exclusion criteria as well as articulating clear key questions and sub-questions. The authors also provide a cadence for presenting the results that is nearly always easy to follow despite the variation in the number and type of interventions for the various chronic pain conditions. The authors provide a useful summary of key findings that can be leveraged to generate omnichannel clinician and patient-centric media that promotes patient</p>	

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		<p>engagement in chronic pain treatment decision-making. This is followed by a discussion that considers the clinical, policy, and research implications of the current review that can serve as conversations starters among subject matter experts within each of these domains as to how to best ensure effective non-invasive, non-pharmacological treatments are appropriately integrated into care for the chronic pain patient.</p> <p>Overall, this review will serve as a key document that marks the state of the field in the mid-2010's. If optimally leveraged, this review will help propel clinicians, researchers, policy-makers, and funders to ensuring that a decade from now, there is a host of highly effective treatment options available for clinicians and patients to choose when addressing the physical, emotional, psychological, and behavioral challenges associated with chronic pain.</p>	
TEP Reviewer #5	Introduction	The authors provide a clear, concise review of the nature and burden of chronic pain as well as the need for effective non-opioid treatment strategies for chronic pain. The rationale for this review is then provided with a nod towards the National Pain Strategy and Institute of Medicine call for evidence concerning the effectiveness of nonpharmacologic interventions. The scope and key questions provide a strong rationale for why assessing the short-, intermediate-, and long-term effects provide significant value when considering chronic pain treatment.	Thank you for your comments.
TEP Reviewer #5	Methods	Overall, the adherence to methodological best practice was commendable. The process employed and the experts consulted during development of the protocol resulted in a strong study design. The literature search strategy appears adequate. The authors provided clarity regarding the inclusion and exclusion criteria surrounding the Patients, Interventions, Comparators, Outcomes, Timing, Studies, and Settings	<p>Thank you for your comments.</p> <p>Chronic migraine was excluded as it was felt that there were a number of effective treatments for this condition, and it has been the subject of previous AHRQ systematic reviews. In order to</p>

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		<p>(PICOTS). The methods used to abstract/manage data, assess study quality, and analyze data were consistent with known best practice from AHRQ and the Cochrane systems. The decision to categorize effects utilized previously published work by this team for chronic low back pain. The methods provide confidence in the utility of the findings.</p> <p>Within the methods, a few issues give one pause when considering how to best assess this review. The authors note that during the public comment phase and interactions with the Technical Expert Panel there were suggestions that additional chronic pain conditions be included. However, the only rationale provided for why certain conditions were included relative to those excluded was “all were considered beyond the scope and resources for this review”. It would help the audience to know what other chronic pain conditions were actively considered and the rationale for deciding to spend resources on the current conditions and not on those excluded. Although not exhaustive of the conditions excluded, two populations in particular are noteworthy for their exclusion: chronic migraine and chronic orofacial pain. These, especially chronic migraine, represent populations that have similar prevalence to some of the conditions selected and both represent conditions with deleterious impact on function. The primary concern here is that given the pre-eminence of this review, without any acknowledgement or rationale for excluding relatively common conditions, uninformed consumers might consider excluded conditions to be less important and/or not amenable to noninvasive, nonpharmacological treatments.</p> <p>The rationale for creating the taxonomy of interventions is another issue that would benefit from further explanation.</p>	<p>maintain a manageable scope for this report, we needed to limit the number of conditions evaluated. Those chosen were considered to be among the most common.</p> <p>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.</p> <p>Risk of Bias assessment was based on the Cochrane Back and Neck Group criteria, and general characteristics of a good, fair, or poor quality trial are described in the protocol; At least two investigators reviewed risk of bias (ROB) ratings and where there were differences, these were discussed to arrive at a final assessment of study quality; ratings across trials were also reviewed for consistency. In general, studies that included</p>

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		<p>Again, the authors note that during the public comment phase and interactions with the Technical Expert Panel there were suggestions that “there was substantial heterogeneity... within categories of nonpharmacological, noninvasive treatment strategies”. However, the authors do not provide insight regarding the process of determining intervention categorization. For example, there would appear to be a significant overlap between psychological therapies and mindfulness practices. The authors do note that Acceptance and Commitment Therapies were included in psychological therapies while Mindfulness-Based Stress Reduction was not. Although experts within psychological and mindfulness treatment domains might strongly advocate for the unique aspects that differentiate them, both treatment categories appear to involve efforts to modulate autonomic function and alter cognitive/behavioral performance. One suspects that the authors considered this and other potential ways to merge or split the modalities among themselves and with the technical experts; however, the lack of insight regarding this process and the rationale behind these decisions is a missed opportunity to enlighten the audience. The concern here is not the taxonomy itself but rather the questions raised by not providing the rationale.</p> <p>The authors do an excellent job laying out the high-level framework for assessing quality of individual studies. However, the actual methodologies for whether a specific study received a Yes/No/Unclear rating for a category was not made explicitly clear. It may well be that these are fully laid out in the Cochrane references noted. However, given that the quality assessment of these studies is critical to the review, a brief note about how the methods for each was operationalized is at least worthy of a footnote to Appendix E.</p>	<p>intervention/comparators that precluded patient blinding were rated as fair as a starting point. Additional information on the risk of bias tool used has been added to the report appendix.</p> <p>Effect size: This is more fully described in Appendix H and in previous reports for the primary outcomes of pain and function. We did not create any additional specific effect sizes for specific quality of life measures as these were secondary outcomes. The magnitude of effects for pain and function were classified with the system used our previous AHRQ review on noninvasive treatment for low back pain. The methods described in the full report and Appendix H provide additional information. Where an minimal clinically important difference (MCID) was known for a measure this was considered the basis for "moderate" effect size. Discussion on the interpretation of effect sizes is found in the Applicability section as well. We acknowledge that small effects using this system may not meet standard thresholds for clinically meaningful effect. Our method provided a consistent benchmark to compare results across trials.</p>

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		<p>Similarly, among the 15 aspects of a study analyzed, was strict criteria set for determining whether a study was good/fair/poor or was it based on subjective agreement between reviewers?</p> <p>Providing guidance regarding what made an effect small or moderate was helpful. It was interesting to see the large/substantial description in the Appendix but not in the text. Also, there are always questions about relative vs absolute change when assessing intervention effectiveness. Did the authors consider relative change as a potential outcome measure and/or was there discussion about the rationale behind this? There is discussion of quality of life measures in the methods and results; do those measures fit within the “Pain or Function” row in Appendix H when assessing effect? If so, it would be helpful to note this in the text and/or footnotes of Appendix H.</p> <p>Two other relatively minor concerns emerged that can be easily addressed and will enhance the quality of the review. First, the timeframe surrounding the literature search is not clear. It would be helpful to know how far back the search went and on what date the final search was conducted. This will be especially helpful for the consumer who might be surprised that a newly published study was not included but then recognize that the final search preceded publication. Second, the exact parameters for short-, intermediate-, and long-term followup are not clear. This is described two ways within the text. First, there is “short-term followup (1 to 6 months following completion of treatment), intermediate-term followup (6 to 12 months), and long-term followup (≥12 months)”. Second is “short-term (up to 6 months), intermediate-term (6 to 12 months) and long-term (at least 1</p>	<p>Interpretation of clinically important differences in mean change for continuous variables is challenging. In some instances, a mean effect size may be small, but may related to a larger effect when the proportion of responders achieving that (or other) level is considered.</p> <p>There is variability across individual patients regarding what may constitute a clinically important effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in function or pain gained by using a treatment that has relatively low cost with no serious harms may be important.</p> <p>We have clarified the search dates and followup time frames.</p>

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		year)". If follow up is 6 months, is it short or intermediate? If it is 12 months, is it intermediate or long? Also, however it is operationalized, it needs to be consistent in the text.	
TEP Reviewer #5	Results	<p>The authors faced a daunting task of tackling the breadth of noninvasive, nonpharmacological interventions for chronic pain. This placed unique challenges on the authors to determine how to best present the results in a manner that were readily consumable. The authors handled this with great aplomb. The ratio of information in the text relative to the appendices is well-balanced. The authors have provided clear, concise summaries of each study as well as useful tables and appendices. The messages for each modality were clear. The summary tables (Tables 47-61) were particularly effective at delivering easy to consume findings.</p> <p>Although the authors have conducted an extremely thorough search of interventions, there appear to have been a few that may have been missed by the authors. Below are a list of specific articles that did not appear to be in the excluded reference section.</p> <ul style="list-style-type: none">- Huguet A, McGrath PJ, Stinson J, et al. Efficacy of psychological treatment for headaches: an overview of systematic reviews and analysis of potential modifiers of treatment efficacy. Clinical Journal of Pain. 2014 Apr;30(4):353-69.- Lami MJ, Martinez MP, Sanchez AI. Systematic review of psychological treatment in fibromyalgia. Current Pain & Headache Reports. 2013 Jul;17(7):345- Minen MT, Torous J, Raynowska J, et al. Electronic behavioral interventions for headache: a systematic review. Journal of	<p>Thank you for your comments.</p> <p>We have assessed each of the citations listed for applicability to our report and reference lists of systematic reviews listed. None of the citations listed met our inclusion criteria. Are they included in the appendix of excluded studies? If yes, please say so.</p>

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		<p>Headache & Pain. 2016;17:51.</p> <p>- Moraska AF, Stenerson L, Butryn N, et al. Myofascial trigger point-focused head and neck massage for recurrent tension-type headache: a randomized, placebo-controlled clinical trial. Clinical Journal of Pain. 2015 Feb;31(2):159-68</p> <p>- Slavin-Spenny O, Lumley MA, Thakur ER, et al. Effects of anger awareness and expression training versus relaxation training on headaches: a randomized trial. Annals of Behavioral Medicine. 2013 Oct;46(2):181-92.</p> <p>- Verhagen AP, Damen L, Berger MY, et al. Behavioral treatments of chronic tension-type headache in adults: are they beneficial? CNS Neuroscience & Therapeutics. 2009;15(2):183-205.</p> <p>Moreover, the February-March 2014 issue of the American Psychologist (volume 69, number 2) is dedicated to Chronic Pain treatment and would be worth the investigators considering (if they have not previously) for identifying other potential studies.</p>	
TEP Reviewer #5	Discussion/ Conclusion	<p>The authors were able to summarize the findings and challenges that exist within the current literature. They accurately state that there is consistent evidence for small to moderate effects of some of the modalities. Their summary that there are few studies available for many conditions among the various modalities is spot on as was their assessment that many of those also struggle to provide long-term follow up. In general, the authors accurately identify a number of gaps in the current literature that limit the ability for clinicians, patients, and decision makers to know how to fully ascertain which noninvasive, nonpharmacological</p>	Thank you for your comments.

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		<p>interventions are best for chronic pain patients. In particular, their statement that “Included trials provided limited information on diagnostic criteria, symptom duration, clinical characteristics, comorbid conditions, and concomitant treatments” is spot on in summarizing the state of the field at this time.</p> <p>The discussion of how certain modalities share characteristics (“active” vs “passive”) helped address the limitation of transparency about categorization noted in the methods section. However, expanding this to discuss this issue in more detail or providing the non-expert with more insight would have provided even more value.</p> <p>Overall, the discussion was outstanding and will provide audience of all types with insight that will be beneficial for years to come.</p>	
TEP Reviewer #5	Clarity and Usability	<p>In general, the report was very well structured, organized, and summarized. The authors clearly helped lay out a vision for what clinicians, researchers, policy makers, and funders can do to help move the field forward in the next 5-7 years.</p> <p>The issues that limit the overall value of the review primarily surround a lack of clarity regarding some of the decisions made regarding certain PICOTS aspects (failure to provide a rationale for population inclusion/exclusion, intervention taxonomy) and specific methods for determining the quality of the study (again a lack of insight regarding the specifics of the process). Besides the other minor technical issues noted within the methods review, the authors would benefit from reviewing the in text reference numbers with the actual references with that number. There were multiple instances where the reference referred to in the text did not match the</p>	<p>Thank you for your comments.</p> <p>The protocol does provide rationale for various decisions and evaluation of study/evidence quality . There is no standard way for categorizing interventions; we aimed to include commonly used interventions that might be available to a broad U.S. population</p> <p>We have checked the references.</p>

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		<p>reference itself. Otherwise, this was a superior review.</p> <p>There are a number of value added components to this review. The breadth of the review, utilizing strong methods for analysis, and a well-crafted discussion are superior and make this a worthy addition to the literature and will serve as a strong reference moving forward.</p>	
Peer Reviewer #4	General	<p>The report is comprehensive and focused on the most common conditions for adults with chronic pain as well as fibromyalgia. Conceptually, the three part format addresses a variety of comparison groups that make some sense. But, there are challenges with all of them. Part A includes a wide variety of controls: sham, attention control would likely have smaller effects than no treatment/waitlist and usual care might be somewhere in the middle. (cf, MacPherson et al. Influence of Control Group on Effect Size in Trials of Acupuncture for Chronic Pain: A secondary Analysis of an Individual Patient Data meta-Analysis. PLoS ONE 9(4): e93739. doi:10.1371/journal.pone.0093739). Although I understand the rationale for the Key Question B comparing a specific non-pharmacological therapy against pharmacological therapy, these studies are quite rare and in practice, many patients seem to use pharmacological therapies and possibly, the non-pharm treatments as adjunctive, so this is a bit forced – although the value for some conditions and populations (e.g., older adults) could be important. Re Key Question C, the comparison with exercise is reasonable for some conditions (i.e., back pain, neck pain, some osteoarthritis sites including hip and knee OA and fibromyalgia). I don't think it makes sense for all osteoarthritis sites (e.g., hand or arm – unless the type of exercise is very specific) or for headaches. Later the authors describe a need to do this analysis against a “common comparator” – such as exercise, which unfortunately is so</p>	<p>Thank you for your comments.</p> <p>We recognize 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. Evaluation of "adjunct" treatments was beyond the scope of this report as described in the protocol. 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.</p> <p>Biofeedback was the common comparator for headache.</p> <p>The full report and evidence summary provide additional information regarding interventions for which there was no evidence. We have also edited to facilitate consistent use of</p>

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		<p>variable within and across conditions as to make such an idea challenging to interpret clearly, even when the comparison intervention is superior to exercise. Was, for example, the exercise chosen to be likely minimally effective versus a ‘bona-fide’ comparative effectiveness trial between two well thought out interventions. Given the relatively small number of trials, these questions are probably “as good as it makes sense” for comparator groups.</p> <p>Moreover, for some conditions, where a treatment package is considered standard care (e.g., exercise plus NSAIDs for knee OA in the UK), it’s reasonable to ask whether a new non-pharmacological therapy (e.g, acupuncture) adds something. Yet, you have absolutely no provisions (so far as I can tell) for a very clinically relevant comparison like this. (cf : Foster NE1, Thomas E, Barlas P, Hill JC, Young J, Mason E, Hay EM. Acupuncture as an adjunct to exercise based physiotherapy for osteoarthritis of the knee: randomised controlled trial. BMJ. 2007 Sep 1;335(7617):436. Epub 2007 Aug 15.).</p> <p>The target populations are quite broad, given the nature of studies of “chronic pain”, where the original and other co-morbidities may be not well characterized.</p> <p>Structured Abstract: There is an overwhelming amount of data to be summarized, given five pain conditions; two primary outcomes (function and pain) at short-term, intermediate term and long term follow-up; multiple therapies (e.g., probably 10 different therapies for chronic low back pain-CLBP) and several types of comparison groups. In addition, there are three effect sizes (small, moderate, large – though no high effect sizes were seen) and then there are low and moderate “strength of evidence”. Not all therapies were</p>	<p>"small" , "slight" for describing effect sizes, have corrected the double listing of "acupuncuncture" and clarified follow-up time frames.</p> <p>It was not the case that a specific effect size observed short term necessarily continued into the intermediate term. We've attempted to highlight what effects persisted. The summary tables in the executive summary and in the full report show the magnitude of effect at various time frames. SOE is not necessarily the same at all time frames as it is also impacted by the quality of studies available at a given time point for the specific outcome, estimate precision and consistency, as described in the protocol.</p> <p>Usual care was the most common comparator for included trials; we've edited for clarity to describe what the comparators are.</p> <p>We</p>



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		<p>tested for all pain conditions or time points or with all comparison groups. So, as it is written, lack of data on some comparisons cannot distinguish between effects that return to normal and comparisons that were never made.</p> <p>The scope of the review makes it tough for the reader to digest the findings, even when it is written fairly clearly, especially for cLBP and to a lesser extent, for fibromyalgia where there are lots more therapies tested. I would recommend that the authors use consistent terminology to describe the effect sizes (is “slightly” or “slightly improved” a small effect size? – cf chronic low back pain section)) and when talking about multiple time points (effects on function continued into the intermediate term for yoga, ... (should we assume that they continued to be moderate at the intermediate term). I believe that the best way to clearly summarize these results would be to create a table. The authors should be very careful to make sure they describe effects at all point (for example, for cLBP, we are told that improvements in pain persisted into the intermediate for some therapies (e.g., exercise, massage and yoga) at a moderate effect - nothing was said about short term – were they all moderate effects. Would we assume the SOE would be the same for those therapies at short term? Comparison groups are not mentioned in all cases. I am not sure what that implies (e.g., only usual care, usual care and sham are equivalent?). Some convention is needed for cLBP at least.</p> <p>Evidence Summary: Overall, this is quite clear, especially with the tables that summarize the evidence across the conditions and by Key questions. Although I understand the rationale for the Key Questions comparing a specific non-pharmacological therapy against pharmacological therapy, these studies are</p>	

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		<p>quite rare and in practice, most patients seem to use pharmacological therapies and possibly, the non-pharm treatments as adjunctive, so this is a bit forced – although it's value for some conditions and populations (e.g., older adults) could be important.</p> <p>On page ES-2, acupuncture is mentioned twice – lines 33 and 36. I suspect this is a mistake.</p> <p>On page ES-4, the time periods (short-term: up to 6 months; intermediate term: 6 to 12 months; long term: at least a year) are defined. Since 6 and 12 month follow-up periods are common for spine pain, it's important to make sure that all 6 month follow-ups are included in the intermediate time period. I am unclear where the 12 month period goes, but it needs to be unambiguous.</p>	
Peer Reviewer #4	Introduction	<p>The introduction is OK, but could be slightly reworked to make some points more clear:</p> <ol style="list-style-type: none">1) emphasis on longer-term (at least 1 month post-treatment outcomes) and the rationale for that2) better graphics to drive home the 5 pain conditions; the various therapies and the various control groups3) Make the analytic frame work a more prominent part of the introduction - now, it looks like an afterthought. In particular the outcomes are spelled out very clearly here, but not so clearly anyplace else in the document. That needs to be consistent throughout.	<p>Thank you for your comments. We have made edits for improved clarity on these points.</p>
Peer Reviewer #4	Methods	<p>The methods are mostly well written and clear. The inclusion and exclusion criteria are fairly well defined. They are reasonable for pain type, but a reference for the chronic tension headache would be helpful. Also for chronic back pain, the new definition from NIH requires at least 90 days of pain over 180 days, so this is a little bit different. This is more a</p>	<p>Thank you for your comments.</p> <p>The chronic pain definition used is consistent with what is reported in the included literature; newer definitions will hopefully be part of newer studies.</p>

