Technical Brief Disposition of Comments Report

Research Review Title: *Prevention, Diagnosis, and Management of Opioids, Opioid Misuse and Opioid Use Disorder in Older Adults*

Draft review available for public comment from May 15, 2020 through June 12, 2020.

Research Review Citation: Zullo AR, Danko KJ, Moyo P, Adam GP, Riester M, Kimmel HJ, Panagiotou OA, Beaudoin FL, Carr D, Balk EM. Prevention, Diagnosis, and Management of Opioids, Opioid Misuse, and Opioid Use Disorder in Older Adults. Technical Brief No. 37. (Prepared by the Brown Evidence-based Practice Center under Contract No. 290-2015-00002-I.) AHRQ Publication No. 21-EHC005. Rockville, MD: Agency for Healthcare Research and Quality. November 2020. Posted final reports are located on the Effective Health Care Program search page. DOI: 10.23970/AHRQEPCTB37.

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.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 1	b background	The background does a good job of pointing to the increasing prevalence of opioid use and adverse events in the older adult population. Although trauma, anxiety and depression all likely contribute to opioid use in the older population (since they contribute in general adult populations), no evidence is offered for a special effect in older adults.	It is yet unclear if there is a "special effect" of trauma, anxiety, and depression on opioid use in older adults. Older adults have a high prevalence of those conditions. Understanding whether special effects exist among older adults could be an area of future inquiry. In the section of the technical brief titled "Research Needs on Predictors of Opioid-Related Disorders", we had included the following sentence: "In addition, more research is necessary to understand the role of stress, anxiety, depression, and other behavioral and mental health conditions in increasing the risks of opioid misuse and development of OUD." We have modified that sentence to include trauma. In addition, we have modified the section titled "Research Needs on Predictors of Long-Term Opioid Use" to include an analogous sentence: "In addition, more research is necessary to understand the role of stress, anxiety, depression, trauma, and other behavioral and mental health conditions in increasing the risk of long-term opioid use".
KI Reviewer 1	b background	I don't think "Opioid treatment is often indicated for older adults" is an accurate heading for the following paragraph, which describes the risks with all pain treatments and the negative associations of untreated pain, and thus is generally about needs for and challenges of pain treatment in older adults.	We have edited the section title to "Needs and challenges of pain treatment in older adults". To avoid any confusion, we have also edited the section title immediately prior to "Pain in older adults".

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KI Reviewer 1	b background	P2: Here it says there is no research on PDMP effect, but elsewhere says it is significant.	We have deleted the following sentences from the Background: “Clinician use of state prescription drug monitoring programs (PDMP) provides information on a patient’s prescription history for controlled medications and may promote safer prescribing practices. However, it is unclear whether PDMP programs have an effect on opioid use in older adults.” These were written prior to the literature search and discovery of empirical studies examining the effects of PDMPs among older adult populations.
KI Reviewer 1	b background	Many questions about opioid dependence in older adults remain to be answered: what predicts inability to taper opioids: dose and duration of exposure, MH conditions, history of SUD?	It is true that these questions still exist. We have added text to the section titled “Research Needs on Predictors of Long-Term Opioid Use” as follows: “Research on how to taper opioids, especially after long-term use, is also critically needed. Future studies should focus in particular on which factors are associated with the inability to taper opioids, including opioid dose, duration of opioid use, mental health conditions, and any prior history of substance use disorders.”
KI Reviewer 1	b background	It is not clear that opioid dependence is principally or solely “physical.”	We appreciate this point and have added the following sentence to the Background section: “ Older adults may also develop psychological and other types of dependence on opioids.”
KI Reviewer 1	c. Guiding Questions	These seem reasonable generally	Thank you
KI Reviewer 1	d. Methods	Reasonable methods adequately described. Key Informants well described. I did not read through Appendix C	Thank you

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KI Reviewer 1	d. Methods	How and who assesses the risk-benefit balance of opioid therapy is important and not addressed.	Research is necessary to answer this question, therefore, we have built upon our existing text in the subsection titled "Research Needs Specific to Tools to Predict Harms During Appropriate Opioid Use" to underscore the need for more research on how to assess the benefit-risk balance and who should perform this assessment.
KI Reviewer 1	d. Methods	The Conceptual Framework diagram is useful in organizing the different domains of concern.	Thank you
KI Reviewer 1	d. Methods	Disagreements on methods in research into dependence indicates some research on alternative definitions and assessment methods needs to be done.	In the section titled "Research Needs on Predictors of Opioid-Related Disorders", we have added the following to incorporate this point from KI Reviewer #1: "More work should also focus on distinguishing opioid dependence from OUD in various data sources, and how changes in definitions and assessment methods for each over time have impacted the findings of research studies."
KI Reviewer 1	e. Findings	Description of proposed intervention: Important point about defining "older adult" and determining age thresholds.	Thank you
KI Reviewer 1	e. Findings	Evidence Map: I found these Heat maps useful summaries at a glance.	Thank you
KI Reviewer 1	f. Summary and Implications	Appropriate focus on multivariable analyses.	Thank you
KI Reviewer 1	f. Summary and Implications	Agree with need to develop and validate measures of opioid misuse among older adults.	Thank you

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KI Reviewer 1	f. Summary and Implications	More detail needed on anxiety as predictor: PTSD?, psychological trauma history, pain-related anxiety? More research needed on tobacco as risk for misuse.	In the section on Research Needs on Predictors of Long-Term Opioid Use, we have added a list of mental health issues, including anxiety, stress, and depression, among others. Essentially all factors need additional research in regard to predictors of risk for opioid misuse (etc.). It is not clear that we should specifically call out tobacco (or anxiety).
KI Reviewer 1	f. Summary and Implications	Need more research on which older adults receiving long-term opioids progress to misuse and OUD.	We believe this need is present in regards to predictors of all outcomes and all interventions. We have added language in the Summary and Implications section (and elsewhere) discussing the need for research about the heterogeneity in characteristics of the older adult population.
KI Reviewer 1	f. Summary and Implications	Need more ethics and policy research to define what is “appropriate reduction in opioid prescriptions.”	In the section titled “Research Needs Regarding Interventions to Reduce Opioid Prescribing for Older Adults For Whom Harms Outweigh Benefits (Triangle I1)”, we have now added the following statements: Future studies should attempt to better focus on minimizing “inappropriate” use. Such attempts might first require ethics research to define “appropriate reductions” in opioid use, as well as policy research to understand the unintended adverse consequences of policies that aim to reduce potentially inappropriate opioid use.
KI Reviewer 1	g. Next Steps	More discussion of the relative importance of population based studies, clinical cohort studies, and randomized clinical trials—based on the current state of the evidence would be useful.	We have focused more on the importance of assessing clinically-relevant, patient-centered outcomes. However, given the early state of the evidence, particularly for interventions (a general paucity of any studies of any given intervention), we refrain from recommending specific study designs.

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KI Reviewer 1	g. Next Steps	The need for research on the role, feasibility, and importance of multidisciplinary and multimodal care is important. Many calls for these, but little guidance on how to get it done.	The following sentence has been added to the section "Research Needs Specific to Multimodal Stepped Care Pain Therapy": Since many different research questions will need to be answered to establish the role, feasible designs, and ideal implementation of multimodal and multidisciplinary care interventions for older adults, qualitative research involving key stakeholders may be necessary to establish a structured research agenda and sequential steps.
KI Reviewer 1	g. Next Steps	What is the relation between age and OUD risk? Do SUDs develop de novo in the over 65 group? If so, who is at risk?	To the section Research Needs on Predictors of Opioid-Related Disorders, we have added that, in particular, research is needed to determine the risk of (and predictors of) de novo opioid-related disorders among older adults.
KI Reviewer 1	g. Next Steps	Important note of the lack of research into Goal Setting and Shared Decisionmaking	We appreciate KI Reviewer 1 acknowledging the importance of Goal Setting and Shared Decisionmaking.
KI Reviewer 1	g. Next Steps	Need more work on the structure of pain outcomes in the older population and on what the ultimate goals of pain treatment should be.	This is an important point and is now addressed through the addition of two sentences to the "Research Needs Specific to Goal-Setting and Shared Decisionmaking" section: Related to goal-setting and shared decisionmaking is the need to identify how to best measure the outcomes of pain management that are of utmost importance to older adults. In particular, research on outcome measures that relate to older adults' goals of pain treatment could help to optimize opioid use and pain treatments more broadly.
KI Reviewer 2	a. General Comments	found the report more than adequate. It was well referenced. It covers a difficult subject very well.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 2	b. Background	The background looked into the current issues with opioid misuse in general. The current epidemic of opioid use disorder	Thank you
KI Reviewer 2	c. Guiding Questions	Very detailed and appropriate for a challenging Subject	Thank you
KI Reviewer 2	d. Methods	Excellent literature review. Well referenced.	Thank you
KI Reviewer 2	e. Findings	Appropriate and objective	Thank you
KI Reviewer 2	f. Summary and Implications	The summary was well developed and cover the subject adequately. The implications of this paper will help clinicians and future researchers better understand the issues.	Thank you
KI Reviewer 2	g. Next Steps	Very well written. The recommendations were appropriate and relevant	Thank you

