Evidence Report Disposition of Comments Report

Research Review Title: *The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain*

Draft review available for public comment from December 19, 2013 to January 16, 2014

Research Review Citation: Chou R, Deyo R, Devine B, Hansen R, Sullivan S, Jarvik JG, Blazina I, Dana T, Bougatsos C, Turner J. The Effectiveness and Risks of Long-Term Opioid Treatment of Chronic Pain. Evidence Report/Technology Assessment No. 218. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) AHRQ Publication No. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality; September 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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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.

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Reviewer	Section	Comment	Response
Peer Reviewers			
Peer Reviewer 1	General	The authors should be commended for undertaking the resource-intensive task of updating and expanding a comprehensive literature review that began for another purpose in 2008. The review's objective is clearly defined, and the Key Questions, with related sub-questions (listed on Pages 2-4), seem appropriate to the study objective (although it must be noted that the alphabetical designations for each subquestion under all Key Questions are not consistent with those provided in the Executive Summary and in the Results section).	Thank you for your comment. We verified the alphabetical designations for each subquestion and they match throughout the report.
Peer Reviewer 1	General	However, the target population and audience are only implied by the Implications for Clinical and Policy Decisionmaking section on Pages 50-51 and Research Gaps sections on Pages 51-52.	Thank you for your comment. As noted in the Introduction, this report will be used by National Institutes of Health to inform a Pathways To Prevention Conference on use of opioids for chronic pain. To clarify, this report does not represent a clinical practice guideline (for which a target population and audience are typically defined).
Peer Reviewer 1	General	It is evident throughout this review that the authors' ability to draw unequivocal conclusions is hampered by empirical literature that is characterized by insufficient- or low-quality evidence. Although this review is valuable to emphasize the paucity of empirical evidence from which to make distinct determinations, it is unclear whether this report can be clinically meaningful or practical for guiding policy decisions. Rather, it seems that the more appropriate and straightforward function of this review is, in the authors' words, to "define and update priorities for further research in this area" (Page 2, Line 4).	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Introduction	Although the authors correctly acknowledge the practice standard that "clinical decisionmaking around long-term opioid therapy [LTOT]…requires individualized assessments of the balance between benefits and harms…" (Page 1, Lines 27-28), the authors also appropriately acknowledge the difficulty in gaining an understanding from empirical evidence about benefits and harms from the current extant literature because of a wide variety of methodological issues. The authors then provide a paragraph in which many of those methodological issues are listed (Page 1, Lines 36-53). Given this empirical reality, however, it seems that the authors could better indicate how these methodological issues influence the interpretability of the following statement: "accumulating evidence indicates important harms associated with prescription opioids…" (Page 1, Lines 14-15). When referring to harms, especially in relation solely to clinical harms, it is critical to take into account the degree to which polypharmacy characterizes these events, and to indicate whether these harms relate exclusively or primarily to LTOT for chronic pain (i.e., ethical prescribing practice with legitimate patients). The authors also should explicitly recognize the degree to which the issue of pharmacogenomics can challenge a generalizable understanding of benefits and risks. It also seems important to note that some of the articles used to reference the above-quoted statement were deemed unworthy to include in the evidence base for this review.	Thank you for your comment. We revised the Intro (p1 line 14-15) to note that prescription opioids may be associated with important harms. The purpose of the citations is to provide context regarding concerns about harms and we think it is appropriate to cite such contextual references here. The Results and Discussion address the findings regarding the available evidence.
Peer Reviewer 1	Introduction	Finally, when describing risk mitigation strategies, the authors cite the "application of maximum dose ceilings" (Page 1, Line 33) as originating from a clinical practice guideline published from the American Pain Society/American Academy of Pain Medicine (Reference 9). Actually, the guideline recommends not a dose ceiling, per se, but rather an amount for which "more frequent and intense monitoring is often appropriate, to sufficiently inform the decision to continue therapy or consider additional dose escalations" (p. 120). The authors should clarify this important distinction and carry it through the entire manuscript when the phrase "maximum dose ceiling(s)" is mentioned.	Thank you for your comment. We revised to "application of dose thresholds that warrant increased caution" and throughout the report revised to refer to "dose thresholds".
Peer Reviewer 1	Methods	The authors explain that the methods used for this manuscript conform to those suggested by the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Page 5, Lines 6-8). Given this, the search strategies (which are explicitly outlined in Appendix A) and the inclusion and exclusion criteria (which are described in Appendix B) seem to appropriately stem from the numerous Key Questions. Outcome measures related to pain, function, various types of harm, etc. are clear, but are operationalized in the individual studies (if at all) and not in this review. No statistical methods were used in this manuscript, due to its review nature, but articles controlling for potential confounders were included in the sample of studies comprising the manuscript's evidence base.	Thank you for your comment. We included outcomes for pain, function, and quality of life as used in the studies.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Methods	Although the authors clearly described the process used to determine study quality according to the various categories of studies (e.g., cohort, cross-sectional, case-control, etc.), a number of issues could be further clarified that may have an impact on conclusions and implications. For example, it seems important to know the degree to which the two investigators' independent assessment of study quality resulted in initially equivalent determinations, given the method behind this process. Also, when describing the categories of article quality, the authors state the following: "Studies rated 'fair-quality' have some methodological shortcomings, but no flaw or combination of flaws judged likely to cause major bias. In some cases, the article did not report important information, making it difficult to assess its methods or potential limitations. The moderate risk of bias category is broad and studies with this rating vary in their strengths and weaknesses; the results of some studies assessed to have moderate risk of bias are likely to be valid, while others may be only possibly valid" (Page 8, Lines 33-39). Given this description, there seems to be a broad degree of "quality" within this single category. Would it be feasible for the authors to report the proportion of studies for which methods or potential limitations were difficult to assess, as well as describe the potential implications of drawing conclusions from such studies? This information seems especially important given the considerable amount of fair-quality evidence comprising the study sample and the seeming equivocal interpretability of this standard. For another issue, even with the information provided in Appendix E it remains difficult to appreciate the extent that included studies controlled for relevant confounds (especially patient and practice characteristics) that could influence assessed outcomes; although controlling for potential confounders was a characteristic used to rate the quality of studies, is there any way to suggest the cumulative ramifications of unmeasured, but nevertheless potentially mediating, clinical confounders across the studies?	Thank you for your comment. Detailed quality assessment of all included studies is available in Appendix F. The evidence tables provide detailed information regarding patient characteristics, other potential confounders, and methods for adjustment.
Peer Reviewer 1	Results	The literature flow diagram (Page 11, Figure 2) clearly illustrates the article selection process used for this review, and the remaining tables, figures, and appendices seem to sufficiently describe the additional characteristics of the study process and relevant article features (except when noted elsewhere in these comments). I am unaware of additional germane studies that were published during the stated timeframe and that would have met inclusion criteria. Also, the studies that ultimately were selected as the evidence base seem apt, given the inclusion criteria described. The key questions guiding this review were represented in the descriptions of review findings, and the review's messages (those identified by the authors as pertinent) were apparent especially in the Detailed Synthesis descriptions.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Results	Although not surprising, the lack of evidence around the effectiveness or comparative effectiveness of LTOT to placebo, no opioid therapy, or other opioid therapy is frustrating and needs to be addressed through a concerted research agenda. The same largely can be said about evidence regarding the three other key questions, the subquestions of which typically are characterized by insufficient- or low-quality evidence. Again, the inconsistent collection of relevant confounds, the potential influence of unmeasured confounds, and the failure to assess predefined outcomes makes it difficult to draw valid implications from this collection of studies. For example, when describing the evidence base for Key Question 2 (Harms and adverse events), the authors state that "No study examined how harms vary depending on the specific type or cause of pain, patient demographics, or patient comorbidities (including past or current substance abuse disorder or being at high risk for addiction)" (Page ES-12, Lines 30-32). In fact, in the Executive Summary, similar statements were made that were relevant to each of the four Key Questions.	Thank you for your comment. Regarding confounders, we limited the inclusion of controlled observational studies to those that performed adjustment on potential confounders. The degree of adjustment of confounders for each study is reported in Appendix F. Please see the above response regarding the operationalization of the outcomes. Regarding Key Question 2, we state that because no RCT or controlled observational study met inclusion criteria, we broadened criteria to discuss evidence on uncontrolled studies for this Key Question.
Peer Reviewer 1	Results	Even though the authors recognize that "A challenge in interpreting the evidence on rates of opioid abuse, addiction, and related outcomes is inconsistency in how these outcomes were defined, as well as variability in methods used to ascertain these outcomes" (Page 16, Lines 39-41), it seems that further explanation is required for the finding that "rates of opioid abuse were 0.6 percent to 8 percent and rates of dependence were 3.1 percent to 26 percent in primary care settings…" (Page ES-12, Lines 13-15). It is unusual for incidence or prevalence rates of abuse to be lower than rates of dependence (if "dependence" is in fact meant to represent the term "substance dependence").	Thank you for your comment. The rates of opioid abuse and dependence were largely from uncontrolled studies that evaluated different populations and used different methods to define these outcomes, as described in the Results and Discussion.
Peer Reviewer 1	Results	Finally, implications from the Portenoy et al. (2007) study warrant additional discussion, where "5.7 percent of the patients were identified by their physician as exhibiting problematic drug-related behaviors…[while] verification by an independent panel resulted in a lower rate of 2.2 percent" (Page 16, Lines 27-31). What is the research or clinical relevance, if any, of this categorization discrepancy?	Thank you for your comment. The data are presented as reported in the study. Some readers might consider assessments from an independent panel to be less potentially biased and therefore more reliable.
Peer Reviewer 1	Results	On Page 20, Line 26: Is something substantive missing at the end of the sentence?	Thank you for your comment. We deleted the left parentheses, which was a typo.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Discussion/ Conclusion	The authors provided a straightforward recitation of the key findings and reiterated the many areas in which available evidence is either non-existent or of low quality, drawing from information contained in the included studies. Throughout the discussion of key findings, the authors acknowledge the difficulty of drawing conclusions from many of these studies based on a variety of methodological limitations (which is again enumerated in the Limitations of the Evidence Base section). When discussing the finding of lower risk of methadone-associated mortality in the VA system, the authors justifiably recommend that "research is needed to understand the factors that contribute to safe prescribing in different clinical settings" (Page 43, Lines 30- 31); it seems important, however, for this recommendation to be considered broadly, beyond methadone. The authors also need to correct the seemingly redundant listing of references that occurs on Page 43, Lines 49-50.	Thank you for your comment. We deleted the duplicated listing of references in this sentence.
Peer Reviewer 1	Discussion/ Conclusion	In the Applicability section, the authors mention what seems a key limitation of conclusions that can be drawn from this review, "One challenge was difficulty in determining whether studies focused on patients with chronic pain" (Page 49, Lines 44-45). This seems a particularly problematic challenge, given that the objective of this review was to understand the "benefits and harms of long-term opioid therapy for chronic pain" (Page 1, Line 36). In light of the foundational nature of this issue, it seems incumbent on the authors to indicate the proportion of included studies for which it was difficult to determine patients with chronic pain, the key questions for which these studies provided evidence, and the implications of this information.	Thank you for your comment. The next sentence after this statement describes that it refers to the observational administrative database studies. As noted in the Methods, we restricted inclusion to studies in which we could infer that patients had chronic pain based on the number of prescriptions or the type of opioid used (e.g., sustained-release opioids).
Peer Reviewer 1	Discussion/ Conclusion	Also, the authors discuss the research use of a run-in period that "preselects patients who respond to and tolerate initial exposure to the studied treatment. Therefore, benefits observed in the trials might be greater and harms lower than seen in actual clinical practice" (Page 50, Lines 8-10). Is it not correct, however, that such a selection and trial process is recommended by current clinical practice guidelines and actually should reflect what is occurring in clinical practice? It would be important for the authors to validate and promote this clinical approach.	Thank you for your comment. Use of run-in periods are recognized as threats to applicability. In clinical practice, clinicians do not know who will respond to or tolerate opioids before initiating them. We added a reference about applicability and run-in periods.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Discussion/ Conclusion	In the Implications for Clinical and Policy Decisionmaking section, the first paragraph seems to represent an accurate description of the current situation. However, messages from the second paragraph would benefit from a more comprehensive context. It seems that opioid-related harms in the clinical setting can result from a number of different scenarios, including (1) appropriate prescribing and appropriate patient use of the medication, (2) appropriate prescribing and inappropriate patient use of the medication, (3) appropriate prescribing and either appropriate or inappropriate use of the medication along with harmful use of other substances, and (4) inappropriate prescribing, which may occur along with a patient's harmful use of other substances. Does the published literature provide an indication of what clinical scenario(s) are most associated with the mentioned harms, which also tend not to account from non-medical use occurring completely outside the clinical setting? If so, does this need to be considered to better aid clinical and policy decisions? When this is not the case, the clinical and policy implications of the current literature are extremely limited and should at least be acknowledged as such. Overall, when addressing the review objective, it seems essential to understand the extent to which documented benefits and harms occur within the ethical practice of pain medicine.	Thank you for your comment. The observational studies that comprise the bulk of the evidence on harms reflect outcomes as observed in clinical practice. As noted in the paragraph, greater adherence to practice guidelines might reduce harms, but there is as yet no evidence to show that this is the case.
Peer Reviewer 1	Discussion/ Conclusion	In the Limitations of the Evidence Base section, the authors specifically acknowledge the foundational shortcomings of the evidence available for this review, that "the critical limitation of our review is the lack of evidence in the target population (patients with chronic pain) and intervention (long-term opioid therapy)" (Page 51, Lines 28-29). Comments regarding this critical limitation are provided for in the Applicability section above.	Thank you for your comment. Please see above for our response.
Peer Reviewer 1	Discussion/ Conclusion	In the Research Gaps section, the authors provide an extensive list of recommendations based on the limitations recognized in the Results section, including the need to clearly and consistently define a variety of clinical outcomes and addressing appropriate and sufficient confounders related to patient and other clinical characteristics. Clinical research also requires, as the authors suggest, the evaluation of confirmed patients with chronic pain. As proposed in the preceding comments, accurately studying the effectiveness, comparative effectiveness, and harms of LTOP for chronic pain additionally requires an ability to operationalize the appropriateness of the prescribing practices, especially given the authors' recognition of "continued wide variation in practice" (Page 1, Line 52) and the potential influences of inappropriate practice on poor or adverse outcomes. Another clinical and empirical consideration is the extent to which the prescribed medications are used as directed, since research has shown that medical misuse can lead to personal harmful consequences. Such a research agenda also would be strengthened by recommendations about methodologies that would better predict benefits and harms within a variety of clinical settings.	Thank you for your comment. We revised the Research Gaps section to suggest studies of patient "clearly with" chronic pain. As our focus is on clinical effectiveness, we are interested not just in outcomes associated with "ideal" use (efficacy) but also those associated with suboptimal use, as observed in clinical practice.