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		<p>note for the future than for this project, since it was recently recommended as a requirement for future studies, none of which could have been completed by the time of this review.</p> <p>I do not think it is reasonable to include systematic reviews as part of this review because there are likely multiple ones, with overlapping trials and that would lead to difficulties in correctly characterizing the outcomes. Better to use good quality reviews to facilitate the review of individual trials.</p> <p>The authors state on page 265, “Many reviews have addressed the effects of interventions for chronic pain management during or immediately following treatments. We focused on evaluating the sustainability of effects for at least 1 month post-intervention.” This should have been noted prominently in the abstract, executive summary and methods. Instead, I had to actually go to the description of the studies to figure it out. Even, then it was not clear that the outcomes needed to be at least 1 month post intervention. This fact alone would explain why many otherwise relevant studies were NOT included. This is an easy fix, but a rather big lack of clarity.</p> <p>Re the outcome measures, clearly the most data are available on pain and function, which are but two of the domains recommended by IMMPACT. I think the authors should clearly note somewhere the focus on pain and function. Somehow tie IMMPACT to the outcome measures proposed in the introduction and provide justification for them via key references.</p> <p>Also needed is a clearer reference to the appendices of excluded studies as well as how data from three arm trials</p>	<p>Full strength of evidence evaluation, including reasons for down grade is provided in the Appendices.</p> <p>Systematic reviews were not used as the basis for the results or conclusions of this report. The bibliographies of systematic reviews were evaluated for includable trials; primary trials meeting the inclusion criteria were abstracted and critically appraised individually.</p> <p>References to IMMPACT and ACTION have been made in the revised discussion regarding future study needs. Included studies did not generally report outcomes based on these suggestion guidelines for outcomes reporting/evaluation.</p>

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		<p>were dealt with in the analyses.</p> <p>Regarding assessing the effect sizes (page xx), line 32, please indicate what the mean difference needs to be for a moderate effect, and also what the SMD should be. This section should be analogous to the small/slight effect.</p> <p>Please provide more evidence on what the difference between low and moderate strength of evidence. Even an example or two – perhaps in an appendix – would be helpful because otherwise, it’s not easy to understand this.</p> <p>I think it would be helpful to note that some therapies could overlap (e.g., manual therapy could include spinal or joint manipulation/mobilization and massage).</p> <p>Other aspects of the methods are well justified and reasonable. The statistics and data analysis section is well-justified on the general level and sensitivity analyses seem reasonable. (I am not a biostatistician).</p>	
Peer Reviewer #4	Results	<p>Overall, the results are appropriately described. I do have concerns that potentially important studies have been characterized inaccurately or omitted completely. For example, in reading the assessment of our own large number of clinical trials on numerous non-pharmacological treatments for cLBP, I note some inaccurate information regarding our large acupuncture trial and the supposedly “unclear” method of randomization, which was clearly described in the trial protocol and was quite rigorous to meet CONSORT recommendations (Cherkin DC, Sherman KJ, Hogeboom CJ, Erro JH, Barlow WE, Deyo RA, Avins AL. Efficacy of acupuncture for chronic low back pain: protocol for a randomized controlled trial [ClinicalTrials.gov NCT00065585]).</p>	<p>Thank you for your comments.</p> <p>We have now included the Cherkin 2011 study and re-evaluated the risk of bias for Cherkin 2008. For any given outcome for specific comparisons vs. sham, the blinding of patients was considered to have been done and this is reflected in the final strength of evidence for the appropriate outcomes.</p> <p>We have reviewed the suggested</p>

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		<p>Trials. 2008; 9: 10. PMID: PMC2774684.) Also, the study was described as “non-blinded” to patients, which was only true for the usual care comparison group and not for the “simulated acupuncture” comparison group or the two treatment groups. Moreover, among those three groups, participants had similar ratings about the acupuncture they received. At least one other acupuncture trial, which included two control groups, was rated differently because of the capacity to mask in the sham arm of that trial.</p> <p>One of our massage studies, a major trial published in Annals of Internal Medicine in 2011, (Cherkin DC, Sherman KJ, Kahn J, Wellman R, Cook AJ, Johnson E, Erro J, Delaney K, Deyo RA. A Comparison of the Effects of Two Types of Massage on Chronic Low Back Pain: A Randomized, Controlled Trial. Ann Intern Med 2011; 155:1-9. PMID:PMC3570565) was not even referenced at all – either it should have been included or appeared in the list of excluded trials, but I could find it in neither. Such omissions with our trials, which have been among the largest US trials, always lead me to wonder about accurate extraction of data from other, less prominent trials. My guess is that there are other errors in the search and data extraction process, but I am not as intimately familiar with all of the trials as I am with our own.</p> <p>To overcome this challenge, I recommend that reviewers who are expert in each of the pain conditions and/or the major therapies be consulted in addition to the regular reviewers.</p> <p>Re acupuncture, combining sham and usual care controls is efficient, but more detailed work by the Acupuncture Trialist Collaboration shows some differences in effect sizes between these types of controls. (MacPherson H, Vertosick E, Lewith G,</p>	<p>publications to assess whether any trials meeting our inclusion criteria were missed; The MacPherson analysis does not meet our inclusion criteria and review of their citations did not reveal additional trials meeting our inclusion criteria with the exception of Berman 2004 which has been included in the final report. Differences between our results and theirs is likely due to differences in methodology.</p> <p>The TEP and peer reviewers included persons with expertise in a variety of conditions of interventions.</p> <p>To evaluate the impact of comparator type, we did sensitivity analyses to separately look at comparisons vs. sham and usual care. The result of these sensitivity analyses are included in the full report.</p> <p>Table 43 lists the psychological therapies for headache by study and the summary tables in the draft report (Tables 60 and 61) provide a summary of psychological therapies for headache. All results were considered insufficient, so the information was not carried forward to the executive summary table to streamline the results in the ES. The summary table in</p>

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		<p>Linde K, Sherman KJ, Witt CM, Vickers AJ; Acupuncture Trialists' Collaboration. Influence of control group on effect size in trials of acupuncture for chronic pain: a secondary analysis of an individual patient data meta-analysis. PLoS One. 2014 Apr 4;9(4):e93739. doi: 10.1371/journal.pone.0093739)</p> <p>Given the way they combined data, it's not likely possible to take this apart for each condition and outcome, but the effect sizes are impacted by the relative proportion of sham (smaller effects) and usual care/wait list (larger effects) controls.</p> <p>To assist in ensuring that key acupuncture trials are not missed, please review: MacPherson et al. The persistence of the effects of acupuncture after a course of treatment: a meta-analysis of patients with chronic pain. Pain 2017 May;158(5):784-793.</p> <p>In some instances, a self-care book was considered an "attention control". I believe that the term in behavioral medicine is intended to be restricted to studies where people get an in-person "attentional" intervention or some other intervention that mirrors the attention in the verum group.</p> <p>The summary tables are extremely helpful, but incomplete (for example) – the head ache summary misses psychological therapies (seeTable 43</p>	<p>the evidence summary (Table M in the draft report) will now include information psychological therapies (CBT plus relaxation), indicating the evidence is insufficient .</p>
Peer Reviewer #4	Discussion/ Conclusion	<p>I thought the discussion section was quite good and addressed, albeit briefly, many of the key challenges in interpreting these findings and translating them to primary care. I especially liked the section on findings in relationship to what is already known. However, this would have been a place to reference findings from the Acupuncture Trialist Collaboration, which uses individual patient-level data for meta-analysis for multiple types of chronic pain. While some</p>	<p>Thank you for your comments. We reviewed the Acupuncture Trialists Collaboration IPD publications. The analyses did not meet our inclusion criteria. We did review the bibliography for trials not captured for the draft report. Berman 2004 was the only study meeting our criteria and has</p>

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		<p>of the analyses lump all types of pain, others are focused on individual pain types. The authors could have discussed how having access to such data might have changed (or not) their estimates of effect size.</p> <p>A little more explicit note of the lack of data on all of the IMMPACT recommended domains (Pain, physical function, emotional state, ratings of improvement and satisfaction with treatment, adverse events and adherence to the treatment regimen) would be valuable.</p> <p>The authors rightly note the challenge of masking patients to treatment group in non-pharmacological studies. Rather than stop there, they could have talked about issues of adherence in trials of exercise and mind-body therapies and the possibility that some of these therapies might need to continue even after formal instruction is over. This is a key issue for the successful adoption of such therapies and bears noting in a report designed to undergird clinical practice recommendations.</p> <p>I thought that the research section was a little weak, mainly stating the problems, with some easy to include fixes in outcome measures and additions of harms. But, the primary challenge is that I don't see a compelling case on the need for more data. Nothing stands out prominently in the findings - the large number of possible treatment with small effects is much too large to mount better trials on all of them. I don't see a nice recommendation of how to prioritize these therapies for further study.</p>	<p>been added to the final report. We have added a sentence to the limitations indicating that our results are based on study-level data versus individual patient-level data and that our overall conclusions regarding some benefit are similar for some conditions.</p> <p>In the discussion we have noted that adherence was not widely reported in included trials and that some interventions would likely be used on continuing basis to optimize effectiveness.</p> <p>We have suggested that future research include more attention to IMMPACT recommendations. We agree that there are numerous gaps in evidence and it is difficult to prioritize based on these findings; additional work on this is needed.</p>
Peer Reviewer #4	Clarity and Usability	<p>I think the authors have overall done an excellent job in structuring the report (with the exceptions noted above). Some of the methodological points of inclusion/exclusion need</p>	<p>Thank you for your comments and suggestions.</p>

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		<p>to be more explicit (e.g., follow-up time points, some definitions of a few therapies, any exclusions based on the length of treatment (e.g., is one 10 minute acupuncture treatment ok if they had a long term follow-up?).</p> <p>The limitations of the data make applicability to care sometimes hard to determine, but overall, the authors have done a great job in mentioning those. I think the conclusions are definitely policy relevant.</p> <p>One thing the authors could do to improve the data on harms is to look for non-clinical trials. For example, there are numerous studies on the safety of acupuncture using prospective surveys (e.g., MacPherson H, et al. The York acupuncture safety study: prospective survey of 34,000 treatments by traditional acupuncturists. Br Med J. 2001;323:486-487; Melchart D, et al. Prospective investigation of adverse effects of acupuncture in 97733 patients. Arch Intern Med. 2004;164:104-105.; White A, et al. Adverse events following acupuncture: prospective survey of 32,000 consultations with doctors and physiotherapists. Br Med J. 2001;323:485-486; Witt CM, et al. Safety of acupuncture: results of a prospective observational study with 229, 230 patients and introduction of a medical information and consent form. Forsch Komplementarmed. 2009;16:91-97.) that could give evidence for acupuncture's relative safety. Other data on exercise could be garnered.</p> <p>While the draft is well organized, the sheer volume of material is mind - boggling. The summary tables are essential to digesting the findings, and even then, are a lot to take in. I wonder if color can be added to make it clearer which time points and outcomes have data and how good the data are.</p>	<p>We have made edits to the report to clarify the points noted.</p> <p>While we recognize the value of non-randomized studies for assessment of harms, the inclusion of such studies was beyond the scope of this review.</p>

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		I think these findings primarily underscore our understanding of treatments for spine pain, which I am most familiar with. The review of treatments for knee OA and fibromyalgia also seems to cover a fairly comprehensive grasp of the literature. I think they serve to reinforce what I've taken away from various other studies of chronic pain and are helpful, but not sure how new they are. What seems to be new is the compilation in one place.	
Peer Reviewer #5	General	<p>Excellent and timely. Will provide significant support for policy and guidelines.</p> <p>Overall comment regarding effect sizes and clinically meaningful improvement: It is difficult for clinicians without an active statistic/research experience to interpret where and whether low, moderate, or high effect sizes correspond to varying degrees of clinically meaningful improvement (CMI). It was not clearly stated at the outset that so few studies were able to meet the CMI criteria that it was rarely mentioned. The challenges of determining CMI was finally addressed in the Applicability section, but not until page 309-310. Consider discussion about this limitation early on in the report, or adding either a separate summary table in the executive summary, or more prominently identify wherever (and describe how) an analysis identifies clinically meaningful outcomes. It may be useful for the reported small effect sizes to also be specified as not having met CMI. For instance, this was footnoted on page 264 (Table 40, line 22-30), but not on page 269 (Table 41). There was a useful mention in KP narrative page 271 (line 41-50), but not in other sections. Summary Tables A-M, (and later Discussion Tables 47-61) are clear and concisely meet stated goals to aid guideline development and identify research gaps; but none mention</p>	<p>Thank you for your comments. We have made some edits accordingly.</p> <p>The magnitude of effects for pain and function were classified with the system used our previous AHRQ review and are described in the Methods section. The discussion contains additional information regarding interpretation of effect sizes. Where an minimal clinically important difference (MCID) was known for a measure this was considered the basis for "moderate" effect size. We acknowledge that small effects using this system may not meet standard thresholds for clinically meaningful effect. Our method provided a consistent benchmark to compare results across trials. Interpretation of clinically important differences in mean change for continuous variables is challenging. In some instances, a mean effect size may be small, but</p>

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		<p>CMI. Similarly, in Key Question(s) section, SMDs are provided, but not whether any of these values are clinically meaningful.</p> <p>This important and likely to be oft quoted report could also then provide support for clinical practice decision-making and/or for guideline development, both highly relevant goals aligning with the non-opioid (and opioid) pharmacological treatments recommended in the CDC and other recently released opioid practice guidelines. The question, “If not opioids, then what?” could be better implemented were positive effect size consistently noted as meeting clinically meaningful improvement.</p> <p>Specific comments: (page 19) Line: 6-7 “Stakeholders” emphasized improved function > pain relief. Which stakeholders were identified: pain experts (presumed) or patients? Line 19-20: Quality of life was not included in the results summary page (7-8) (page 38) More of a “Limitations” than “Applicability”? Consider section title change, or combine with “Limitations of Evidence Base...” (Page 40, Line 30 and following) Line 6-7: Important to seek benefits duration after treatment compared with the continuing “non-curative” relief (if any) from medications Line 37-39: Important to identify that populations and methods studied are not representative of real-world patients. Also, gender and other differential efficacies in study populations were important to note. (pages 39-40) Very important discussion, pleased to see policy discussion</p>	<p>may related to a larger effect when the proportion of responders achieving that (or other) level is considered. There is variability across individual patients regarding what may constitute a clinically important effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in function or pain gained by using a treatment that has relatively low cost with no serious harms may be important.</p> <p>Stakeholders include those who formally provided input as Key Informants (which included patient representation) and/or Technical Experts who were from a variety of background. Individuals who served in these capacities are listed in the final report.</p> <p>Quality of life measures were secondary outcomes and thus not part of the executive summary; the executive summary has been edited to reflect this. Availalbe evidence for these outcomes is in the full report.</p> <p>Appendix H is in the appendix to the</p>

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		and guideline support (page 41) (page 44) Lines 10-16: Seems redundant, since reiterates with few differences the Evidence Summary of page 16 (page 50) Line 42-3: PICOT table footnotes; consider revising: physical and biopsychosocial (since physical is the “bio” dimension); Important that clinicians are advising patients on which exercise is best, note that the difference between exercise form appears not to be important. This is highlighted on page 62, line 39. Consider that this be noted on page 50, too. (Page 52) Line 17: Who are the “stakeholders”? See above re page 19 (Page 54) Line 31: For function: as a mean difference of ...? Line 35: “No appendix H” appears in the document	report, which was available to reviewers upon request to the AHRQ Scientific Resource Center. Due to the length, the report appendix is not automatically included in the PDF review file.
Peer Reviewer #5	Introduction	Please see attached file.	Comments from the attached PDF are transcribed into the spreadsheet under "General Comments", row 54.
Peer Reviewer #5	Methods	Please see attached file.	Comments from the attached PDF are transcribed into the spreadsheet under "General Comments", row 54.
Peer Reviewer #5	Results	Please see attached file.	Comments from the attached PDF are transcribed into the spreadsheet under "General Comments", row 54.
Peer Reviewer #5	Discussion/ Conclusion	Please see attached file.	Comments from the attached PDF are transcribed into the spreadsheet under "General Comments", row 54.
Peer Reviewer #5	Clarity and Usability	Please see attached file.	Comments from the attached PDF are transcribed into the spreadsheet under "General Comments", row 54.

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Public Commenter #1 [Anonymous]	General	<p>This war on “opioids” is actually a war on chronic incurable diseases. A war on chronic pain disease patients who benefit from opioid medications. Medications that enable millions of Americans relief of chronic debilitating pain associated with these diseases.</p> <p>The fiction, widespread hysteria and distorted truths about this “opioid epidemic”, is killing legitimate chronic pain disease patients who use their medications responsibly. We are patients.</p> <p>100 million Americans have one or more chronic incurable pain Diseases. As the CDC, DEA, FDA, Medicaid and Medicare, and numerous other government agencies, are blaming Doctors for the over prescribing of opioid medication.</p> <p>NOBODY, is looking at or reading the statistics from chronic pain disease patients. How about NOT addressing these drugs as dangerous and addictive. When all else fails: physical therapy, exercise, over the counter medications and numerous injections etc, we chronic pain disease patients, are left with one option to help us cope, opioid pain medication. Lets address this medication as lifesaving and medically necessary for the million of Americans with chronic diseases. Chronic pain is a disease. Chronic pain disease patients are now the epidemic. The addiction rate of chronic pain disease patients is .02-.6 %. We do not misuse or abuse our medications.</p> <p>No other disease medication is scrutinized. We, as patients, are being denied, dismissed, overlooked and discriminated against, by our physicians, due to all the scrutiny associated with treating chronic pain disease with opioid medications.</p> <p>Our Dr's are afraid to treat us humanely, ethically and adequately. We have a disease that medication is readily accessible and beneficial to us and we are being denied. We, pain patients, are being discriminated against, due to people who abuse illegal heroin and illegal fentanyl. This is a direct</p>	<p>Thank you for your comments. We appreciate the many challenges faced by patients with chronic pain and their families and health care providers.</p>

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		<p>hunt for Doctors who prescribe life saving medication, for pain disease patients, that benefit from them. We have our privacy invaded, we no longer are able to have doctor/patient confidentiality. We now have insurance agencies, pharmacists, and other government agencies in our physicians offices, monitoring, prosecuting and policing our physicians. Though the statistics show a reduction in opioid medications distributed, due to the CDC guidelines, death rates of overdoses from illegal opioids is rising.</p> <p>The specific causes of deaths also needs to be closely investigated. The opioid in the person's system needs to be specified. Was it an illegal opioid, was it opioid medication specifically for that person, was there other drugs or alcohol involved? These statistics need to come out. These Government agencies do not want that information out, due to the fact that this "opioid epidemic", would then be debunked.</p> <p>Let's put the shoe on the other foot. Restricting or taking away our medications is like FORCING people who do not want this medication to take it. One day those against these medications will need them but they will be denied.</p> <p>We have a chronic disease. We want to be able to take care of our homes, our children, ourselves, as much as possible. Without access to these life saving medications, we are unable to do so. We want to live, not just exist in pain 24/7.</p> <p>We need the government agencies to look at the real statistics, not the hand picked. These agencies are not physicians. They are trying to doctor us, patients, without a medical license. They are also trying to police our physicians. This is a war on a disease, medications, physicians and patients.</p> <p>We, chronic pain disease patients, need help. All the</p>	

