Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Nonopioid Pharmacologic Treatments for Chronic Pain

Draft report available for public comment from October 15, 2019, to November 12, 2019.

Citation: McDonagh MS, Selph SS, Buckley DI, Holmes RS, Mauer K, Ramirez S, Hsu FC, Dana T, Fu R, Chou R. Nonopioid Pharmacologic Treatments for Chronic Pain. Comparative Effectiveness Review No. 228. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2015-00009-I.) AHRQ Publication No. 20-EHC010. Rockville, MD: Agency for Healthcare Research and Quality; April 2020. DOI: https://doi.org/10.23970/AHRQEPCCER228.

Comments to Draft Report

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each draft report is posted to the EHC Program Web site or AHRQ Web site 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' comments to revise the draft report.

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

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

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 Ashley Walton, American Society of Anesthesiologists (ASA)	Question 1	Regarding the evidence summary, the estimated number of patients affected by chronic pain is listed as 50 million people, which is from a MMWR paper and not from the quoted reference. The quoted reference is from the IOM paper, which states that "chronic pain alone affects approximately 100 million U.S. adults" not 50 million people as suggested in the Introduction.	Thank you for pointing this out. The correct reference to the MMWR was accidentally omitted in the evidence summary but has been corrected.
Public Reviewer 6 Anna Bono	Question 1	Personal anecdote including potentially private information (please see attachment). Statement redacted for posting purposes.	Thank you for the comment.
Public Reviewer 1 Karl Lorenz	Question 2	I find it quite problematic: That you omit studies of “end of life” – setting of care e.g., hospice would be more appropriate. There is no clear distinction for the “eol” category and your report points out that almost none of the studies of interest focus on serous chronic conditions in older adults (as the median age of the median study appears to be around 50). This content area is understandably distinctive but the fact that you found no overlapping studies despite not (apparently) explicitly rejecting them points to a large gap in the literature (e.g. understanding pain and its management in ESRD, CHF, COPD, dementia etc…) none of the latter are at “end of life” – it would also help if your exclusion criteria were clearer by condition if you made these implicit judgements.	Thank you for the valuable input. As the reviewer notes, "end of life" is not described in the same terminology across studies; our criterion was life expectancy <= 6months (see exclusion criteria), and is consistent with the other reports on chronic pain being conduced by our center. We agree that chronic disease co-morbidities may alter pain management, and would have included such studies if we had found any that met our criteria. To be clear, we did not find any studies that specifically enrolled these patients or that analyzed subgroups of such patients.
Public Reviewer 11 Ashley Walton, American Society of Anesthesiologists (ASA)	Question 2	ASA would ask AHRQ to reconsider how the information in the background and objectives sections of the draft are represented regarding the IOM report and the MMWR paper. The quoted material has conflicting values in the number of patients suffering from chronic pain. The MMWR paper quoted says 50 million estimated but the latest IOM report says 100 million (downgraded from a prior estimate of 116 million). One could argue the IOM report is more authoritative in this regard, though the MMWR paper is more recent	Thank you again for pointing this out. Please see our comments above as the citation for the MMWR was missing. All three chronic pain reports used the more recent MMWR paper.
Public Reviewer 4 Jacob Marzalik, American Psychological Association	Question 2	We appreciate the continued efforts to review and report subgroup information, especially of racial/ethnic and gender minorities as there continues to be disparities across the underserved populations (Samuel et al., 2019). Likewise we appreciate the emphasis on considering patient characteristics when selecting treatment. We were wondering if you could further explain your definition of the “other” racial/ethnic category (in tables for example).	Thank you for the commentary. This review adopted race and ethnicity categories as defined by the United States Census Bureau. One caveat is that the literature often reported an "other" category which we felt was important to capture . Categories were only listed if reported in the literature.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 4 Jacob Marzalik, American Psychological Association	Question 3	We also appreciate noting the limited evidence on long term outcomes, comparative effectiveness data, and quality of life. Nice job including information on potential harms of treatment as well as information on withdrawals due to adverse events.	Thank you for the comment.