Reviewer	Section	Comment	Response
Peer Reviewer 1	Discussion/ Conclusion	The Conclusions section is too brief and does not provide readers with important messages that would be beneficial to the anticipated audience. Also, the authors should provide additional justification when highlighting "increased risk of serious harms that appears to be dose-dependent" (Page 52, Line 39) as the only reported finding. From the information provided, it was determined that low quality evidence characterizes the findings under Key Question 2b (itemized in Appendix G). If, as the authors state, "A 'low' [strength of evidence] grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate" (Page 9, Lines 44-47), and low quality evidence characterizes many findings from this review, why is this the only finding mentioned? Was it because of its potential clinical significance? Because it was determined that these harms were associated with ethical prescribing practice with legitimate patients? Because potential confounders were better controlled? Because the study limitations were predominantly moderate? It seems that the authors should give explanations for the messages provided in the Conclusions.	Thank you for your comment. To clarify, the Conclusions are not intended to provide practice or policy recommendations, but to briefly summarize the findings of the evidence review. Most of the evidence was "insufficient", we focused on effects of dose since there is low quality evidence for a number of harms, and it is a potential target for risk mitigation strategies (other areas supported by low quality evidence, e.g. risk of opioids in general, effects of long vs. short-acting opioids, etc. do not lend themselves to actionable measures).
Peer Reviewer 1	Clarity and Usability	The report is well-structured and well-organized, and presents a clear indication of the utility and quality of the current literature related to the benefits and harms of LTOT for chronic pain. That being said, and as noted in the Discussion/Conclusions comments, the conclusions are now insufficient to be useful for informing practice or policy decisions. Although this may be largely a product of being limited by an insufficient or low-quality evidence base, it is up to the authors to determine the messages that can be validly drawn from the current literature and to justify their importance to clinicians and policy-makers, if this is even possible given the evidence.	Thank you for your comment. Please see above for our response.
Peer Reviewer 2	General Comments	The report differs from previous reviews in that it focuses on the benefits and harms and additional key questions related to long term opioid therapy. It is directed at those who use opioids to manage chronic pain patients and those who study this population. Key questions are right on target	Thank you for your comment.
Peer Reviewer 2	General Comments	On ES-18 HR is defined as heart rate should be hazard ratio	Thank you for your comment. We corrected this typo.
Peer Reviewer 2	Introduction	The structured Abstract report should indicated that the review includes chronic pain patients on long term opioids with cancer and noncancer pain—this statement is buried on pg ES-6 in the Summary	Thank you for your comment. We added this to the Structured Abstract.
Peer Reviewer 2	Methods	The methodology of the Chou group is well established and recognized as the standard for evidence based reviews. Each step is clearly described in the methods section.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 2	Methods	The Methods should include some information on why HR vs OR (or other estimates) were selected for the analysis.	Thank you for your comment. We reported relative measures of effects as reported in the studies. For studies that did not report relative measures of effects, we calculated relative risks when data were available to do so, as noted in the Methods (Data Extraction section).
Peer Reviewer 2	Results	Clearly presented –no concerns An appropriate amount of detail is presented. The characteristics of the studies are clearly described. The key messages are explicit and applicable. The figures, tables and appendices are adequate and descriptive. Not aware of any additional studies that ought to have been included studies that ought to have been excluded.	Thank you for your comment.
Peer Reviewer 2	Discussion/ Consclusion	The implications of the major findings are clearly stated as are the limitations of the review. The future research section is clear and easily translated into new research.	Thank you for your comment.
Peer Reviewer 2	Discussion/ Consclusion	Need some statement in the discussion on whether the dose dependent increased risk of serious harms like overdose does or does not apply to cancer pain patients. Many clinicians that manage cancer pain believe that longer term opioid use is associated with tolerance to respiratory depression and that these patients are protected from RD in a manner that patients initiation opioid therapy are not.	Thank you for your comment. As noted in the Methods, we excluded patients receiving opioids at end of life. We do not believe there is a strong rationale that patients with non-terminal cancer pain would be more or less likely to overdose when treated with long-term opioid therapy as patients with chronic pain due to a non-cancer condition.
Peer Reviewer 2	Clarity and Usability	The reader will come away with a much better appreciation of the limits of the current evidence and the need for additional focused research. Given the limitation imposed on the conclusions by the lack of evidence in many critical areas, the identified research gaps provide a roadmap of where we need to go.	Thank you for your comment.
Peer Reviewer 3	General Comments	In general this is a superb effort to respond to the questions posed. However, I only ranked the quality as “good”. That is because I am concerned that there may have been bias to reach a conclusion that very little is known about the use of opioids for chronic pain, that prompted the authors to set a minimum duration of observation of 1 year as a criterion for study inclusion in the meta-analysis (see below).	Thank you for your comment. The National Institutes of Health working group and Technical Expert Panel members selected the 1 year minimum duration, as shorter-term benefits and harms of opioid therapy were felt to be better understood.
Peer Reviewer 3	Introduction	Nothing to criticize here, very well-done.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 3	Methods	"Are the inclusion and exclusion criteria justifiable?" In my view the inclusion criterion of at least a 1-year interval of observation requires more justification. As the authors likely know, over a decade ago the FDA established a 12-week duration of observation as a requirement for approval of drugs for use in chronic pain. Hence, with some exceptions, there was little or no requirement to conduct pharma-sponsored trials beyond 12 weeks. Indeed, the authors of the present systematic review themselves defined "chronic opioid use" as 3 months or longer. Although it is hard for me to tell from the flow diagram how many studies were rejected based upon their having a duration of observation less than 12 months, given the large number of excluded studies this number may have been substantial. Hence I feel it would be important to conduct a sensitivity analysis to determine how the results and conclusions of this systematic review might have been altered if the inclusion criterion were reduce either to 6 or 3 months of observation during the study. I am not saying that the information and conclusions about 12-month studies is unimportant—it's very important—but one wonders whether relevant studies might have been needlessly excluded by the 12-month criterion.	Thank you for your comment. We added a sentence to the Limitations of the Review Process section noting that applying a shorter duration threshold for inclusion could have provided additional evidence. However, we identified no placebo-controlled trials of opioid therapy for at least 6 months.
Peer Reviewer 3	Results	In general I have little to criticize regarding this superb effort. However, to address the question "Did the investigators overlook any studies that ought to have been included" I would refer to section d above, in this scoring sheet.	Thank you for your comment. Please see above for our response.
Peer Reviewer 3	Discussion/ Conclusion	To address the question "did the investigators omit any important literature?" I would refer to section d above, in this scoring sheet.	Thank you for your comment. Please see above for our response.
Peer Reviewer 3	Clarity and Usability	This report is very clearly written. Because its conclusions emphasize how little is known, it is not appropriate to look to it to inform policy decision directly. Rather, its value in its present form (setting aside my concerns about the duration of observation in the studies included) is as a guide to the research that must be carried out to close important knowledge gaps.	Thank you for your comment.
Peer Reviewer 4	General Comments	This report addresses and clinically important and timely topic. It provides an update on previous systematic reviews on the efficacy and safety of long-term opioids for patients with chronic non-cancer pain. The key questions considered in the report were clearly enumerated	Thank you for your comment.
Peer Reviewer 4	Introduction	The rationale for the report was clearly defined. There is no question that there are a large number of individuals with chronic, non-cancer pain (CNCP) in the US population and a substantial proportion of whom are prescribed opioids on a long-term basis. The evidence for the increased incidence of misuse, abuse, morbidity, and mortality of individuals for whom these drugs are prescribed and more broadly in the general population is clear and disconcerting.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 4	Methods	Although the inclusion criteria for studies considered is clearly presented, I was somewhat surprised that the authors decided not to include tramadol, despite the weak mu opioid affinity. Given the frequency with which tramadol is prescribed, I believe it would have been useful to include the studies on this medication, especially in light of the inclusion of tapentadol, a drug with a number of commonalities. The search strategies used, the inclusion criteria for studies, an analytic strategies are clearly presented and therationale well-documented. The criteria for quality ratings is also clearly specified.	Thank you for your comment. The National Institutes of Health working group and Technical Expert Panel recommended exclusion of tramadol because it has very weak mu-affinity (~100 fold less than tapentadol).
Peer Reviewer 4	Results	The report is quite detailed and precise in the results presented. The characteristics of the studies included are clearly described. The Tables and figures are clearly presented and compliment the narrative text. The authors do an excellent job of relating the outcomes of the available studies to the key questions addressed and the conclusions provided based on the available body of research.	Thank you for your comment.
Peer Reviewer 4	Results	I believe the report does include all of the relevant studies, however, not my question regarding the failure to consider studies reporting on the safety and efficacy of tramadol.	Thank you for your comment. Please see above for our response.
Peer Reviewer 4	Discussion/ Conclusion	Although the report is comprehensive, clearly presenting the major findings, the disappointing outcome is that so little research was available to address the key questions that were pre-specified and the low quality of many of those studies that were available. This leads to concern as to the actual clinical utility of the conclusions. There is no question that the review identifies the paucity of high quality research that greatly limits the actual conclusion. The results may should serve as a guide to necessary research that needs to be conducted to permit better clinically meaningful guidance to practitioners and policy makers.	Thank you for your comment.
Peer Reviewer 4	Clarity and Usability	Although the report is carefully conducted and the results of the analyses are discussed in depth and appear to accurately reflect the current state of knowledge, the ability to inform policy and practical decisions is limited by both the availability and quality of the research. After the extensive review and analysis the actual contribution to practice and policy is limited as it is based on very weak evidence. Thus, the recommendations are largely based on inadequate results from clinical trials and epidemiological data on misuse, abuse, morbidity and mortality. At best the results demonstrate the inadequacy of the evidence to answer the key question. This is not a fault of the report but rather the state of knowledge. One could ask the question as to what clinical practice and policy decisions should be altered as a result of the review and analysis that could not have been made had the analyses not been conducted.	Thank you for your comment.
Peer Reviewer 5	General Comments	This is a timely review of evidence paper. It confirms that many if not most of the key questions that need to be asked and answered to support widespread chronic opioid therapy have less than sufficient data to come to meaningful conclusions. The paper would benefit, in my opinion from a summary/key points to address some of the more contentious issues. The length of the document is daunting.	Thank you for your comment. The brief Structured Abstract and Executive Summary are provided for this purpose.