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		<p>headlines, topics and stories on how opioids are bad and how people are abusing, misusing, overdosing, becoming addicted or dying from them. We need to look at the good they do and how they help our disease of chronic pain and the million of Americans who use them for some relief.</p> <p>The government needs to put the focus on illegal drugs coming into, being manufactured and distributed in this country, illegal fentanyl, illegal heroin, methamphetamine, cocaine and all other ILLEGAL DRUGS. Not the legally prescribed and medically necessary medications we patients need. We chronic pain disease patients need help, but we are helpless due to the government and government agencies. There is stigma, scrutiny and discrimination against us due to a category of medications we desperately need and benefit from, opioid medications.</p> <p>WE ARE PATIENTS NOT ADDICTS! !</p>	
Public Commenter #2 [Rachel Couban McMaster University]	Appendix	<p>See attached document for search strategy.</p> <p>Hi, thanks for the opportunity to comment. I have 2 comments about the search strategy, first about the search terms used for the P section of the PICO question, and second about the search terms used to limit the set of results to the study designs of interest.</p> <p>My comment about the search terms used for the concept of chronic low-back pain portion of the patient population or “P” concept (lines 1-3 of the search) is that the set of terms does not include any free-text synonyms for the condition, such as chronic adj4 pain.mp or sciatica. This means you are going to miss certain trials that may be eligible for the review if they are not indexed with the included MeSH terms. For example, these three RCTs are not captured by the strategy: PubMed PMID: 27550953, PubMed PMID: 28328324, PubMed PMID: 27333534 (citations below, and I have uploaded a doc showing</p>	<p>Thank you for your insights and comments.</p> <p>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. Our strategy used both MeSH terms and key words that we hoped would maximize precision. While text terms such as those suggested increase the total number of retrieved citations, the relevance of the additional citations is likely low. While we do not have a published reference for the validity of</p>

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		<p>the strategy I used to test this concept in MEDLINE.) Maybe these trials are not eligible for the review, but when I have searched for the concept of chronic low back pain, I have been asked to use broader terms by my review teams, with the idea that eligibility would better be determined through title and abstract screening. Given that the same strategy is also used in Cochrane Central register of controlled trials, any EMBASE-only records will not be captured by the search (trials added to Central from other databases or from Cochrane review groups are not indexed using MeSH, as far as I know.) This will limit your set of results to only those papers in MEDLINE that are indexed with the specific MeSH terms.</p> <p>My comment about the search terms used to limit the set of results to the study designs of interest is that the approach used is not consistent with the approach described in the methods section, wherein it states that “The methods for this systematic review follow the Agency for Healthcare Research & Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.” In particular, it appears that the “Publication Type” limiter provided by Ovid has been applied to the set for this domain, whereas the AHRQ Methods Guide specifies that “we recommend the use of any validated hedges (filters)” for concepts such as randomized controlled trial. I have not tested the approach here, but last week I tested a search strategy using the Publication Type limits in PubMed and found that this approach was inadequate to search comprehensively for the study design concept. It may be that the approach is valid, but I would expect to see a demonstration of this at the next session of the Medical Library Association before I would be prepared to let it pass without comment.</p> <p>Low back pain studies not captured by strategy:</p>	<p>the filters used in the OVID interface, here is what Ovid says about their filters: “Filters are tried and tested search strategies that help you narrow down your search and that enhance the precision of your results. Filters are used typically to identify articles containing a particular piece of evidence—for example, randomized control trials (rcts) or systematic reviews—types of clinical query (e.g., diagnosis, etiology, therapy), or results for a specific population or specialty (e.g., pediatrics).” We have used these filters with numerous previous reviews and have rarely missed important, relevant citations. It is reassuring to note that overall, citations suggested by expert reviewers and public commenters were captured by our search and/or did not meet our inclusion criteria.</p> <p>Regarding the 3 citations they can all be excluded at title/abstract (and likely would not have been picked up in the search) for the following reasons: Manning 2017: radiculopathy is an excluded condition Mathieson 2017: pharmacological therapies are not an intervention of interest; they are only of interest as a comparison to one of our included</p>

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		<p>Manning DC, Gimbel J, Wertz R, Rauck R, Cooper A, Zeldis JB, Levinsky DM. A Phase II Randomized, Double-Blind, Placebo-Controlled Safety and Efficacy Study of Lenalidomide in Lumbar Radicular Pain with a Long-Term Open-Label Extension Phase. <i>Pain Med</i>. 2017 Mar 1;18(3):477-487. doi: 10.1093/pm/pnw212. PubMed PMID: 27550953.</p> <p>Mathieson S, Maher CG, McLachlan AJ, Latimer J, Koes BW, Hancock MJ, Harris I, Day RO, Billot L, Pik J, Jan S, Lin CC. Trial of Pregabalin for Acute and Chronic Sciatica. <i>N Engl J Med</i>. 2017 Mar 23;376(12):1111-1120. doi: 10.1056/NEJMoa1614292. PubMed PMID: 28328324.</p> <p>Wang G, Gao Q, Li J, Tian Y, Hou J. Impact of Needle Diameter on Long-Term Dry Needling Treatment of Chronic Lumbar Myofascial Pain Syndrome. <i>Am J Phys Med Rehabil</i>. 2016 Jul;95(7):483-94. doi: 0.1097/PHM.0000000000000401. PubMed PMID: 27333534; PubMed Central PMCID: PMC4902326.</p>	<p>nonpharmacological interventions (in this case, pregabalin is compared with placebo). Wang 2016: dry needling is an excluded intervention.</p>
Public Commenter #3 [Celia Bucci, LMT]	Evidence Summary	<p>The report notes "...focusing on whether improvements are seen for at least one month post-intervention." While a worthwhile marker, many suffering from chronic pain require ongoing treatment. One cannot take one or two antibiotic pills and expect to be symptom free. And while a single non-invasive treatment may provide improvements a month out for an injury or post-surgery pain, the focus for people suffering from chronic pain should be long term. We need to study their improvements over time when they continue receiving treatment regularly - just as they would take opioids regularly.</p>	<p>We acknowledge that those with chronic pain may use various interventions on an ongoing basis. 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 such interventions may not be continued longer in real world application. The review also included trials that had</p>

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			intervention periods of 6 or 12 months where available.
Public Commenter #4 [Jeffrey Lackner, PsyD University at Buffalo]	Methods	The biggest limitation of this impressive effort is the inattention to the efficacy of non invasive, non pharmacological treatments for chronic abdominal pain disorders. Irritable bowel syndrome for example is one of the most common chronic pain disorders affecting 20 million Americans. Its core symptom is abdominal pain. IBS has been subjected to a number of clinical trials many of which feature non Rx treatments whose efficacy profile rivals if not exceeds that of medical and dietary treatments (see Mayer, NEJM, 2008, Ford et al., AJG, 2013, 2009; van Oudenhoove, Gastroenterology, 2016). This is a non trivial omission as one could seriously argue that IBS is a disease state where we see change in cardinal symptom of disorder (vs LBP where we see change in function)	We acknowledge that there are a number of chronic pain conditions that were beyond the scope of this report; they should be evaluated perhaps in future reports. Musculoskeletal pain, particularly related to joints and the back, is the most common single type of chronic pain. The report focuses on 5 of the most common chronic pain conditions for which opioids might be prescribed.
Public Commenter #5 [Anonymous]	Evidence Summary	<p>I believe that there needs to be some clarification on a couple items. I don't see a clear definition of multidisciplinary rehabilitation. (Chiropractic is not noted although chiropractors perform physical rehabilitation.) So I don't know what this includes but I do see a reference to physical therapy in text within the document. Also the definition of spinal manipulation notes "osteopathic and spinal manipulation". Chiropractors deliver the highest volume of spinal manipulation but there is no clarity as to whether they are including review of chiropractic literature or spinal manipulation performed by chiropractors.</p> <p>I would find the preceding concerning as there is suggestion of using this review for clinical and policy decision making. It would seem important to note whether chiropractic manipulation or chiropractic rehabilitation was included or</p>	Multidisciplinary rehabilitation (also known as interdisciplinary rehabilitation), is defined in the report (Table 1 of the full report) as a coordinated program with both physical and biopsychosocial treatment components (e.g., exercise therapy and cognitive behavioral therapy) provided by professionals from at least two different specialties. The definition does not specify specialty or provider type. Studies involving spinal manipulation, including that which may be done by chiropractors, osteopaths, or other provider types, were included if the PICOTS inclusion criteria were met.

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		intentionally omitted as readers assess rationale for inclusion in clinical algorithms or coverage policies.	
Public Commenter #6 [Mitchell Haas, MA, DC University of Western States]	Results	The following systematic review has a positive assessment for spinal manipulation for chronic neck pain, whereas the current review does not. Is this due to review methodology or cutoff date for trial inclusion? Hidalgo B, Hall T, Bossert J, Dugeny A, Cagnie B, Pitance L. The efficacy of manual therapy and exercise for treating non-specific neck pain: A systematic review. J Back Musculoskelet Rehabil. 2017 Nov 6;30(6):1149-1169.	Thank you for suggesting this review. We have assessed the bibliography of the review to assure that studies meeting our inclusion criteria have been included. The focus and inclusion criteria for this systematic review differ from those used in our review, thus findings from this review may differ from ours.
Public Commenter #7 [James Specker Government & Industry Relations Director American Massage Therapy Association (AMTA)]	Executive Summary	While the report provides good information about massage therapy in certain settings, the criteria for inclusion of research studies is too limiting to give an adequate picture of available, quality research on the value and efficacy of massage therapy for the types of chronic pain examined. The American Massage Therapy Association appreciates AHRQ's interest and efforts to provide this important analysis and we look forward to working with you to ensure that patients suffering from chronic pain have access to effective integrative treatments, including massage therapy.	Thank you for your comments.
Public Commenter #7 [James Specker Government & Industry Relations Director American Massage Therapy Association (AMTA)]	Methods	While the report provides good information about massage therapy in certain settings, the criteria for inclusion of research studies is too limiting to give an adequate picture of available, quality research on the value and efficacy of massage therapy for the types of chronic pain examined. The American Massage Therapy Association appreciates AHRQ's interest and efforts to provide this important analysis and we look forward to working with you to ensure that patients suffering from chronic pain have access to effective integrative treatments, including massage therapy.	Thank you for your comments. We acknowledge that immediate/short-term relief of pain or improvement in function is of value, however, given that the conditions are chronic, evaluation of the sustainability of effects for at least 1 month was felt to be most informative. Studies with at least 1

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		<p>The most restrictive element for research inclusion is that the studies cover a period of at least one month post-intervention. Likewise, the focus on “evaluating the persistence of effects for therapies beyond the course of treatment at short-term follow-up (1 to 6 months following completion of treatment), intermediate-term follow-up (6 to 12 months), and long-term follow-up (≥12 months)” assumes massage therapy will have lasting effects well beyond its application. The result is the inclusion of only four massage therapy studies. The vast majority of massage therapy research covers a shorter period of intervention – often only two weeks. We strongly recommend the inclusion of other quality massage therapy research to ensure a more complete analysis of its efficacy. The methodology of the report also suffers from the decision to only include randomized control trials and to not include studies where massage therapy was an integrative part of patient treatment. In many cases, massage therapy is most effective when combined with other therapies and treatments.</p> <p>Below are some examples of additional research for your consideration. The meta-analyses, while not specific to the five common chronic pain conditions examined in the AHRQ report, include such research in their findings.</p> <ul style="list-style-type: none">• Pedersen K, Björkhem-Bergman L. Tactile massage reduces rescue doses for pain and anxiety: an observational study. <i>BMJ Support Palliat Care</i>. 2017 Nov 4. pii: bmjspcare-2017-001421. doi: 10.1136/bmjspcare-2017-001421. [Epub ahead of print]• Crawford C, et al. The Impact of Massage Therapy on Function in Pain Populations—A Systematic Review and Meta-Analysis of Randomized Controlled Trials: Part I, Patients Experiencing Pain in the General Population. <i>Pain Med</i> (2016) 17 (7): 1353-1375.• Boyd, C, et al. The Impact of Massage Therapy on Function in	<p>month of followup were included.</p> <p>We recognize 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 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 and would vastly expand the scope of the report beyond available resources.</p> <p>All citations provided were reviewed; studies were either previously excluded or did not meet the inclusion criteria.</p>

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		<p>Pain Populations—A Systematic Review and Meta-Analysis of Randomized Controlled Trials: Part II, Cancer Pain Populations. <i>Pain Med</i> (2016) 17 (8): 1553-1568.</p> <ul style="list-style-type: none">• Lin, Yuan-Chi, Wan, Limeng, Jamison, Robert N. Using Integrative Medicine in Pain Management: An Evaluation of Current Evidence. <i>Anesthesia & Analgesia</i>: December 2017 - Volume 125 - Issue 6 - p 2081–2093. doi: 10.1213/ANE.0000000000002579	
Public Commenter #8 [Angelo McClain, PhD, LICSW Chief Executive Officer National Association of Social Workers (NASW)]	General	<p>Re: Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>Dear Mr. Khanna,</p> <p>The National Association of Social Workers (NASW), representing 125,000 social workers, submits comments for the Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review. NASW is the largest professional social work organization in the United States.</p> <p>The social work profession promotes the well-being of individuals, families and communities and social workers serve vulnerable populations with chronic mental and physical conditions. Social workers work as private practitioners and are employed in a variety of health care settings. They provide psychosocial support to patients and families and help individuals reach their personal goals while living with illness. Clinical social workers provide clinical assessment and treatment for mental health conditions and are the largest group of providers of mental health services in the U.S. NASW is encouraged by the Agency for Healthcare Research and Quality's (AHRQ) findings, that nonpharmacological treatments can be helpful for chronic pain conditions and psychological therapies can moderately improve chronic low back pain and fibromyalgia. Using a biopsychosocial model, social workers have training and expertise in delivering a range of therapies such as those described in the report (cognitive</p>	Thank you for your comments.

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		<p>behavioral therapy, biofeedback, relaxation techniques, acceptance and commitment therapy), and mindfulness practices (meditation, mindfulness-based stress reduction practices).</p> <p>While the trials examined in the report did not include comorbid mental health conditions, individuals living with chronic pain and functional impairments often experience distress, depression and anxiety that exacerbate pain. It is important to understand the relationship between chronic pain and mental health conditions. NASW hopes that further research will be done to clarify this link and identify the specific treatment modalities that should be employed within behavioral health services to address pain and function for a variety of chronic pain conditions. NASW supports nonpharmacological treatment for chronic pain and recommends licensed clinical social workers as one of the disciplines to be involved in providing treatment. Provider teams across health settings should consider alternatives to pharmacological treatments and apply integrative, multimodal care models for chronic pain conditions. As CMS has encouraged through their Transforming Clinical Practice Initiative to advance integrated care (https://innovation.cms.gov/initiatives/Transforming-Clinical-Practices/), there is a need for physicians and nurses to partner with behavioral health providers in the community. Establishing connections between mental health and physical health providers facilitates the referral and follow-up process and leads to better health outcomes and cost savings throughout the system.</p> <p>Thank you for the opportunity to provide comments. Should you have any questions about NASW comments, please do not hesitate to contact me at naswceo@socialworkers.org or 202-408-8600, Ext. 200.</p>	

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Public Commenter #9 [Linda Wheatland Smith, D.C Hands on Health]	NA	<p>Response to the 2017 AHRQ Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review Linda Wheatland Smith, D.C. St. Louis, MO</p> <p>My clinical experience as a chiropractic physician and certified acupuncturist spans 35 years of managing low back pain, neck pain, tension headaches, osteoarthritis of the knee and hip, rotator cuff tendinopathies, plantar fasciitis, and lateral epicondylitis with manual therapies including spinal manipulation, deep specific therapeutic massage, acupuncture, dry needling, physical agents, meditation, and physical rehabilitation. It has been a very satisfying professional career of interrupting many challenging pain patterns while providing safe, effective care with essentially no side effects.</p> <p>Myofascial pain patterns, degenerative joint disease and joint dysfunction form the basis for the majority of non radicular back and neck pain. In my experience integrating therapies including physical agents, deep specific therapeutic massage, and spinal manipulation into one treatment session is significantly more effective than applying each therapy individually. Dry needling and deep tissue massage specific to an area i.e. hip, shoulder or foot is another effective integrated protocol for managing damaged soft tissues in these areas.</p> <p>Poor postural habits, weak lower abdominal muscles, weak lower trapezius muscles, weak gluteus medius muscles and stiff tight hips contribute to recurrent episodes of low back pain. These issues must be addressed in addition to the application of manual therapies or the pain patterns will recur.</p> <p>Chronic stress and chronic pain can be effectively interrupted</p>	Thank you for your comments.

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		<p>with meditation and mindfulness training. It is helpful to my patients that I practice these techniques myself and provide resources for them to learn MBSR and meditation. In addition, a quiet setting for the acupuncture with soft classical music creates an atmosphere conducive to the production of endorphins and the elicitation of the relaxation response.</p> <p>It is inspiring and hopeful to see this 2017 AHRQ Review of Noninvasive, Nonpharmacological Treatments for Chronic Pain in addition to the Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians (2017). Chronic non-radicular pain patterns of the back and neck require a thoughtful, comprehensive hands on approach that excludes wasteful, harmful imaging, the chronic use of antiinflammatories that raise blood pressure and increase the risk of stroke, and addictive pain medications that intensify the cycle of pain.</p>	
Public Commenter #10 [Edward Kelty, PhD American Psychological Association]	General	<p>Chronic pain can be associated with an interruption in life's upward trajectory. Most people expect that their lives will improve and objectives achieved as they grow older. However, there can be mid-age interruptions in this path such as not receiving any promotion, disappointment in partner, or even the kids going away to college or to work elsewhere. Life looks empty. This is the time that an accident or other injury will produce chronic pain.</p> <p>First, in full disclosure, I want to give my credentials and personal experience with pain. Trained at McGill and Duke in clinical neuropsychology. Worked for 26 years at NIMH before retiring and joining a medical practice dealing with chronic pain. Several of our clients were recuperating from failed back surgery. I had a personal event in which I was suddenly struck</p>	Thank you for your comments.

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		<p>with incredible back pain while picking up an 8 oz package of cream cheese at the supermarket. Spinal imaging was ordered, but I could not spend a half hour in the tube. The next day they gave me oxycontin, with no relief. Instead of surgery, I elected physical therapy which eliminated the need for questionable cutting. Some years later I had open heart surgery to install an aortic valve. After a day on oxycontin, I switched to Tylenol and was discharged in three days. Why do patients differ in response to spinal surgery and to Oxycontin?</p> <p>Working in a clinical setting focused on chronic pain, we had a variety of patients ranging from neural problems to fibromyalgia and chronic fatigue syndrome. It was hard to get them to follow an exercise routine as they were always too fatigued. So, I explored aspects of their current lives.</p> <p>It turns out that people who were middle aged had hit a ledge where their life expectations were suddenly disrupted. This could be as simple as kids going away to school or jobs, failure to get a promotion after years at the company, or disappointment in marital relations. If they had an accident or a medical complication, this was the time when chronic pain would set in and be difficult to treat without examination of the life situation and options for the future.</p> <p>I gave a talk once on this at a national pain conference, but it needs to be verified by research. Although, I have clinical records, it would be a great doctoral research project about the timing of clinical pain onset.</p>	
Public Commenter #11 [Tim Bertelsman, MD Brandon Steele, MD]	General	See attachment	Thank you for your comments. All citations provided were reviewed; studies were either already included,

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			previously excluded, or did not meet the inclusion criteria.
Public Commenter #12 [David A. Herd, D.C. President, The American Chiropractic Association (ACA)]	Introduction	<p>Re: Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>Dear Dr. Kato:</p> <p>The American Chiropractic Association (ACA) appreciates the opportunity to provide comment on the Agency for Healthcare Research and Quality's (AHRQ) draft report Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review. ACA, the largest organization in the United States representing doctors of chiropractic, is leading the chiropractic profession in the most constructive and far-reaching ways – by working hand in hand with other health care professionals, by supporting meaningful research, and by using that research to inform chiropractic practice. ACA members pledge to adhere to the highest standards of ethics and patient care, contributing to the health and well-being of the estimated 35 million individuals across the country who seek chiropractic care each year.</p> <p>We are encouraged by the AHRQ findings that indicate a number of nonpharmacological interventions can provide beneficial effect on pain and/or function in patients with chronic low back pain, chronic neck pain, osteoarthritis, fibromyalgia, and chronic tension headaches. The conditions evaluated constitute the majority of chronic pain diagnoses in the United States. Additionally, the evidence is especially supportive for those with moderate or severe intensity of pain that has persisted for greater than one year.</p>	Thank you for your comments.
Public Commenter #12 [David A. Herd, D.C.]	Results	<p>We would like to recommend consideration of the following, should they meet the inclusion criteria:</p> <p>Chronic Low Back Pain</p>	Thank you--all citations provided were reviewed and none met the inclusion criteria.