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KI Reviewer 3	a. General Comments	The clarity in the "main points" section needs to be sharpened. Is there a diagram that could highlight some of the main points from this technical brief? The structure is hard to follow. It starts with "35 studies" and then when you try to understand the main findings from those 35 studies it bounces around. Many people scan the executive summary but don't read the rest of the document. I believe there are two summary points made: - Risk factors for long-term opioid use in older adults surgery (8 studies), higher dosage (6 studies) - Opioid misuse/OUD Interventions for older adults only 1 RCT... Could there by a more lay language executive summary before the main points? The main points are quite technical.	Although there is a lot of detail covered in the Main Points, we believe that it is clearly laid out in a logical order in relatively straightforward English. We do not agree that it “bounces around” but is laid out in a rational order (by type [predictor/intervention], outcome, and consistency of evidence), with bolding and underlining to further guide the reader. The two major (black) bullets are largely what you have stated as the two summary points. However, we believe it is necessary to add more detail. The only technical language relates to definitions of strength and consistency of associations. But these are necessary to explain our terminology. We would be happy to revert to prior templates for the structure of the report to preface the document with Key Messages, if AHRQ prefers. It is not clear to us what type of diagram would be helpful. A pie chart or bar graph? We think Table 1 (and Table 14) in the main report summarize the data succinctly, but there is no room for them in the Main Points section.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 3	b. Background	"Opioid-related hospitalizations, emergency department (ED) visits, and deaths are increasing among older adults even as rates of nonopioid-related hospitalizations and ED visits are decreasing." Could we have diagram for this? Is it possible to state that part of this work is to try and understand why this is happening?	In the "Overview of the Technical Brief" section we write that "This Technical Brief comprises a conceptual framework and a focused evidence map of the current evidence base **with the goal of understanding the issues that are driving the current rise in opioid-related morbidity, mortality, and events in older adults, and what evidence is needed** to support effective interventions to prevent and manage harms from opioids in this population." Given the page limits required in Technical Briefs, we have chosen to allocate space to displaying new data and provide references to previous work.
KI Reviewer 3	b. Background	Conceptual framework: is this meant to be a general conceptual framework or a framework for older adults? how might those conceptual frameworks differ?	In the "Conceptual Framework" subsection of the "Findings" section, we have added the following sentence: "The framework is intended to remain general enough to accommodate the considerable differences among older adults across the population.." We have also added examples specific to older adults throughout the section to help readers understand how the Conceptual Framework applies.
KI Reviewer 3	b. Background	I find the section " The challenge of pain management in older adults " to be strong and the heart of the matter why this work is so challenging.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 3	c. Guiding Questions	An addition challenge for this work is understanding the difference between those with lifelong risk factors for SUDs/mental health disabilities versus those who experience a stressful life event and develop an OUD later in life.	We have now added a future research need to the section “Research Needs About Birth Cohort, Age, and Substance Use” as follows: “In addition, more research is necessary to understand the differences that may exist between older adults with lifelong risk factors for substance use disorders and mental health conditions who develop OUD versus older adults who experience a stressful event later in life and develop OUD. Some forthcoming research may help to provide some evidence on these topics; American Institute for Research investigators have recently tested the use of the Current Opioid Misuse Measure (COMM) for use with people with disabilities caused by arthritis, severe spinal osteoporosis and spinal stenosis who use opioids to manage chronic pain. Preliminary results suggest that a subset of the COMM items is valid for assessing opioid misuse in this population.”
KI Reviewer 3	c. Guiding Questions	One challenge with the guiding questions is it may imply older adults are a homogeneous group when there's a great deal heterogeneity. For older adults, their historic experience is a strong predictor...there's continuity in the experience, behavior, personality through the life course.	While we cannot modify the guiding questions, this is an excellent point that we have addressed by adding language throughout the report to better emphasize the heterogeneity of the older adult population.
KI Reviewer 3	e. Findings	With the risk factors, I worry some of the description treats them as independent predictors (e.g. tobacco use) when it is related to broader SES circumstances and early life experiences. How many older adults START to use tobacco out of the blue?	Yes, we (and the included multivariable analyses) treat each risk factor as independent. This analytic assumption does not imply that the factors are unrelated to each other. Throughout, we discuss “independent” variables/factors. Regarding tobacco use, the risk factor is not starting tobacco use, but instead current tobacco use.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 3	e. Findings	We should be careful to clarify which behaviors and risk factors may have origins in early life (tobacco use) as opposed to later life (surgery).	Our general approach is to minimize making assumptions about the evidence. Many risk factors clearly existed in early life (e.g., race, gender). Other specific risk factors very likely occurred in later life (e.g., surgery, dementia). But many are variable (e.g., mental health). For at least several risk factors, studies use variable definitions (or do not define), such as (current vs. history of) tobacco use, "substance misuse," and duration of anxiety/depression. While we could lay this out for each of the 30-plus risk factors we included, this Technical Brief is not the right place for such a detailed assessment.
KI Reviewer 3	f. Summary and Implications	We should be careful about making "age-based" associations because we don't have the data to tease out age-period-cohort effects. For example, in the multiple-provider analysis, younger older adults were more likely to have Rxs from multiple providers. They were also the group more likely to be in their 40s/50s when the opioid crisis was ramping up. The older "older adult" population was less likely. Is it age or historic experience? I would argue it isn't age but a combination of historic factors (increase in opioid Rxs) and unlucky events (need for surgery, traumatic injury, adverse event) that is driving those age-based effects.	This is an excellent point, which we have now incorporated into the subsection entitled "Research Needs About Birth Cohort, Age, and Substance Use". We thought it was most important to highlight this as a research need while simultaneously pointing out the pitfalls of interpreting age-based association without age-period-cohort studies.
KI Reviewer 3	g. Next Steps	agree with next steps	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	a. General Comments	Page xi, Line 56 - Insert “education and training of the healthcare workforce”	While we agree that a distal goal of this report is to improve education and training of the healthcare workforce, these specific items fall within the listed concepts in the sentence (page xi, last line of Background and Purpose). There are numerous other equally important specific items that could, but are not included in this general statement (eg, prediction tools, patient education, dosage guidance). We have, though, added the specific issues to Page 2 of the Introduction.
KI Reviewer 4	a. General Comments	Page 3, Lines 26- 27 – Insert after improve health outcomes in older adults “identify evidence-based practices to educate and train the healthcare workforce”	We have added a similar statement on page 2 under “Needs and challenges of pain treatment in older adults”.
KI Reviewer 4	a. General Comments	Page 41 – change 75 as oldest old to 85	We agree, and have made the change (page 46).
KI Re**viewer 4**	a. General Comments	Page 46, line 32; Page 47, line 10; Page 49, line 26; and Page 55, line 9 refer to Table 15 in the report. It appears these studies are listed in Table 14. There is no Table 15 in the report.	Thank you. These were meant to be call outs to Table 14. Corrected.
KI Reviewer 4	b. Background	The background is complete and thoroughly describes the clinical problem which is the increase in opioid related harms among older adults. The conceptual framework is comprehensive and describes the relevant evidence to outline a process of care that identifies risks and opportunities for intervention. The Technical Brief identified the following contextual factors: opioid related hospitalizations, emergency department visits, death, challenges of pain management and comorbidities, adverse drug reactions, and opioid misuse.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	c. Guiding Questions	No changes to the guiding questions were noted. The draft conceptual framework was revised based on feedback from a panel of 15 Key Informants.	The substance of the questions was not changed in any major way, but the questions were greatly shortened and simplified. We've made this clearer in Appendix B.
KI Reviewer 4	d. Methods	The Technical Brief clearly describes the methodology used for data collection. To address the Guiding Questions, a conceptual framework was developed which was informed by a 15-member panel consisting of six individuals employed by federal agencies and nine individuals employed by nonfederal entities. Key Informants participated in three teleconferences and over email until all of the relevant themes were sufficiently discussed. They also provided input into the draft Conceptual Framework and identified relevant peer-reviewed publications.	Thank you
KI Reviewer 4	d. Methods	Per Appendix C, the Key Informants consisted of representation to address the issue and included a patient/patient advocate, a practicing geriatrician, a pharmacist, a pain and addiction medicine expert, a pain medicine specialist practicing in an outpatient or community-based setting, a state-level health policymaker or policy advisor, an expert in psychiatry, a non-pharmacist allied healthcare professional, and an expert in psychology. It would be helpful to list the representation of the 15-member panel to show the diversity of backgrounds of the panel.	We have added the following statement to the Key Informants and Discussions section of the report: The expertise of the Key Informants included geriatrics, pain medicine, addiction medicine, psychiatry, nursing, psychology, pharmacy, emergency medicine, and health policy.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	d. Methods	The literature search was thorough. It informed and further refined the Conceptual Framework and the evidence map. Articles were identified that predominantly addressed harms from opioids in older adults and interventions that appropriately reduce opioid prescribing and risk of harms, or identify and treat misuse and opioid use disorders in older adults. Studies were also identified that focused on the likelihood of opioid use, preventing opioid misuse and opioid use disorder and reducing opioid-related harms. The evidence map reflects information from studies that directly addressed questions pertaining to the management of opioid use and misuse in older adults.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	e. Findings	The findings summarize the development of a comprehensive Conceptual Framework that depicts the stages for older adults (> 65 years) who require or use opioids, it also includes the results of the evidence map. The Conceptual Framework identified factors that have an impact on management decisions, interventions, and patient outcomes for 1) reducing opioid use/prescriptions where harms outweigh benefits, 2) preventing opioid misuse and opioid use disorder, and 3) reducing other opioid-related harms (benefit-risk assessments). These factors include assessment of pain, selection of pain treatment, choice opioid regimen, assessment for opioid misuse or opioid use disorder, and management of misuse or opioid use disorder. The Conceptual Framework identifies two pathways, pain pathway and recreational use pathway, by which older adults start using or misusing opioids. Predictors of opioid misuse were identified and include system (insurer reimbursement, copayment size), societal expectations, pain, provider (multiple providers, multiple pharmacies), patient, setting, guidance (clinical guidelines, federal laws), and substance use factors. Interventions to support benefit-risk assessment can be employed	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	e. Findings	An extensive review of the literature was performed using terms related to older age/aging, crossed with terms on opioid use, opioid-related disorders, opioid misuse, and opioid-related adverse events yielding 5402 citations. The literature review confirmed a paucity of relevant studies in these areas. From these citations, 35 studies were identified with multivariable models of factors associated with opioid use, and opioid-related harms and adverse outcomes among and 14 intervention studies were identified. The population was older adults greater than 65 years of age.	Thank you
KI Reviewer 4	e. Findings	The evidence map is comprehensive and detailed. It refers back to and aligns with the Conceptual Framework. The evidence map categorizes the 35 studies of multivariable models of factors associated with opioid use, and opioid-related harms and adverse outcomes into 7 types of outcomes (long-term opioid use, opioid-related disorders, multiple opioid prescribers/pharmacies, clinical harms related to mental or physical health conditions, opioid-related hospitalization or emergency department visits, opioid overdose, and death). Half (17/35) of the multivariable analysis studies evaluated factors associated with long-term opioid use. A few studies evaluated outcomes pertaining to opioid-related harms (such as overdose or opioid use disorder or high-risk or undesirable behaviors (such as opioid misuse). The factors most commonly evaluated included demographic factors, comorbidities, medication factors, history of pain or opioid use, social conditions, and history of substance use.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	e. Findings	Fourteen (14) intervention studies were identified and examined screening tools to predict opioid-related harms, prescription drug monitoring programs, multidisciplinary pain education for patients, an educational pamphlet for patients, provision of patient information and pain management training for clinicians, a bundle of educational modalities for clinicians, a nationally-mandated tamper resistant opioid formulation, and motivational interview training for nursing students. Each intervention was evaluated by a single observational study except for one of the clinician education studies which was evaluated by a randomized controlled trial. Almost none of the intervention studies were replicated. None of the screening tools were tested in clinical practice to assess real-world results.	Thank you
KI Reviewer 4	e. Findings	The Table/Heat Maps summarize the narrative and are particularly helpful in visualizing the results of the studies and the measure of association in a given category.	Thank you
KI Reviewer 4	e. Findings	Gaps in knowledge and future research needs are identified throughout the Technical Brief.	Thank you
KI Reviewer 4	e. Findings	Although research needs specific to cost and reimbursement of nonopioid therapies are discussed on page 57, there is no discussion of cost of opioid use/misuse to the individual and society.	In the subsection “Research Needs Specific to Cost and Reimbursement of Nonopioid Therapies”, we have added the following text to address this point: “Finally, research is necessary on the costs of opioid misuse and OUD at the individual and society levels, though this topic was outside the scope of the current report. Cost could be studied as either as an outcome of nonopioid therapy use (e.g., cost savings through avoidance of misuse or OUD) or as a stand-alone topic.”

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	f. Summary and Implications	A summary of studies on the multivariable models of factors associated with opioid use, and opioid-related harms and adverse outcomes are included at the end of each section along with identified research needs for the section. For example, page 17 summarizes the studies on factors associated with opioid use and page 17 identifies research needs of predictors of long-term opioid use; page 26 summaries studies on factors associated with opioid-related disorders and identifies research needs of predictors of opioid-related disorders; page 30 summarizes studies on factors associated with multiple opioid prescribers, and pages 30 and 31 identifies research needs of predictors of multiple opioid prescribers.	Yes, we summarize findings in multiple locations.
KI Reviewer 4	f. Summary and Implications	Key Informants identified future research needs related to the definition of “older adult” and the need to quantify the interaction between birth cohort, age, and nonopiod substance use (e.g. alcohol) as predictors of opioid misuse and opioid use disorder.	We have added the following statement to the “Future Research Needs” section: “As a precursor to that work, it may be necessary to define “older adult” in a principled way and better understand the relationship between age, period, and birth cohort”
KI Reviewer 4	f. Summary and Implications	The Summary on page 59 succinctly discusses the relationship of the Conceptual Framework to the evidence base. The most-studied interventions are screening tools to predict opioid-related harms but none have been tested in clinical practice to assess real-world results. Of note is that the recreational pathway was addressed by empirical evidence.	Thank you
KI Reviewer 4	f. Summary and Implications	The Conceptual Framework and the evidence base serves as a starting point from which a research agenda could be developed.	Thank you

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 4	g. Next Steps	Several future areas of research are identified at the end of each section throughout the technical brief. Two immediate next steps for future research are noted and include 1) conducting additional research focused on multivariable analyses replicating findings for factors that already have some information available, and 2) further validating and adapt screening tools for identifying opioid misuse in older adults. Areas of future research that were not discussed but should be considered include intervention studies on educating and training of 1) patients, families, and caregivers, and 2) direct workers, and health professions students, faculty, and providers. Educational intervention studies should focus on reducing the risk of opioid prescribing where harms outweigh benefits and increase access to non-opioid treatments, preventing opioid related misuse or opioid use disorder, and reducing opioid related harms.	We agree with these points and have now included them in the "Research Needs Specific to Tools to Predict Harms During Appropriate Opioid Use" as follows: "In addition to research that helps to answer how benefits and harms should be assessed, research is also necessary to identify exactly who is poised best to perform the benefit-harm assessment. It is possible that some individuals may become well-poised to assess the balance of benefits and harms of opioids through education or formal educational interventions. Families and caregivers, for example, might be such persons. Clinicians, direct care workers, health profession students, and faculty are likely to be identified as persons for whom educational interventions might be impactful. Educational intervention studies should focus on training these individuals to quantify the benefits and risks of opioids, and then reduce opioid prescribing where harms outweigh benefits. They will also need to train individuals to better understand how to increase access to non-opioid treatments, prevent opioid misuse or OUD, and reduce the risk of opioid-related harms when opioid use is necessary."