Reviewer	Section	Comment	Response
Peer Reviewer 5	Introduction	I believe that the key questions asked by the authors are those that are on many clinicians minds, or should be on our minds. I think that the issue of abuse/addiction was handled particularly well in that the lack of uniformity in definitions (and the lack of consistent application of even what consensus there is in the pain/addiction world) did not lead the investigators to come to overly absolute conclusions. Clearly more data must be developed to put the practice of chronic opioid therapy into a meaningful and rational context. Personally, I think that the lack of precision is inevitable when dealing with problematic behavior in persons with a legitimate (if not always appropriate) need to use the opioid class of drugs. We need to focus more on issues beyond "opioid addiction is X in the chronic pain population". It simply isn't that clear.	Thank you for your comment.
Peer Reviewer 5	Methods	Well described and executed	Thank you for your comment.
Peer Reviewer 5	Results	Well done	Thank you for your comment.
Peer Reviewer 5	Discussion /Conclusion	Conclusions and the pathway the authors took to reach these conclusions were easy to follow. The sad fact that we are as far into chronic opioid therapy in chronic pain management in the absence of so much basic evidence of support is fightening.	Thank you for your comment.
Peer Reviewer 5	Clarity and Usability	This is really well done. Not really directly applicable to clinical practice except to say "Higher doses tend to have greater risk" and (cautiously) that methadone may actually be safer (in the correct setting) than morphine extended release. This paper really needs to spawn more research initiatives. Perhaps FDA will be able to use this to require pharmaceutical companies to help answer some of these previously unanswered and sometimes unasked questions.	Thank you for your comment.
Peer Reviewer 6	General Comments	This is a rigorously conducted and well reported systematic review. The target population and intervention are clearly described and appropriate. The key questions address the most important and clinically relevant questions related to long-term opioid therapy. In general, the methods are appropriate, the results are clearly described, the introduction and discussion sections are well written, and the conclusions are appropriate. The primary limitation, as the authors report, is the small number of available studies relevant to the key questions.	Thank you for your comment.
Peer Reviewer 6	Introduction	The introduction concisely summarizes the the problem of chronic pain, the dilemma of clinical decision-making about long-term opioid therapy, and the state of the evidence to date. In some locations, the definition of long-term opioids is described as ">1 year" (for example, Key Question 1a on page 11). The text should be clarified to indicate that the definition of long-term is inclusive of 1 year.	Thank you for your comment. We edited the typo where it should have said ≥1 year.