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President, The American Chiropractic Association (ACA)]		<p>Goertz CM, Long CR, Vining R, Pohlman KA, Kane B, Corber L, Walter J, Coulter I. Assessment of chiropractic treatment for active duty, U.S. military personnel with low back pain: a study protocol for a comparative effectiveness clinical trial with adaptive allocation (ACT 1). Trials 2016;17:70. doi: 10.1186/s13063-016-1193-8.</p> <p>This trial evaluated the effects of the addition of chiropractic care to usual medical care on LBP pain and disability. A pilot study¹ compared chiropractic care plus standard medical care with standard medical care alone for active duty military personnel with acute LBP. Improvements in pain and disability were significantly greater in the chiropractic care group. This comparative effectiveness study evaluated whether these prior findings can be reproduced in a larger sample, across multiple sites and with varied populations, including individuals with subacute and chronic LBP.</p> <p>Chronic Neck Pain</p> <p>Côté, P., Wong, J.J., Sutton, D. et al. Management of neck pain and associated disorders: A clinical practice guideline from the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. Eur Spine J (2016) 25: 2000. doi.org/10.1007/s00586-016-4467-7. The OPTIMa guidelines included similar studies; however, they concluded with a stronger recommendation than the AHRQ review, advocating use of spinal manipulation/mobilization combined with exercise and massage for chronic neck pain.²</p>	
Public Commenter #12 [David A. Herd, D.C. President, The American	Discussion	As the AHRQ report findings demonstrate, there is a current lack of published data on the impact of noninvasive, nonpharmacological therapies for chronic pain. Although data on harms was limited, no study in the AHRQ reported serious harms. Risk of harm should be reported alongside risk of	Thank you for your comments and suggestions. Strength of evidence is assessed separately for primary outcomes (benefits as well as safety/harms) as

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Chiropractic Association (ACA)]		<p>benefit for all treatments and considered when comparing treatments to one another. Since the evidence identifies such a low risk profile for the nonpharmacological therapies reviewed in this paper, we suggest there is rationale for elevating the enthusiasm of recommendations for therapies with limited or low strength of evidence.</p> <p>ACA generally supports the conclusions reached but would like to bring attention to the Implications for Clinical and Policy Decision-making on page 267. Nonpharmacological therapies have become a vital part of managing chronic pain. These can be used as stand alone therapies; however, nonpharmacological treatments often are used to augment and complement pharmacological treatments. Choice of nonpharmacological intervention is determined by the nature of each case, what works for a specific patient and the skills of the clinician. Noninvasive, nonpharmacological interventions may present less risk to the patient than invasive or pharmacological measures and therefore present the need for greater access to and integration of safe and affordable alternatives. If you have any questions regarding our comments or need more information, please contact Angela Kennedy, Senior Vice President of Education and Health Policy at the American Chiropractic Association, akennedy@acatoday.org or 703-812-0242.</p>	<p>described in the report and published protocol.-Harms/safety were poorly reported in included studies, but the limited data found were presented in the report. We have noted in the discussion and other places that there is no suggestion of serious harms.</p> <p>We acknowledge that in clinical practice many of the include interventions are used in combination with pharmacological and other treatments. Given the multitude of combinations of therapies and 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, and their inclusion would vastly expand the scope of the report beyond available resources.</p>
Public Commenter #13 [Erik Groessel, PhD University of California San Diego and San Diego VA]	Results	<p>The report does not seem to include a full-scale RCT of yoga for low back pain published online in July 2017. Yoga for Military Veterans with Chronic Low Back Pain: A Randomized Clinical Trial. Groessel EJ, Liu L, Chang DG, Wetherell JL, Bormann JE, Atkinson JH, Baxi S, Schmalzl L. Am J Prev Med. 2017 Nov;53(5):599-608. doi:</p>	<p>This trial was also captured by our updated search (performed during the peer review and public comment period) and meets the inclusion criteria; it was added to the final report.</p>

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		10.1016/j.amepre.2017.05.019. Epub 2017 Jul 20. PMID: 28735778	
Public Commenter #14 [Bruce A. Weiner, DNP, MSNA, CRNA President, American Association of Nurse Anesthetists (AANA)]	General	See attachment	Thank you for your comments. All citations provided were reviewed; studies were either already included, previously excluded, or did not meet the inclusion criteria.
Public Commenter #15 [Kara R. Gainer, JD Director of Regulatory Affairs American Physical Therapy Association (APTA)]	Evidence Summary	We recommend that AHRQ 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.	<p>Thank you for your comments.</p> <p>We acknowledge that there are many ways to organize the evidence as well as the follow-up time frames and attempted to present information in a way that was most informative.</p> <p>Harms/safety were poorly reported, but the limited data found were presented in the report. We have noted in the discussion and other places that there is no suggestion of serious harms.</p>
Public Commenter #15 [Kara R. Gainer, JD Director of Regulatory Affairs American Physical Therapy Association (APTA)]	Introduction	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	<p>Thank you for your comments.</p> <p>There is no standard method for categorizing many of the interventions. We realize that other may categorize interventions differently than we have and that there is heterogeneity within intervention categories.</p>

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		<p>like cognitive behavioral therapy or physical therapy (which are often compromised of individual approaches). A better approach may be to separate the approaches into single and multimodal approaches. This would also be consistent with recent International Association for the Study of Pain recommendations. 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.</p> <p>While we appreciate that the systematic review acknowledges that exercise and movement therapy are critical to improving function and pain outcomes, there also are similar issues with the term exercise – such term can be defined in a number of ways, and describing it as only one intervention is a continuing problem that this report will perpetuate, if not resolved. Exercise is an effective tool for improving mood and cognition, which often are a challenge for many patients with chronic pain. Moreover, we encourage AHRQ to be more descriptive of what commonly utilized exercise approaches may be more successful and effective than others.</p> <p>Additionally, we recommend that AHRQ include a statement within the Introduction that explains how there is a 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.</p>	<p>Where data were available, we did sensitivity analyses on exercise type, which are described 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.</p> <p>The magnitude of effects for pain and function were classified with the system used our previous AHRQ review and are described in the Methods section. The discussion contains additional information regarding interpretation of effect sizes. Where an minimal clinically important difference (MCID) was known for a measure this was considered the basis for "moderate" effect size. We acknowledge that small effects using this system may not meet standard thresholds for clinically meaningful effect. Our method provided a consistent benchmark to compare results across trials. Interpretation of clinically important differences in mean change for continuous variables is challenging. In some instances, a mean effect size may be small, but may related to a larger effect when the</p>

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			proportion of responders achieving that (or other) level is considered. There is variability across individual patients regarding what may constitute a clinically important effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. For some patients a small improvement in function or pain gained by using a treatment that has relatively low cost with no serious harms may be important. Additional clarification has been added in the methods and discussion.
Public Commenter #14 [Kara R. Gainer, JD Director of Regulatory Affairs American Physical Therapy Association (APTA)]	Results	<p>AHRQ has the opportunity to guide future work, especially as it relates to better treatment effect moderation opportunities. To that end, we recommend that AHRQ consider a discussion of stratification and treatment matching, and potential for the results to be affected by such, in moving forward.</p> <p>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 AHRQ provide additional clarification on why the factors of age, sex, and presence of comorbidities were selected a priori for consideration. Moreover, in regards to Key Question 6, AHRQ indicates 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</p>	<p>Thank you for your comments.</p> <p>Where data were available we did sensitivity analyses, stratifying on various factors (e.g., types of exercise), and results are presented in the report.</p> <p>KQ 6: Trials did not provide adequate information to evaluate heterogeneity of treatment effect (i.e., effect modification) by the factors listed in the KQ or any other factors.</p> <p>As described in the report and protocol, we acknowledge that usual care was defined variably across trials</p>

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		<p>example, what are the main barriers to addressing this question and what are key research priorities in this area?</p> <p>Moreover, in using the term usual care as a comparator – we expect that this included pharmacological therapies and exercise. However, there is little information on how AHRQ is defining usual care and what it encompasses. We request that AHRQ provide additional clarification on what comprises usual care and how it was included as a comparator.</p>	<p>and likely did include components of a range of pharmacological and nonpharmacological interventions. We did not impose a single strict definition, but reported information as it was provided by study authors. This is a limitation of including usual care as a comparator.</p>
Public Commenter #15 [Kara R. Gainer, JD Director of Regulatory Affairs American Physical Therapy Association (APTA)]	Discussion	<p>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.</p> <p>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 and whether nonpharmacological treatments can, in fact, be emphasized as preferred over pharmacologic treatments.</p>	<p>Thank you for your comments.</p> <p>We acknowledge that immediate/short-term relief is of value; however, given that the conditions are chronic, evaluation of the sustainability of effects for at least 1 month was felt to be most informative.</p>
Public Commenter #15 [Kara R. Gainer, JD Director of Regulatory Affairs American Physical Therapy Association (APTA)]	Tables	<p>APTA recommends that within the final report, AHRQ include a table that is organized by treatment, as we believe this will offer readers an easy to understand description of each intervention that is considered most beneficial for each problem. Additionally, while we find the tables and figures informative, we believe it would be beneficial for AHRQ include “intervention first” summaries. Such modifications to the tables could assist with the development of “choosing wisely” statements and guide intervention selection for ongoing care pathways.</p>	<p>Thank you for your comments.</p> <p>We acknowledge that there are many ways to organize the evidence and various groups and individuals will view the organization differently. Within each condition, evidence for each intervention is provided. Organizations may be able to organized our findings in ways the best suit their needs.</p>

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Public Commenter #16 [David Hebert, JD Chief Executive Officer American Association of Nurse Practitioners (AANP)]	General	<p>Re: Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>Dear Dr. Kato,</p> <p>The American Association of Nurse Practitioners (AANP), representing more than 234,000 nurse practitioners (NPs) in the United States, appreciates the opportunity to comment on AHRQ's evidence report titled "Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review."</p> <p>NPs are advanced practice registered nurses (APRNs) who are prepared at the masters or doctoral level to provide primary, acute, chronic and specialty care to patients of all ages and walks of life. Daily practice includes: assessment; ordering, performing, supervising and interpreting diagnostic and laboratory tests; making diagnoses; initiating and managing treatment including prescribing medication and nonpharmacologic treatments; coordinating care; counseling; and educating patients and their families and communities. NPs practice in nearly every health care setting including clinics, hospitals, Veterans Affairs and Indian Health Care facilities, emergency rooms, urgent care sites, private physician or NP practices (both managed and owned by NPs), nursing homes, schools, colleges, retail clinics, public health departments, nurse managed clinics, homeless clinics, and home health. NPs hold prescriptive authority in all 50 states and the District of Columbia. It is important to note that 89.2% of NPs are certified in primary care, the majority of whom see Medicare and Medicaid patients. NPs complete more than one billion patient visits annually. Pain management is an integral part of the care they provide.</p> <p>As AHRQ evaluates the research conducted regarding</p>	<p>Thank you for your comments.</p> <p>Any trials that met the inclusion criteria are included in the review, regardless of discipline.</p> <p>We recognize 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 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 and would vastly expand the scope of the report beyond available resources for this report.</p> <p>Some trials did include patients with various comorbidities and these data were abstracted as available; there were inadequate data to evaluate the role of comorbidities based on included trials. Many trials excluded individuals with comorbidities.</p>

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		<p>noninvasive, nonpharmacological treatments for chronic pain there are three areas that are needed to obtain the most robust and complete data regarding these treatments. First, AHRQ needs to ensure that data from all disciplines, including nursing and nurse practitioners, is examined and included in the evidence report. Nurse practitioners are the primary care providers for many patients dealing with chronic pain, and literature on the outcomes of treatment that they provide is essential for a complete picture of the treatment landscape. Second, studies need to be included that involve multiple treatment modalities. Clinicians treating patients with chronic pain will often use a combination of treatments simultaneously, and studies need to be included that account for the real-world application of these treatments. Third, studies need to be included that involve patients suffering from comorbidities in addition to or in conjunction with chronic pain that will have an impact on the pain status of the patient.</p> <p>This review is an important step in evaluating noninvasive and nonpharmacologic chronic pain treatment. We note the importance of continued funding and study of these treatments to fill the gaps in knowledge of treatment outcomes and encourage you to explore the three areas we have identified above.</p> <p>We thank you for the opportunity to comment on this evidence report. We look forward to continued discussion with AHRQ related to the evaluation of noninvasive and nonpharmacological treatments for chronic pain. Should you have comments or questions, please direct them to MaryAnne Sapio, V.P. Federal Government Affairs, msapio@aanp.org, 703-740-2529.</p>	

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Public Commenter #17 [Lynn Bufka, PhD American Psychological Association (APA)]	Evidence Summary	<p>We appreciate the opportunity to review and provide comments on this draft report. Please note, these are not official comments from the American Psychological Association.</p> <p>ES-23 It would be helpful to describe how the ICER report regarding chronic pain differs from this AHRQ report, rather than merely noting that differences exist.</p> <p>Tables A-M are very helpful.</p>	Thank you for your comments.
Public Commenter #17 [Lynn Bufka, PhD American Psychological Association (APA)]	Introduction	<p>Page 2 lists psychological therapies as cognitive-behavioral therapy (CBT), biofeedback, relaxation techniques, acceptance and commitment therapy (ACT). While we would agree that biofeedback and relaxation techniques are routinely used as part of psychological care, we are concerned that relaxation techniques, delivered solely in the context of physical therapy (Viljanen 2003 as an example) by physical therapists be classified as a psychotherapy. We recommend that this intervention be reviewed separately from CBT or ACT when multiple studies with “psychological therapies” are identified and when only one study, featuring relaxation strategies taught by a physical therapy constitutes this category for the category to actually be labeled as relaxation. (See results described on page 93 as a concerning example.)</p>	Thank you for your comments. Details regarding individual psychological therapies, as provided in the trials, are in the full report and we have provided additional detail in the executive summary. We have included relaxation techniques under psychological therapies, recognizing that others may not classify things the way that we have. We have focused on the techniques used as described, recognizing that in some cases, different provider types might administer them. We do not indicate that the relaxation techniques are equated with “psychotherapy”
Public Commenter #17 [Lynn Bufka, PhD American Psychological Association (APA)]	Results	<p>Overall, it is disappointing that so little evidence exists to compare noninvasive, nonpharmacological therapies to pharmacological therapies across conditions.</p> <p>Page 67- It appears that an errant decimal point precedes 39.6% (95% CI 31.7, 49.5) in the 'function and pain outcomes' column.</p>	We have checked the accuracy of the reported data and made appropriate edits.

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		Page 69- Are the numbers reported correctly for 6 months, McGill Pain Questionnaire for the Turner study? Intuitively, it appears the first two numbers should be reversed. At present, it is reported as 9.5 (15.7) vs. 15.7 (9.2). (I am not able to review the original study.)	
Public Commenter #18 [Anonymous, from the American Academy of Pain Medicine]	General	<p>Comments from the American Academy of Pain Medicine</p> <p>The American Academy of Pain Medicine supports the AHRQ's efforts to review and evaluate the effectiveness of noninvasive, nonpharmacologic treatments for many common chronic pain states. We acknowledge the tremendous amount of work that was required to prepare this extremely thorough and rigorous report. We thank you for the opportunity to provide feedback and offer a constructive critique for your consideration.</p> <p>General comments:</p> <ul style="list-style-type: none">• We would initially point out that the stated title of the review is overly broad, and could be qualified by the types of "non-pharmacological" treatments undergoing review, namely psychological/physical therapy/rehabilitative. We suggest acknowledgement that of "non-pharmacological" treatments for pain, many of the techniques employed by pain specialists, for example spinal cord stimulation and radiofrequency ablation, were not included in the review, and that non-inclusion in this review does not imply these treatments are less useful or important considerations in the "non-pharmacological" category of pain management.• The goals of this report were ambitious and important, and the conclusions, although not surprising, once again confirm that much of what is done in medicine is not supported by robust literature, unfortunately. We have concerns, given the	<p>Thank you for your comments.</p> <p>We looked at an array of non-invasive, nonpharmacological treatments, using these broad terms to encompass various types of treatment (e.g. physical modalities, manual therapy, etc.). The focus of the report is on noninvasive, nonpharmacological treatment. In the discussion we have acknowledged that there are additional interventions that were beyond the scope of this report. It would not be possible to list and acknowledge all possible treatments that were excluded. Exclusion doesn't imply anything regarding the efficacy or safety of such treatments. The inclusion criteria for interventions are described more fully in the methods and published protocol.</p> <p>Where data were available we did sensitivity analyses, stratifying on various aspects of interventions (e.g., types of exercise, different psychological therapies, etc.) and results are presented in the report. We</p>

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		<p>limitations of the literature, that this report itself has significant limitations and that the conclusions should be tempered.</p> <ul style="list-style-type: none">• Due to the scope of the work, it is very dense reading which makes it very difficult to read the data sections. Nevertheless, the tables are well laid out and easy to find details if so inclined. The figures and the summary tables in the discussion section are excellent. In addition to publishing the full document, we would like to see an accompanying “Executive Summary” (with key points, the meta-analysis figures, and summary tables with their discussion section). It would be much easier to find clinically useful summary information than it is in the full document.• Regarding RCTs and psychobehavioral treatments; two commonly overlooked factors are patient preferences and therapeutic alliance.<ul style="list-style-type: none">o Patient Preferences. Treatment outcomes may be diminished by failing to include a key patient participant variable: treatment preference. If patient did not wish to be assigned to CBT and was hoping to get MBSR, it may not be surprising when treatment adherence rates are low. A literature exists on the importance of “equipoise” considerations in RCTs (e.g., https://www.ncbi.nlm.nih.gov/pubmed/11720698; Lavori, Rush et al, Biol Psychiatry 2001). This may be a point for the authors to consider in the conclusions and recommendations for future research.o Therapeutic Alliance. Similarly, recent research suggests that the therapeutic alliance is a critical variable in psychosocial	<p>have made some edits to the evidence summary for clarification regarding specific psychological therapies.</p> <p>We acknowledge that factors such as patient preferences and therapeutic alliance are important; these were generally not reported in included trials; to focus the report the primary outcomes reported were function and pain.</p>

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		treatment outcomes, and it could explain a portion of the variance seen between studies conducted in similar populations using the same protocols. (e.g., https://www.ncbi.nlm.nih.gov/pubmed/25119513 Burns, Neilson, Jensen, Heapy, Czapinski, Kerns. “Does change occur for the reasons we think it does? A test of specific therapeutic operations during cognitive behavioral treatment for chronic pain.” Clin J Pain 2015). Again, perhaps salient points of consideration that add texture to our understanding that these behavioral treatments involve dynamic psychosocial interactions that deeply impact ongoing treatment across weeks and months.	
Public Commenter #18 [Anonymous, from the American Academy of Pain Medicine]	General	<ul style="list-style-type: none">• Treatment Responders. An overemphasis on general effects harms our overall understanding regarding a fundamental question: For whom do these treatments work best? No single treatment is right for everyone. With this publication, an opportunity exists to encourage researchers to better characterize treatment responders and non-responders so that clinicians can be provided with the evidence as to which treatments will be most effective for each patient and thereby improving cost effectiveness. With this information in hand, clinicians could focus on phenotyping and evidence-based treatments that are optimal for each patient, supported by their individual characteristics, preferences and the available treatment choices.• Methodology. As with most reviews that result in guidelines, the randomized controlled trial study is used as the gold standard. This approach is typical in much of medical research. It should be noted that questions have been raised as to whether RCTs should be considered the “gold standard” in all research situations as it is not necessarily the most valid or reliable way to assess outcomes in all situations. This is	<p>Thank you for your comments on future research directions. We agree that it would be nice to be able to describe for whom which treatment work best, what the characteristics of responders and non-responders are and that future research should include appropriate methods for evaluation of this.</p> <p>RCTs: While there are limitations to RCTs, their design still provides the potential for the least bias and facilitates understanding of whether or not a treatment works under ideal conditions. Well designed and rigorously conducted observational studies may provide additional information to complement RCTs for treatments that have demonstrated some level of efficacy.</p>