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	This review provides a useful review of a subset of studies on opioid prescribing focused on older patients. The general conclusions seem reasonable. I also understand that this is a Technical brief and perhaps does not include all of the elements of a traditional SR of comparative effectiveness. Nonetheless I have a number of general concerns that I believe lower the overall usefulness of the review in its current format, and I make some suggestions for areas I think could be improved:	Thank you.
KI Reviewer 5	a. General Comments	1. The introduction does a nice job highlighting why issues related to opioid use may play out differently in older patients than younger ones. Indeed in some studies of long term opioid use, overdose deaths seem to diminish with age. Other factors such as drug interactions, falls, depression, osteoporosis would likely be bigger issues in older patients. Yet these age-specific issues are under-emphasized in the analytic framework and the research recommendations.	We appreciate this comment, and also agree that drug interactions, falls, depression, and osteoporosis are important issues in older patients. Our intention was not to downplay the importance of those issues, but rather, to highlight the importance of emerging ones like OUD in older adults, for which there is substantially less information or evidence available. For example, one of the studies we included in the report (Pasquale et al. 2017) suggests that OUD might be present in over 11% of the study population, yet the frequency of OUD in older populations appears to be significantly underappreciated. Regardless, we have made changes to the Conceptual Framework section of the report to provided more emphasis on some of the issues identified by KI Reviewer 5.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	2. The individual studies are inadequately described. This includes details of the study populations, the settings, the risk factors examined, and the definitions of specific outcomes. The meanings of many of the important outcomes or risk factors are not clearly defined – for example, what is included under "opioid misuse". Distinctions between population-based studies and specialized cohorts such as patients with polyneuropathy or knee replacement are not made.	We have added brief descriptions of the study designs (retrospective, longitudinal vs. cross-sectional) and populations (eligibility criteria) into the tables. Appendix Tables D-3-1 to D-3-3 provide details about the predictors and outcomes for each included study.
KI Reviewer 5	a. General Comments	3. Different study designs are combined without reference to their implications. Prospective studies with individual level data are lumped in with cross-section studies with group data (e.g Grigoras study). The questions addressed by these different studies are often quite distinct.	None of the studies regarding associations was prospective in design. We have added information about design and study eligibility into the tables (and briefly in the descriptive text).
KI Reviewer 5	a. General Comments	4. The Tables are poorly linked to the references – there is no reference # listed in Tables and the references are not alphabetical so there is no way to move from Tables to original study.	We have added reference callouts to the tables.
KI Reviewer 5	a. General Comments	5. There is no quality assessment of the individual studies. While I recognize there is no consensus on tools to assess risk of bias in observational studies, there are accepted reporting standards in STROBE, and frequently used assessments of bias in the Downs-Black and Ottawa Newcastle assessments. Some application of these tools if only to identify areas of weakness in individual studies would have been useful.	True. Risk of bias assessment is not conducted for AHRQ Technical Briefs, which are intended to identify next steps for research. A deeper dive, including application of risk of bias tools would be an excellent next step.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	6. The section on risk factors for long-term opioid use appears to mix studies of opioid use for acute pain (i.e. in ED or surgical settings) with studies of opioid use for chronic pain. These are very different clinical issues and certainly their potential for leading to long term use are very different.	It is the case that we did not distinguish among reasons for opioid use (except to the degree that they were evaluated within multivariable analyses). We were looking for signals, rather than definitive associations. More detailed analysis stratified by clinical setting would be an excellent next step.
KI Reviewer 5	a. General Comments	7. Comparitors are sometimes difficult to discern in individual studies. Given the framing of Question #2, it would seem that most studies are restricted to patients taking opioids and looking for differences within that group. But some studies seem to be making comparisons to non-users of opioids (e.g., Zeng and tramadol study which compared to NSAIDs). Such comparisons are not addressing Q2 or telling you about risks among opioid types.	Thank you. We agree and have changed the Zeng study to be an association between opioid use (vs. NSAID) instead of opioid type.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	8. The exclusion criteria may exclude literature that would seem to be very relevant to older patients. For example, population-based studies that included substantial numbers of older patients were excluded if the mean age was below 60. This appears to have excluded numerous studies from the VA, which has a generally older population and which has generated a substantial body of literature on the risks of opioid prescribing, including risks for overdose, suicide, and death. One important VA study appears to have been excluded because the mean age was 59. As a result, for critical outcomes such as overdose death, the report is left with only 5 studies, and only one looking at benzodiazepine co-prescribing. An alternate approach would be to include the largest and most representative population-based studies that included substantial numbers of older patients and see whether they examined age as an independent risk factor. If age was not significant, findings should be relevant to older subjects.	We aimed to ensure that the evidence being review was as applicable as possible specifically to older adults (although variably defined). Studies with mean ages below 60 will (the large majority of the time) include participants fewer than half of whom are "older". We did not consider that VA studies are fully representative of older adults simply because the studies have older mean ages than studies from most other populations. We did include studies that reported subgroup analyses of older adults (regardless of the mean age of the overall study population). We did not include analyses of "older" vs. "younger" adults, as we were not looking for evidence about whether findings may differ in older than younger people. We did not make the leap to assume that because no significant association was found by age that studies are representative across age groups.
KI Reviewer 5	a. General Comments	Suggestion: Set the context by what we already know about risk factors in the general population, regarding dose, duration, co-prescribing, etc. These have been reviewed in existing reviews and could be summarized in the intro.	The following statement is now included in the "Needs and challenges of pain treatment in older adults" section of the Introduction: Prior published evidence and guidelines focused on a general population has suggested that restricting opioids to severe pain or pain that has not responded to non-opioid therapy, using the lowest effective dose of short-acting opioids for the shortest duration possible, and co-prescribing opioids with non-opioid analgesics, but not other interacting medications, is the optimal approach. References have been added.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	Suggestion: Consider a second diagram to supplement the analytic framework to more succinctly describe the literature to address the questions #2 and #3 that are the focus of the review (see comments below).	We believe the tables (particularly Tables 1 and 14) are sufficiently succinct and descriptive.
KI Reviewer 5	a. General Comments	Suggestion: Add a table that describes Patient population, Design (cohort, cross section, case control, etc.), Risk factors or Comparisons, Outcomes, Timing	We have added information about the study design and study population in the summary tables. Additional information is included in Appendix tables.
KI Reviewer 5	a. General Comments	Suggestion: Include a separate bibliography of included studies alphabetically by first author. It is difficult otherwise to look for studies one thinks should be included.	We have added citations to the tables.
KI Reviewer 5	a. General Comments	Suggestion: More clearly distinguish study designs in discussion. Don't mix group level data (e.g. studies with counties as unit of analysis) with individual level data.	Where association factors are at the population level, we call these out. We have also added notation to distinguish longitudinal and cross-sectional studies. However, since the purpose of the Technical Brief is to provide a high level description of the evidence base and identify signals, and given the time, space, and resource constraints, additional detail would not be feasible. We believe the additional details would not change the conclusions for this Technical Brief.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	a. General Comments	Suggestion: Separate discussion of studies looking at new prescribing for acute pain with studies that examine prevalent use of opioids.	The distinction between new use and prevalent use is important, and one that pharmacoepidemiologists, including those on our research team, have emphasized for several decades. In many of the tables and much of the text in this report, we distinguish new use of opioids. In a future systematic review, ideally after more evidence has accrued, we agree that distinguishing new and prevalent use of opioids would be valuable. However the evidence base has not yet reached the point where this level of detail would be very informative.
KI Reviewer 5	a. General Comments	Suggestion: In discussion, more clearly distinguish the policy questions of interest from the types of studies relevant to the question. Clinical questions about who is at risk of developing long-term opioid dependency need to examine incident use and control for indications for use. Studies of who is at risk of dying from overdose need to look at prevalent use and examine opioid characteristics as well as underlying conditions.	To the section titled “Research Needs on Predictors of Opioid-Related Disorders”, we have added the following statements: When examining such questions, consideration must be given to the temporality and type of opioid use. For example, studies examining the relationship between OUD and risk of opioid overdose death would likely focus on prevalent opioid use, while studies examining the transition from initial opioid use to long-term use to OUD would likely focus on new use of opioids and follow individuals longitudinally over time. These opioid use definition and study design decisions merit consideration in future work to maximize the ability of studies to address research needs.
KI Reviewer 5	a. General Comments	Suggestion: Give more emphasis in research recommendations to issues that are most specific to older patients and where generalizing from research in younger patients is problematic	Thought the various Research Needs subsections, we have added statements to further emphasis issues that are most specific to older patients and where generalizing from younger patients *might* be most problematic, though the latter is a research need in and of itself.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	b. Background	Background is generally clear and appropriate. No suggestions.	Thank you.
KI Reviewer 5	c. Guiding Questions	The conceptual framework is reasonable for displaying the complexity of the interacting factors that influence long tem opioid use. However, it is less successful in depicting the type of evidence you sought or the classification of studies. I think it would have been cleaner to have the boxes represent outcomes measured in studies , as done by the USPSTF rather than questions: e.g. , long term opioid use, OUD, overdose, death. I realize you cannot change the framework since you developed it with your committee but I wonder if you could add a framework that better aligns with the literature you found. The left-hand box would depict the different populations under study, the octagon the risk factors examined and the right hand box the outcomes measured. E.g. – populations of patients receiving an opioid prescription for post-op pain; risk factors: demographics, medical history, opioid dose, co-prescribing, etc. Outcomes: LTOT (opioid use > 12 months; opioid overdose; suicide; all cause mortality).	The conceptual framework was designed to be a framework across the full field, including existing and (potentially) future. It was created and (essentially) finalized prior to the review of the literature. It is not meant to describe the existing evidence base. The full Technical Brief is designed to describe the evidence base in order, in part, to identify the evidence gaps in the conceptual framework. Tables 1 and 14 summarize much of what you are suggesting.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	c. Guiding Questions	I also think one might need to more clearly separate out two clinical questions which might be informed by different literature: 1) in which patients does the initial use of opioids have a higher risk of progressing to long term use, misuse and other adverse effects? and 2) in which patients currently on opioids is the risk of adverse outcomes highest? The first question informs decision making in initial treatment of pain, but requires identifying populations not currently on opioids. The second informs strategies to taper and reduce opioids in patients already taking them.	While we are unable to modify the Guiding Questions, we agree with these important points. In several places throughout the report, we discuss them. For example, in the "Research Needs on Predictors of Long-Term Opioid Use" section, we added the following: Older adults with problematic opioid use may need interventions to reduce opioid use, whereas those with uncontrolled pain may require other interventions to better treat the underlying condition. Specifically, research on how to successfully taper opioids, especially after long-term use, is also critically needed. Future studies should focus in particular on which factors are associated with the inability to taper opioids, including opioid dose, duration of opioid use, mental health conditions, and any prior history of substance use disorders.
KI Reviewer 5	d. Methods	Xiv: You should provide more information on your inclusion and exclusion criteria for finding relevant studies using a PICOTS frameworks: What criteria did you have for the population – i.e. restricted to older patients, high average age, subgroups analysis with ages > 60? What restrictions related to indications for opioids: chronic pain, acute pain, etc?	This is fully laid out in Appendix B.
KI Reviewer 5	d. Methods	Please briefly define terminology in the Exec Summary – what did studies use to define misuse or LTOT? I realize these are in the definitions but a brief mention should be included in the Executive Summary	We have revised the ES to add full descriptions of outcomes.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	d. Methods	Comparing RR for continuous variables such as dose and RR for categorical variables (eg back pain) is problematic. If using continuous variables you should use some consistent frame of comparison – eg top quartile to bottom quartile, etc.	Ideally, we would have been able to extract consistent analytic methods (e.g., frames of comparison) across studies, but unfortunately, studies do not all use equivalent methods nor do they provide sufficient data to allow adequate re-analyses (e.g., to determine statistical significance). While our approach may not have been ideal, but we believe it is reasonably accurate for identifying signals of strong association from a group of highly heterogenous studies that were not designed for the same purposes as our Technical Brief.
KI Reviewer 5	d. Methods	Please clarify that you are considering long term opioid therapy as an outcome. This becomes clear later but wasn't immediately clear to me here	In the Methods, we have added additional explanation of long-term opioid use as a specific outcome of interest.
KI Reviewer 5	d. Methods	Please clarify "substance abuse" as a risk factor – do you mean pre-existing substance abuse prior to opioid prescribing?	We do so in the pertinent parts of the results. We allowed (included) past and ongoing "abuse", etc. We have also added this explanation "(past or current)" to the list of factors (i.e., predictors) we included (start of the section *Factors Associated With Opioid-Related Outcomes in Older Adults*).