Reviewer	Section	Comment	Response
Peer Reviewer 6	Methods	Overall, the eligibility criteria, definitions, and methods are appropriate and well described. I have one major concern about the eligibility criteria for the overdose and injury harms addressed under Key Question 2. When evaluating overdose and injury harms, which may occur early in therapy (and may be especially likely to occur during early initiation and titration phases of therapy), I do not think it makes clinical sense to exclude studies based on duration of therapy, as long they address the target population (patients with chronic pain). Especially in the case of fatal overdose, excluding studies based on duration of therapy < 3 months (or unclear duration of use) could result in underestimating risk associated with initiation of long-term therapy for chronic pain. For these specific harms, just as an exception was made for outcomes occurring before 1 year of opioid therapy, I think an exception ought to be made for duration of therapy < 3 months. It appears this change would result in inclusion of 1-2 additional studies addressing overdose outcomes among patients with chronic pain.	Thank you for your comment. As described in the Methods, we included studies of any duration for overdose and injuries. In general, studies of overdose and injuries were excluded not because of duration of opioid use, but because we could not determine whether patients were prescribed opioids for chronic pain.
Peer Reviewer 6	Results	Overall, the results are clearly described and summarized. The inclusion/exclusion criteria seem to have been appropriately applied. In Summary Tables A and 6, the conclusion column sometimes includes a brief description of the source/quantity of evidence (e.g., "Two randomized trials found…") and sometimes does not (e.g., "No difference between various long-acting opioids."). It would improve the usefulness and clarity of the tables if information about the source of evidence was consistently included.	Thank you for your comment. More detailed information about the number and type of studies is presented in Appendix G.
Peer Reviewer 6	Discussion/ Conclusion	The findings are clearly summarized and their implications are appropriately stated. Comparisons with prior reviews are concisely and clearly discussed. Limitations are adequately described. The future research section is clear. One comment: Long-term randomized controlled trials are challenging for the reasons stated, but they are still critically important to fill many of the research gaps identified in this report. The research section emphasizes observational research and registries as ways to address these challenges. I think it is also important to briefly mention clinical trial designs (e.g., pragmatic trials) that could be useful in addressing challenges of conventional "efficacy" trial design.	Thank you for your comment. We added a sentence noting that pragmatic and other non-traditional RCT approaches could help address some of these challenges.
Peer Reviewer 6	Clarity and Usability	Overall, the report is very clear and well organized. The conclusions can be used to inform decisions, to the extent that relevant data are available. One policy implication not explicitly stated is the need for investment in research funding. An underlying reason for the lack of data is the historic lack of research resources directed to chronic pain management.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 7	General Comments	Limiting the analysis to studies with one year outcomes severely limits the usefulness of the report. It would have been better had this EPC assessment independently addressed both the RCTs previously assessed by the Furlan analysis (Ref #43) and the observational studies addressed by Noble (Ref #8), and any other studies that may not have been included in those two systematic reviews. As it is, on the effectiveness side, there is really not much new in here.	Thank you for your comment. The mentioned reviews and others are Discussed for contextual purposes. However, the focus of the report as determined by the National Institutes of Health Working Group and Technical Expert Panel was on long-term benefits and harms of long-term opioid therapy.
Peer Reviewer 7	General Comments	Again, limiting the scope to patients already on chronic opioids and with one year outcomes, the report misses the very important topic of the evidence on whether even starting chronic opioid therapy is prudent.	Thank you for your comment. We agree, which is why the focus is on long-term benefits and harms. Short-term benefits and harms have been fairly well delineated in placebo-controlled RCTs.
Peer Reviewer 7	General Comments	Re effectiveness, it would have been useful had the report adressed the extent to which any report has used a definition of clinically meaningful improvement in pain and function, or at a minimum to recommend that this issue be addressed in future research.	Thank you for your comment. As no study regarding effectiveness versus placebo (or no opioid) met inclusion criteria, whether effects met criteria for minimum clinically important differences was not relevant.
Peer Reviewer 7	General Comments	The issue of the relationship between chronic opioid use and both dependence and disability are not adequately assessed. As such, inclusion of such studies as the Martin study (J Gen Int Med; 2011; 26: 1450-7) on discontinuation rates would help provide at lease indirect evidence as to how long term opioid use is in the majority of cases. Similarly, the large prospective study in WA workers compensation on the relationship between early opioid use and later (1 year) disability (Franklin et al, Spine 2008; 33: 199-204), along with several other crosssectional studies of longer duration, should be cited even if these studies do not strictly meet the inclusion criteria.	Thank you for your comment. The studies you mention are not in chronic pain patients and do not meet our inclusion criteria.
Peer Reviewer 7	Introduction	Page ES-1, lines 17-18, the Furlan systematic review (Ref 43) should be cited, even though it doesn't meet the report criteria.	Thank you for your comment. The Furlan review is cited elsewhere in the report.
Peer Reviewer 7	Introduction	Page ES-1, lines 29-30-Ref 25 is about hyperalgesia-this should be mentioned in the sentence	Thank you for your comment. We added "hyperalgesia".
Peer Reviewer 7	Introduction	Page ES-1, lines 36-37-, and throughout manuscript-These aren't maximum dose ceilings-they are thresholds anchored to measured improvements, as in the WA AMDG guidelines-it would be extremely important not to perpetuate this myth. The actual language from the WA guidelines states" The total daily dose of opioids should not be increased above 120 mg oral MED without either the patient demonstrating improvement in function and pain or first obtaining a consultation from a practitioner qualified in chronic pain management."	Thank you for your comment. We revised to refer to "dose thresholds". (See similar comment above.)

Reviewer	Section	Comment	Response
Peer Reviewer 7	Introduction	ES-5, line 24- "The protocol for this CER was developed prior to initiation of the review"-it should be very transparent as to which criteria were pre-specified on the task order, vs which criteria were added by the expert panel or EPC.	Thank you for your comment. The Protocol for the review is posted on the AHRQ website.
Peer Reviewer 7	Methods	Again, limiting the scope to studies with outcomes greater than one year has severely limited the usefulness of this report	Thank you for your comment. Please see above for our response.
Peer Reviewer 7	Results	Page 21-KQ1-on effectiveness, the population-based prospective study in WA workers compensation demonstrating increased doses over one year, and baseline and one year pain and function using a definition of clinically meaningful improvement, should be cited and discussed (Franklin et al, Clin J Pain 2009; 25: 743-751)	Thank you for your comment. The article evaluates a cohort of patients with acute back injuries and did not compare outcomes between those who received opioids and did not receive opioids.
Peer Reviewer 7	Results	Page ES-23, lines 18-23-here and in subsequent sections, the description of the existing high quality observational studies relating opioid dose to overdose events is severely lacking. The four relevant studies (Dunn, Bohnert, Gomes, and Paulozzi) should be summarized in a Table, with a summary of the risk ratio at diferent doses. You can cite the limitations, but at least you will have summarized for readers a range of risks and doses. We calculated from the Dunn study almost 2 overdoses per 100 person years, and 1.5 overdose deaths/100 person-years in the Bohnert study.	Thank you for your comment. Only the Dunn and Gomes studies met inclusion criteria and are described in detail in the Results. The Bohnert and Paulozzi studies were not included because they did not include patients with chronic pain or we were unable to determine duration of opioid use.
Peer Reviewer 7	Discussion/Conclusion	Implications are not as robustly stated as they could be, related to the narrow scope of the review	Thank you for your comment. The Discussion and Conclusion present the findings of the evidence review. The purpose of the review is not to provide clinical or policy recommendations.
Peer Reviewer 7	Clarity and Usability	This is fine	Thank you for your comment.
Peer Reviewer 8	General Comments	OK	Thank you for your comment.
Peer Reviewer 8	Introduction	OK	Thank you for your comment.
Peer Reviewer 8	Methods	OK	Thank you for your comment.
Peer Reviewer 8	Results	I found Table A. Summary of evidence, difficult to read. Suggest dividing into one table for each key question. Also suggest carrying the text that gives each subquestion across all 3 columns, i.e., merging the cells in that row. This will remove a lot of white space. You might also then widen the last column so it doesn't wrap so much.. Finally, I'd left rather than right justify the individual health outcomes.	Thank you for your comment. The formatting of the table follows AHRQ guidance.
Peer Reviewer 8	Discussion/ Conclusion	OK	Thank you for your comment.
Peer Reviewer 8	Clarity and Usability	OK	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 9	General Comments	This is an excellent, well-defined, and thorough review of the state of the science in relation to long-term opioid use for chronic pain. The key points were that the published studies to date show little evidence to guide practice or policy, other than some weak recommendations that risks are related to long-acting opioids in a dose-response fashion. All studies to address the questions asked in the review had evidence that was either low or insufficient. The only two studies with moderate evidence were those examining the 2 hour post-medication benefit of either buccal fentanyl or intranasal fentanyl vs oral opioids on break-through pain. However, these were shortterm effects without looking at long-term sequelae of use of these short-acting break-through pain opioids. Given all the attempts across states at public policy and laws regulating opioid use and prescribing practices, the critical review provides the current state of the evidence that we have little to guide either practice or policy. The highlight of the report is the recommendations for research directions.	Thank you for your comment.
Peer Reviewer 9	Introduction	Excellent background and introduction.	Thank you for your comment.
Peer Reviewer 9	Methods	The methods are well described with what I consider appropriate inclusion and exclusion criteria. The search strategies are nicely explained and logical. The descriptions of the categorization of outcome measures are appropriate. The statistical methods also seem appropriate in that no meta-analyses could be performed based on the numbers and qualities of the studies found to meet inclusion criteria.	Thank you for your comment.
Peer Reviewer 9	Results	The descriptive summaries, tables, and data including references are well described in enough detail and provided in multiple formats. The key messages are noted in a clear and repeated fashion. I could not find any studies missed by the authors.	Thank you for your comment.
Peer Reviewer 9	Discussion/Conclusion	The discussion, study limitations, and study finding implications are clear and direct. The directions for future research section is especially informative and based nicely on the review findings.	Thank you for your comment.
Peer Reviewer 9	Clarity and Usability	This is a well described, clearly written report, based on a well-defined literature review with clear inclusion and exclusion criteria. The results are noted clearly in various formats, both descriptively and including table formats. The main points are nicely highlighted and the conclusions are based on the evidence presented and nicely highlight the need and directions for future research.	Thank you for your comment.
Peer Reviewer 10	General Comments	This is a high impact article that is long overdue. With the increase controversy over use of opioids for chronic pain, risk/benefit needed a thorough assessment. This article has achieved this. The findings and conclusions are not surprising and is consistent with the growing clinical experience with chronic opioid use. The key questions are complete.	Thank you for your comment.
Peer Reviewer 10	Introduction	Introduction is excellent and summarizes the reasons behind the need for this article. Deaths and overdoses from chronic opioid use has skyrocketed over the past decade and now surpasses MVA as a cause of death.	Thank you for your comment.