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		<p>especially true as it relates to psychotherapy outcomes. Many of the studies, as noted in the AHRQ review, are of poor quality and do not report important information about this very mixed population, which unfortunately makes generalizability very difficult. Large data sources (“big data”), in the form of data registries, are becoming one way to supplement RCTs while still producing reliable, valid and relevant results. If data registry information is available pertaining to the topics reviewed, that data should be at least considered for inclusion.</p> <ul style="list-style-type: none">• Many of these treatments are often delivered concurrently rather than sequentially in clinical practice. The authors may want to note that future research may wish to focus on what combinations of treatments are appropriate, for which patients, and in which order.• We note that Yoga was not included as a treatment in the Fibromyalgia section. We would draw the author’s attention to the studies of Carson, JW and Langhorst, J (Rhumatol Int 2013). These studies are RCTs (perhaps they did not meet inclusion criteria?). <p>About AAPM The American Academy of Pain Medicine is the premier medical association for pain physicians and their treatment teams with some 2,000 members. Now in its 34th year of service, the Academy’s mission is to optimize the health of patients in pain and eliminate pain as a major public health problem by advancing the practice and specialty of pain medicine through education, training, advocacy and research. Information is available on the Academy’s website at</p>	<p>We recognize 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 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 and would vastly expand the scope of the report beyond available resources.</p> <p>Regarding the last bullet: Yoga was considered as an intervention for Fibromyalgia (FM); however, none of the trials evaluating yoga for the treatment of FM met inclusion criteria. We did include one trial (Altan 2009) that looked at Pilates for FM - this trial was included under the Exercise category as it was considered to be more indicative of muscle performance exercise as compared with more "traditional yoga". Regarding the two trials cited, both were excluded at full text review (see Excluded Studies List in the Appendix:</p>

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		www.painmed.org. Submitted December 23, 2017	# 122 (Carson 2010) and #432 (Langhorst 2013)
Public Commenter #19 [Alexander Walley, MD, MSc Boston University School of Medicine]	Results	Please describe how and why the five pain categories were selected for review, as well as, why other pain categories were not included. Consider broadening the review to include other common pain conditions. Here are some examples: Shoulder pain due to rotator cuff problems is a common source of chronic pain, not addressed by this review. Peripheral neuropathy is particularly common in patients with diabetes and HIV infection and not addressed in this review. Cancer-related pain is common among patients with cancer, and much may be learned from including a review of non-pharmacological approaches to cancer-related pain that are effective.	Musculoskeletal pain, particularly related to joints and the back, is the most common single type of chronic pain. The report focuses on 5 of the most common. We acknowledge that there are a number of chronic pain conditions that were beyond the scope and resources of this report the should be evaluated perhaps in future reports.
Public Commenter #20 [Andrew Vickers, PhD Acupuncture Trialists' Collaboration]	General	To whom it may concern We are writing to you on behalf of the Acupuncture Trialists' Collaboration. The Acupuncture Trialists' Collaboration is an international group of trialists, biostatisticians, pain experts and acupuncture content experts that was established in 2006 and has been supported by NIH R21 and R01 grants. It is chaired by myself, Andrew Vickers, a biostatistician at the rank of Attending, equivalent to full Professor, in the Department of Epidemiology and Biostatistics at Memorial Sloan Kettering Cancer Center. The purpose of the Acupuncture Trialists' Collaboration is to obtain raw data from high-quality randomized trials of acupuncture for chronic pain and conduct individual patient-data meta-analyses. Our main findings were originally published in the Archives of Internal Medicine[1], with updates published in JAMA[2] and the Journal of Pain[3]. We have both a general and a number of specific criticisms of	Thank you for your comments and perspective. We have reviewed the citation: Vickers, A. J., et al. (2012). "Acupuncture for chronic pain: individual patient data meta-analysis." Arch Intern Med 172(19): 1444-1453. We acknowledge the authors' efforts to perform a quality analysis. We did not include full systematic reviews in our report but reviewed their bibliographies to assure that relevant citations meeting our inclusion criteria were included. Berman 2004 was the only additional study meeting our criteria and has been added to the final report. We have added a

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		<p>the AHRQ report “Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review”. Our general criticism is that the report makes no reference whatsoever to the findings of the Acupuncture Trialists' Collaboration. It has not open to doubt that individual patient data (IPD) meta-analysis – as conducted by the Acupuncture Trialists' Collaboration - is a superior methodology to analysis of summary data. If the results of an IPD meta-analysis conflict with those of a meta-analysis based on summary data, our conclusions would be exactly as for any other situation where the results of a superior and inferior methodology conflict: we trust the superior methodology. At a very bare minimum, we should attempt to understand and explain the differences in results.</p> <p>The AHRQ report completely omits any reference whatsoever to the Acupuncture Trialists' Collaboration. So when the report concludes, for instance, that “there were no clear differences between acupuncture versus control interventions on [osteoarthritis] pain” this is stated baldly, sui generis, and there is no comment that the Acupuncture Trialists' Collaboration found statistically significant differences between acupuncture and both sham and no treatment control for the treatment of osteoarthritis. Now maybe there is a good explanation, for instance, the Acupuncture Trialists' Collaboration combined different types of osteoarthritis and different time periods. But then this would at least have to be discussed and analyzed, for example, why we might expect acupuncture to have different effects on osteoarthritis pain depending on pain site, or why the effect differs importantly by time period, and why the conclusions of the AHRQ are more reliable than those of the Acupuncture Trialists' Collaboration in the light of methodological differences.</p>	<p>sentence to the limitations indicating that our results are based on study-level data and that our overall conclusions regarding some benefit are similar for some conditions.</p> <p>While we appreciate the advantages of individual patient data meta-analysis(IPD), the objectives and focus for this report differ from those in described in the IPD, and thus our inclusion criteria and methods, also differ as does our focus on effects at various timeframes. These factors likely contribute the discrepancies between our report and the IPD.</p>

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		<p>We have a number of more specific criticisms of the report that may explain the differences between some of the findings of the Acupuncture Trialists' Collaboration in comparison to the AHRQ report. In the interests of time, we have not done an entire point-by-point comparison of the many items of difference between the Acupuncture Trialists' Collaboration and AHRQ. Given below, we choose three obvious examples where the AHRQ findings are grossly at odds with the published literature.</p>	
Public Commenter #20 [Andrew Vickers, PhD Acupuncture Trialists' Collaboration]	Abstract	<p>1. Regarding the evidence of neck pain (Page viii) it states that there was “no improvement in pain was seen at any time frame”. However, one large study (MacPherson et al 2015[4]), which measured outcomes with the Northwick Park Neck Pain Questionnaire (NPQ), this trial was wrongly listed as measuring function, when it was actually measuring pain. With reference to our initial point, the Acupuncture Trialists' Collaboration reported a highly significant difference between acupuncture and sham for neck pain (SMD 0.83; 95% C.I. 0.64, 1.01; $p < 0.0001$); we also show that the effects of acupuncture for neck pain dissipate over time 3. These two findings are never referenced in the authors’ conclusion that there is “no improvement in pain ... at any time frame”.</p>	<p>Our reported results are based on the trials that met our inclusion criteria, based on our objectives and published protocol. We have verified the accuracy of the data.</p> <p>Many outcome measures incorporate aspects of pain and function and a judgement is made regarding where it may fit best given the objectives of the report. The NPQ measures how neck pain <i>affects one's ability to manage in everyday life</i>. The questionnaire is composed of 9 sections, only the first of which addresses pain intensity, while the remaining 8 address consequent levels of disability resulting from neck pain: neck pain and sleeping; pins and needles or numbness in the arms at night; duration of symptoms; carrying; reading and watching television;</p>

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			working and/or housework; social activities; and driving. (At the end there's a tenth question which aims to compare the current state to the state when the questionnaire was last completed.) Because this questionnaire does not simply address the patients level of pain but explores how that translates into the patient's ability to function in daily life, this questionnaire is considered a measure of function/functional disability.
Public Commenter #20 [Andrew Vickers, PhD Acupuncture Trialists' Collaboration]	Results	2. It is of interest to compare the osteoarthritis plots on page 165 with those published by the Acupuncture Trialists' Collaboration. First, it is obvious that several trials are missing, including Berman 2004[5], Vas 2004[6], Scharf 2006[7]. There is no explanation as to why these trials were excluded in the AHRQ report. Second, the effect sizes and 95% C.I. are often discordant with the published literature. For instance, Witt 2005 is given as a not significant SMD 0.22, with a confidence interval -0.06, 0.49. The Acupuncture Trialists' Collaboration gives 0.41 95% C.I. 0.18, 0.63. In the original paper, acupuncture was significantly superior to both sham and no acupuncture control leading the authors to conclude: "After 8 weeks of treatment, pain and joint function are improved more with acupuncture than with minimal acupuncture or no acupuncture in patients with osteoarthritis of the knee". It is difficult to understand how the AHRQ report can report a non-significant difference between groups for this trial.	The PICOTS in the published protocol and report describe the exclusion criteria; trials excluded at full text and reason for exclusion are identified in the report appendix. Regarding the trials indicated as missing: Berman 2004 was excluded previously in error. This study will be included in our final report for the comparison of acupuncture vs. sham acupuncture only; the third arm which underwent a self-management education program is excluded as it does not meet our inclusion criteria (self-management and education were ineligible comparators). Vas 2004 was excluded at the title/abstract triage phase because it was considered adjunctive to pharmacological therapy

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			(adjunctive/additive/incremental therapies were excluded): both treatment groups received diclofenac with the addition of acupuncture (intervention group) or sham acupuncture (control group). Scharf 2006 was excluded at full text review (see list of excluded studies in Appendix) because the intervention was additive/incremental in nature: Patients underwent up to 6 physiotherapy sessions and as-needed anti-inflammatory drugs plus 10 sessions of acupuncture (group 1), 10 sessions of sham acupuncture (group 2), or 10 physician visits within 6 weeks (conservative therapy) (group 3).
Public Commenter #20 [Andrew Vickers, PhD Acupuncture Trialists' Collaboration]	Results	3. One might similarly compare the forest plots for low back pain. There are again missing studies (e.g. Molsberger[8]) and obvious errors. For instance, the Brinkhaus trial[9] is described as a study compared acupuncture to sham acupuncture, when in fact it is a three arm trial with both a sham and a usual care group. For the Haake trial[10], the means and SDs for the acupuncture and (presumably combined) controls groups are 33.2 (SD 23.1) and 41.1 (SD 22.9). These numbers do not appear anywhere in the paper. The effect size given is 0.34. Even if correct, this would be an average of two very different estimates: as per the Acupuncture Trialists' Collaboration, a SMD of 0.56 versus usual care and 0.13 versus sham acupuncture. This is, of course, a more general problem with the AHRQ report. Effect sizes in comparison to sham and no	The PICOTS in the published protocol and report describe the exclusion criteria; trials excluded at full text and reason for exclusion are identified in the report appendix. We have verified the accuracy of the data in our report against the original publications. Our report includes results of stratified analyses by control type and reporting of instances where results differ when sham vs. usual care are used as controls.

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		acupuncture control are combined, an unusual methodologic approach for which no justification is provided and which is applied arbitrarily in the case of three arm trials, with controls being combined in some but not all cases.	<p>Molsberger - This study did not meet our inclusion criteria and was excluded at the title/abstract review phase. Studies of adjunctive treatment did not meet our inclusion criteria.</p> <p>Brinkhaus 2006 - the waitlist group was excluded from this report because they received 12 sessions of acupuncture 8 weeks after randomization (i.e., immediately after the true and sham groups completed their treatment periods); thus, the "pure" waitlist group did not have any data 1 month post-"treatment" (an inclusion criteria) that could be compared to the true acupuncture group. A note to this effect was included in the detailed data abstraction tables in the Appendix.</p> <p>Haake 2007 (GERAC trial) - was included in the report.</p> <p>Stratified analysis by control type (sham versus usual care/no acupuncture) were done and are reported in the full report.</p>
Public Commenter #20 [Andrew Vickers, PhD Acupuncture Trialists']	General	In sum, the AHRQ reports bases its findings on a meta-analytic methodology that is known to be inferior to IPD, but completely ignores the findings of an IPD meta-analysis. Even a cursory review of the AHRQ report reveals missing papers, miscategorized papers, and effect size estimates discordant	Thank you for your comments. We have added a sentence to the disucssion indicating that our results are based on study-level data and that our overall conclusions regarding some

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Collaboration]		<p>with the published literature. These are clearly extremely serious issues that would need to be addressed in any revised report.</p> <p>Yours, Andrew Vickers On behalf of the Acupuncture Trialists' Collaboration.</p>	<p>benefit are similar for some conditions.</p>
Public Commenter #21 [Paul Gerrard, MD American Academy of Physical Medicine and Rehabilitation (AAPMR)]	General	<p>Re: Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>To whom it may concern:</p> <p>This is comprehensive review in both breadth and depth that covers a wide range of mostly non-pharmacologic approaches to the treatment of pain. However, there are a number of limitations.</p> <p>While this review is comprehensive in its depth and breadth, it makes the error of treating movement-based and mind-body interventions like oral medications, which they are not. In particular it does not appropriately assess for heterogeneity of the interventions. Such assessments require a careful examination of the details of intervention protocols. This is a challenge that many researchers have in understanding and interpreting movement and mindfulness-based healthcare interventions, which is what most non-interventional non-pharmacologic interventions are.</p> <p>While this review does not present many strong conclusions for nearly any of the interventions studied, the categorization approach of a large and influential organization like AHRQ may be used as a precedent for future guideline development, which makes it essential that the method of categorizing</p>	<p>Thank you for your perspective. 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 are different perspectives on where various interventions could be classified.</p> <p>Details of the intervention (as provided in the trials) were abstracted and presented in the report tables; as noted in the discussion, there is substantial heterogeneity with regard to components of interventions even those within the same general type of intervention. We are aware that there is a lack of standard terminology for describing (or categorizing) various types of therapies, including those related to mind-body interventions. We are aware that styles of Tai-Chi, Yoga, and other interventions may differ and that naming of various styles is a function of the lineage to which they are ascribed. Even though all</p>

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		<p>studies in this review being given careful thought.</p> <p>The review explicitly separates Tai-Chi, Yoga, Qi-Gong, and exercise. However, it lumps Pilates in with exercise-based therapy. It is critical to keep in mind that Tai Chi, Yoga, and Qi Gong are all kinds of exercise-based interventions, and each of which also includes a mind-body component. Pilates, like Tai Chi, Yoga, and Qi Gong, is also an exercise-based therapy with a particular set of movements and its own mind-body approach. As such, the categorization of studies in this review is essentially arbitrary, but that is really a symptom of the larger problem. The real question that both researchers and health care providers need to know is: What kinds of movements are important for movement-based therapy to succeed, and what kinds of mindfulness based interventions are needed? Is there a benefit in integrating the two? What someone chooses to call the intervention is not important. For example, in Table 40, describing the results of mind body interventions for fibromyalgia, the Wang, 2010 study compares Tai Chi to an attention control. This study is considered to examine a mind-body therapy. However, if one looks at the details of the two interventions in the Wang study, the Tai Chi group does active movements (i.e. exercise), and the attention control does stretching. While philosophically, a Tai Chi practitioner might agree with calling Tai Chi a mind-body therapy, what is <i>de facto</i> being studied is exercise vs stretching.</p> <p>Additionally, none of these named approaches truly represents a homogenous or regimented approach to rehabilitation. While Tai Chi, Yoga, and Qi Gong all have a deep history in East Asian culture, there are many different modern variants on each. In some respects, this review recognizes this</p>	<p>movement-related Yoga is considered under the umbrella of "hatha" yoga, some styles may be more alignment-based (e.g., Iyengar Yoga, Anusara Yoga) than others (e.g. hot yoga, power yoga), so providing labels as described by the investigators may confer some information regarding the approach taken and its potential benefits and risks and suitability for a given patient.</p> <p>We did sub-analyses based on intervention subtype as well as type of control and study quality to assess these as potential sources of heterogeneity. The results are described in the full report. We noted when heterogeneity was present in an analysis and attempted to ascertain why. In some instances, it is not clear what factors may have influenced heterogeneity.</p>

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		<p>in the information it presents in the tables but not in its synthesis and conclusions. For example, Iyengar Yoga (studied in low back pain in reference 174) is widely considered a style of Hatha Yoga (which is recognized as a distinct yoga approach in other studies in Table 11). Iyengar Yoga is quite literally the yoga approach of a single practitioner, BKS Iyengar. Since BKS Iyengar is well known enough in the yoga community, his approach to Hatha Yoga has been given its own name, however, lesser known Hatha yogis may have equally unique takes on Hatha yoga that do not get distinguished with their own names and as such simply get called “Hatha Yoga.” The name assigned to the movement based therapy may have more to do with the educational tradition in which the instructor who is teaching the set of movements has been educated than the actual movements used in the therapies. However, the name has no physiologic impact on the patient; the movements do.</p> <p>In summary, this review distinguishes interventions based on the name that study investigators chose to assign to the movement-based therapy rather than based on the substance of the activities done within the interventions, particularly in the discussions of the results. This is where movement and mindfulness intervention studies must be read in a different way than pharmacologic studies. Put another way, the names that study investigators choose to assign to their interventions do not have a clear meaning in the same way that other terms (e.g. the names of drugs) in healthcare do, yet this study relies on those names.</p> <p>Perhaps the most dangerous element of this review is that by relying too heavily on names of the interventions healthcare providers, policy makers, and patients could easily be misled</p>	

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		<p>into believing or not believing that an intervention is worth pursuing (or paying for) based on its name rather than based on what is actually done for patient.</p> <p>This review assesses for statistical heterogeneity of the outcomes of the studies and in a number of places finds it. A key question when statistical heterogeneity is found in the outcomes of studies is: What is causing that heterogeneity? In this case, arbitrary binning of heterogeneous interventions under the same heading may be one of the major sources, but this is not adequately assessed.</p> <p>Such limitations in this review should either be corrected or explicitly acknowledged.</p> <p>Sincerely, Paul Gerrard, MD on behalf of the American Academy of Physical Medicine and Rehabilitation</p>	
Public Commenter #21 [Paul Gerrard, MD American Academy of Physical Medicine and Rehabilitation (AAPMR)]	Evidence Summary	<p>On behalf of The American Academy of Physical Medicine and Rehabilitation:</p> <p>In summary, this comprehensive review does not adequately assess the actual activities that comprise the interventions studied. Unlike medications for which a name means something very clear, a single pharmacologic substance, movement-based and mind-body interventions, especially those that come from cultural traditions, are not reliably and accurately described by the names assigned to them. This review relies heavily on assigned names chosen for the study interventions by investigators rather than examining the actual substance of the interventions regardless of the name. A full explanation is presented in the submitted word document.</p>	<p>Thank you for your perspective. There is no standard method for categorizing many of the interventions. We realize that other may categorize interventions differently than we have and that there are different perspectives on where various interventions could be classified.</p>

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Public Commenter #22 [Anonymous]	General	<p>Point and Counterpoint to the Prevailing Narrative about Opioids and the “Opioid Epidemic” By Maxx Lamb</p> <p>Comments on “Policy for Prescribing and Dispensing Opioids” Pain has extremely serious physiological consequences that can and do lead to death if the pain is left unrelieved, particularly when it is severe (Middleton, 2003) (Epel, 2004) (McEwen, 2004) (WHO, 2000) (Tennant, 2011). The seriousness of these consequences are not to be understated, as pain slows wound healing (Middleton, 2003), which is particularly pertinent post-surgically, but is equally so in chronic conditions involving repetitive tissue damage. Infections are more likely if pain is left unrelieved post-surgically (Walder, 2001), and it slows down wound healing</p> <p>More than 85% of “overdose” deaths from opioids were in fact not due to opioids obtained from a doctor’s prescription, but illicitly manufactured fentanyl, as this is responsible for the vast majority of the deaths (Kertesz, 2016). As such, it is illogical to restrict prescription opioids, as this will only worsen the situation. I anticipate others who comment will describe why, or if you review any of the cited articles herein, it will become apparent (Scholten and Henningfield, 2016).</p> <p>Less than 1% of the global need for opioids for pain relief is met (Knaul et al., 2017). This is the case despite the fact that opioids are used for far more often for legitimate purposes than they are abused (Mizonni et al., 2012) (Bartleston, 2002). Further, fewer than 0.7% of people filling prescriptions for opioids are doctor shoppers in the U.S. (McDonald and Carlson, 2013), and 89% of “prescription opioids” that end up on the street are from thefts of pharmacies, hospitals, etc.</p>	Thank you for your comments.