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	d. Methods	p. 6 – I am not sure consistency is sufficient as the sole determinant of quality of evidence for risk factor epidemiology, especially given the fairly broad inclusion criteria for study design. I would give more weight to prospective cohort designs than cross-sectional studies , to studies that assess initial opioid prescribing than continued prescribing, and studies that attempt to control for confounding factors or study a consistent indication for prescribing.	We set a basic standard for quality with our somewhat restrictive inclusion criterion of multivariable analysis. However, individual study quality assessment is beyond the scope of a Technical Brief. We agree that prospective longitudinal designs are more likely to yield accurate results than (retrospective) cross-sectional studies and have added this information to the table (although, all studies were retrospective). However, given the sparseness and heterogeneity of the available studies for most specific analyses, we do not believe re-analysis would change the high-level identification of signals, which was the goal of the Technical Brief.
KI Reviewer 5	d. Methods	p. 9 – A summary or flow chart of included and excluded studies would help	Appendix D includes a flow diagram (Figure D-1) and Appendix E lists rejected articles with reasons.
KI Reviewer 5	d. Methods	p. 10 – I have concerns about grouping the studies by outcomes only, rather than by patient population or opioid indication. It seems that studies that examined risks related to incident use (primarily for acute pain in ED or post op). are fundamentally different than risks associated with prevalent use.	We agree that a more nuanced analysis would be preferable, However, given the general sparseness and heterogeneity of the available studies, we chose this approach as the best option to identify high-level signals within the time and resource constraints or a Technical Brief.
KI Reviewer 5	d. Methods	Treating multiple prescribers as an outcome is problematic. Research has identified that multiple prescribers increases risk of dangerous patterns of opioid use and overdose. It would be important to know if that was true in older patients, where one might think it may reflect increased number of providers rather than doctor-shopping.	The outcome of interest is multiple prescribers, not multiple providers. The problematic concept is that multiple prescribers are prescribing opioids to the same patient, possibly without coordination. It does not necessarily equate to doctor-shopping.
KI Reviewer 5	e. Findings	p. 38 – Was suicide included? There is a growing literature on opioids as a risk factors for suicide yet none is mentioned.	Studies that evaluated suicide would have been included (within the framework of ED, hospitalization, or death).

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	e. Findings	p. 39 – The Grigora study is a study of county level risk factors not individual risk factors. It is a study that examines the spread of the opioid epidemic but not the risks to individuals. Thus it should not be included as it is at risk for ecological fallacy. Counties that are poor and white have higher risk of opioid deaths because there is higher use of opioids there. It says nothing about whether among opioid users, white or poor people have a higher risk of dying than black or non-poor patients.	Thank you. We have added additional text to the Table to differentiate longitudinal and cross-sectional studies. In the descriptive text (eg, in the description of the evidence base for *Factors Associated With Death*) and in the relevant summary tables (eg, Table 14), we have pointed out and described possibility of ecological fallacy due to use of population-level measures. We included the studies with population-level predictors because our goal was to describe the evidence that may support different predictors on risk of outcomes.
KI Reviewer 5	e. Findings	It would be good to include a discussion about potential risks of discontinuing or reducing opioid dosage. I don't know if there have been specific analyses in older patients but VA data has indicated increased risk around time patients are discontinued. It is not known if this is causal (i.e. they may have been reasons that also are risks for overdose (i.e. diversion or use of illegal drugs).	These are excellent points which we have incorporated as follows in the "Research Needs Specific to Deprescribing Protocols and Sharing Responsibility" subsection: It is possible that deprescribing or tapering opioids may cause adverse events or confer a risk of harms (e.g., suicide). Research is necessary to better understand the causal effects of deprescribing and tapering approaches on harms to ensure that all approaches employed are safe in addition to being effective. Antecedent non-interventional research using secondary data might be necessary to understand the relationships between real-world discontinuation or tapering patterns and subsequent outcomes. Such information, if obtained using methods that properly account for biases (e.g., confounding and selection biases), could be valuable for informing the design of interventions.

Section	Commentator & Affiliation	Comment	Response
KI Reviewer 5	e. Findings	The section on interventions is generally clear and well presented. But more attention should be given to issues that are likely to be important in designing interventions to reduce opioid use or harms in older patients – this includes dealing with multiple providers, non-opioid strategies most likely to be feasible in older patients, and addressing cognitive impairment and caregiver issues. The issue of harms and benefits of dose reduction in patients on LTOT is a complicated issue in all patients, and even more so in older patients who seem to be managing on current dosing.	We appreciate the positive assessment of the section on interventions. The findings are limited to what the intervention studies report on, but we address the issues mentioned (dealing with multiple providers, non-opioid strategies, etc.) among the research needs.
KI Reviewer 5	f. Summary and Implications	The summary is reasonable but could be more focused on the critical issues for older patients.(see discussion in Next Steps)	Thank you, and please see the response immediately below.
KI Reviewer 5	g. Next Steps	p. 51 – The review of research needs would benefit from some more focused judgments about which research is most important for advancing questions specific to older patients. Many of these read as questions to be addressed for any age group. More emphasis on harms such as falls, cognitive impairment, osteoporosis, dependency, depression is recommended. After reading this review, I feel we don't have the information we need to really assess harms and benefits for patients who are currently on long-term opioids. I think practice is already shifting in reducing use of opioids in the ED and post-operatively, for young and old alike. But the clinical question of lowering opioid doses safely, and to what level, while trying to deal with dependency and pain is especially complex for older patients.	We have updated the "Future Research Needs" section and now address some of these suggestions by KI Reviewer 5.
KI Reviewer 5	g. Next Steps	p. 58--The conclusions should again emphasize the critical questions and the gaps in the evidence for answering those questions	We have added to the Conclusions. We believe it covers the main themes.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 1	a. General Comments	There are clear strengths of this technical brief, but also glaring weaknesses. The most startling omission in this document is that while one of the research questions included, "What interventions have been studied to help providers identify and treat opioid misuse or opioid use disorder in older adults?" there is barely any mention of the evidence-based, life-saving treatment of medications for opioid use disorder (MOUD) including methadone, buprenorphine, or naltrexone. If there are no studies examining older adults on these medications, then maybe this brief should not cover the management of OUD. An important question for older adults is what MOUD is best? This is not addressed here. Also, issues surrounding MOUD in settings where older adults receive care such as post-acute care settings and skilled nursing facilities is a major issue in geriatrics.	Although we searched for studies addressing MOUD, we found none focused on older adults (as per our eligibility criteria). Thus, we have no evidence to summarize. We have repeated this more explicitly in the Results section of the Evidence Summary and main report's Overview of Literature. We have also better emphasized it in sections on Research needs; for example, "There is also a need for more empirical evidence about which medications (methadone, buprenorphine, naltrexone) and treatment regimens for OUD are most effective and safe for older adults. A related need is information on how to implement SBIRT and medications for OUD in settings where older adults often receive care, but that may not have the necessary resources or infrastructure to implement interventions to treat OUD in older adults. Post-acute care settings like skilled nursing facilities and nursing homes are likely to be one such setting."

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 1	a. General Comments	I also note that among the key informants, there does not appear to be anyone with expertise in addiction medicine. This is evident not only with the use of stigmatizing language around drug use throughout the document, but the glaring lack of discussion of MOUD. If this document will include treatment for OUD, then this document is simply not acceptable. For example, it is not okay to have this paragraph on page 8, "Older adults identified with opioid misuse or OUD require management to reduce or stop associated harms (Rectangle F). Potential management options include interventions to coordinate care or improve healthcare transitions, pharmacological, nonpharmacological, and behavioral treatments, and combinations thereof. Examples include naloxone availability (to acutely counteract opioid overdose), ensuring proper nutrition, and preventing homelessness among older adults with misuse or OUD." The first example should be the large evidence-base supporting methadone or buprenorphine. I also do not understand what "proper nutrition" has to do with OUD. Furthermore, adding "homelessness" here without any further mention of it throughout the entire document is disingenuous, if you are going to bring up people experiencing homelessness, then you need to take space and discuss it and how it relates to older adults with OUD.	Our KI panel did include a specialist in addiction medicine (Maria Sullivan at Columbia University). She also reviewed the draft report. As we also describe in response to another comment, we decided it was best to maintain the original wording of interventions, variables (factors), and outcomes used by the authors of the studies included in this technical brief. We do not wish to misrepresent the original studies, even if they used language that today, to some readers, might be considered inappropriate. However, we realize that modern language is preferred and less stigmatizing. Thus, in our overall summaries of study findings, we aim to use neutral, non-stigmatizing language. We have removed the whole sentence with examples.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 1	a. General Comments	The strengths of this document are not surprisingly in areas where there is a stronger evidence base including factors associated with long-term opioid use. I believe this document covers this area well and guides us on how this evidence base is useful for the development of policy. I would suggest that this technical brief focus in this area where there is more evidence rather than quickly cover areas (such as management of older adults with OUD) where there are only a handful of studies.	We cover all areas equally, as the evidence allows. An important finding is where there are research gaps.
Peer Reviewer 1	a. General Comments	The authors do a good job in defining opioid misuse, however, to be more accurate it should be prescription opioid misuse unless the authors meant to include heroin in their definition. Unfortunately, the authors use the term “alcohol misuse” and “abuse of substances” throughout the document, these are antiquated terms that are no longer recommended by the American Society of Addiction Medicine or the United States Preventive Services Task Force and should be avoided. Even when citing papers that use these terms, the authors should not use them in their own writing.	Our purpose was not to restrict to prescription opioid misuse (as per Pathway A2), although it is the case that the evidence base focuses on opioid prescriptions. Within the text we use standard, neutral terms for opioid and substance misuse etc. However, when discussing or describing specific studies, we present their terminology. Many studies described and defined these concepts variably. We aim to avoid misrepresenting the studies.