Public Reviewer 1 Karl Lorenz	Question 4	Pain is in fact more common among older adult and those with serious conditions. Therefore, even the absence of evidence, highlighting this gap more strongly is appropriate. At least in older adults with such chronic conditions, there is evidence that they value treatments such as NPT that preserve cognition (Steinhauser, Tulsky JAMA 2000) and there is also evidence that social, emotional, and functional dimensions of the pain experience are more common.The report should more clearly call out this gap. Assuming that older adults and family members are indifferent to these tradeoffs because of frailty is not appropriate, but these issues and the use of CIH and NPT alternatives are understudied.	Thank you, this has been more clearly defined in our research gaps section. For more information regarding non-pharmacologic therapies please see the associated Noninvasive Nonpharmacologic Treatments of Chronic pain report.
Public Reviewer 11 Ashley Walton, American Society of Anesthesiologists (ASA)	Question 4	The conclusion derived in the results section under antidepressant, SNRI, indicates that at 52 weeks there is no improvement in pain. "A long-term RCT (N=257) found no differences between duloxetine 40 mg/day versus 60 mg/day in pain scores at 52 weeks (Appendix H)". This is moderate strength of evidence. However, going to the source, #33 on the reference list, Yasuda et al. indicates that these studies suggest that duloxetine continues to be analgesic over the long term in patients with DNP. This source actually shows that there was a 2-point improvement in pain over the 52-week period regardless of the 40 or 60 mg/day dose. Thus, the conclusion should be that the 40mg was as efficacious as the 60mg dose, but that both reduced pain at 52 weeks.	We appreciate the commenters in-depth reading of the report. This sentence is meant to convey results comparing the two doses and not the overall (combined) change from baseline. That is, there are no differences in pain improvement between 40mg/daily and 60mg/daily. This sentence has been altered in the report for clarity.
Public Reviewer 15 Celeste Cooper	Question 4	RE: Most effects were small; long-term evidence was sparse. Function and/or pain did not improve with... Although evidence was limited, serious harms were not reported with the interventions. The goals were not met. Escaping serious harm is not an acceptable objective of any intervention. Among these are treatments suggested in the CDC chronic pain guidelines, many of which are not accessible to chronic pain patients and if they are, they are limited by Medicare to the point they would not be therapeutic.	Thank you, the purpose of this review was to synthesize current literature. We do not offer recommendations

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 4 Jacob Marzalik, American Psychological Association	Question 4	We would appreciate if you could expand more on the role industry funding has played in funding the nonopioid pharmacological research, and the potential subsequent impact on this systematic review.	We appreciate the comment and certainly understand the interest in the role of the funder. This review caputred only the funding source which can be found in Appendix E and reported on under the Results of Literature Search. However, expanding on the role industry plays in funding research was outside the scope of this review. It is certainly an important consideration for future research.