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		<p>(Joranson and Gilson, 2005).</p> <p>With the understanding that fewer than 7% of the world’s population has access to pain relief when it is desperately needed (acute situations like broken arms and other injuries, people with chronic intractable pain, and the terminally ill), the statement that the U.S. consumes more opioids than any other country, and even more than all of them combined illustrates the profound lack of availability of these drugs for medical uses. Increases in the past of opioid use should not be alarming –in fact, they should be encouraging–because worldwide, pain is undertreated, and people suffer and die in agony needlessly (Seya, 2011).</p> <p>Despite being used as an excuse to permit the needless suffering of millions worldwide, opioids do not produce addiction in between 96% and 99..81% of the time (Fishbain et al., 2008) and overdose occurs less than a fraction of a percent of the time in regards . Mizonni et al., and Mcauliffe et al. found similarly low rates of addiction occurring due to administration of opioids for pain, as did Furlan and colleagues (Minozzi et al., 2012) (Mcauliffe et al., 2013) (Furlan et al., 2006). In a Cochrane review on the matter, the authors likewise concluded that there was not a significant risk for addiction upon exposure to opioids long term (Noble et al., 2010) (Bartleston, 2002), it becomes clear that the U.S. consuming more opioids than anyone else simply reflects the fact that the United States was managing pain better than it is now (Laires et al., 2017) (Tennant, 2015), but that we have slumped down towards where much of the rest of the world lies—that is in a place where people needlessly suffer by the millions (Knaul et al., 2017). Reports of patient suicides due to inadequate treatment and being forcefully tapered off of their</p>	

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		<p>previously stable does of opioids abound in the U.S. (Kline and Lamb, 2017) since availability has been drastically reduced.</p> <p>There are serious physiological consequences to pain being left untreated (Middleton, 2003) (Seminowicz et al., 2011) (Masart et al., 2016) (WHO, 2000).</p> <p>Chronic pain is a form of chronic stress, as all pain is an extreme form of stress (Blackburn-Munro, 2001) The consequences of chronic pain when left untreated or undertreated include, but are not limited to:</p> <ul style="list-style-type: none"> • “Stress could potentially lead to oxidative stress by means of chronic activation of the autonomic and neuroendocrine stress responses.” This leads to accelerated DNA damage and aging (Epel, 2004) (Mcewen, 2004) • So called chronic non-malignant pain predicts death within 10 years (Grol-Prokopczyk, 2016) • Cognitive issues, (brain fog) and memory problems (Porta et al. 2015) • “Atrophy of nerve cells in the brain” (Mcewen, 2004) • Changes in DNA (Massart et al., 2016) • “Impaired immunity” (Mcewen, 2004) • “Major depressive illness and may be expressed also in other chronic anxiety disorders” (Mcewen, 2004) • “Obesity” (Mcewen, 2004) • “Bone demineralization” (Mcewen, 2004) • Disability, (Lohman, 2010) • Suicide and/or a desire for death (WHO, 2000) • Heart Attack and/or Stroke (Tennant, 2011) (Middleton, 2003) <p>“Unrelieved pain can impair all aspects of a person’s life, including appetite, mood, self-esteem, relationships with</p>	

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		<p>others, and even the ability to move. In some countries, it has been reported that unrelieved pain can lead to the wish for death and inquiries about euthanasia and assisted suicide. Relief of pain has been demonstrated to improve quality of life.” (WHO, 2000)</p> <p>Chronic pain reduces the lifespan substantially. As Grol-Prokopczyk, 2016 noted, “...higher pain at baseline predicts death even 10 to 12 years later. Pain serves as a long-term mortality risk,” It causes heart conditions, accelerated cellular aging, and death from suicide (Masart et al., 2016). Memory impairment, shortened life expectancy, depression, and decreases in brain volume that are reversible with adequate treatment (Seminowicz et al., 2011) are on the list of reasons why pain must be adequately treated.</p> <p>“Unrelieved pain can impair all aspects of a person’s life, including appetite, mood, self-esteem, relationships with others, and even the ability to move. It has been reported that unrelieved pain can lead to the wish for death and inquiries about euthanasia and assisted suicide. Relief of pain has been demonstrated to improve quality of life.” (WHO, 2000)</p> <p>As if these consequences were not enough, “Chronic pain is a one of the most significant causes of suffering and disability worldwide,” (Lohman, 2010) Yet, people in chronic pain have little-to-no access to treatment in the U.S. though, it is worse elsewhere in the world, particularly where they have no access at all. This is precisely why our overall opioid consumption was not too high as many political figures have stated, and the recent decreases in opioid prescribing have caused a great deal of harm to a multitude of people. One need only seek out the nearest Facebook support group for chronic pain patients</p>	

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		<p>to see the people who are now bedridden due to pain, whereas before they lost access to adequate treatment they were functional, productive human beings, often holding down jobs. This is the context surrounding the statement that the United States consumes more opioids than any other country.</p> <p>Sources</p> <p>Bartleson, J. D. "Evidence For and Against the Use of Opioid Analgesics for Chronic Nonmalignant Low Back Pain: A Review: Table 1." Pain Medicine 3.3 (2002): 260-71. Web.</p> <p>Blackburn-Munro, G., and R. E. Blackburn-Munro. "Chronic Pain, Chronic Stress and Depression: Coincidence or Consequence?" Journal of Neuroendocrinology 13.12 (2001): 1009-023. Web</p> <p>Cowan, David T., Jenifer Wilson-Barnett, Peter Griffiths, and Laurie G. Allan. "A Survey of Chronic Noncancer Pain Patients Prescribed Opioid Analgesics." Pain Medicine 4.4 (2003): 340-51. Print.</p> <p>Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. The changing face of heroin use in the United States: a retrospective analysis of the past 50 years. JAMA Psychiatry. 2014;71(7):821–826. doi:10.1001/jamapsychiatry.2014.366. Notes:</p> <p>Daniulaityte, Raminta, Matthew P. Juhascik, Kraig E. Strayer, Ioana E. Sizemore, Kent E. Harshbarger, Heather M. Antonides, and Robert R. Carlson. "Morbidity and Mortality Weekly Report (MMWR)." Centers for Disease Control and Prevention. Centers for Disease Control and Prevention, 31 Aug. 2017. Web. 03 Nov. 2017.</p> <p>Epel, E. S., E. H. Blackburn, J. Lin, F. S. Dhabhar, N. E. Adler, J. D. Morrow, and R. M. Cawthon. "Accelerated Telomere Shortening in Response to Life Stress." Proceedings of the</p>	

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		<p>National Academy of Sciences 101.49 (2004): 17312-7315. Web.</p> <p>Fine, P. G. (2011). Long-Term Consequences of Chronic Pain: Mounting Evidence for Pain as a Neurological Disease and Parallels with Other Chronic Disease States. <i>Pain Medicine</i>, 12(7), 996-1004. doi:10.1111/j.1526-4637.2011.01187.x</p> <p>Fishbain, David A., Brandly Cole, John Lewis, Hubert L. Rosomoff, and R. Steele Rosomoff. "What Percentage of Chronic Nonmalignant Pain Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction And/or Aberrant Drug-Related Behaviors? A Structured Evidence-Based Review." <i>Pain Medicine</i> 9.4 (2008): 444-59. Web.</p> <p>Furlan, Andrea D., Juan A. Sandoval, Angela Mailis-Gagnon, and Eldon Tunks. "Opioids for Chronic Noncancer Pain: A Meta-analysis of Effectiveness and Side Effects." <i>Canadian Medical Association Journal</i> 174.11 (2006): 1589-594. Web</p> <p>Grol-Prokopczyk, Hanna. "Sociodemographic Disparities in Chronic Pain, Based on 12-year Longitudinal Data." <i>Pain</i> 158.2 (2017): 313-22. Web.</p> <p>Inturrisi, Charles E. "Clinical Pharmacology of Opioids for Pain." <i>The Clinical Journal of Pain</i> 18.Supplement (2002): n. pag. Web.</p> <p>Joranson, David E., and Aaron M. Gilson. "Drug Crime Is a Source of Abused Pain Medications in the United States." <i>Journal of Pain and Symptom Management</i> 30.4 (2005): 299-301. Web.</p> <p>Kertesz, Stefan G. "Turning the Tide or Riptide? The Changing Opioid Epidemic." <i>Substance Abuse</i> 38.1 (2016): 3-8. Web.</p> <p>Kline, Thomas, and Maxx Lamb. "Suicides: Associated with Non-consented Opioid Pain Medication Reductions." <i>Medium</i>. Medium, 29 Sept. 2017. Web. 03 Nov. 2017.</p> <p>Knaul Et Al., Felicia Marie. "Alleviating the Access Abyss in Palliative Care and Pain Relief-an Imperative of Universal</p>	

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		<p>Health Coverage: The Lancet Commission Report." The Lancet. Elsevier, 12 Oct. 2017. Web. 03 Nov. 2017.</p> <p>Kreek, M. J., and K. S. Laforge. "Stress Responsivity, Addiction, and a Functional Variant of the Human Mu-Opioid Receptor Gene." Molecular Interventions 7.2 (2007): 74-78. Web.</p> <p>Kroenke, Kurt, and Andrea Cheville. "Management of Chronic Pain in the Aftermath of the Opioid Backlash." Jama (2017): n. pag. Web.</p> <p>Laires, Pedro A., Jorge Laíns, Luís C. Miranda, Rui Cernadas, Srinirajagopalan, Stephanie D. Taylor, and José C. Silva. "Inadequate Pain Relief among Patients with Primary Knee Osteoarthritis." Revista Brasileira De Reumatologia (English Edition) 57.3 (2017): 229-37. Print.</p> <p>Lohman, Diederik, Rebecca Schleifer, and Joseph J. Amon. "Access to Pain Treatment as a Human Right." BMC Medicine 8.1 (2010): n. pag. Web.</p> <p>Massart, Renaud, Sergiy Dymov, Magali Millecamps, Matthew Suderman, Stephanie Gregoire, Kevin Koenigs, Sebastian Alvarado, Maral Tajerian, Laura S. Stone, and Moshe Szyf. "Overlapping Signatures of Chronic Pain in the DNA Methylation Landscape of Prefrontal Cortex and Peripheral T Cells." Scientific Reports 6.1 (2016): n. pag. Web</p> <p>Mcauliffe, William E., Silvia Minozzi, Laura Amato, and Marina Davoli. "A Critique of Minozzi et al.'s Pain Relief and Dependence Systematic Review, and Authors' Response." Addiction 108.6 (2013): 1162-171. Print.</p> <p>McDonald, Douglas C., and Kenneth E. Carlson. "Estimating the Prevalence of Opioid Diversion by "Doctor Shoppers" in the United States." PLOS ONE. Public Library of Science, 17 July 2013. Web. 03 Nov. 2017.</p> <p>Mcewen, Bruce S. "Protection and Damage from Acute and Chronic Stress: Allostasis and Allostatic Overload and Relevance to the Pathophysiology of Psychiatric Disorders."</p>	

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		<p>Annals of the New York Academy of Sciences1032.1 (2004): 1-7. Web.</p> <p>Middleton, Carolyn. "Understanding the Physiological Effects of Unrelieved Pain." Nursing Times. N.p., 16 Sept. 2003. Web. 07 May 2017.</p> <p>Minozzi, Silvia, Laura Amato, and Marina Davoli. "Development of Dependence following Treatment with Opioid Analgesics for Pain Relief: A Systematic Review." Addiction 108.4 (2012): 688-98. Print.</p> <p>Morgan, Michael M., and Macdonald J. Christie. "Analysis of Opioid Efficacy, Tolerance, Addiction and Dependence from Cell Culture to Human." British Journal of Pharmacology 164.4 (2011): 1322-334. Print.</p> <p>Noble, Meredith, Jonathan R. Treadwell, Karen M. Schoelles, Philip J. Wiffen, Clarisse Akafomo, Vivian H. Coates, Stephen J. Tregear, and Roger Chou. "Long-term Opioid Management for Chronic Noncancer Pain." Wiley. John Wiley & Sons, Ltd, 20 Jan. 2010. Web. 03 Nov. 2017.</p> <p>O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016. MMWR Morb Mortal Wkly Rep 2017;66:1197–1202. DOI: http://dx.doi.org/10.15585/mmwr.mm6643e1</p> <p>Scholten, Willem, and Jack E. Henningfield. "Negative Outcomes of Unbalanced Opioid Policy Supported by Clinicians, Politicians, and the Media." Journal of Pain & Palliative Care Pharmacotherapy 30.1 (2016): 4-12. Web.</p> <p>Seminowicz, D. A., T. H. Wideman, L. Naso, Z. Hatami-Khoroushahi, S. Fallatah, M. A. Ware, P. Jarzem, M. C. Bushnell, Y. Shir, J. A. Ouellet, and L. S. Stone. "Effective Treatment of Chronic Low Back Pain in Humans Reverses Abnormal Brain Anatomy and Function." Journal of Neuroscience 31.20 (2011): 7540-550. Web.</p>	

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		<p>Seya, Marie-Josephine, Susanne F. A. M. Gelders, Obianuju Uzoma Achara, Barbara Milani, and Willem Karel Scholten. "A First Comparison Between the Consumption of and the Need for Opioid Analgesics at Country, Regional, and Global Levels." <i>Journal of Pain & Palliative Care Pharmacotherapy</i> 25.1 (2011): 6-18. Web.</p> <p>Tennant, Forest. "Editor's Memo: The Inhumane and Dangerous Game of Forced Opioid Reduction." <i>Practical Pain Management</i>. Practical Pain Management, Sept. 2015. Web. 03 Nov. 2017.</p> <p>Tennant, Forest, MD. "Treat the Pain... Save a Heart." <i>Practical Pain Management</i>. Practical Pain Management, 7 Mar. 2011. Web. 03 Nov. 2017.</p> <p>Walder, B., et al. "Efficacy and Safety of Patient-Controlled Opioid Analgesia for Acute Postoperative Pain." <i>Acta Anaesthesiologica Scandinavica</i>, Munksgaard International Publishers, 20 Dec. 2001, onlinelibrary.wiley.com/doi/10.1034/j.1399-6576.2001.045007795.x/full.</p> <p>WHO. "ACHIEVING BALANCE ACHIEVING BALANCE IN NATIONAL IN NATIONAL OPIOIDS OPIOIDS CONTROL POLICY." N.p., 2000. Web.</p> <p>WHO. "Achieving Balance In National Opioids Control Policy." N.p., 23 Jan. 2010. Web. 08 May 2017.</p>	
Public Commenter #22 [Anonymous]	Evidence Summary	<p>It is imperative to recall that unrelieved chronic pain, particularly intractable, severe chronic pain when left unrelieved will cause often deadly consequences, and when pain is intractable—not responsive to more conservative treatments—it is important to acknowledge the utility and importance of alleviating suffering, and how opioid analgesics are often a part of the multimodal, interdisciplinary care required to manage particularly extremely painful disorders,</p>	Thank you for your comments.

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		like Ehlers Danlos Syndrome (Hypermobility Type), arachnoiditis, cancer, spondylitis, CRPS/RSD, etc.	
Public Commenter #23 [Matthew Bauer, L.Ac. Acupuncture Now Foundation]	General	<p>See attachment for further details. The authors make 3 recommendations:</p> <p>Recommendation #1. Separate effectiveness rates for the types of controls employed especially to segregate sham controls from other types of controls.</p> <p>Recommendation #2. Consider conducting a subgroup analysis for clinical quality issues such as treatment number/frequencies over time or at least explain your reviewers rational for how clinical quality issues such as these were considered or not considered in developing the research inclusion criteria. Also consider adding the 2007 E. Miller “Delayed Effects” trial to your review.</p> <p>Recommendation #3. Where possible, this review should make note of the training level of the practitioners.</p>	<p>#1: Data from stratified analyses based on control type were done and and results reported in the full report; in some instances there was little difference. We've edited the evidence summary to note instances where they differed.</p> <p>#2: Data on intervention frequency, duration, etc. were abstracted as reported in the trials are are reflected in the report results tables. There were insufficient data to conduct subgroup analyses based on treatment characteristics. Adherence was poorly reported across trials and was assessed as part of the risk of bias assesement. <i>Miller E, Maimon Y, Rosenblatt Y et al. Delayed Effect of Acupuncture Treatment in OA of the Knee: A Blinded, Randomized, Controlled Trial. Evid Based Complement Alternat Med. 2011;2011:792975. doi: 10.1093/ecam/nen080. PMID: 19124552.</i></p> <p>This study was excluded at the title/abstract triage phase: the abstract states that standard therapy could include "NSAIDS, cyclooxygenase-2 inhibitors,</p>

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			acetaminophen, intra-articular hyaluronic acid and steroid injections." Other references were also reviewed and studies were either already included, previously excluded, or did not meet the inclusion criteria. #3: Training/licensure of practioners was not routinely collected.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	Evidence Summary	The executive summary correctly notes some of the shortcomings inherent in research on non-pharmacological treatments for pain. The lack of trials with extended follow-up and with active comparator arms including opioids and other pharmacological treatments can be traced, in most cases, to the inadequacy of funding for this line of research. Many studies of non-pharmacological treatments also are challenged by the difficulty inherent in adequately blinding both subjects and providers. We also note that, in this review, unblinded studies of various psychotherapies are rated as 'fair' in quality, at best; obviously, it is not possible to blind therapists to the type of therapy they are allowing, so other reviews have treated such studies as being of a higher quality. As a result, the body of research tends toward low-to-moderate quality of evidence, and a large number of studies needed to be excluded due to lack of adequate follow-up. It should be noted that the lack of follow-up is most acutely noticed in the 6-to-12 month range, and that this same limitation is found in much of the research for pharmacological treatments for pain, especially opioids. Nonetheless, the finding that the research supports the efficacy of a variety of interventions across a number of common painful conditions is encouraging, and the summary rightly notes the need for improving research in the future.	Thank you for your comments. Yes, there is less evidence in the 6-12 month and >12 month time-frames. We have added information to the discussion regarding the parallels with pharmacological treatments.