Peer Reviewer 1	b. Background	In general, the background is well written and frames the problem of opioid use among older adults very well. They balance the need/indication for opioids with the potential harms well. I would avoid the term "polypharmacy" in favor of "potentially inappropriate medications." The last paragraph on page 2, I should better clarify that physical dependence on opioids is not the same as opioid use disorder. This is an important distinction. Furthermore, I find the sentence, "Once OUD develops in an older adult, its symptoms may resemble those of common geriatric syndromes like cognitive impairment, Alzheimer disease and related dementias, delirium, and depression.50" very problematic. As a clinician and researcher who cares for older adults with OUD, I don't agree with this broad statement and I don't believe your citation supports it either. You can state that older adults with OUD may be at higher risk for common geriatric conditions or you can elaborate on how diagnosing OUD in older adults is challenging, but I find this statement very problematic	Polypharmacy and potentially inappropriate medications are distinct, if somewhat overlapping concepts. Polypharmacy is nonjudgmentally descriptive of an event. We have retained it. We have added the sentence: Physical dependence on opioids may be a precursor to, but does not indicate, opioid misuse or OUD. In the article "Maree RD, Marcum ZA, Saghafi E, Weiner DK, Karp JF. A Systematic Review of Opioid and Benzodiazepine Misuse in Older Adults. Am J Geriatr Psychiatry. 2016;24(11):949-963. doi:10.1016/j.jagp.2016.06.003", the authors write the following: "Complicating the identification of substance misuse problems in late-life is the fact that addiction or intoxication may present similarly to depression, delirium, or dementia." For that statement, the authors cite two references: 1. Koechl B, Unger A, Fischer G. Age-Related aspects of addiction. Gerontology. 2012;58(6):540–544. doi: 10.1159/000339095. 2. 13. Luijendijk HJ, Tiemeier H, Hofman A, Heeringa J, Stricker BHC. Determinants of chronic benzodiazepine use in the elderly: a longitudinal study. Br J Clin Pharmacol. 2007;65(4):593–599. doi: 10.1111/j.1365-2125.2007.03060.x. We have now edited the report to more closely concord with the authors' statement, as follows: "Some clinicians have postulated that the identification of substance misuse problems in later life, such as opioid misuse or OUD, may be complicated by a clinical

Section	Commentator & Affiliation	Comment	Response
			presentation that is similar to depression, delirium, or dementia in older adults." We have added the additional references.
Peer Reviewer 1	c. Guiding Questions	These are important guiding questions; however, I do not think you have answered any of them. From your document, I am convinced that we do not have the evidence base to answer any of these questions. I believe the issues answered by this document is who among older adults who is at risk for long-term opioid use and what are some interventions to reduce opioid use in this population.	We do not aim to answer the guiding questions, but instead to describe the literature base that addresses them. Your conclusion that we do not have the evidence base to describe them is fair.
Peer Reviewer 1	d. Methods	I find the methods to be strong and the development of the conceptual framework well thought out. The definitions of strong and weak associations are well defined. As discussed above, there needs to be someone with expertise in addiction medicine added as a key informant if you are going to cover management of OUD.	As noted, our Key Informant panel did include a psychiatrist who specializes in addiction medicine.
Peer Reviewer 1	e. Findings	The strength of this document is reviewing factors associated with long-term opioid use as well as interventions to decrease opioid use among older adults. The authors do an excellent job in reviewing the literature and summarizing it, especially the section on interventions to reduce opioid prescribing. As above, I find the factors associated with opioid-related disorders to be problematic, and I think it is more of a reflection of the lack of literature. This is also true for factors associated with harms. There are only a handful, and this is the limiting factor.	Thank you
Peer Reviewer 1	e. Findings	The big limitation of this document is "Interventions to Manage Opioid-Related Disorders (Rectangle F and Triangle I3)" on page 55. There is just a limited discussion on MOUD and this needs to be expanded.	We have added to various summaries of the evidence in the Evidence Summary and the main report to make more explicit that there were no eligible studies on treatment of OUD. We have also added to the Research Needs.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 1	f. Summary and Implications	This is a nice summary of your document, which emphasizes the limited available evidence.	Thank you
Peer Reviewer 1	g. Next Steps	This is quite limiting and I would suggest the authors be more ambitious about what next steps should be. This country is experiencing an opioid epidemic that is also affecting older adults, we need to expand on best practices for safer opioid prescribing, emphasize screening (which is difficult in older adults), and expand MOUD treatment in all care settings where older adults receive care.	It is true that the recommended next steps are focused. The technical brief is intended to inform AHRQ and other agencies' development of evidence-based research agendas and how to feasibly achieve continued scientific progress. While there are many potential next steps, those recommended are intended to be the most feasible and achievable in the short term. However, we have added a statement about intermediate-term work that should be conducted: Intermediate-term next steps should include developing interventions to 1) increase the uptake of best practices for safer opioid prescribing that does not compromise pain control in older adults, 2) overcome barriers to screening for opioid misuse and OUD in older adults, and 3) expand treatment for OUD in all settings where older adults receive care.
Peer Reviewer 2	a. General Comments	This technical brief assesses and summarizes the issues relating to the prevention, diagnosis and management of opioids, opioid misuse and opioid use disorder in older adults. The authors should be commended on this well written report which clearly and concisely outlines key issues for both policy and practice.	Thank you
Peer Reviewer 2	a. General Comments	Page 10, Line 21: '(see Figure)' – the figure number is missing.	The ES has only a single (unnumbered) figure. This will clearer in the final formatting of the published document.
Peer Reviewer 2	a. General Comments	Page 12 is empty – is this intentional?	Thank you. This was an artifact of formatting the draft report that will be addressed in the final posting.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	a. General Comments	Page 13, Line 3 - Title of figure - the figure number is missing.	The ES has only a single (unnumbered) figure. This will clearer in the final formatting of the published document.
Peer Reviewer 2	a. General Comments	Page 14, Line 7: '(see Figure)' – the figure number is missing.	The ES has only a single (unnumbered) figure. This will clearer in the final formatting of the published document.
Peer Reviewer 2	a. General Comments	Page 15, Line 33: it would be useful to include the reason why studies published prior to 2000 are not included here. Although reason is given later it is not provided until much later in the manuscript.	The Evidence Summary has strict page limitations, and we felt other information was more important to include. In the Methods section of the full report (page 6) we have added a fuller description of our reasoning for restricting to 2000 onward.
Peer Reviewer 2	a. General Comments	Page 18, Line 8: The opening paragraph provides a background relating to the period 2010-2015. Is it possible to provide more recent figures to describe the current problem?	We have confirmed that more recent estimates are not available at this time. 2016 data on hospitalizations is here https://www.ahrq.gov/opioids/map/index.html

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	a. General Comments	References: references should be checked for formatting. Below is a list of issues noted, but is not an exhaustive list. Page 80, Line 17: empty line in left hand column between #45 and #46. See also after references #58, #122, #125. Page 80, Line 41: reference #48 contains 'Language: English'. There are 15 instances of this throughout the references. Page 80, Line 44: reference #48 contains 'Publication Type: journal article'. There are 15 instances of this throughout the references. Page 80, reference #53 and #56 both relate to documents published online, however the method of referencing is different, see 'retrieved from' versus 'accessed on'	Thank you, we appreciate your attention to detail. We did not conduct a complete clean up of references (which we knew would be changing) for the draft report. The final reference list is considerably cleaner.
Peer Reviewer 2	b. Background	The issue is adequately described as are the contextual factors. However, the age cut-offs used are not standardized and should be addressed. Up to page 18, older age is listed as 60+. On page 18, Line 8, age 65+ is given. It is important to either standardize the age cut off used to describe 'older', or justify why different ages are used.	We describe how we used 60 as a threshold and have elaborated further why. We added a comment that most studies used a threshold of 65 (which accounts for the focus on a threshold of 65 in much of the background). As we note in the Methods for the Evidence Map (page 6), "Based on discussions with the Key Informants and the variable definitions of "older adults" across studies, we focused on studies that included adults aged 60 and over. There is no standard definition of "older adult." Most studies, especially those based in the US, used a threshold of 65 years, in keeping with Medicare eligibility criteria. We decided that a threshold of 60 was reasonable to be more inclusive."

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	c. Guiding Questions	The guiding questions clearly define the scope of the review, they are both well developed and focused. The guiding questions are linked to the conceptual framework. The report states that the conceptual framework was revised based on feedback from a panel of invited Key Informants, however it is not clear if changes were made to the guiding question.	We have clarified that they differ. The original questions can be found in Appendix B.
Peer Reviewer 2	d. Methods	The methods section is clearly written and describes how the data for this report was gathered and integrated. Key informants and their inputs are well described. Adequate details of the literature screening and extraction processes are provided.	Thank you
Peer Reviewer 2	d. Methods	On page 20, line 45 it states that this brief focuses on adults aged 60 years and over. It would be useful to provide the reader with the reasoning behind selecting this particular age cut-off.	We describe how we used 60 as a threshold and have elaborated further why. We added a comment that most studies used a threshold of 65 (which accounts for the focus on a threshold of 65 in much of the background).
Peer Reviewer 2	e. Findings	The evidence map clearly and concisely summarizes research to date and matches the evidence to the key questions. Each factor is set out in turn and gaps are adequately described. The size and direction of the evidence is nicely presented through heat maps.	Thank you
Peer Reviewer 2	e. Findings	Evidence Map, Page 32, Line 17-21: This sentence is confusing to read and difficult to understand it meaning. Suggest that it could be more reader friendly. Does it mean that participants with opioid prescriptions that were of short duration and for low-dose, short-acting opioids, were up to 25% less likely to use opioids for a minimum of 12 months?	This paragraph (on page 19) has been re-written, but we maintain the directionality of the studies (and tables), i.e., discussing long-acting and long-duration opioids and increased likelihood of long-term use.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	e. Findings	Evidence Map, Page 32, Line 20/21: 'were less than one-fourth as likely to use opioids for at least 12 months'. It would be useful to give the comparison, less likely than whom?	We have clarified the comparator, which is basically not any of the listed opioid types (i.e., the complement to those listed; i.e., longer duration, higher dose, or longer-acting opioid regimens).
Peer Reviewer 2	e. Findings	Evidence Map, Page 32, Line 6: give the full word 'benzodiazepines' in the column heading.	"Benzo" is defined in the abbreviation list of the relevant tables.
Peer Reviewer 2	e. Findings	Schedule II opioids are mentioned on page 50 (row 17), page 51 (row 13 and 27). It would be useful to indicate/define what Schedule II is.	Thank you. We have added this to the abbreviation list.
Peer Reviewer 2	e. Findings	Page 56, Line 49-56: this is a very important issue. The statement regarding aging of the "baby boomer" cohort, patterns of substance use and misuse is somewhat narrow. Current literature provides many more reasons, including demographic changes, drug availability, increased life expectancy, improved treatment access and the development of harm reduction services. For example see Crome I., Wu L., Rao R. & Crome P. (2015) Substance use and older people. 1 edn. John Wiley & Sons Inc., West Sussex, UK.	The following statement has been added to expand upon the issues mentioned by Peer Reviewer 2: Such research should also take into account temporal trends in other important factors that might influence opioid use and misuse, such as demographic changes, increased life expectancy, greater illicit drug availability, improved access to healthcare, and the development and implementation of harm reduction and substance use disorder treatment services.
Peer Reviewer 2	e. Findings	Page 57, Line 8: Is it intended for this line to be by itself?	We do not find the orphaned line. Final formatting is still pending.

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	e. Findings	Page 63, Line 36 onwards: what is meant by 'deprescribing'? Is it dose-reduction or ceasing use of opioids?	Deprescribing is the clinically supervised process of dose-reducing or completely stopping medications that could cause harm or that no longer provide benefits that outweigh potential risks. It is not an action that the patient and/or caregiver takes independent of the prescriber. It occurs under the guidance and direction of the healthcare provider. We have now included this information in the section titled "Research Needs Specific to Deprescribing Protocols and Sharing Responsibility".
Peer Reviewer 2	f. Summary and Implications	This section nicely summarizes the most important issues as identified by the evidence review and ties these issues together. The authors discuss areas where strong evidence exists and also where evidence is lacking. The evidence base is nicely tied back to each of the components of the conceptual framework. Areas lacking in evidence are clearly stated.	Thank you

Section	Commentator & Affiliation	Comment	Response
Peer Reviewer 2	f. Summary and Implications	Given the evidence presented, it would seem that prevention and the early identification of problematic opioid use would be particularly beneficial. Collaboration and integrated approaches between healthcare and social care providers may be useful, particularly as many older people may already be in regular contact with services due to health issues, and these providers are well placed to identify substance use problems among this population. The changing composition of this cohort implies a wide range of services will be required into the future and integrated approaches across addiction and other health care services would be beneficial in identifying and treating problem opioid use among older people. It also seems that education programmes in screening, assessing and diagnosing problem substance use in ageing populations would be valuable for health and social care providers. Although these items are presented in the report, it would be useful to highlight them more strongly.	We have now emphasized the suggested points more strongly in the report.
Peer Reviewer 2	g. Next Steps	There are many gaps in the literature. The authors have clearly outlined future research needs which are grounded in the evidence gaps. A roadmap of key priorities in this area is nicely presented.	Thank you
Public Reviewer 1: APA	a. General Comments	We appreciate the call for research on defining the age group that would meet the “older adult” criteria as this will provide further clarification in future research studies and developing recommendations.	Thank you