Reviewer	Section	Comment	Response
Peer Reviewer 10	Methods	Methods are adequate. The only thing I would add is to research the impact of sleep apnea on opioid death. There is a lot of suspicion that coexisting sleep apnea and use of long acting opioids is a significant cause of death.	Thank you for your comment. We found no studies on the association between long-term opioid use and risk of death in patients with sleep apnea.
Peer Reviewer 10	Results	See above about comment on sleep apnea.	Thank you for your comment. Please see above for our response.
Peer Reviewer 10	Discussion/Conclusion	Great discussion and balanced.	Thank you for your comment.
Peer Reviewer 10	Clarity and Usability	Good	Thank you for your comment.
Peer Reviewer 11	General Comments	This report entitled "The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain" is clinically meaningful. The topic of the report is timely given the epidemic of opioid related deaths in the US. The report has important clinical, research, and policy implications. The key questions were appropriate and explicitly stated. Although KQ 2a's statement "related outcomes" is a little vague. Unfortunately, the answers several of the key questions were unanswered due to the paucity of research in multiple areas related to chronic opioid therapy. I may have missed it; but I don't remember if the target population and audience was explicitly stated. Overall, this is an excellent report that will be helpful to the field.	Thank you for your comment. We were intentionally broad in describing outcomes related to pain, function, and quality of life in order to be inclusive. We added a sentence to the Introduction to be clearer that the report was commissioned by the National Institutes of Health to inform a Pathways To Prevention Workshop.
Peer Reviewer 11	Introduction	Structured abstract (page v): Minor point-- I generally consider adverse opioid related outcomes on a spectrum from least severe (most common) to most severe (least common). For example, I would consider reordering the mention and discussion of the outcomes: misuse (least severe, most common), abuse, addiction, and overdose (most severe, least common). I'm not sure if the authors agree with my contention, but it makes more sense to structure/order these outcomes this way than how they are mentioned in the abstract and throughout the report (overdose --> misuse).	Thank you for your comment. The order of the outcomes is not intended to be a marker of their relative frequency or severity.
Peer Reviewer 11	Introduction	Structured abstract and throughout report the word "percent" is written out. I realize this is a very minor point, but according to JAMA manual of style use of the symbol % is recommended for specific percentages unless at the start of a sentence. This change would save some space too if implemented. Also can simply use 95% CI's rather than 95 percent CI's.	Thank you for your comment. We spelled out the word "percent" per AHRQ style use requirements.
Peer Reviewer 11	Introduction	Yet another point: Would avoid qualfiers such as "extremely" or "very limited." This is used in the abstract in reference to data from the ORT ("... were extremely inconsistent and other risk assessment.)	Thank you for your comment. As evidence was generally lacking, we think using such qualifiers is appropriate to distinguish situations with very low quality from less low quality evidence.
Peer Reviewer 11	Introduction	I question whether opioid therapy and the possible link with OSA and sleep disordered breathing should be mentioned or some rationale of why if was not evaluated as part of the report.	Thank you for your comment. We identified no studies on the association between long-term opioid therapy and sleep apnea or related consequences.

Reviewer	Section	Comment	Response
Peer Reviewer 11	Methods	The inclusion/exclusion criteria are justifiable. The only controversy may be exclusion of tramadol given its recent DEA scheduling decision and implementation. This may deserve at least a brief mention.	Thank you for your comment. Tramadol is a very weak opioid agonist and the National Institutes of Health Working Group and Technical Expert Panel felt that it was qualitatively different from "true" opioids. Tapentadol was included because it is a much stronger opioid agonist.
Peer Reviewer 11	Methods	The search strategies are explicitly stated and logical.	Thank you for your comment.
Peer Reviewer 11	Methods	The definitions and diagnostic criteria for the outcomes are appropriate.	Thank you for your comment.
Peer Reviewer 11	Methods	Appropriate statistical methods used? Due to the paucity of data, meta-analytic methods were not used which is appropriate.	Thank you for your comment.
Peer Reviewer 11	Methods	Minor point: The analytic framework figure should explain in a footnote or write out the abbreviation KQ.	Thank you for your comment. We added a footnote explaining the abbreviation.
Peer Reviewer 11	Methods	Minor point (page ES 11) related to the literature flow diagram. I was a little put off by the statements "wrong population," "wrong intervention," "wrong outcomes." It might come across less harsh if it was stated that eligibility criteria were not met (or failed to meet eligibility criteria) for XXX studies for population, intervention, outcomes, etc.	Thank you for your comment. We used standard systematic review language for categorizing the excluded studies.
Peer Reviewer 11	Results	The amount of detail presented is generally adequate. In the tables, I like mention of the study setting (if available) since this seems to moderate certain harms such as misuse, abuse, and addiction. Especially for studies on harms and the predictive accuracy of risk prediction instruments	Thank you for your comment.
Peer Reviewer 11	Results	As mentioned above, I view harms along a spectrum: from misuse, abuse, overdose, and addiction-- listing of terms in this order reflect this spectrum (from least severe, most common to most severe, least common). I would also recommend consistency in the report in the order in which these are discussed.	Thank you for your comment. Please see above for our response.
Peer Reviewer 11	Results	While the discussion of opioid related harms is well done, some additional detail may be helpful. I'm interested in the biological connection between the opioid-MI relationship. What is the biological plausibility of this finding? This association is not intuitive and is not commonly discussed. Same question for opioids and fractures (I assume mediated through falls)?	Thank you for your comment. We elected not to speculate about the biological connection between opioids and falls or myocardial infarction, but to present the evidence regarding the potential association.
Peer Reviewer 11	Results	Minor point: would use symbol % throughout report rather than writing out percent, except for when a percentage starts a sentence (AMA Manual of Style).	Thank you for your comment. Please see above for our response.
Peer Reviewer 11	Results	Table 1: Setting of the study would be useful to include (if available).	Thank you for your comment. Study settings are abstracted in the main evidence tables.
Peer Reviewer 11	Results	Table 2 (page 30): Minor editing needed, i.e., change form to from	Thank you for your comment. We have corrected this typo.

Reviewer	Section	Comment	Response
Peer Reviewer 11	Discussion/Conclusion	The implications of the major findings are clearly stated.	Thank you for your comment.
Peer Reviewer 11	Discussion/Conclusion	The limitations of the review/studies included are well described.	Thank you for your comment.
Peer Reviewer 11	Discussion/Conclusion	The future research section is helpful and should be easily translated into new research.	Thank you for your comment.
Peer Reviewer 11	Discussion/Conclusion	I'm curious why opioid therapy's potential effecs on OSA or sleep disordered breathing were not explored or at least mentioned?	Thank you for your comment. No study reported effects of long-term opioid therapy on outcomes related to sleep apnea.
Peer Reviewer 11	Discussion/Conclusion	I agree with the author's statement and ultimate conclusion that "...most clinical and policy decisions regarding useof long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence."	Thank you for your comment.
Peer Reviewer 11	Clarity and Usability	The report is well structured and organized. The main points are clearly presented. The conclusions will likely inform practice, policy, and research decisions. My hope is that this report will stimulate funders to earmark more money towards pain related research.	Thank you for your comment.
Peer Reviewer 11	Clarity and Usability	Minor point: SIPs is not a common acronym and is not used all that often in the report. Thus, would consider simply writing it out.	Thank you for your comment. We define this acronym at first use.
Peer Reviewer 11	Clarity and Usability	Minor point: The summary of evidence tables could benefit from slight modification. I would recommend including the outcomes assessed in its own column rather than underneath the KQ verbiage. This modification would likely require changing the table to a landscape format.	Thank you for your comment.
Peer Reviewer 11	Clarity and Usability	Minor point: SOE is not a common acronym and is not used all that often in the report. Thus, would consider simply writing it out.	Thank you for your comment. We define this acronym at first use.
Peer Reviewer 11	Clarity and Usability	Additional discussion on how the strength of evidence was determined. Who made this determination?	Thank you for your comment. We discuss our methods for assessing strength of evidence on page 9 of the report.
Peer Reviewer 11	Clarity and Usability	Minor point: PLR is not a common acronym and is not used all that often in the report. Thus, would consider simply writing it out in the text.	Thank you for your comment. We define this acronym at first use.
Peer Reviewer 12	General Comments	This is a well written article on a topic that is very clinically relevant and timely. The authors decide to search and review articles from 2008 forward because they assume that the APS review up to 2008 was complete and thorough. Much attention is given to the key questions and the methodology used to help answer these questions based on the current literature. Overall the authors found the literature to be lacking in rigorous studies that could address key questions about the long-term use of opioids for chronic pain. This is a very useful article in identifying gaps in the literature.	Thank you for your comment.
Peer Reviewer 12	Introduction	Throughout the paper the authors chose to use the word "harms" rather than "harm." The assumption is that there are many different kinds of harm. It would be useful to briefly describe why this term was used rather than the more familiar "harm."	Thank you for your comment. There are indeed many kinds of harms, so we preserved this language.

Reviewer	Section	Comment	Response
Peer Reviewer 12	Introduction	It would help to briefly describe the results of the APS review, since it seems that this review is an extension of the previous APS review.	Thank you for your comment. The results of the American Pain Society review are discussed throughout the report.
Peer Reviewer 12	Methods	Care us given in identifying the inclusion and exclusion criteria of the studies considered for review. It is hard for the reader to be clear about what these are and this paper would benefit from a concise list of the inclusion and exclusion criteria in a table.	Thank you for your comment. Inclusion and exclusion criteria are provided in Appendix B.
Peer Reviewer 12	Methods	A number of papers were excluded because of inadequate duration. It would help to be clear about what the cutoff off the study duration is.	Thank you for your comment. Inclusion and exclusion criteria are provided in Appendix B.
Peer Reviewer 12	Methods	A number of risk assessment tools were not considered. It would help the reader to identify these tools (e.g., COMM, SISIP) and to state why they were not included.	Thank you for your comment. The inclusion and exclusion criteria for studies of risk assessment instruments in Appendix B. We focused on studies evaluated for predicting risk of abuse/misuse in patients prior to initiating opioid therapy (the COMM and others have been evaluated for monitoring patients already on opioids).
Peer Reviewer 12	Methods	I was surprised to see that Jamison et al, Pain 2010 was not included to help answer the Key Question 4c.	Thank you for your comment. The study you mention was excluded because the duration was only 6 months.
Peer Reviewer 12	Results	I appreciate that the authors were very conservative in their report of the results. A surprise conclusion was that methadone was associated with lower risk of mortality and that the study designs for the efficacy of buccal or intranasal fentanyl were the best. I would think that these results would be balanced with reports of difficulties with these medications.	Thank you for your comment. Issues regarding buccal or intranasal fentanyl and methadone are presented in the Discussion.
Peer Reviewer 12	Discussion/ Conclusion	There is no real discussion on the assessment of craving associated with opioid addiction, abuse or misuse. There are a number of measures on the predisposition of craving and dependence of dependent/addictive substances (e.g., cigarettes) in the literature.	Thank you for your comment.
Peer Reviewer 12	Discussion/ Conclusion	This article would benefit from more discussion of the impact of abuse-deterrent opioid formulas in reducing opioid abuse.	Thank you for your comment. We identified no studies on the association between use of abuse-deterrent formulations and improved clinical outcomes.