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Public Commenter #24 [Robert Twillman, PhD] The Academy of Integrative Pain Management (AIPM)]	Introduction	<p>The introduction succinctly describes the rationale for the study and the overall outline of the methods. It lists interventions that were included, but does not indicate the basis on which those interventions were selected. Additionally, the "lumping" of interventions raises some concerns. For instance, in the psychological therapies category, there are two distinct types of psychological therapies listed; cognitive-behavioral therapy (CBT) and acceptance and commitment therapy (ACT) are very similar to each other, and use similar therapeutic techniques, while biofeedback and relaxation techniques are very similar to each other, but are different from CBT and ACT. Similarly, a wide variety of techniques is considered together in the physical modalities category. A justification, or at least an explanation, for these decisions would be welcomed, and if possible, sub-analysis of the various therapies is warranted.</p>	<p>Thank you for your comments.</p> <p>Where data were available we did sensitivity analyses and stratification on various aspects of interventions (e.g., types of exercise, different psychological therapies, etc.), and results are presented in the report. We have made some edits to the evidence summary for clarification regarding specific psychological therapies.</p>
Public Commenter #24 [Robert Twillman, PhD] The Academy of Integrative Pain Management (AIPM)]	Methods	<p>The exclusion of studies evaluating the incremental value of adding a noninvasive, nonpharmacological intervention to another noninvasive, nonpharmacological intervention creates a situation in which treatments are being evaluated in something other than a real-world application. In most clinical settings, these types of treatments are combined into a "package" of interventions specific to each individual patient. By excluding these "additive" studies, the current review does zero in on the unique effects attributable to each intervention, but it removes the findings one step from real world applications of those interventions. Again, this method is consistent with the manner in which most systematic reviews are conducted, but we wonder if there might be benefit in analyzing these excluded studies to produce a result that is more meaningful to clinicians treating people with chronic pain.</p>	<p>We recognize 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 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 and would vastly expand the scope of the report beyond available resources.</p>

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Public Commenter #24 [Robert Twillman, PhD] The Academy of Integrative Pain Management (AIPM)]	Results	The Results section is comprehensive and meticulously organized. Some of the sub-analyses suggested above are presented in the results section, which begs the question as to why note was not made of that fact in previous sections.	Where there are substantial differences in effect estimates based on sub-analyses these are noted in the report. The use of subanalyses is described in the methods. For some areas, there were insufficient data to do subanalyses.
Public Commenter #24 [Robert Twillman, PhD] The Academy of Integrative Pain Management (AIPM)]	Discussion	The discussion is thorough and considers a number of factors related to selection of studies for this review, as well as the applicability of these findings to clinical practice and policymaking. Limitations and research recommendations are identified, and are comprehensive in their scope. Given the a priori decisions about the criteria used to select studies, the discussion is on point and offers valuable insights into the existing data. Of course, there are many studies of nonpharmacological treatments that were not included as a result of the selection criteria, and perhaps a point should be made that systematic reviews containing those studies could still yield some valuable guidance for clinicians and policymakers. The discussion calls out the need for pragmatic trials of these individual interventions and of combinations of these interventions, a point with which we agree wholeheartedly. In our experience, in real-world clinical settings, these treatments are often combined with each other, as well as with pharmacological treatments, and systematic study of all the available combinations via RCT methodology is impractical. Therefore, focusing more on the effectiveness of what currently happens in the real world seems as though it would be more productive, in a shorter time frame.	Thank you for your comments
Public Commenter #24 [Robert Twillman,	Tables	The tables are presented in a well-organized and intuitive manner.	Thank you.

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PhD The Academy of Integrative Pain Management (AIPM)]			
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	Figures	The tables are presented in an intuitive manner.	Thank you.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<p>Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>Supplemental comments submitted to the Agency for Healthcare Research and Quality December 21, 2017</p> <p>The Academy of Integrative Pain Management (AIPM) is the nation's largest organization for pain management professionals. As its name implies, AIPM promotes an integrative model of pain care, one that conceptualizes pain as a biopsychosocial-spiritual experience and uses all available treatments to design a unique comprehensive care plan for each person with pain, with a goal of restoring that person to optimal health and wellness. AIPM collaborates with many organizations representing the full range of licensed and certified healthcare professionals and a wide variety of treatment modalities. These comments were informed by discussions with the groups listed at the end of the document.</p> <p>We are grateful for the efforts of the Agency for Healthcare Research and Quality (AHRQ) in pulling together this</p>	Thank you for your comments.

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		systematic review. This was a very large-scale undertaking, and the effort required to complete this review was substantial. The review follows standard scientific methodology for systematic reviews, and as such, presents a robust set of findings that are very well-grounded in the evidence that was considered for the study. The review finds that there is at least some evidence of efficacy for a wide variety of nonpharmacological pain treatments, both in terms of pain intensity and degree of functioning. The review also identifies shortcomings in the existing body of literature, and recommends research strategies designed to overcome these shortcomings.	
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<p>In discussion with our collaborators, several themes have emerged. We will enumerate those themes and briefly present our concerns related to each.</p> <ul style="list-style-type: none"> • <i>Psychological Therapies</i>: In the review, four specific types of psychological therapy are grouped together for purposes of analysis. Specifically, cognitive-behavioral therapy, acceptance and commitment therapy, biofeedback, and relaxation therapy are all subsumed under the category of psychological therapies. While it is true that these are all psychological therapies, they have differences foci for their interventions and probably should not be considered as one aggregate category. Cognitive-behavioral therapy and acceptance and commitment therapy focus primarily on modifying the thoughts patients have regarding their painful experiences. Biofeedback and relaxation therapy, on the other hand, focus primarily on inducing a state of relaxation, rather than modifying thought patterns. We suggest that, if possible, these therapies be subjected to sub-analyses as delineated here. 	The types of interventions are labeled in the forest plots and sub-analyses based on type of therapy; these are presented in the full report where there were sufficient data to do so.
Public Commenter #24	General	<ul style="list-style-type: none"> • <i>Massage Therapy</i>: Our massage therapy collaborators raise a concern that the review's inclusion criteria for studies are too 	We acknowledge that immediate/short-term relief is of

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[Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]		restrictive to capture the best and most relevant massage therapy research. Massage therapy studies typically last only two to three weeks, causing most of the massage therapy literature to be excluded. Additionally, the review's focus on the persistence of results over follow-up periods of up to a year suggests an assumption that massage therapy's effects extend well beyond the intervention period; this assumption is not supported by the profession. Recommendations for additional studies that should be considered are attached at the end of this document.	value, however, given that the conditions are chronic, evaluation of the sustainability of effects for at least 1 month was felt to be most informative. Studies with at least 1 month of follow-up were included. We have noted that some treatments may be continued into a longer term in a real clinical setting. All citations provided were reviewed; studies were either previously excluded or did not meet the inclusion criteria.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<ul style="list-style-type: none">• <i>Acupuncture</i>: Our collaborators recommend that you acknowledge the Australian Acupuncture Evidence Project¹ as a resource regarding the effectiveness and safety of acupuncture. They also note the previous publication of an AHRQ/CG CAHPS survey² regarding patient satisfaction, quality of service, and response rate in acupuncture patients, and suggest a reference to this in the discussion section of the review. Additionally, they note a recent publication in The Integrative Medicine Journal³, which raises some concerns about the ability for acupuncture studies to be designed in a manner consistent with the standards for drug trials—a factor that can lead to the exclusion of many acupuncture trials from a systematic review such as this. Recommendations for additional studies that should be considered are attached at the end of this document.	Thank you for your comments; Where data were available, information on quality of life for all interventions is reported. These were considered secondary outcomes are described in the full report. All citations provided were reviewed; studies were either previously excluded or did not meet the inclusion criteria.
Public Commenter #24 [Robert Twillman, PhD The Academy of	General	<ul style="list-style-type: none">• <i>Combinations of interventions</i>: Several of our collaborators noted that, while the review studies the efficacy of interventions in isolation from each other, in the real world, patients often receive combinations of nonpharmacological treatments, +/- pharmacological treatments. While the results	Thank you for your comments. We recognize that in practice, individuals would not receive a single therapy. An important first step to evaluating the efficacy of a therapy is

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Integrative Pain Management (AIPM)]		of this study are informative, studies that take a more pragmatic, real-world approach to the delivery of integrative pain care should be conducted. It is possible that the effects of combined treatments are synergistic, and that studies demonstrating this point could have a significant impact on insurance coverage. This point can easily be made in the discussion section of the review.	to evaluate it as an isolated therapy. In addition, given the multitude of combinations of therapies and 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 and would vastly expand the scope of the report beyond available resources.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<ul style="list-style-type: none">• <i>Delivery of services:</i> It is unclear from this review if the efficacy of the interventions differs if those interventions are delivered by licensed providers for those therapies (e.g., licensed acupuncturists, licensed massage therapists) or by primary care or other providers who are not specifically licensed to provide the treatments (e.g., massage therapy delivered by a physical therapist, or acupuncture delivered by a physiatrist).	Thank you for your comments. We did not abstract information regarding the licensure status of providers.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<ul style="list-style-type: none">• <i>Role of patient education:</i> Several collaborators raised questions about the role of patient education about pain as a nonpharmacological intervention. It is the feeling of our collaborators that education can have a beneficial effect for a variety of reasons, including improved treatment adherence. The suggestion was made to expand the review to include patient pain education as an additional nonpharmacological intervention.	Thank you for the suggestion. Self-management and self-management education programs were considered, however their inclusion would have expanded the scope of this project beyond available resources; thus they were excluded from this report.
Public Commenter #24 [Robert Twillman, PhD The Academy of	General	<ul style="list-style-type: none">• <i>Support groups and patient self-management programs:</i> These are additional nonpharmacological interventions with bodies of existing evidence demonstrating their efficacy. The suggestion was made to include them in the review.	Thank you for the suggestion. Self-management and self-management education programs were considered, however their inclusion would have expanded the scope of this project beyond available resources,

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Integrative Pain Management (AIPM)]			particularly given the variability in such programs; thus they were excluded from this report.
Public Commenter #24 [Robert Twillman, PhD The Academy of Integrative Pain Management (AIPM)]	General	<ul style="list-style-type: none"> • <i>Patient selection and comorbidities:</i> The draft notes that the issue of comorbid physical and mental conditions is beyond the scope of the review, and that the presence of these conditions might not even be mentioned in most studies. However, a few of our collaborators point out that these are key factors that can significantly influence the efficacy of nonpharmacological therapies. At a minimum, this should be a specific point in the discussion section, with a call for further research to delineate these effects. Patient selection for future trials should consider these factors. 	Thank you for your comments. We recognize the importance of such factors. There were insufficient data in included studies to evaluate their impact. Perhaps future research can include such evaluations.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	1. The title of the report does not accurately reflect the work product: Given the stated objective to assess the effectiveness of opioid alternatives, being clear and factual is imperative. “Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review” implies that all noninvasive and nonpharmacologic treatments for chronic pain are included in this analysis. Further, it suggests an analysis of the whole body of evidence has been conducted. Neither are factually accurate. In truth, chiropractic care has not actually been reviewed. One cannot with any credibility conduct a systematic review of five conditions with just eight studies.	<p>Thank you for your perspective. The review scope, framework, Key Questions, PICOTS inclusion/exclusion criteria were honed based on input a group of Key Informants and a Technical Expert Panel to obtain broad perspective and expertise as described in the front matter of the report in order to make best use of the resources available for this review. The EPC used methodology prescribed in the AHRQ Methods guide to provide a methodologically sound report and mitigate the potential for bias.</p> <p>Studies of included interventions, including any which may be done by chiropractors, osteopaths or other provider types were included if the PICOTS inclusion criteria were met.</p>

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			There was no intent or attempt to exclude any provider type.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	2. All noninvasive, nonpharmacological treatments are not represented with equal vigor: A review of both the search strategy and the review methods confirm that chiropractic was never a specific search term, while other therapies were included as specific search terms. These include acupuncture, massage, mind-body therapies, meditation, qi-gong, and yoga. As a result, the term chiropractic only appears once in the text of the report, on page 219. The term appears only in passing, not as part of the review. There are only 8 out of 884 papers listed as part of the appendix bibliography in which the word chiropractic appears in the title. The authors of this report have merged osteopathic and chiropractic research into one category as if there are no distinctions in the professions and practices. Chiropractic is a distinct profession that warrants equal inclusion, equal treatment, and equal mention.	Thank you for your comments. The MeSH Search term "Musculoskeletal Manipulations" is an umbrella term, under which is the the specific term "manupulation, chiropractic"; using the broad umbrella term captures "chiropractic". This "Musculoskeletal Manipulations" search term was used in our search. Studies of chiropractic were identified (whether or not this term is in the title) and those that met the inclusion criteria were included.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	3. Given the chronic pain crisis, the <i>a priori</i> determination to conduct a Cochrane style meta-analysis and include only specific clinical trials does not serve the best interest of the public. The current need is not simply to conduct an academic exercise evaluating the quality of certain previous research. The current chronic pain crisis warrants a comprehensive review of all types of evidence in order for the review to build a full picture of the evidence base on opioid alternatives rather than a narrow, one dimensional report that will do more to cloud inclusion and reimbursement rather than bring clarity to the issues. The limited number of chiropractic clinical trials, as well as the specific selection of trials included raises concerns. Our review of the chiropractic and spinal manipulation provisions of this report confirm that the report does not provide a full picture of the body of evidence confirming the benefit of chiropractic care. The detrimental	Thank you for your comments. The scope, research questions and inclusion criteria were developed through a public process with input from stakeholders, including patientes, clinical and methodological experts. We address specific comments related to study selection as they are presented elsewhere.

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		effect of the handling of chiropractic care in this study may result in consumers opting for opioids, rather than finding recovering from pain through chiropractic care. Further it may harm access to insurance reimbursement or expansion of availability through federal health programs for veterans, the military and their dependents, and Medicare and Medicaid recipients.	
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	4. There are numerous research reviews ongoing related to alternatives to opioids for pain management. It is unclear if these various government activities build upon each or not or have been created in stove pipes, devoid of cross agency communication. For example, is the AHRQ conduction of a meta-analysis supportive of the CMS patient centered care activities?	Thank you for your comments.-The White House Office of National Drug Control Policy and the Departments of Health and Human Services, Department of Justice, Department of Veterans Affairs, and Department of Defense meet regularly to coordinate federal efforts to address the opioid epidemic and identify opportunities for additional collaboration between government and external stakeholders. (See https://www.hhs.gov/opioids/about-the-epidemic/index.html .)
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	5. The design of the inquiry itself may be biased: Given the failure to search specifically for chiropractic, the limited number and specific selection of a handful of studies, and a rigid drug model style analysis, this report has inherent bias against chiropractic and likely other therapies. The interventions included in the analysis: <ul style="list-style-type: none">• Exercise• Psychological therapies• Physical modalities• Manual therapies• Mindfulness practices	Thank you for your comments. The review scope, framework, Key Questions, PICOTS inclusion/exclusion criteria were developed by the reviewers after consideration of input from a group of Key Informants and a Technical Expert Panel. These stakeholder groups were consulted to obtain broad perspective and expertise (as described in the front matter of the report) in order to make best use of the resources available for

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		<ul style="list-style-type: none"> • Mind-body practices • Acupuncture • Functional restoration training • Multidisciplinary/interdisciplinary rehabilitation <p>The key questions for adults covered the following conditions:</p> <ul style="list-style-type: none"> • Chronic low back pain • Chronic neck pain • Osteoarthritis-related pain • Fibromyalgia • Chronic tension headache <p>Our review of the report focuses on the specific statements and outcomes listed for spinal manipulation. (Given that there is no specific analysis conducted for chiropractic care.) At no point in this report do the authors suggest that a specific review of the chiropractic literature has been conducted. There is not even a specific mention of chiropractic in the Executive Summary.</p>	<p>this review. The EPC used methodology prescribed in the AHRQ Methods Guide to provide a methodologically sound report and mitigate the potential for bias. The MeSH Search term "Musculoskeletal Manipulations" is an umbrella term that includes chiropractic specifically and was used in our search strategy. We also looked at the bibliographies of systematic reviews (including those which involved chiropractic) for relevant citations. Studies of chiropractic were identified (whether or not this term is in the title), and those that met the inclusion criteria were included.</p> <p>We evaluated the intervention and how it was conducted without consideration of the type of provider performing the intervention.</p>
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	General	<p>Summary of Concerns and Recommendations</p> <p>From the title page throughout the report, it is obvious that the (as yet, unnamed) authors have either consciously chosen to ignore the diversity of professions within the complementary and integrative health community; or have chosen to ignore the chiropractic profession specifically.</p> <p>With so few studies included, both for the overall review but specifically for spinal manipulation, one must consider if the problem is the</p>	<p>Thank you for your comments.</p> <p>We focused our review on the evidence of benefits of included interventions, which were conducted by a range of providers. The MeSH Search term "Musculoskeletal Manipulations" is an umbrella search term that includes chiropractic interventions specifically. This search term was used in our literature search</p>

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		<p>availability of scientific data, or if the real problem is with the study design and implementation? Policy makers and the public are likely better served by a comprehensive review of existing data, both clinical trials, other research styles, and data from real world datasets such as workman's compensation data in states where these exist.</p> <p>It is important to acknowledge that when designing and evaluating research in nonpharmacologic approaches, trying to retrofit the drug study model into this nonpharmacologic frame is not going to provide the most accurate or useful information.</p> <p>It would appear the authors have attempted to utilize a drug study model to evaluate over 20 non-drug approaches. Doing so, short changes these therapies but also those who are likely to turn to this report as a conclusion of what the policy maker and general public will assume has been a fair and comprehensive analysis.</p> <p>If the study designs of the existing body of clinical trials are of poor or fair quality, there is an urgent need to address research design quality issues going forward and to stipulate an urgency with federal research agencies in funding well designed, useful studies that can address the management of pain in real world situations.</p> <p>The ICA requests a meeting with AHRQ to discuss the lack of inclusion of chiropractic in this report, to discuss the existing whole body of evidence on the benefits, and cost saving potential of chiropractic care for the treatment of the five</p>	<p>strategy. Studies of chiropractic were identified (whether or not this term is in the title) and those that met the inclusion criteria were included. We also looked at the bibliographies of systematic reviews and included trials (including those which involved chiropractic) for relevant citations.</p>

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		<p>conditions noted in this report.</p> <p>The ICA actively engages in collaborations domestically and internationally to promote the field of chiropractic, advance research, access, and appropriate regulations and compensation. The ICA is also actively engaged in advancing the broader field of integrative health care; plays a leadership role in the Integrative Health Policy Consortium; and engages in educating policy makers about the value of non-drug options for care for pain management.</p> <p>The doctor of chiropractic as the primary care provider resulted in a 52 percent reduction in pharmaceutical costs, 43 percent decrease in hospital admissions, and 43 percent fewer outpatient surgeries and procedures. This was the finding in a four-year study begun in 1999 of doctors of chiropractic in a primary care role in a large Chicago HMO.</p> <p>(Sarnat RL, Winterstein J. Clinical and cost outcomes of an integrative medicine IPA. Journal of manipulative and physiological therapeutics. 2004;27(5):336-47. doi: 10.1016/j.jmpt.2004.04.007. PubMed PMID: 15195041.)</p> <p>There are dozens of other studies that support the safety, benefit, and value of chiropractic care. Upon request, ICA will provide a bibliography of relevant research.</p>	
Public Commenter #25 [Beth Clay Director of	Key Messages	<p>The following statement is included:</p> <p>"Exercise, acupuncture, multidisciplinary rehabilitation, mind-body and mindfulness practices, and psychological therapies</p>	<p>This statement is based on the evidence presented in the report of our systematic review.</p>

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Government Relations International Chiropractors Association (ICA)]		such as cognitive behavioral therapy may improve function or pain outcomes for specific chronic pain conditions." Manual therapies in general and chiropractic care specifically are not included.	
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Abstract	Page vii. Results. 205 publications (192 trials) were included in review...Chronic low back pain: Function improved slightly in the short term with massage, yoga, and psychological therapies (Strength of evidence [SOE]: Moderate) and with exercise, acupuncture, lowlevel laser therapy, mindfulness-based stress reduction (MSR), spinal manipulation, and multidisciplinary rehabilitation (SOE: Low), and psychological therapies (SOE: Moderate). ...Improvements in pain persisted into the intermediate term for exercise, massage and yoga (moderate effect, SOE: Low)...as well as spinal manipulation...(small effects, SOE” Moderate) No further reference to spinal manipulation for other conditions are mentioned in structured abstract.	This statement is based on the evidence presented in the report of our systematic review.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Evidence Summary	Page ES-1. The section on non-pharmacological treatments for chronic pain includes: exercise and physical therapy, mind-body practices, psychological therapies, interdisciplinary rehabilitation, mindfulness practices, osteopathic and spinal manipulation, acupuncture, physical modalities, and acupuncture. There is no mention of chiropractic care specifically.	This statement is based on the evidence presented in the report of our systematic review.
Public Commenter #25 [Beth Clay Director of	Evidence Summary	Page ES-2. Chiropractic not included in the specific strategies considered in the review: The authors of this report exclude chiropractic from specific mention in detailing the types of therapies included in the	Chiropractic care is considered under the subject heading of musculoskeletal manipulation, included in our search.