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 1: APA	a. General Comments	P. 26 – please provide clarification for the following statement. Did the one study find a negative relationship between college education and risk of OUD? "Older age, college education, and a prior history opioid misuse were each found to be associated with high risk obtainment of prescription opioids (in one study)."	Clarified. Increased risk.
Public Reviewer 1: APA	a. General Comments	Interventions to Reduce Opioid Prescribing for Older Adults for Whom Harms Outweigh Benefits o We recommend noting a call for more research on the mechanisms of the cognitive-behavioral model used along with exercise, stress management, and other modalities in the multidisciplinary setting such as the setting in the Darchuk, 2010. It would also be important to note the specialists who provided treatment using principles from the cognitive-behavioral model (i.e., physical therapists, psychologists, nurse practitioners, etc.).	We have expanded our existing discussion of cognitive behavioral therapy for pain to further emphasize the need for research in older adults. Thank you for the recommendation.
Public Reviewer 1: APA	a. General Comments	We appreciate further examining the management of opioid use in older racial/ethnic minority adults and recommend emphasizing the need for more research in this domain. In measuring opioid use/misuse it is important that the measures are culturally appropriate (see Booker et al., 2015 for an example on developing an assessment tool based on self-report from African American older adults). Booker, S., Pasero, C., & Herr, K. A. (2015). Practice recommendations for pain assessment by self-report with African American older adults. Geriatric Nursing, 36(1), 67-74. https://doi.org/10.1016/j.gerinurse.2014.08.014	We have now added the following to the section titled "Research Needs Specific to Validation of Existing Tools to Identify Opioid Misuse or OUD": An assessment of the cultural appropriateness of various tools and their performance across subgroups of race and ethnicity is a remaining research need. Given the existing evidence that suggests race and ethnicity are potentially important predictors of opioid-related outcomes, a rational next step is to study how tools (and management of opioids more broadly) might need to differ for older racial/ethnic minority adults with pain.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 1: APA	a. General Comments	We also recommend adding more information about the management of opioid use disorder in any other diverse racial and ethnic older adults as well or note if that information is lacking in the literature.	To address this point, the following sentences have been added to the "Research Needs Specific to Settings for OUD Treatment" section fo the report: More information is also necessary to understand whether certain settings are more effective for specific subgroups of older adults. For example, while more research is necessary in general about the management of OUD for diverse racial and ethnic minority older adults, research might be particularly helpful on which settings result in the best outcomes for racial/ethnic minority seniors with OUD.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	Reference: "We developed a Conceptual Framework outlining the stages of care for older adults who require or use opioids, and factors that have an impact on management decisions and patient outcomes (see Figure). The framework prioritizes three potential targets to determine factors associated with and interventions for: 1) reducing opioid prescriptions where harms outweigh benefits, 2) preventing opioid misuse and opioid use disorder (OUD), and 3) reducing other opioid-related harms." although the conceptual framework identifies many factors associated with long-term opioid use in all patient populations, it offers no useful evidence beyond outright surmise concerning reliable measures which justify restriction of opioid prescriptions on a basis of risk. We know from multiple published sources including the US CDC that there is no actual correlation between rates of opioid prescribing in any patient population versus risk of overdose-related mortality on a US State-by-State basis (Ref 1). We also know that risk of overdose-related mortality in persons age 62 and older is the lowest of any age cohort, while their rate of opioid prescribing is highest. (ibid) This demographic inversion cannot be explained as an outgrowth of any factor directly relating to prescribing of opioid pain relievers to legitimate pain patients. Ref 1: Richard A Lawhern, PhD "Stop Persecuting Doctors for Legitimately Prescribing Opioids for Chronic Pain", STAT News, June 28, 2019, https://www.statnews.com/2019/06/28/stop-persecuting-doctors-legitimatelyprescribing-opioids-chronic-pain/	The conceptual framework is not intended to "offer evidence", but rather, to serve as a foundation for understanding opioid use in older adults and to help organize the current and future literature on the topic. As we wrote, "The Conceptual Framework (Figure 1) outlines the stages of care for older adults who use (or may use) opioids and factors that impact management decisions and patient outcomes, including assessment of pain, selection of pain treatment, choice of opioid regimen, assessment for opioid misuse or OUD, and management of misuse or OUD."