Reviewer	Section	Comment	Response
Peer Reviewer 12	Discussion/ Conclusion	It would be helpful to point out to the reader that this area of study is constantly evolving and that studies are underway that will help to answer these important key questions. A review in another 5 years will likely offer different conclusions.	Thank you for the comment. However, we elected not to speculate about whether there would be more and higher-quality evidence in the future.
Peer Reviewer 12	Clarity and Usability	This article is worthy of publication and helps to summarize the current literature. I did not especially find it easy to read and kept having to go back to understand the assumptions for inclusion and exclusion of articles. Any way to help the reader understand why certain articles were not included in the review would help to support the overall conclusions.	Thank you for your comment. We provide a detailed list of inclusion and exclusion criteria in Appendix B.

Reviewer	Section	Comment	Response
Public Reviewers			
International Adhesions Society	NA	Thank you for commissioning this report on an important topic and for the opportunity to submit comments as follows. The report is written against the backdrop of recent public debate involving various US government agencies about pain in general and opioid use in particular. In its introduction, the report summarizes some of the main issues around opioid use. This report was, appropriately, commissioned in an attempt to provide a scientific basis for sound decision-making related to the long term opioid use. The authors appear to have been diligent in their charge. What is alarming was not so much what they found, but more so what they did not or could not find. To answer a well thought-out set of questions, the authors could find only 38 studies that met the quality criteria, but only minimally. Indeed for some questions, no studies met the criteria. The dearth of good quality studies is even more alarming considering recent estimates (2012) of opioid US sales at around $9 billion and societal costs of opioid abuse and misuse (2007) at $56 billion. This latter figure is almost double the 2012 appropriation ($32b) for NIH, 158 times its budget for chronic pain research and only 30% less than the 2013 Federal budget sequester. Simply put, the extensive long-term use of opioids is not supported by good quality studies concerning their safety and efficacy. Accordingly, one could argue that opioid use must be curtailed pending conduct of studies supporting their continued use, funded from the $9 billion or so of annual opioid sales. Such a policy would deprive legitimate patients of what may be their only means analgesia, despite the potential harms. Against the backdrop of the recent debates about opioid use one of the report's main conclusions needs discussion: "More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies." We are concerned that, unqualified, these sorts of statements will be used to support a "quick-fix" solution to the opioid problem that denies legitimate pain patients their only means of analgesia while failing to wean the nation from opioids. Such an effort must be undertaken through an integrated public policy that includes funding and developing alternatives such as the one we have evaluated for pelvic pain[1] - and found to reduce opioid use in some patients. Accordingly we propose amending this conclusion to: "More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies that include use of other non-opioid modalities." More specific comments are as follows and in the full version of this comment as an appended file IntAdhesionSoc-081514AHRQLongTermOpioids.doc.	Thank you for your comment. Because there is not even good evidence examining the effectiveness and harms of long-term opioid use versus no opioids, we felt that the main conclusion should reflect this before discussing comparative effectiveness with other (non-opioid) modalities.

Reviewer	Section	Comment	Response
International Adhesions Society	NA	1. Appropriate framing of conclusions in abstract Given the intent of reports of this nature to be used as the basis for policy making, and the strong likelihood that some policy makers may only read the Executive Summary, it is essential that the conclusions from the body of the report be fully represented in the executive summary. Accordingly the ES states: (p5) "Conclusions. Evidence on long-term opioid therapy for chronic pain is very limited, but suggests an increased risk of serious harms that appears to be dose-dependent. More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies." The term "very limited" does not convey fully the dearth of information used to formulate the report which is more fully captured in the main body on page 89: "Based on our review, most clinical and policy decisions regarding use of long-term opioid therapy must necessarily still be made on the basis of weak or insufficient evidence." It is suggested that the paragraph from p89 be merged into that on p5.	Thank you for your comment. While the Conclusions in the Executive Summary and full Report currently match verbatim, we agree and added the requested sentence to both sections.
International Adhesions Society	NA	2. Tabulation of conditions and gender Given the complexity of pain as well as the report's limitations vis-à-vis the weak or insufficient evidence on which it is based, it is all the more important to qualify the few conclusions that can be made by framing them in the context of the types of pain conditions (e.g. back pain, headache etc.) and the study populations (particularly gender) described in the referenced studies. Particular populations for which data is completely absent (e.g. women, minorities etc.) should be identified.	Thank you for your comment. Key Question 1b examines the effectiveness of opioid use based on type of pain and patient demographics, including race and gender, and other factors, and no studies met inclusion criteria. We added this sentence to the Discussion: "No studies examined how effectiveness varies based on various factors, including type of pain and patient characteristics."
International Adhesions Society	NA	3. Research Gaps The section on Research Gaps (pES24, p51) should include the following questions: a) What the conditions of non-opioid treatment failure that head to the prescribing of long-term opioids? b) How do the answers to the research questions posed by the report vary with gender, type of pain condition, age, minorities and other special populations? c) What treatment strategies should be employed to optimize the use of non-opioid pain treatments in order to obviate the use of opioids?	Thank you for your comment. Suggested questions A and C were outside the scope of this systematic review. Suggestion question B is addressed by the Key Questions in the report.

Reviewer	Section	Comment	Response
International Adhesions Society	NA	4. Implications for Clinical and Policy Decisionmaking (pES22, p89) The report is written against the backdrop of recent discussions (e.g. at FDA) regarding mitigation (by the placement of dose or duration limits) of risks associated with use of opioids. Indeed pES22 states: "Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some support for clinical policy efforts aimed at reducing harms." Given the lack of data and its general low quality, this statement appears a little too strong and should be amended: "Based on low-quality evidence regarding harms associated with long-term opioid therapy, our review provides some LIMITED support for clinical policy efforts aimed at reducing harms." We have previously submitted comments to FDA regarding "Impact of Approved Drug Labeling on Chronic Opioid Therapy; Public Hearing; Request for Comments" (Docket FDA-2012-N-1172) on March 9 2013. These previously submitted comments are to be found at: www.synechion.com/IAS2013-FDAOpioidSurvey.pdf with a video review at: https://www.youtube.com/watch?v=ODmVHD8qB5w Relevant to the current report are two main concerns discussed more fully in the referenced earlier comments: a) Concern that the report will be used to support restrictions of opioids to legitimate users While we certainly agree that reduced usage of opioids is medically and socially desirable, we are concerned that this report will be used to support what appears as a "knee jerk" response to opioid use that involves restriction of opioids to legitimate users, beyond what the conclusions from this report can support.	Thank you for your comment. We revised as suggested.

Reviewer	Section	Comment	Response
International Adhesions Society	NA	Con't: In response to FDA's request for comments on this issue, we conducted (with the collaboration of 9 other patient groups) a study with 2840 mainly female patients representative of, conservatively, 30 million Americans with chronic pain related to pelvic, abdominal & spinal adhesions, endometriosis, interstitial cystitis and related conditions. These data highlight concerns that the current report may be used to support policies that will reduce the ability of a large majority (>80%) of these patients to access pain medication or to be reimbursed for it. In these patients, the use of opioids: *exceeds 90 days (85.5%), and often more than 2 years (54.8% of patients). sometimes exceeds 100mg morphine equivalent daily (24.3% of patients). *treats pain that is less than severe (46.3%). *is necessary, even with non-severe pain because other approaches have failed to provide relief. *would be regarded as "off-label" in 92.4% of patients if the labeling restrictions are implemented. Accordingly, as mentioned in section 2 above, the conclusions of the report need to be qualified by tabulating the types of patients and conditions described by the studies used in the report's analysis.	Thank you for your comment. Unfortunately, there are no studies that examine the effectiveness of opioid use based on type of pain and patient demographics, including race and gender, and other factors (see Key Question 1b.)