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Government Relations International Chiropractors Association (ICA)]		review. Individual pain management strategies considered in the review include exercise and physical therapy, mind-body practices (yoga, tai chi, qigong), psychological therapies (cognitive-behavioral therapy, biofeedback relaxation techniques, acceptance and commitment therapy), interdisciplinary rehabilitation, mindfulness practices (mediation, mindfulness-based stress reduction practices), osteopathic and spinal manipulation, acupuncture, and physical modalities (traction, ultrasound, transcutaneous electrical nerve stimulation [TENS], low level laser therapy, interferential therapy, superficial heat or cold bracing for knee, back, or neck, electro-muscular stimulation and magnets), acupuncture, and functional restoration training. It is inconceivable to conclude that a true comprehensive review of more than 20 therapies for multiple conditions can be achieved when less than 200 studies were included total. For Spinal Manipulation, only eight studies were included.	The nine studies met the inclusion criteria.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Evidence Summary	<p>Page ES-7: Manual Therapies for Low Back Pain</p> <ul style="list-style-type: none">• Spinal manipulation was associated with slightly greater effects than sham manipulation, usual care, and attention control, or placebo interventions in shortterm function (3 trials, pooled)...and intermediate-term function (3 trials, pooled)...• There was no difference between spinal manipulation versus sham manipulation, usual care, and attention control or a placebo intervention in short-term pain (3 trials, pooled...) but manipulation was associated with slighter greater effects than controls on intermediate-term pain (3 trials, pooled)...(SOE: low for short-term, moderate for intermediate term). <p>If the true objective of this report was to provide a true analysis of the evidence related to spinal manipulation, a pooling of just three studies is not sufficient. The National Center for Complementary and Integrative Health at the</p>	All citations provided were reviewed. They did not meet inclusion criteria, with the exception of one, which was already included in the report (Ferreira 2003).

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		<p>National Institutes of Health provides an information page online describing spinal manipulation that provides more than the eight studies, including the prior report from AHRQ. (https://nccih.nih.gov/health/pain/spinemanipulation.htm)</p> <ol style="list-style-type: none">1. Bialosky JE, Bishop MD, Robinson ME, et al. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. <i>Physical Therapy</i>. 2009;89(12):1292–1303.2. Bronfort G, Haas M, Evans R, et al. Effectiveness of manual therapies: the UK evidence report. <i>Chiropractic & Osteopathy</i>. 2010;18(3):1–33.3. Bronfort G, Haas M, Evans R, et al. Evidence-informed management of chronic low back pain with spinal manipulation and mobilization. <i>Spine Journal</i>. 2008;8(1):213–225.4. Bronfort G, Haas M, Evans RL, et al. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: a systematic review and best evidence synthesis. <i>Spine Journal</i>. 2004;4(3):335–356.5. Cagnie B, Vinck E, Beernaert A, et al. How common are side effects of spinal manipulation and can these side effects be predicted? <i>Manual Therapy</i>. 2004;9(3):151–156.6. Cherkin DC, Sherman KJ, Deyo RA, et al. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. <i>Annals of Internal Medicine</i>. 2003;138(11):898–906.7. Chou R, Huffman LH. Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. <i>Annals of Internal Medicine</i>. 2007;147(7):492–504.8. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low-back pain: a joint clinical practice guideline from the	

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		<p>American College of Physicians and the American Pain Society. Annals of Internal Medicine. 2007;147(7):478–491.</p> <p>9. Dagenais S, Tricco AC, Haldeman S. Synthesis of recommendations for the assessment and management of low back pain from recent clinical practice guidelines. Spine Journal. 2010;10(6):514–529.</p> <p>10. Elder WG Jr, King M, Dassow P, et al. Managing lower back pain: you may be doing too much. Journal of Family Practice. 2009;58(4):180–186.</p> <p>11. Ferreira ML, Ferreira PH, Latimer J, et al. Comparison of general exercise, motor control exercise and spinal manipulative therapy for chronic low back pain: a randomized trial. Pain. 2007;131(1-2):31–37.</p> <p>12. Ferreira ML, Ferreira PH, Latimer J, et al. Efficacy of spinal manipulative therapy for low back pain of less than 3 months' duration. Journal of Manipulative and Physiological Therapeutics. 2003;26(9):593–601.</p> <p>13. Furlan A, Yazdi F, Tsertsvadze A, et al. Complementary and Alternative Therapies for Back Pain II. Evidence Report/Technology Assessment, no. 194. Rockville, MD: Agency for Healthcare Research and Quality; 2010. AHRQ publication no. 10(11)–E007.</p> <p>14. Hoiriis KT, Pflieger B, McDuffie FC, et al. A randomized clinical trial comparing chiropractic adjustments to muscle relaxants for subacute low back pain. Journal of Manipulative and Physiological Therapeutics. 2004;27(6):388–398.</p> <p>15. Hurwitz EL, Morgenstern H, Kominski GF, et al. A randomized trial of chiropractic and medical care for patients with low back pain: eighteen month follow-up outcomes from the UCLA low back pain study. Spine. 2006;31(6):611–621.</p> <p>16. Kinkade S. Evaluation and treatment of acute low back pain. American Family Physician. 2007;75(8):1181–1188.</p> <p>17. Machado LAC, Kamper SJ, Herbert RD, et al. Analgesic</p>	

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		<p>effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials. <i>Rheumatology</i>. 2009;48(5):520–527.</p> <p>18. National Institute of Arthritis and Musculoskeletal and Skin Disorders. Handout on Health: Back Pain. National Institute of Arthritis and Musculoskeletal and Skin Disorders Web site. Accessed at www.niams.nih.gov/health_info/back_pain/default.asp on April 11, 2012.</p> <p>19. Oliphant D. Safety of spinal manipulation in the treatment of lumbar disk herniations: a systematic review and risk assessment. <i>Journal of Manipulative and Physiological Therapeutics</i>. 2004;27(3):197–210.</p> <p>20. Rubinstein SM, van Middelkoop M, Assendelft WJ, et al. Spinal manipulative therapy for chronic low-back pain. <i>Cochrane Database of Systematic Reviews</i>. 2011;(2):CD008112. Accessed at www.thecochranelibrary.com on April 11, 2012.</p> <p>21. Santaguida PL, Gross A, Busse J, et al. Complementary and Alternative Medicine in Back Pain Utilization Report. Evidence Report/Technology Assessment no. 177. Rockville, MD: Agency for Healthcare Research and Quality; 2009. AHRQ publication no. 09–E006.</p> <p>22. van Tulder MW, Koes B, Malmivaara A. Outcome of non-invasive treatment modalities on back pain: an evidence-based review. <i>European Spine Journal</i>. 2006;15(suppl 1):S64–S81.</p>	
Public Commenter #25 [Beth Clay Director of Government Relations International	Evidence Summary	<p>Page ES-9: Comparative Effectiveness of Interventions for Chronic Low Back Pain</p> <ul style="list-style-type: none">• There were no differences between spinal manipulation versus exercise in shortterm function (3 trials, pooled....) or intermediate-term function (4 trials, pooled....) (SOE: Low)	This statement is based on the evidence presented in the report of our systematic review.

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Chiropractors Association (ICA)]		<ul style="list-style-type: none">• There were no differences between spinal manipulation versus exercise in shortterm (3 trials, pooled...) or intermediate-term pain (4 trials, pooled...) (SOE: Low).	
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Evidence Summary	Page ES-15: Key Question 5: Chronic Tension Headache Spinal manipulation therapy was associated with small to moderate improvements respectively, in function compared with usual care....and with moderate improvements pain intensity...over the short term (SOE: Low) Approximately a quarter of the patients had comorbid migraine	This statement is based on the evidence presented in the report of our systematic review.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Evidence Summary	Page ES-23: Findings in Relationship to What is Already Known Consistent with the prior review, small to moderate effects of exercise, yoga,.....spinal manipulation...were identified. This review suggests that most effects are at short or intermediate-term followup: long-term data are sparse.	This statement is based on the evidence presented in the report of our systematic review.
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Evidence Summary	Page ES-24: Implications for Policy and Decision Making Our review provides evidence that an array of nonpharmacological treatments provide small to moderate improvements in function and pain that are durable for more than 1 month for the five conditions addressed in this review....The evidence synthesized in this review may help inform guidelines and healthcare policy (including reimbursement policy) related to the use of noninvasive, nonpharmacological treatments as alternatives to	Thank you for your comments. Studies of musculoskeletal manipulation (which includes chiropractic) were sought and included in our review if they met the inclusion criteria.

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		<p>opioids....and inform policy decisions regarding funding priorities for future research....Importantly, some interventions such as exercise...and some complementary and integrative medicine therapies such as acupuncture and spinal manipulation were associated with some sustained effects on function. At the same time, there was no evidence suggesting serious harms...</p> <p>As the report acknowledges, this report is likely to have significant policy implications. The ICA is greatly concerned that this limited review of existing data on spinal manipulation in general and absent analysis of chiropractic care specifically will bring a chilling effect to the efforts of the ICA and others to advance the profession, improve access for consumers and improve reimbursement for providers.</p>	
Public Commenter #25 [Beth Clay Director of Government Relations International Chiropractors Association (ICA)]	Results	<p>Page 57: Detailed Synthesis of Spinal Manipulation for Low Back Pain</p> <p>A total of eight studies were considered for this review, six reported as of fair quality and two of poor quality.</p>	This statement is based on the evidence presented in the report of our systematic review.
Public Commenter #25 [Beth Clay Director of Government Relations	Results	<p>Page 247: Manual Therapies Compared with Pharmacological Therapy</p> <p>The summary notes that a single poor-quality trial was reviewed, providing insufficient evidence to determine effect of spinal manipulation compared with amitriptyline over the short term.</p>	This is correct.

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International Chiropractors Association (ICA)]			
Public Commenter #26 [Robert B. Saper, MD MPH Academic Consortium for Integrative Medicine and Health Boston University School of Medicine]	General	<p>Re: Public Comments on Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review</p> <p>On behalf of the Academic Consortium for Integrative Medicine & Health (the “Consortium”), thank you for the opportunity to comment in response to the draft AHRQ evidence report “Noninvasive, Nonpharmacological Treatment for Chronic Pain: A Systematic Review.” The Consortium is comprised of over 70 academic health centers and health systems in North America committed to an evidence-based approach to integrating mainstream therapies with well-studied effective and safe complementary therapies. We commend AHRQ, the authors, and research staff involved in producing this comprehensive report. The rationale for the report on this topic is well-articulated, sound, and timely. The systematic review methodology is rigorous. The appendices describing the individual included and excluded studies, reasons for exclusion, and rationale for strength of evidence ratings are thorough and will be particularly useful for investigators in the field. Tables and figures summarizing evidence for different indications, therapies, and comparators are clear and well-organized. The important limitations in the literature are appropriately highlighted – in particular, the relatively fewer studies in fibromyalgia and tension headache; lack of blinding patients and providers to allocation concealment; and the paucity of studies with long-term follow-up. Factors impacting external generalizability are similarly well highlighted including study heterogeneity, the low numbers of RCTs used in individual meta-analyses, and variability of intervention style, dose, and methods of delivery.</p>	Thank you for your comments.

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		We agree with your recommendations for research, particularly the need for pragmatic trials, standardized outcomes, and assessment of proportion of responders in addition to differences in mean changes. Trials with long-term follow-up are particularly critical. Implications for reimbursement policies are well-stated, particularly the emphasis on prioritizing effective 'active' therapies with passive therapies reserved for more impaired and complicated patients.	
Public Commenter #26 [Robert B. Saper, MD MPH Academic Consortium for Integrative Medicine and Health Boston University School of Medicine]	Appendix	<p>One area which was unclear was why several studies of spinal manipulation for neck pain were excluded from the review (namely #91, #207, and #496 in Appendix C).</p> <p>Again, thank you for your efforts and we look forward to reviewing the final version.</p> <p>Sincerely, Robert B. Saper, MD MPH</p>	A legend explaining the Exclusion Codes is provided at the beginning of Appendix C. Specifically regarding: #91 (Bronfort 2001, exclusion code 10): this study is a systematic review (SR) and while SRs were not directly used in this report the bibliographies of all relevant SRs (including this one) were checked for potential inclusion. #207 (Evans 2002, exclusion code 3): this trial was excluded because, based on the information provided, the population most likely had radiculopathy, which is an ineligible population for this report. #496 (Maiers 2014, exclusion code 4): this trial was excluded because it was considered to be assessing the additive/incremental value of adding spinal manipulation therapy (SMT) to exercise (SMT + home exercise vs. home exercise alone and vs. home exercise + supervised exercise).

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Public Commenter #27 [Rajal Cohen, PhD University of Idaho]	Results	Alexander Technique was found effective for chronic low back pain in a large RCT comparing it to usual care and exercise: http://www.bmj.com/content/337/bmj.a884	The trial referenced here was included in our report: Little P, Lewith G, Webley F, et al. Randomised controlled trial of Alexander technique lessons, exercise, and massage (ATEAM) for chronic and recurrent back pain. BMJ. 2008 Aug 19;337:a884. doi: 10.1136/bmj.a884. PMID: 18713809.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University- Purdue Univeristy Indianapolis]	General	<p>AHRQ Report:</p> <p>Overall comments: This represents an important and impressive report. It is important and timely in the context of the National Pain Strategy and published opioid treatment guidelines (CDC, VA/DOD, and Canadian) that are emphasizing non-pharm treatments for chronic musculoskeletal pain conditions. The report is comprehensive by focusing on the 5 most common and disabling chronic pain conditions (low back, neck, OA, fibromyalgia, and chronic tension headache). The methods are rigorous and results valid. The clinical, research, and policy implications are well-articulated and do not over-reach from the data presented. I think the report is well-organized and presents the data in several helpful ways (text, tabular, figures, forest plots, and text summaries for each treatment modality and pain condition). The amount of work that went into producing this report is substantial and appreciated by me (pain researcher and primary care physician)</p> <p>How could the report be improved? Overall, I think it's excellent and do not have substantive recommendations for improvement; only minor edits that should be considered.</p>	Thank you for your comments.

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		Below are my specific recommendations (1-18):	
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Methods	1. While the description of how strength of evidence is determined is fairly detailed, I found the differentiation between “low” and “moderate” sounding fairly arbitrary for certain treatment modalities for select conditions. Some further explanation of how this classification was determined specially could improve the “transparency.”	Thank you for your comments. Details of how each outcome was assess/graded are found in Appendix G. We have reviewed ratings for consistency.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Abstract	2. Shouldn't psychological therapies be mentioned in the conclusions of the abstract? Seems like CBT has some of the strongest evidence across conditions for effects on pain and function.	Thank you for your comments. We have made edits to further describe psychological therapies
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	General	3. Very minor: Throughout the report, there is inconsistency in how percentages are reported. Sometimes a value will be listed as 37%; sometimes written out as 37 percent. I think 37% is preferred. Would make this consistent throughout the report.	Thank you. We have reviewed for consistency in reporting percentage values. (Note: The EPC follows a government publication style guide that calls for percent to be spelled out in text, and the for symbol (%) to be used in tables and within parenthetical expression.)
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Evidence Summary	4. In the executive summary, some abbreviations were not defined early. Examples include: SMD and NDI	Thank you. We have edited the section so that the acronyms are defined upon their first usage.

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Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Results	5. In exercise for OA of the knee, why is 9 trials considered low SOE?	Thank you for your question. For function and pain across the nine trials at intermediate-term, the study limitations were moderate (downgraded 1) and there was substantial inconsistency across trials (downgraded 1) leading to a low strength of evidence rating. Appendix G provides additional information.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	General	6. Be consistent throughout the report in use of hyphenation for "short-term," "intermediate-term", and "long-term."	Thank you. We have reviewed and make edits as appropriate.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	General	7. Because there are no head-to-head trials with opioids, we cannot state these non-pharm treatments are more effective than opioids. However, we can state that they are likely safer than opioids since no significant adverse events were found across multiple treatment trials of these modalities.	Thank you for your comments.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	General	8. There is a belief that not all control arms are "created equal." Attention-control may be more effective than usual care. The producers of this report do an excellent job of stratifying their analysis by control group to show that it is ok to "lump" usual care, sham treatment, and attention control.	Thank you.

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Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Methods	9. Page 11 of report: need to edit “clinically importance effect” to clinically important effect.	Thank you. We have made this correction.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Results	10. Table 4—would not hyphenate “pharmaco-logical”—to be consistent with the text.	Thank you. The word cannot fit on one line and thus is hyphenated to continue on the line below.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Results	11. For consistency in how results are presented in tables, could probably round to the nearest tenth rather than nearest hundredth (which is done at times).	Thank you. We have reviewed and edited for consistency.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Results	12. What is SNA for acupuncture intervention?	SNA stands for "stand needle acupuncture" (see definitions at the bottom of the tables and figures as applicable).
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue University Indianapolis]	Results	13. Table 15: Is this correct...that use of analgesics was exactly the same at 1- and 3 months? Why are these figures repeated?	We have checked the accuracy of the reported data and made appropriate edits.

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Purdue Univeristy Indianapolis]			
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue Univeristy Indianapolis]	Results	14. Page 94: minor edit: should read trial rather than “trail.”	Thank you. We have made this correction.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue Univeristy Indianapolis]	Results	15. Page 110: should read acupuncture...not psychological therapies for use of opioid therapies and health care utilization.	Thank you. We have made this correction.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue Univeristy Indianapolis]	Results	16. Bottom of page 127: minor editing needed—where CI are repeated twice	Thank you. We have corrected this.
Public Commenter #28 [Matthew Bair, MD, MS Indiana University-Purdue Univeristy Indianapolis]	Results	17. Bottom of page 179: minor editing needed for “treatmen,t”	Thank you. We have made this correction.
Public Commenter #28	Results	18. Page 219—should read analgesics rather than lay-term of “pain killers”	Thank you. We have revised this.

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Commentator & Affiliation	Section	Comment	Response
[Matthew Bair, MD, MS Indiana University- Purdue Univeristy Indianapolis]			

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