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	It is likewise unequivocally clear that rates of diagnosis for substance use disorder in otherwise opioid-naïve post-surgical patients of all ages who are treated with opioid analgesics are on the order of a maximum of 0.6% (Ref 2). Rates of protracted opioid prescribing (prescriptions renewed longer than 120 days) are less than 1% for at least 11 common surgical procedures; these rates in all likelihood represent failure of surgical procedures and emergence of chronic pain, rather than any drug-seeking behavior on the part of patients themselves. Rates of protracted prescribing in non-surgical patients are on the order of 0.136%. (Ref 3) Ref 2: Gabriel A Brat, Denis Agniel, Andrew Beam, Brian Yorkgitis, Mark Bicket, Mark Homer, Kathe P Fox, Daniel B Knecht, Cheryl N McMahill-Walraven, Nathan Palmer, Isaac Kohane, "Postsurgical prescriptions for opioid naïve patients and association with overdose and misuse: retrospective cohort study", BMJ 2018;360:j5790 http://www.bmj.com/content/360/bmj.j5790.long Ref 3: Eric C. Sun, Beth D. Darnall, Laurence C. Baker, Sean Mackey, "Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naïve Patients in the Postoperative Period", JAMA Internal Medicine 2016;176(9):1286-1293. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2532789	Although the study focused on those Medicare patients its model found to be high risk, in one included study (Pasquale 2017) about 10% had de novo OUD. We have highlighted this finding. Nonetheless, it is likely that OUD is uncommon in older adults. However, given the lack of focus on screening for and diagnosing OUD in older adults, the previously reported estimates may be subject to substantial measurement error and represent an under-ascertainment of the true incidence and prevalence of OUD among seniors. Confirmation of other points made by Public Reviewer 2 are worthwhile future research needs that have already been addressed throughout the report. We have examined the suggested references but did not find them to be specific to the older adult population.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	The combination of these data should inform us that quantifiable risk of addiction or mortality in patients of any age who are diagnosed and treated for chronic pain with prescription opioid analgesics, is very low. In fact, it is so low that there is no possibility of usefully predicting individual patient risk. This fundamental principle is supported by no less an authority than Nora Volkow, MD, Director of the National Institutes on Drug Abuse: “Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with pre-existing vulnerabilities...” “Older medical texts and several versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct from those responsible for tolerance and physical dependence, in that they evolve much more slowly, last much longer, and disrupt multiple brain processes.” Ref 4: Nora D Volkow, MD, and Thomas A McLellan, Ph.D., “Opioid Abuse in Chronic Pain — Misconceptions and Mitigation Strategies” . NEMJ 2016; 374:1253- 1263 March 31, 2016]. http://www.nejm.org/doi/full/10.1056/NEJMra1507771	This is an assumption that we are not willing to make. Pasquale 2017, for one, seems to contradict this (10% had de novo OUD, although, admittedly of a preselected high-risk population). Of note, prediction modeling is possible even for very rare outcomes. For an example of a paper included in the report that demonstrates this fact, please see the included study by Lo-Ciganic et al., 2019, PMID: 30901048.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	Reference: "35 studies assessed factors independently associated with opioid-related outcomes among older adults (≥60 years). ● While the 35 studies reported multivariable analyses, none of the analyzed models was designed or evaluated as a screening or prediction tool. ● 17 multivariable studies evaluated long-term opioid use, which may sometimes be a high-risk behavior, but is not necessarily evidence of problematic opioid use. o All 8 studies that looked at prior or early postoperative opioid use found mostly strong associations (e.g., relative risk [RR] >2.0) with long-term opioid use. o All 6 studies that examined greater amounts of prescribed opioids (higher number of opioid prescriptions or higher opioid dose) found mostly strong associations with long-term opioid use." The assertion of long-term opioid use as a high-risk behavior is unsupported by any reference and is in fact wrong on the evidence. We should expect strong associations between prior post-operative opioid use and long term use. Likewise, we should expect associations between higher opioid dose levels and long term use. Neither is an issue of risk per se.	We do not describe it as a high-risk behavior. We have revised language to better clarify that it is an indicator of use, not high risk use, and may indicate untreated pain.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	The typical course of progression for many underlying medical disorders and the typical course of dose titration is toward higher levels over time, to address more intense, intractable or multi-factorial pain. We must also keep in mind the relatively tiny size of the population in which these effects have been documented. It is highly inappropriate to extrapolate rules of all medical practice or to infer "risk" in the general population of patients, based on this relatively small patient cohort (under 1%).	The goal of this review was to find evidence specific to the "older adult" population so that we would not need to infer from the general population.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a1. Evidence summary	"14 studies addressed interventions related to opioid use and opioid-related disorders in older adults. ● Only 1 study was a randomized trial. Each intervention was evaluated by only 1, or rarely, 2 studies. ● The most-studied interventions were screening tools to predict opioid-related harms but none of these tools has been tested in clinical practice to assess real world results. ● 2 studies found that prescription drug monitoring programs have been associated with less opioid use (at the State level)." My Comments: While it is true that no presently available screening tool has been tested in clinical practice, other AHRQ reports (Ref 5) go further to report that no two available screening tools produce mutually consistent results even in non-clinical settings. Very illuminating from this source is the realization that genomic testing also provides no reliable risk predictions for tolerance, addiction or mortality in individual patients (ibid). Nor should we expect such predictions. Ref 5: US Agency for Healthcare Research and Quality, "Opioid Treatments for Chronic Pain" - Draft Comparative Effectiveness Review, circulated October 2019 for public comment, pp 202-204.	We have no evidence comparing screening tools in this population.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a2. Key Messages	Reference: “No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse “ Even more concerning in the present report is that it makes no reference to genomic testing or opioid metabolism even as marginal concerns in modeling relationships between opioid exposure versus addiction. This omission appears to reflect a consistent and unreported anti-opioid bias among the (unnamed) writers group that produced the report. If the writers had acknowledged the existence of an extensive medical literature on genetically mediated polymorphism in P450 enzymes which govern opioid metabolism, they might also have been forced to assess whether metabolism is a significant confounding factor in any “one size fits all” criterion that might be proposed – as the 2016 CDC Guidelines did – as a basis for evaluating risks versus benefits.	The purpose of this Technical Brief was to describe research specifically in older adults. We are not able to expand the scope other interesting topics.
Public Reviewer 2: Richard A. Lawhern	a2. Key Messages	It is unsurprising that existence of PDMPs at State level is associated with reduced opioid prescribing. These databases are actively being exploited by State Medical Boards and regional prosecutors as a means of suppressing opioid prescribing by singling out and warning doctors who prescribe most often. Thus the tangential reference in this report can only be construed as a deliberate confusing of cause and effect to support a preexisting anti-opioid agenda.	Thank you. We have made it more explicit wherever we describe the PDMP studies that they did not evaluate whether changes in opioid use was “appropriate” or beneficial to patients.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	Rerefece: “We formed a 15-member panel comprising…” I find it very difficult to believe that the Key Informants group included any” recognized advocates for older adults in pain. “ The draft report offers no evidence of even considering the lived experience of the 30 million US residents whose lives are constrained by daily severe pain which impacts quality of life and function.	Per AHRQ policy, these individuals were redacted from the draft. They will be named in the final report.
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	The conceptual framework proposed in this Technical Note incorporates a fundamentally faulty assumption unsupported by medical evidence: that interventions are needed to “reduce risk of opioid prescribing where harms outweigh benefits and increase access to non-opioid treatment.”	It seems fundamental that all interventions should follow the mantra of first do no harm. All interventions where harms outweigh benefits should be minimized.
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	As noted above, it is not at all clear either that (a) interventions involving restrictions on prescription opioid availability are actually needed, or (b) that non-opioid treatments are available and effective as replacements for opioids. A compelling case can be made for the finding that our US “opioid crisis” is not and never was the result of physicians prescribing to their patients -- and is not being sustained from that source. Indeed, the conceptual framework as introduced pointedly ignores the existence of multiple socioeconomic factors which are in fact directly pertinent.	We have better highlighted that the included studies (mostly) did not evaluate pain and that reducing opioid use is not a clinical goal in and of itself.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	The economic crisis of 2008 contributed directly to ongoing structural unemployment and the hollowing-out of small communities across the US rust belt, Appalachia, the deep south and rural west. Job loss from automation and international out-sourcing has caused family breakups in all of these areas, placing people of all ages – including some seniors – under enormous situational pressure. Street drugs become an attractive distraction from such factors. This phenomenon has been discussed under the designation “a Crisis of Despair.”	Macroeconomic phenomena are beyond the scope of this Technical Brief.
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	Even granting that recent years have seen somewhat increased rates of opioid related mortality in seniors, the increases seen have been small in absolute terms and in comparison to mortality in youth, young adults and people of middle age. The Figure below is a plot of mortality data by age cohort over a period of nearly 20 years [Ref 7]. It is based on direct data downloads from the CDC-Wonder database. [Ref 7] Richard A Lawhern, PhD, “Over-Prescribing Did Not Create America’s Opioid Crisis”, Understanding Cronic Plain - Online Blog of Lynn Webster, MD, April 6, 2019, https://www.lynnwebstermd.com/over-prescribing/	We agree that younger age groups have suffered greater increases in opioid related mortality. However the goal of this particular body of literature and this Technical Brief is to focus on older adults..
Public Reviewer 2: Richard A. Lawhern	a3. Conceptual Framework	We should also note that behavioral and non-invasive therapies may play constructive roles as adjuncts to opioids, NSAIDs, off-label use of anti-seizure and anti-depressant medications. But there are simply no published trials of such therapies as replacements for opioids. Moreover, medical evidence for nearly all “alternative” pain therapies is exceptionally weak.	We do not claim there is evidence that behavioral or noninvasive therapies can/should replace prescription drugs.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	b. Introduction	In large-cohort demographic studies, incidence of opioid overdose related mortality in patients prescribed opioids is on the order of 0.022% (22 deaths per hundred thousand). In a definitive study of a full year of medical records for the entire State of North Carolina, nearly 2 million people were found to have been prescribed both a benzodiazepine and an opioid. But only 386 died of an overdose where both were implicated in the span of 1 year. Every overdose death is a heart break; but the numbers clearly speak to a general safe use of the meds together. Dasgupta N, Funk MJ, Proescholdbell S, et al. "Cohort study of the impact of high-dose opioid analgesics on overdose mortality".[Erratum appears in Pain Med. 2016 Apr;17(4):797-8; PMID: 27025778]. Pain Med. 2016 Jan;17(1):85-98. PMID: 26333030	We agree that the evidence base is inadequate regarding risks of opioid and benzodiazepine coprescription. We have revised the sentence to remove the concept of concurrent benzodiazepine use.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	b. Introduction	The assertion that effectiveness of long-term opioid therapy is “unclear” is strongly contradicted by literally hundreds of thousands of reports in social media, grounded upon patient lived experience. This assertion is largely an artifact of the rarity of long term double-blind trials due to patients dropping out of the placebo arms in such trials. The 2016 CDC guidelines on opioid prescribing in adults with chronic non-cancer pain deliberately conflated this rarity with lack of effectiveness. However had the same criteria been applied to behavioral and non-opioid analgesic trials, none of these therapeutic approaches would have been able to demonstrate strong evidence of effectiveness. (Ref 9) Baraa O. Tayeb, Ana E. Barreiro, Ylsabyth S Bradshaw, Kenneth K H Chui, Daniel B Carr, “Durations of Opioid, Nonopioid Drug, and Behavioral Clinical Trials for Chronic Pain: Adequate or Inadequate?” Pain Medicine, Volume 17, Issue 11, 1 November 2016, Pages 2036–2046. https://academic.oup.com/painmedicine/article/17/11/2036/244788	We have edited the text to emphasize the lack of data to support effectiveness.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	b. Introduction	Reference: “It is plausible that many older adults misuse prescribed opioids by taking them in greater amounts, more often, or for longer than they were directed to by a prescriber, or even resort to illicit opioids to alleviate untreated or undertreated pain, increasing the risk of overdose.46” It is indeed “plausible”, but the logic of this passage is profoundly outrageous: are we to presume that patients are at fault for the unwillingness of their physicians to prescribe and manage adequate pain control? And if they are at fault, are clinicians justified in refusing them adequate treatment? The withholding of treatment for pain when it is available is widely considered to be a violation of human rights.	We have edited the text to further highlight the role of the prescriber in such misuse.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	b. Introduction	Reference: “As with younger individuals, opioid misuse may transition to OUD. Regardless of age, individuals may become physically dependent on opioids (i.e., the body adjusts its normal functioning around regular opioid use) and continue taking them to avoid uncomfortable withdrawal symptoms.48, 49 Long-term opioid use—use of opioids on most days for longer than 3 months— may predispose individuals to developing OUD; although, this connection has not been established in younger or older adults. “ And later in the draft: “Opioid use in older adults may eventually result in opioid misuse or OUD, and a variety of factors may predict transition to misuse, OUD, or both (Octagon R2). Pharmaceutical, non-pharmaceutical (e.g., behavioral), nonmedical (e.g., educational, community-based), and other interventions could, at least conceptually, help older adults to safely use prescription opioids and prevent or reduce the risks of transition to opioid misuse and OUD (Triangle I2).” If the connection has not been established between long term opioid use and OUD then why are the writers at pains to introduce the idea at all? Is this not obvious evidence of disqualifying anti-opioid bias?	These are descriptions of the Conceptual Framework. There is little controversy that opioid use may transition to misuse and use disorder. The goal of the Technical Brief is to describe the evidence base for these hypotheses.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	b. Introduction	Likewise, the phrase “at least conceptually” reveals an uncritical and unsupported. surmise that goes far beyond any real medical evidence. Reality on the ground, as summarized by Dr Nora Volkow (ibid Ref 4), is that prescription opioid misuse or addiction are not predictable outcomes of prescribing for any age group – and most certainly not for Seniors over age 62 who have the highest rates of prescription use and the lowest rates of overdose-related mortality. What is actually going on in this phrasing and in the construction of the conceptual model amounts to an exercise in hype and overstatement that is utterly unsupported by real evidence. This deliberate distortion is by itself sufficient grounds for retraction of the Technical Note in total.	We have removed the phrase. It was included because the statement in the Introduction was made prior to evaluation of the evidence base. The goal of the report is to describe the evidence base.
Public Reviewer 2: Richard A. Lawhern	d. Methods	Although the process of developing a draft conceptual document is reviewed, the identities and professional positions of the Key Informants are withheld in the draft report. Thus is impossible for readers to assess the experience, biases, professional or financial self-interest of those who have shaped the methodology and conclusions of the report. This represents a fundamental and ethically unacceptable failure of public transparency, and should be grounds for rejection of the Technical Note out of hand.	Per AHRQ policy, these individuals were redacted from the draft. They will be named in the final report.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 2: Richard A. Lawhern	e. Findings	Reference: “While opioids are an option (Rectangle C), nonopioid medications could be used to manage pain. These medications include acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ibuprofen, naproxen), corticosteroids, antidepressants, antiepileptics, and others (e.g., topical capsaicin products). Nonpharmacological options are available as well and include a wide array of potential interventions, such as yoga, massage therapy, and acupuncture. Importantly, older adults may start “multimodal” treatment (of more than one intervention) that comprises a pain treatment approach that 1) combines medications from different pharmacologic classes and 2) combines pharmacologic and nonpharmacologic therapies or multiple nonpharmacologic therapies.” As documented in a 2019 AHRQ systematic outcomes review, the state of medical literature on the effectiveness of non-pharmacological methods is abysmal. No trial for yoga, massage therapy, acupuncture or behavioral therapies has progressed beyond Phase II, and almost all published trials are at Phase I. Moreover, the strength of medical evidence for almost all of the so-called alternatives is assessed as weak, and the degree of improvement in pain levels or quality of life is strictly marginal and temporary [ibid Ref 6]. No trials have been published which directly compare opioid therapy with non-pharmacological techniques on an either-or basis. These documented outcomes give the lie to any assertion that Nonpharmacological alternatives are “available”. They simply are not.	We describe common clinical practices to manage pain. We do not describe their effectiveness. These interventions are commonly used and available.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 3: Masimo	a. General Comments	We applaud your recognition of the dangers of respiratory depression in the Technical Brief and we agree with your assessment that fundamental research is needed to identify interventions and technologies that can reduce opioid-related harms among older adults and to determine which factors may predict opioid-related harms	Thank you
Public Reviewer 3: Masimo	a. General Comments	While progress has been made to address a rising death toll caused by opioids, major gaps in protection against opioid risks for older adults remain. The Department of Health and Human Services Office of. Inspector General (HHS OIG) recently recommended that steps should be taken to mitigate the risk of misuse and overdose in Medicare beneficiaries.x For the reasons highlighted, we feel that medical technology must be a part of any strategy to prevent opioid overdose and death, and that additional research should be conducted on the benefits of the use of such technology in keeping our older adults safe. According to the HHS OIG, an astonishing 71,260 Part D beneficiaries were at serious risk of misuse or overdose in 2017.xi From 1999 to 2013, the rate of opioid poisoning deaths increased more than 7- fold among adults aged 55 to 64 years,xii and older adults experience the highest rates of adverse drug events resulting in emergency department visits. Sadly, they are 4-7 times more likely than younger persons to have an adverse drug event that requires hospital admission. [references in original document]	Thank you for highlighting the recent OIG report. Notable is that 75% of those in Medicare who were found to have “OUD” were eligible based on disability, not age. Therefore, their findings are not specifically pertinent to older adults. In addition, their definition of OUD lumped opioid dependence (which may have to do with unrelieved pain) with “abuse”.

Public Reviewer 3: Masimo	a. General Comments	What We Know The Dangers of Opioid-Induced Respiratory Depression in Older Adults In older adults with a higher risk of cognitive impairment, opioids may result in further deficiency of cognition and decision making function,xiv and there is a risk of death from these drugs due to opioidinduced respiratory depression.xv Opioids are potent respiratory depressants and can cause shallow and decreased respiration rate and decreased blood oxygen saturation. Older adults (>65 years old) are more sensitive to the sedating effects of opioidsxvi and are at increased risk for respiratory depression.xvii Further, advanced age, in combination with other risk factors that are. common in older adults such as obstructive sleep apnea,xviii chronic obstructive pulmonary disease (COPD), chronic kidney disease,xix cardiac disease, and neurological diseasexx increase the risk of. opioid-induced respiratory depression. Advanced age, coupled with coexisting COPD, necessitates greater vigilance in monitoring older patients who are at greatest risk for serious consequences if respiratory function is compromised from anesthesia and postoperative analgesia.xxi Some older adults suffer from cognitive impairment, which can increase their risk for medication errors and make opioid-related confusion even more dangerous.xxii Older adults are also more likely than younger adults to experience comorbid medical conditions and are more likely to receive multiple medications, which can negatively interact with opioids (ex: benzodiazepines).xxiii These comorbidities also make the diagnosis and treatment of pain in older adults more complex.xxiv Chronic pain is one of the most common, expensive, and incapacitating conditions in older adults,xxv and the elderly are more susceptible	We believe we have covered the major points raised in the Introduction (and elsewhere). The body of the report (Results) focuses on the evidence base addressing specific questions in older adults. Where they address the issues raised, they have been summarized.

Section	Commentator & Affiliation	Comment	Response
		and less tolerant of severe and continuous pain than young adults.xxvi However, many clinicians are hesitant to prescribe needed pain medication to the elderly because of the dangers of respiratory depression.xxvii Clinicians face difficult challenges in monitoring patients taking prescribed opioids. Due to concerns regarding post-surgery opioid-related adverse events particularly among older patients, hospitals have integrated risk assessment tools to identify high risk patients and adjust their prescription and/or monitoring efforts, in an effort to minimize the likelihood opioid induced respiratory events and adverse events.xxviii Further, over 12 million Americans over age 65 live alone,xxix where there may not have an available caregiver to provide medical assistance in emergencies, and major health emergencies can be overlooked as “age-related changes” (general weakness, dizziness, and upset stomach) when in fact the person is experiencing respiratory depression.xxx Without someone else in the home or the availability of remote physiologic monitoring, older adults may lack the ability to notify emergency medical assistance. Fortunately, technology exists today that can meet those challenges by enabling physicians to prescribe the medications that they feel are appropriate to manage pain and keep their patients safe from opioidinduced respiratory depression, catastrophic permanent injury, and death.	