Public Reviewer 6 Anna Bono	Question 4	Several studies in controlled settings have concluded that the risk of addiction is less than 1%. If we use the statistics released by government agencies, i.e. 1 out of 4 will addict, then there would be ~25 million Americans addicted, and actively seeking illicit drugs to replace their once prescribed pain medication. This is a slippery slope that our government has inserted itself into, and has evolved into a complete nightmare for legitimate pain patients and our compassionate doctors who are terrified to prescribe controlled substances for the treatment of pain. Honestly, I don't blame them. However, the mass hysteria over a non existent "prescription drug crisis"; will eventually come to light and the public will realize that they've been hoodwinked by manipulated statistics that have no correlation with prescribing rates whatsoever. People are overdosing and dying from ILLICIT DRUGS adulterated with deadly illicitly manufactured fentanyl (IMF) coming from China, Mexico, and the U.S. postal service. Let's be realistic for a moment. If opioid prescribing rates were a tool to measure the number of overdose deaths, then the number would be dropping significantly each year as the prescribing rate has dropped (over 33% since 2012). However, it is the complete opposite. Overdose deaths have skyrocketed since 2012, and shows no signs of leveling off anytime soon because prescribing & abuse rates are NOT connected. In fact, if the government continues to force doctors to undertreat pain and the DEA continues to decrease opioid production, the overdose rate will continue to RISE & millions of Americans will continue to suffer the consequences of the collateral damage we have become.	Thank you for your comment

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 6 Anna Bono	Question 5	As a pain patient & advocate, I communicate with thousands upon thousands of Americans who suffer from daily pain who HAD achieved adequate analgesia in the form of a responsible opioid pain management regime. However, as a result of government overreach and intervention, there are now MILLIONS of patients suffering from acute & chronic pain due to cancer, sickle cell, fall or motor vehicle accident, post operative pain, pancreatitis, lupus, fibromyalgia, Crohn's, and countless other diseases that are now UNABLE to ACCESS the aforementioned life saving medications to achieve pain relief. Even stage 4 cancer patients on their death bed are suffering in torturous pain because doctors are afraid they'll become "addicted". Come on, that's ridiculous! If you had 2 weeks left to live & suffering like a dog would you be concerned about getting addicted? This has gone too far, and we are begging you to put the brakes on before it gets any WORSE. The large majority of patients have been FORCED to reduce their stable, effective pain medications to a non therapeutic level, followed by those who were completely ABANDONED by their health care providers without warning out of fear of law enforcement or regulatory repercussions. The health care providers we communicate with have said they're faced with increased scrutiny, time consuming burdensome paperwork, pop visits from the DEA, and thinly veiled threats advising doctors to curtail their prescribing significantly. Basically, the government has inserted itself into the sacred physician/patient relationship which is eroding trust and public confidence in our nation's health care system. We have been ABANDONED by our health care system. We have been ABANDONED by our government. It seems as if our lives are expendable and our voices do NOT matter because our government (NOT our doctors) know what's best for us. Unfortunately, these stories are NOT folklore. However, certain anti opioid zealots refuse to acknowledge their existence as anything more than "anecdotal" evidence. In any other situation, this abhorrent behavior would be setting off alarm bells across the entire country & our elected officials would be organizing & working across party lines to put an immediate stop to this BARBARIC practice of TORTURE against its own citizens. Where's the ACLU? Where's the mainstream media talking heads? Funny, when it comes down to the health & well being of American citizens we hear NOTHING but CRICKETS from the people who are in a position to champion our cause.	Thank you for the comment. The goal of this report is to review the research on specific interventions and compare their effectiveness in reducing pain and improving function and quality of life.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 Ashley Walton, American Society of Anesthesiologists (ASA)	Question 6	Mazza et al in 2010 showed that duloxetine was associated with reduced pain at 12 weeks. This was a 13-week randomized trial comparing escitalopram with duloxetine and showed that both drugs reduced pain at 13 weeks in chronic low back pain patients. This study is not included in the review. Mazza M, Mazza O, Pazzaglia C, Padua L, Mazza S. Escitalopram 20 mg versus duloxetine 60 mg for the treatment of chronic low back pain. Expert Opin Pharmacother.2010;11,1052. Hwang et al conducted a randomized blind multicentered parallel-group non-inferiority trial comparing fentanyl to gabapentin and showed significant improvement in neuropathic pain.	Thank you for the additional references. Both of the suggested were screened for this review.The first study was not eligible for this review because escitalopram was not an included intervention for the review, based on expert input at the protocol development stage. The second study was not eligible for this review because comparisons to opioids were not included here. However, this comparison was covered in our related report on the use of opioids in chronic pain and this study would have been evaluated for inclusion in that review.