Reviewer	Section	Comment	Response
International Adhesions Society	NA	b) Concern that the strategic approach underlying the report is flawed The tone of the report set by the Background section (ES1) is consistent with FDA's statement (from its 2013 panel on chronic opioid therapy) that it and other policymakers are "striving to find a balance between minimizing opioid drug abuse and misuse, while simultaneously enabling appropriate access to pain-relieving drugs." This "balance" statement and hence the strategy that it represents is flawed because it assumes that: • opioids are the analgesic drugs of choice • drugs are the treatment of choice for pain These assumptions demonstrate just how addicted we are as a society to opioids. Even if scientifically based restrictions (supported only by weak evidence in the current report) could be defined to reduce opioid misuse, abuse will continue. Further, we may be lulled into a false sense of accomplishment that we have solved the dilemma of our need for analgesia, with opioids, by reducing slightly the high societal price we are willing to pay for it. Without considering how opioids should be used in the context of other drugs, devices or techniques, the war on opioid abuse and misuse is doomed to failure. We therefore propose that the guiding principle of any policy related to opioids should strive to "to find a balance between minimizing opioid drug abuse and misuse, while simultaneously enabling appropriate access to pain-relieving drugs, devices and other modalities." Accordingly we propose that this section contains language addressing this principle as a matter of public policy. This is essential if adequate funding is to be allocated for not only the research identified in the "Research Gaps" section of the current draft, but also funding and policies that will allow for: • Expedited FDA approval for alternatives • Streamlined reimbursement approval for alternatives. • Reimbursement that allows modalities such as physical and psycho-therapy to be used adequately for pain relief. • Review of cost centers related to treatment of pain • Allocation of funds to develop and deploy effective alternatives. Parenthetically we are hopeful that the National Pain Strategy, scheduled for release by IPRCC in the Fall of 2014, will also address this point. Please note that we have submitted comments to IPRCC on this subject June 3rd 2013 (see www.prweb.com/releases/2013_chronic_pain_pelvic/06_adhesions_hysterectomy/prweb10845881.htm and https://www.youtube.com/watch?v=ZI1SXnQ_AwY.	Thank you for your comment. This report will be used by the National Institutes of Health to inform a Pathways To Prevention Workshop, and any findings from the Workshop will be published separately. The purpose of this report is not to present clinical or policy recommendations, but to summarize the available evidence.

Reviewer	Section	Comment	Response
Pain Action Alliance to Implement a National Strategy (PAINS)	NA	An Institute of Medicine (IOM) report, Relieving Pain in America, published in 2011 called for a shift from a strictly biomedical to a bio psychosocial approach to chronic pain management, defined as an interdisciplinary emphasis on assessment and treatment that integrates medical, behavioral health and rehabilitation-focused treatment approaches with the goal of maximizing comfort and function for individuals suffering with chronic pain. A bio-psychosocial approach recognizes that opioids may only be a small piece of a comprehensive pain management program, and may even be unnecessary in many patients. With regard to the current tension between those who advocate for more restrictions on prescribing these medications and those who warn about the harmful unintended consequences of such restrictions for those pain patients who benefit from these medications, the IOM committee referenced several publications based on peer reviewed individual studies and systematic reviews of opioid use in chronic pain. Relieving Pain in America cautioned that those research findings "need to be set against the testimony of people with pain, many of whom derive substantial relief from opioid drugs" and suggested that "this tension perhaps reflects the complex nature of pain as a lived experience, as well as the need for bio-psychosocial assessments and treatment strategies that can maximize patients' comfort and minimize risks to them and society." The IOM report went on the state that "Regardless, the majority of people with pain use their prescription drugs properly, are not a source of misuse, and should not be stigmatized or denied access because of the misdeeds or carelessness of others." (Relieving Pain in America. A Blueprint for Transforming Prevention, Care, Education and Research. Institute of Medicine of the National Academies. The National academies Press, Washington DC, 2011, p. 145). The Pain Action Alliance to Implement a National Strategy (PAINS) is an organization that formed in response to Relieving Pain in America, with a commitment to work together with many pain advocacy groups to "transform the way pain is perceived, judged and treated in America". PAINS agrees with the conclusions of the many research studies such as the Cochrane Systematic Review done by Nobel M et. al (Noble, M., S.J. Tregear, J.R. Treadwell, and K. Schoelles. 2008. Long-term opioid therapy for chronic non-cancer pain: A systematic review and meta-analysis of efficacy and safety. Journal of Pain and Symptom Management 35(2):214-228.), and the report prepared for the Agency for Healthcare Research and Quality about which we are reporting, that "evidence on long-term opioid therapy for chronic pain is very limited" and "more research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies."	Thank you for your comment. This report will be used by the National Institutes of Health to inform a Pathways To Prevention Workshop, and any findings from the Workshop will be published separately. The purpose of this report is not to present clinical or policy recommendations, but to summarize the available evidence.

Reviewer	Section	Comment	Response
Pain Action Alliance to Implement a National Strategy (PAINS)	NA	Con't: Specifically, PAINS strongly advocates for federally funded research to enable longitudinal studies of long term opioid use in persons suffering chronic pain to address issues of safety and efficacy, including the impact of these medication on long term physical and emotional functioning, and an assessment of the risks of iatrogenic addiction. We urge policy makers at the state or national levels to pursue only those actions which are scientifically based, and to pursue a balanced policy agenda—one that recognizes the World Health Organization designation of opioids as "essential medications" for pain management as they develop policies to addresses concerns about abuse, misuse and diversion. Sound policy can only be based on sound scientific evidence generated through research. Furthermore, it is critical that we anticipate the unintended consequence of opioid policies and regulations on the lives of those who live and suffer with chronic pain. We have a moral obligation to do so.	Thank you for your comment. Please see above.

Reviewer	Section	Comment	Response
PEW Charitable Trusts	NA	The Pew Charitable Trusts applauds the Agency for Health Care Research and Quality (AHRQ) for its work to evaluate the effectiveness and risks of long-term opioid treatment for chronic pain. Pew is an independent, nonpartisan research and policy organization dedicated to serving the public. Our prescription drug abuse project works to develop and support policies that will help reduce the inappropriate use of prescription drugs while ensuring that patients with legitimate medical needs have access to effective pain management. We appreciate the opportunity to comment on the draft report prepared by your contractor. As the report is revised, we encourage AHRQ to add context regarding harms associated with methadone as a pain therapy and to ensure that qualifications regarding the quality of the evidence are included in the structured abstract. Harms associated with methadone as a pain therapy Without additional context regarding the dangers of methadone as a pain therapy, readers could interpret the report to be more positive about the use of methadone than evidence warrants. In the section entitled Key Findings and Strength of Evidence, the authors briefly state that the use of methadone as a pain therapy is associated with a disproportionate share of patient harm. However, the scope and nature of this harm is not fully described in the report. Pew encourages AHRQ to provide additional details about harms associated with the use of methadone as a pain treatment within the detailed discussion of this therapy. Data from the Centers for Disease Control and Prevention (CDC) indicate that methadone accounts for just 2 percent of opioid prescriptions, but 30 percent of opioid-related overdose deaths. i According to an analysis of data from 2009 in selected states, methadone was implicated in 40 percent of deaths that involved only one opioid-more than double the deaths attributed to other drugs in its class. ii Methadone's unique properties distinguish it from other opioid drugs. Pain relief from methadone lasts four to eight hours, but its effects on other organs, such as the lungs and heart, can continue for eight to 59 hours. iii As a result, patients may put themselves at risk by taking more of the drug before the original dose has been fully metabolized. When taken too often or at too high a dose, methadone can cause life-threatening respiratory depression and heart rhythm or heart rate abnormalities. iv Other commonly prescribed drugs, such as anxiety medications, can amplify these effects. Based on this and other information, the Food and Drug Administration (FDA) and professional societies representing pain specialists have recommended against the use of methadone as a first-line treatment for pain. v The CDC expands this precaution by stating that insurers should not list methadone as a preferred drug for the treatment of noncancer pain. vi	Thank you for your comment. Studies examining methadone were included in Key Question 3c on the comparative effectiveness of different long-acting opioids. In the report, we state that, "The SOE was rated…Low for mortality risk associated with methadone versus morphine..." and in Table 2 we provide detailed tables on the two fair-quality studies examining methadone (Hartung 2007 and Krebs 2011). We think that the wording in the report accurately reflects the evidence.

Reviewer	Section	Comment	Response
PEW Charitable Trusts	NA	This clarification is especially important given that this systematic review is intended for use by health plans and government programs, as described in the Preface. Given this proposed role in public health policy, it is essential that the report include specific epidemiologic and other information about harms and precautions associated with the use of methadone as a pain therapy. Inclusion of this information would provide readers with appropriate context to support a critical evaluation of the role of methadone in the treatment of chronic pain. It would also be consistent with the approach the authors used in presenting a similar FDA safety warning for buccal fentanyl within this report. Quality of evidence The report states that relatively few studies met the inclusion criteria defined for this systematic review. Pew appreciates that evidence limitations frequently prevent the development of strong recommendations or conclusions. It is not our intent to critique the inclusion of specific studies or their outcomes, but rather to ensure that this information is provided with appropriate context. As currently written, some sections of the report do not provide adequate qualifications regarding the limits of the evidence comparing mortality between methadone and morphine. We encourage AHRQ to ensure that evidence limitations are reinforced throughout the report, including within the Structured Abstract. As drafted, the Structured Abstract places strong emphasis on an observational cohort study that found methadone was associated with lower all-cause mortality compared to long-acting morphine. However, the abstract fails to highlight that the authors rated the quality of that evidence as low. There is a statement earlier in the abstract that notes the overall low quality of evidence for the full report, but it is unclear if this statement is applicable to the methadone study or other studies highlighted in the Results section of the Structured Abstract. Other limitations of the methadone study, including the extent to which it is applicable to other populations given the unique characteristics of the Veterans Affairs population that was studied, are described only within the detailed text where they may be overlooked or misinterpreted by some readers. Given the prominent presentation of these study results in the Structured Abstract, it is important to balance that information with a more prominent statement about limitations within that same section.	Thank you for your comment. Please see above.