Public Reviewer 4 Jacob Marzalik American Psychological Association	Question 8	We appreciate including the summary of findings in your appendices as this will be very helpful for guideline developers that may use your systematic reviews for clinical practice guideline development.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 5 Melanie Bowzer, National Academies of Practice	Question 9	Thank you for your leadership on the Opioid Crisis and Substance Abuse Disorders statement. As a stakeholder health professional society, we believe that National Academies of Practice (NAP) can bring a unique perspective to this issue. The National Academies of Practice consists of fourteen distinguished healthcare professions committed to advancing interprofessional healthcare by fostering collaboration in practice and advocating for quality health care processes for the individuals and communities we serve. NAP firmly believes that close collaboration and coordination among healthcare professions, aligned with a vision for quality healthcare can make significant progress toward quality outcomes while reducing regulatory and administrative burdens for all involved in the health care continuum. In as much as the opioid crisis and substance abuse is affecting a large number of people in the United States, it has become clear that diverse perspectives and a variety of professions and clinical disciplines are necessary in order to effectively identify and address the complexities of this issue. As a cadre of distinguished professionals advancing healthcare by fostering collaboration and advocating for the best interest of individuals and communities, the National Academies of Practice appreciates the opportunity to contribute to this project. Please find NAP's comments and considerations accompanying this letter by way of attachment. We share these through an "interprofessional lens" in partnership to improve our US healthcare system. NAP endorses the use of the full spectrum of all professionals and service providers to be effectively used toward quality healthcare. These comments and recommendations are respectfully submitted in anticipation of ongoing collaboration and future research that is interprofessionally planned and collaboratively provided. Please see attachment 1 for full letter.	Thank you for the comment.
Public Reviewer 9 James Specker American Massage Therapy Association	Question 9	Letter contains: - Introduction to the American Massage Therapy Association. - References a pamphlet designed by the American Academy of Spine Physicians and AMTA on uses of massage for spine care. - Notes research on massage therapy utilization rates for associated with Medicare Advantage coverage. - Acknowldeges that the recent report includes massage therapy for pain relief low back and neck pain. - Note other reports indicating support for use of massage therapy. Please see attachment3 for full comment.	While this comment appears to be directed at all three chronic pain reports with an emphasis on the Noninvasive Nonpharmacologic Treatments for Chronic Pain review, we would like to thank the reviewer for their comments regarding the reports.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 11 Ashley Walton, American Society of Anesthesiologists (ASA)	Question 9	ASA agrees that the limitations of the review process and the evidence base were appropriately discussed in the draft. We offer some specific comments on different sections of the report (above), as well as some general concerns/observations here: ASA is concerned about how the conclusions of this review will be interpreted. Specifically, with the conclusions made about nonopioids and the effect vs. the placebo, we do not want the takeaway to be that "doing nothing" is the better pain treatment option than opioids. In addition, there is room for interpretation regarding the variability of the evidence. ASA does not want to see payers interpret the AHRQ document to further restrict coverage or augment preauthorization requirements for nonopioids, which can be very burdensome for both patients and provider causing delays in care. Furthermore, there were a lack of studies examining co-prescription of neuropathic agents and the synergistic effects on risk ratio were not included in this review. The basis of multimodal analgesia, which is a standard of care for pain management, is coadministration of multiple classes of medication. Several studies have demonstrated this synergy between SNRI and gabapentinoids and TCA and gabapentinoids. Lastly, neuropathic pain conditions, while described as "typical" in the conclusions section is far too general of a diagnosis taxonomically speaking to be lumped together. ASA recommends greater specificity in this section.	Thank you for the comment. While we can appreciate the concerns expressed, this report synthesizes current evidence and does not make recommendations. To maintain the scope of this review we excluded any combination therapies; it is noted under our section on limitations of the review on page 59-60. Future updates of this report could expand to include these. We certainly appreciate the comments regarding lumping neuropathic pain together. Our results section is specific with regard to the types of neuropathic pain (mostly diabetic peripheral neuropathy and postherpetic neuralgia) included in studies. However, our conclusions are simply a summary of the overall evidence and the type of neuropathic pain is specified only where needed to emphasize differences (e.g., demographics).

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 12 Angie Stengal, American Society of Regional Anesthesia and Pain Medicine	Question 9	ASRA appreciates AHRQ's review of nonopioid pharmacologic treatments and opioid treatments for chronic pain; however, we are concerned that the research presented in the first report does not fully address the risks and benefits for each nonopioid medication included in the analysis. In addition, it does not appropriately balance the use of nonopioid drug regimens against patients' comorbid conditions. Each of the pharmaceuticals studied have unique profiles that make them clinically appropriate for managing chronic pain in key patient populations, including those studied. More importantly, nonopioid drug therapies are not necessarily a replacement for the use of opioids in managing chronic pain. As the first report suggests, "…evidence on long-term treatment effectiveness, comparative effectiveness, and quality of life for nonopioid drugs and indications studied is limited." And, findings from a small set of randomized controlled trials (RCTs) are not robust enough to drastically alter clinical practice in the management of chronic pain with nonopioid therapies. In addition, and despite the second report's finding that "…evidence on long-term effectiveness [of opioids] is very limited and there is evidence of increased risk of serious harms that appear to be dosedependent," clinical experience suggests that long-term opioid therapy may be helpful in some patient populations. In fact, Thornton, et.al., found four key predictors (i.e., the opioid's duration of action, the parent opioid compound, presence of chronic pain, and drug use disorders) that physicians can use to determine the potential for a patient to transition to chronic opioid therapy when first prescribing opioid therapy1. ASRA recognizes that all drugs – opioid and nonopioid – carry risks. Clinicians managing patients with chronic pain should consider those risks, balanced against the patient's comorbid conditions and available alternatives (i.e., noninvasive, nonpharmacologic and multimodal pain management therapies), in developing a long-term treatment strategy with patients. While it is the position of ASRA that clinicians should not completely eliminate opioids from treatment protocols, nonopioids and alternative therapies should be considered and prescribed first, until they are not effective. In such cases, opioids can and should be tested on a trial basis, and the use of opioids for chronic pain management should be well-controlled and demonstrate clear benefits over available alternatives. We note that the type, dosage, and duration of any pain treatment, including opioid therapy, is best determined by the treating clinician in accordance with each individual patient's need. We encourage AHRQ to consider additional studies as it modifies its aforementioned reports. Further, we encourage AHRQ to work with the pain management community to establish a more comprehensive evidence base around these topics. Please see attachment 4 for full letter.	We appreciate the commenter's perspective and recognize that there are inherent limitations in the review process and the evidence base as noted in the report. We agree that continued research on this topic is needed and important.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 14 Celeste Cooper	Question 9	The evidence speaks for its self. Thank you.	Thank you for the comment.
Public Reviewer 15 Celeste Cooper	Question 9	I hope you will keep looking seriously at evidence to support treatment of chronic pain. I am glad to see alternatives explored, they can be helpful as an adjunct to effective pain care. However, the evidence in this report does not support these CDC recommendations as a viable alternative to treating chronic pain with opioids.	Thank you, we do appreciate this view-point. Since, this review did not compare evidence to treatment with opioids we cannot speak to its viability as an alternative.