Reviewer	Section	Comment	Response
PEW Charitable Trusts	NA	Conclusion Thank you for the opportunity to provide comment on the draft report. The Pew Charitable Trusts recognizes prescription drug abuse as a public health crisis in the United States that must be addressed. Comparative effectiveness reviews, such as this draft report, will also play an important role in improving the use of pain management therapies. Should you have any questions or if we can be of assistance with your work, please contact me by phone at 202-540- 6916 or via email at creilJy@pewtrnsts.org. i Centers for Disease Control and Prevention (CDC), "Vital Signs: Risk for Overdose from Methadone Used for Pain Relief-United States, 1999-201O," Morbidity and Mortality Weekly Report 61 no. 26 (2012): 493-97, http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6126a5.htm; CDC, "Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller" (2012), http://www.cdc.gov/vitalsigns/MethadoneOverdosesL. ii CDC, "Vital Signs: Risk for Overdose from Methadone Used for Pain Relief-United States, 1999- 2010. iii Food and Drug Administration (FDA), "Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat" (2006), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetylnformationforPatientsandProviders/DrugSafetylnformationforHeathcareProfessionals/PublicHealthAdvisories/ucm24346.htm. iv W. Chen et al., "Benzodiazepine Use and Misuse among Patients in a Methadone Program," BMC Psychiatry 11 no. 90 (2011), http://www.ncbi.nlm.nih.gov/pmc/articles/PMC37775/, CDC, "Methadone for Pain Management: The Clinician's Role in Reducing the Risk for Overdose" (2012), http://www.bt.cdc.gov/coca/ppt/2012/080112MethadoneFIN.pdf. v FDA, "Public Health Advisory: Methadone Use for Pain Control May Result in Death and LifeThreatening Changes in Breathing and Heart Beat" (2006); The American Academy of Pain Medicine, "The Evidence Against Methadone as a 'Preferred' Analgesic: A Position Statement From the American Academy of Pain Medicine" (2014), http://www.painmed.org/files/the-evidence-against-methadone-as-a-preferred-analgesic.pdf. vi CDC. "Vital Signs: Risk for Overdose From Methadone Used for Pain Relief-United States, 1999- 2010.	Thank you for your comment. Please see above.

Reviewer	Section	Comment	Response
Academy of Managed Care Pharmacy	NA	The Academy of Managed Care Pharmacy (AMCP) would like to thank the Agency for Healthcare Research and Quality (AHRQ) for the opportunity to comment on the Draft Comparative Effectiveness Review: The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain. AMCP is a national professional association of pharmacists and other health care practitioners who serve society by the application of sound medication management principles and strategies to improve health care for all. The Academy's nearly 7,000 members develop and provide a diversified range of clinical, educational and business management services and strategies on behalf of the more than 200 million Americans covered by a managed care pharmacy benefit. It celebrated its 25th anniversary in 2013. For more news and information, visit www.amcp.org. AMCP believes that the report's conclusions are reasonable and agree more research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies. AMCP members are actively engaged in the management of long term opioid treatment of chronic pain. Many strategies are employed such as provider lock-in programs, innovative medication therapy management (MTM) strategies for targeted management of individuals, and risk mitigation strategies. However, there is a need for published studies evaluating the effectiveness of risk mitigation studies for improving outcomes related to overdose, addiction, abuse or misuse to validate these endeavors. AMCP will be convening a summit in the Fall of 2014 with key stakeholders in the industry to develop best practice activities and programs and prioritize those that AMCP can promote to improve pain management, prevent substance abuse and improve substance abuse treatment outcomes. AMCP's goals for the summit are to develop and encourage managed care organizations to adopt measurable goals and initiatives to improve pain management while reducing the potential for abuse. AMCP will share the findings publicly with stakeholders, including AHRQ. We appreciate this review has highlighted the need for robust studies to validate managed care organizations' endeavors. If you feel that there are unique studies or pilot program opportunities our members can help contribute to this area, please contact me at 703-683-8416 or by email at erosato@amcp.org.	Thank you for your comment.
Dave Beeker	Introduction	Opioids have been around for thousands of years and science has failed to prove their efficacy for chronic noncancer pain. It is time to stop wasting money on research on opioids for noncancer pain and time to look for better treatments for people in pain. We all know NIH and IPRCC has many staff who are friends of the "opioid economy". Our Nation, instead, needs staff and researchers who are friends to people in chronic pain.	Thank you for your comment.

Reviewer	Section	Comment	Response
Jeni Bastean	Results and Tables	Page 28: Limitations for efficacy results in Wild study: study not designed to measure efficacy primarily. 1. Table 2 (Wild 2010): for clarity of efficacy results, consider restating to: mean pain intensity scores decreased from 7.6 (0.05) and 7.6 (0.11) at baseline to 4.4 (0.09) and 4.5 (0.17) for tapentadol ER and oxycodone CR, respectively; For Global assessment: change to "very much improved or much improved" 2. Table 2 (Allan 2005): Significance appears to be reported to the third digit – Adjust the p value for severe pain on movement to p=0.611 from p=0.61 3. Table 2 (Hartung 2007): Add additional values for ED encounters, including "fentanyl HR 0.73 vs oxycodone 0.45 vs methadone 0.71" 4. Table 2 (Hartung 2007): Consider removing "or overdose symptoms" from the last bullet in the table as a significant difference was identified in risk of overdose between methadone and long-acting morphine (HR 1.57, 95% CI 1.03 to 2.40)	Thank you for your comments. We have incorporated some of these clarifications to Table 2.
Paul Coelho	Discussion	Although two studies found an association between opioid dose and increased risk of overdose starting at relatively low doses (20 to 49 mg MED/day), estimates at higher doses were variable (adjusted HR 11.18 at >100 mg MED/day versus adjusted OR 2.88 for >200 mg MED/day).43,47 At least six additional studies not included in your analysis have also shown a positive relationship between dose and risk of overdose. Including these studies in the analysis strengthens the conclusion that overdose risk is strongly correlated with dose. 1. Emergency department visits among recipients of chronic opioid therapy. Braden JB, Russo J, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD.Arch Intern Med. 2010 Sep 13;170(16):1425-32. 2. Association between opioid prescribing patterns and opioid overdose-related deaths.Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, Blow FC.JAMA. 2011 Apr 6;305(13):1315-21. doi: 10.1001/jama.2011.370. 3. A history of being prescribed controlled substances and risk of drug overdose death. Paulozzi LJ, Kilbourne EM, Shah NG, Nolte KB, Desai HA, Landen MG, Harvey W, Loring LD. Pain Med. 2012 Jan;13(1):87-95 4. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. Gwira Baumblatt JA, Wiedeman C, Dunn JR, Schaffner W, Paulozzi LJ, Jones TF. JAMA Intern Med. 2014 May;174(5):796-801. 5. Prescription Histories and Dose Strengths Associated with Overdose Deaths (pages 1187–1195) Anne Hirsch, Scott K. Proescholdbell, William Bronson and Nabarun Dasgupta Article first published online: 15 FEB 2014 | DOI: 10.1111/pme.12391 6. Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, Rajan P, Baser O, Murrelle L. Pain Med. 2014 Jun 14. doi: 10.1111/pme.12480.	Thank you for your comment. As we discuss in the report, the Bohnert and Paulozzi studies were excluded because the duration of opioid use was not reported, and the Braden study was excluded because it combined emergency room (ER) visits for opioid-related overdose with ER visits for alcohol. Likewise, the Baumblatt, Hirsch, and Zedler studies are not in chronic pain patients population.

Reviewer	Section	Comment	Response
Public Reviewer	Discussion	Twenty months ago, I suddenly developed debilitating pain in my gluteal muscles. Under the care of a pain specialist, I have been prescribed opioids and Lyrica and will have an infusion pump implanted in two weeks. I have struggled to work even part time with the pain. I am hopeful that the pump will allow me to work full time and not have to apply for permanent disability. Because of my education and profession, I understand experimental design. This report concludes that there has been insufficient research to answer the posed questions. I wonder if any one of the highly qualified people involved have experienced chronic pain that can only be controlled by opiods. If not, then perhaps they cannot understand that it would be cruel and, in some cases life-threatening, to enroll patients in a study and restrict them to placebos. If patients could only get access to opioids by participating in a study, then coercion is replacing medical necessity. I fear regulations that will cause more primary care physicians to stop prescribing opioids. Of course, abuse and addiction are important issues that must be addressed. But, promoting a culture of fear of opioids could result in much more suffering.	Thank you for your comment.

Reviewer	Section	Comment	Response
David Wiseman	Discussion	Thank you for commissioning this report on an important topic and for the opportunity to submit comments as follows. The report is written against the backdrop of recent public debate involving various US government agencies about pain in general and opioid use in particular. In its introduction, the report summarizes some of the main issues around opioid use. This report was, appropriately, commissioned in an attempt to provide a scientific basis for sound decision-making related to the long term opioid use. The authors appear to have been diligent in their charge. What is alarming was not so much what they found, but more so what they did not or could not find. To answer a well thought-out set of questions, the authors could find only 38 studies that met the quality criteria, but only minimally. Indeed for some questions, no studies met the criteria. The dearth of good quality studies is even more alarming considering recent estimates (2012) of opioid US sales at around $9 billion and societal costs of opioid abuse and misuse (2007) at $56 billion. This latter figure is almost double the 2012 appropriation ($32b) for NIH, 158 times its budget for chronic pain research and only 30% less than the 2013 Federal budget sequester. Simply put, the extensive long-term use of opioids is not supported by good quality studies concerning their safety and efficacy. Accordingly, one could argue that opioid use must be curtailed pending conduct of studies supporting their continued use, funded from the $9 billion or so of annual opioid sales. Such a policy would deprive legitimate patients of what may be their only means analgesia, despite the potential harms. Against the backdrop of the recent debates about opioid use one of the report's main conclusions needs discussion: "More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies." We are concerned that, unqualified, these sorts of statements will be used to support a "quick-fix" solution to the opioid problem that denies legitimate pain patients their only means of analgesia while failing to wean the nation from opioids. Such an effort must be undertaken through an integrated public policy that includes funding and developing alternatives such as the one we have evaluated for pelvic pain - and found to reduce opioid use in some patients. Accordingly we propose amending this conclusion to: "More research is needed to understand long-term benefits, risk of abuse and related outcomes, and effectiveness of different opioid prescribing methods and risk mitigation strategies that include use of other nonopioid modalities." More specific comments are as follows and in the full version of this comment as an appended file IntAdhesionSoc081514AHRQLongTermOpioids.doc.	Thank you for your comment.