Public Reviewer 2 Tom Supinka, National Safety Council	Question 9	Given the complexity of treating chronic pain and concerns regarding the safety and long-term effectiveness of opioids, there is a need for a comprehensive understanding of the benefits and harms of nonopioid pharmacologic treatments for chronic pain. This report examines the evidence-base for nonopioid drugs used to treat chronic pain, varying by pain population (e.g. neuropathic pain, fibromyalgia, etc.) and nonopioid drug intervention (e.g. NSAID, acetaminophen, etc.), examining outcomes, harms and effectiveness. This review provides evidence that can be considered when addressing specific, common chronic pain conditions – evidence which has been lacking to this point. The findings in this report may also support updates of current guidelines of the benefits, harms and risks of short-, intermediate- and long-term nonopioid pharmacological therapies. Careful consideration of patient-specific characteristics is critical, given the highly individualized nature of chronic pain, and individual risks for development of an opioid use disorder require an individualized approach. This review can provide medical professionals with specific interventions for patients who wish to avoid an opioid prescription, who are at risk for development of an opioid use disorder, or who have other contraindications against opioids.	Thank you for the comment.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 6 Anna Bono	Question 9	The state & federal government continues to "shrug off" our repeated of cries for help, and voluminous stories depicting the negative outcomes happening as a direct result of the barbaric policies THEY'VE put in place. Stories of endless suffering, grieving our once productive lives, losing our careers, jobs, families, children, friends, and worst of all, stories of thousands who felt they had no other choice to escape their debilitating pain, so they chose suicide. So where's the nonstop media coverage? Where's the moral outcry from lawmakers, human rights groups, ACLU, or media outlets? Oh, that's right...they can't shed light on our issue because it doesn't fit the anti opioid agenda... opioids = BAD marijuana, alcohol, cigarettes, sugar = A OK So you see, WE are NOT the problem. Our doctors are NOT the problem. However, we ARE the ones taking the proverbial fall for the transgressions of others. We WANT to live. We WANT to be productive and present for our loved ones. Unfortunately, what WE want doesn't matter, because we're NOT important to the "puppet masters"	Thank you for the comment. The goal of this report is to review the research on specific interventions and compare their effectiveness in reducing pain and improving function and quality of life.
Public Reviewer 7 Anonymous	Question 9	Thank you for this important contribution. One area that is lacking is a discussion of the evidence behind the non opioid nutraceuticals such as magnesium.	Thank you for your comment. This area of focus may be a potential opportunity for future research.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 8 Terri Roberts, American Holistic Nurses Association	Question 9	The American Holistic Nurses Association (AHNA) is extremely grateful to the Agency for Healthcare Research and Quality (AHRQ) for its work in producing the evidence reviews regarding non-pharmacological approaches to pain. We do not have any substantive comments to make regarding the process of developing these reports, or about the contents of the reports, we believe them to be very important in helping healthcare providers and people with pain find the safest and most effective treatments available. We were very impressed with the report Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians that was supported by AHRQ and published in 2017. Here at AHNA, we have developed a Pain Tool Kit for Registered Nurses for non-pharmacological approaches to pain treatment and it was released in 2017. The Holistic Pain Relief Toolkit is used to educate and support nurses in the use of evidence-based non-pharmacologic approaches in their nursing practice and for self-care. The Toolkit includes educational content about using essential oils, physical and energetic touch, thermal applications, progressive muscle relaxation, Meditation Based Stress Reduction, visualization, yoga, tai chi, and more for pain management and relief. The Holistic Nurses' Pain Relief Tools for Patients & Self-Care is a 2-page pdf designed to be a quick guide to nursing pain management interventions that are simple, safe and effective. Nurses are encouraged download, print, and share the Holistic Nurses & Pain Relief Tools for Patients & Self-Care: www.AHNA.org/holistic-pain-tools. This Pain Tool Kit has been translated into Spanish, Portuguese, Italian and Japanese in an effort to spread this to registered nurses globally. This report on noninvasive non-pharmacological treatments is especially important, due to the limited understanding of these treatments by many healthcare professionals and the even more limited insurance payment coverage by third party payers. Having a continuously updated compendium of the evidence is extraordinarily valuable as both an educational tool for registered nurses. Registered nurses must be one of the targeted audiences for disseminating and promoting this work because of our vast spectrum of interactions with clients/patients in pain, both chronic and acute. Thank you again for your excellent and substantial work on these reports, and we look forward to the final version's publication. See attachment 5 for the AHNA Pain Relief Toolkit 2018.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 10 Britinia Galvin, American Academy of Physical Medicine and Rehabilitation	Question 9	The American Academy of Physical Medicine and Rehabilitation (AAPM&R) appreciates the Agency for Healthcare Research and Quality's (AHRQ) distribution of and opportunity to provide feedback on the Noninvasive Nonpharmacological Treatments for Chronic Pain: A Systematic Review Update, the report on Opioid Treatments for Chronic Pain, and the report on Nonopioid Pharmacologic Treatments for Chronic Pain. AAPM&R appreciates AHRQ's efforts to assess the effectiveness of common treatments for chronic pain, including opioids, nonopioid pharmacologic treatments, and noninvasive nonpharmacological treatments. Many physiatrists are leaders of health care teams that provide care for patients presenting both acute and long-term chronic pain management needs. Physiatrists treat countless conditions resulting in the manifestation of pain including spinal cord injury, multiple sclerosis, post-stoke pain, fibromyalgia, peripheral neuropathy, and limb amputations. AAPM&R strongly advocates that the treatment for acute, subacute, and chronic pain management should be multimodal. While many physiatrists aim to provide interdisciplinary, nonpharmacological regimens; treatment plans may also include the use of non-opioid medications, opioids and interventional medicine. Regarding the Noninvasive Nonpharmacological Treatments for Chronic Pain: A Systematic Review Update, AAPM&R notes that a review of interventional treatments (e.g. nerve blocks, neuromodulation, etc.) were excluded from this review. AAPM&R believes that an additional report regarding advanced interventional, nonpharmacological treatments would be beneficial and would appreciate such a review by AHRQ. Lastly, regarding the report on Opioid Treatments for Chronic Pain, AAPM&R notes that with meta-analysis, effects tend to homogenize. As such, we would like to emphasize that pain is a subjective and personal experience that widely varies by patient and condition. It is important to evaluate and treat each patient individually, using the best available data to inform personalized treatment	Thank you for the comment. While this comment does seem to be primarily directed at the Noninvasive Nonpharmacologic Treatments for Chronic Pain review we would like to note that our report also calls attention to the need for multimodal pain management in our background section (page 1), and higlights the inclusion of monotherapy as a limitation of the review on pages 59-60. Unfortunately, reviewing evidence for a multimodal approach was outside the scope of this review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer 3 Robert Twillman Integrative Health Policy Consortium	Question 10	The Integrative Health Policy Consortium (IHPC) is grateful to the Agency for Healthcare Research and Quality (AHRQ) for its work in producing these three evidence reviews. Although we do not have any substantive comments to make regarding the process of developing these reports, or about the contents of the reports, we believe them to be very important in helping healthcare providers and people with pain find the safest and most effective treatments available. We are struck by the fact that all three of these reports find much the same thing: low-to-moderate quality evidence of a modest effect on pain over the short term. Where things diverge, however, is with respect to evidence of potential harms, which varies from essentially no evidence of harms from noninvasive nonpharmacological treatments, to modest harms associated with nonopioid pharmacologic treatments, to the potential for serious harms from opioid therapy if safe prescribing practices are not followed. Taken together, these three reports support the recommendations recently issued by the HHS Inter-Agency Pain Management Best Practices Task Force, which focus on an integrative, multimodal, interdisciplinary approach to treating chronic pain. Such an approach allows for additive or synergistic benefits derived from combining treatments, while minimizing risks by minimizing doses and durations of opioid and nonopioid pharmacologic treatments. Please see attachment 2 for full letter.	Thank you for the comment.
Public Reviewer 4 Jacob Marzalik American Psychological Association	Question 11	Thank you for the opportunity to comment on AHRQ's draft report Nonopioid Pharmacological Treatment for Chronic Pain. Overall this was a very well-written report in that it is user-friendly, and it provides comprehensive information on nonopioid pharmacological treatments for chronic pain. We have several comments and suggestions below for your consideration.	Thank you for the comment.