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 3: Masimo	a. General Comments	Remote Physiologic Monitoring Saves Lives Continuous physiological electronic monitoring can save lives. Technology available today will enable seniors to wear a device that can be worn continuously to monitor oxygen saturation, pulse rate, and respiratory rate, transmit that data to a smart phone or remote view station, send alerts based on device alarms through an escalation protocol, and offer healthcare providers to use remote viewing stations that enable real-time monitoring of devices, and communication with device and connected smart phones associated with the device. This alarm system can create a true safety net for elderly patients, with will decrease anxiety and save lives. Researchers at Dartmouth-Hitchcock Medical Center, over a ten year period, found improved outcomes following installation of continuous postoperative monitoring in a post-orthopedic unit. Specifically, researchers were able to eliminate preventable deaths and brain damage due to opioid overdose in post-surgical unitsxxxi as well as reduce rapid rescue events by 60%,xxxii ICU transfers by 50%,xxxiii and cost by an estimated $7 million annually.xxxiv This technology can provide earlier identification of the deteriorating patient condition which will increase the chance of a positive outcome.	We focused on the evidence base specific to older adults. Studies of remote physiologic monitoring (and the like) would have been included if they had been conducted in the population of interest.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 3: Masimo	a. General Comments	Adequate Medicare Coverage and Reimbursement for Remote Monitoring Technologies In order to ensure that life-saving remote physiologic monitoring technology is available to patients and providers, the federal coverage and reimbursement structure must be sustainable and equitable. In the past, reimbursement policies and restrictions have impeded the patient access to available. breakthrough remote monitoring technologies. We urge AHRQ to support the elimination of these restrictions and increased coverage and reimbursement of remote monitoring technologies that will increase access, decreases costs, and save lives.	AHRQ does not advocate for or against policies.

Public Reviewer 3: Masimo	a. General Comments	Research Is Needed to Increase Safety and Provide Effective Pain Management in Older Adults. Taking Opioids In order to reduce adverse outcomes of opioid use among older adults, we recommend that the following research be conducted on patients/individuals taking opioids: ● The benefits of remote physiologic surveillance technology and devices on adverse events. ● Preferably, the technology studied should monitor blood oxygen levels and provides escalating alerts when oxygen levels fall below predetermined thresholds and provides measure-through motion and low perfusion technology. ● Granular analysis of the use of this technology on specific outcomes, including, but not limited to the instances of: o opioid-induced respiratory depression; o pneumonia; o death; o emergency department visits. ● The impact of comorbidities on the benefits of remote physiologic surveillance, including, but not limited to: o age o gender o mental health status/cognitive function; o obstructive sleep apnea o ASA score o chronic obstructive pulmonary disease (COPD) o cardiac disease o neurological disease	We agree that more research is needed to increase safety and provide effective pain management in older adults.

		o concomitant administration of sedatives o patient diagnosis o patient's level of acuity and risk for complications o treatments and medications that the patient is receiving o trends in the patient's vital signs ● Relationship between the use of remote physiologic monitoring and better patient outcomes both short- and long-term. ● The role of home or facility monitoring of older adults and anxiety reduction. ● The relationship between the number of opioid prescriptions written by providers when remote physiologic monitoring is used versus not used (i.e., are providers more likely to prescribe opioids for the elderly if remote physiologic monitoring is used to monitor that patient for adverse events?). ● Benefits of the use of remote physiologic surveillance technology that monitors blood oxygen levels and provides escalating alerts when oxygen levels fall below predetermined thresholds versus other monitoring equipment (i.e., "spot checks" or systems that do not provide escalating alerts to notify the physician). ● Benefits of the use of inpatient continuous physiologic continuous electronic patient monitoring with measure-through motion and low-perfusion pulse oximetry surveillance technology that transmits information	

Section	Commentator & Affiliation	Comment	Response
		on blood oxygenation and respiration versus other monitoring equipment (i.e., “spot checks” or systems that do not transmit information to providers). ● Benefits of educating clinicians on opioid-induced respiratory depression (OIRD) and the technology available that can be used to prevent OIRD causing overdose. ● Benefits of educating patients and caregivers on opioid-induced respiratory depression (OIRD) and the technology available that can be used to prevent OIRD causing overdose. As we all face the challenges of keeping patients safe during the tremendous health threats we face with the opioid crisis, we need to ensure that the private and public sectors work together in a coordinated effort. Masimo stands ready to work with you as you address these important patient safety issues for older adults.	

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 4: Britinia Galvin, American Academy of Physical Medicine and Rehabilitation	a. General Comments	The AHRQ Draft Report on Prevention, Diagnosis, and Management of Opioids, Opioid Misuse and Opioid Use Disorder in Older Adults provided a framework for understanding how to reduce adverse outcomes of opioid use among older adults and described the evidence available for different factors associated with and interventions to reduce adverse outcomes related to opioid use in this population. The literature search resulted in the analysis of 35 studies and the analysis was well done. However, we question why the panel did not conduct a review of the researched articles emphasizing methodological quality (see Limitations), as this process would have strengthened the assessment of the studies included in the report. We also have concerns that the software that was used, which uses machine learning algorithms to predict and sort citations based on likely relevance, may have missed relevant studies that could have added more important information, as discussed in the section on limitations	AHRQ's preliminary survey of the literature suggested that there were too few studies of sufficient quality to warrant a full systematic review at this time. Therefore, it was decided to commission a Technical Brief, designed to describe the state of the evidence. It was not designed to fully systematically review and evaluate the evidence base. Thus, we did not fully elaborate studies, study results, study quality (risk of bias), or summary conclusions. Based on many years of experience with the software, we are quite confident that the machine learning software was accurate in regards to ensuring that all potentially relevant articles (found by the searches in the electronic databases) were screened by humans. The expert, peer, and public review process has not identified additional studies, confirming that the learning algorithm was sufficiently sensitive.
Public Reviewer 4: Britinia Galvin, American Academy of Physical Medicine and Rehabilitation	a. General Comments	Overall, we believe that the report is well done and appreciate AHRQ's efforts to review and summarize the limited research currently available regarding prevention, diagnosis, and management of opioids, opioid misuse and opioid us disorder in older adults. We also appreciate AHRQ's acknowledgement that additional research is necessary in this area.	Thank you

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 5: Anonymous	a. General Comments	The acknowledgment that long-term opioid use is "not necessarily evidence of problematic opioid use"; is appreciated. Long-term opioid; should not be categorized as a negative outcome in itself. As the Introduction acknowledges, for patients with certain medical conditions (often rare ones), where non-opioid therapies have failed or are contraindicated, long-term opioid use may be the best outcome possible. Because policymakers often assume long-term opioid use is automatically bad, and because policymakers do not always read to the end of AHRQ reports, it would help to state this qualification directly in the Evidence Summary, featured prominently throughout the report.	We have further elaborated on this concept and clarified language to distinguish long-term opioid use from problematic use. We have also better added that long-term use may indicate inadequate treatment of the underlying condition, rather than a problem with opioid use, per se.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 5: Anonymous	b. Background	The Introduction states “occurrence of disability... may increase the probability that an older adult uses opioids. However, opioid medication can also *prevent* disability. For certain disabilities, daily opioid medication may enable normal daily function, for decades or a lifetime.” The next paragraph correctly notes: “Appropriate use of opioids under clinicians” supervision may provide many older adults with necessary pain relief, allowing them... a higher quality of life.” As an example, opioids are often mentioned in connection with risk of hip fracture. AHRQ’s report does not mention conditions such as refractory dyskinesias, or autoimmune disease damaging the bowel or bladder, where opioid use can result in lower risk of hip fracture. Without opioid medication, sleep might be impossible, or bathroom trips every 10-20 minutes might be necessary. Amid nationwide incentives to reduce opioid prescribing (currently at an 18-year low), rapid and non-consensual taper has emerged as a major risk factor for overdose and death. AHRQ’s list of risk factors for overdose and death ignores this important factor. Any discussion of opioid risks should also include the risks of rapid, inappropriate, forced tapering, plus the risks of not having access to opioid medication when medically necessary.	This is an important point and we agree. We have now added a statement immediately after the one highlighted by the Reviewer, which reads “In turn, opioids may help prevent or delay disability for years among many older adults.” In addition, we have now added text to caution against any “forced” or “non-consensual” deprescribing of opioids. The decision to deprescribe should be one that is shared with the patient and deprescribing should occur with the consent of the patient and their legally authorized representatives. We have also added the following statements to the “Research Needs Specific to Deprescribing Protocols and Sharing Responsibility” section of the report: Information is also necessary to identify for which conditions deprescribing might be inappropriate and represent a deprivation of important, medically necessary therapy. For example, deprescribing opioids for older adults with refractory dyskinesias might be highly inappropriate and result in severely impaired quality of life, extreme insomnia, and suicidal depression. Qualitative research could help to confirm that opioids are essential and equipoise does not exist for interventional research on deprescribing in such circumstances.

Public Reviewer 5: Anonymous	e. Methods	The methods section could benefit from an additional Guiding Question: What harms are associated with mandatory system-wide reductions in opioid prescribing? The Conceptual Framework could use another triangle: Interventions to reduce harms from mandatory system-wide reduction in opioid prescribing. Much of the evidence on pain and prescription opioid use rests on the premise that increased access to non-opioid treatments will prevent or reduce long-term opioid use. For some populations, regardless of age, this is a false premise. For some patients, all existing non-opioid protocols have already failed. Interdisciplinary pain rehabilitation programs have failure rates. For some medical conditions, palliative management with opioid medication is the only viable option. Some older Americans have lived with these conditions their entire lives. Triangle I1, recommending interventions to increase access to non-opioid treatments, will not be helpful for this population, because access to non-opioid treatments has never been the issue for them.	While we cannot change the Guiding Questions, we believe the additional question is covered by Guiding Question 3 and Conceptual Framework Triangle I1). We included studies of (mandated) system-wide interventions (such as tamper proof medications and an opioid safety intervention). However, we have added the following statements to the section "Research Needs Specific to Provider Perception of OUD Risk": The perceptions and beliefs of various stakeholders are also important because they might result in erroneous expectations about the effects of mandatory system-wide interventions to reduce opioid prescribing. While such system-wide interventions could potentially reduce the risk of OUD across all age groups, they might also result in significant harms to older adults who require opioids and are unable to substitute alternative non-opioid treatments. In addition, the following has been added to the "Research Needs Specific to Comparative Effectiveness of Opioids and Nonopioids in Older Adults" section: Nonetheless, research may still be necessary to answer questions such as "What are the unintended harms of implementing mandatory system-wide interventions to reduce opioid prescribing and substitute alternative nonopioid treatments?" It is highly important to study the premise that increased access to nonopioid treatments will prevent or reduce suboptimal opioid use. For many subpopulations of older adults, the premise may be false and system-wide interventions may cause considerable harm if they do not exempt such subpopulations. Therefore, in addition to understanding the comparative effectiveness of opioids and nonopioids in

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			older adults, research is necessary to both identify subgroups of older adults for whom long-term opioid may be the only viable option and how to best ensure that system-wide interventions do not mistakenly attempt to replace their opioid therapy with non-viable non-opioid therapies.

Public Reviewer 5: Anonymous	f. Findings	The Findings section focuses on opioid-related harms, with little mention of opioid-related benefits. With an evidence base dominated by studies of common musculoskeletal pain, people with rare disease and catastrophic permanent injury are not adequately represented. Had such studies been undertaken and/or reviewed, results might be very different in certain populations. Bialas P1, Maier C2, Klose P3, HÃ¤user W. Efficacy and harms of long-term opioid therapy in chronic non-cancer pain: Systematic review and meta-analysis of open-label extension trials with a study duration â‰¥26 weeks. Eur J Pain. 2019 Oct 29. doi: 10.1002/ejp.1496 Nor did AHRQ include studies showing serious harm, including death, associated with mandatory system-wide reductions in opioid prescribing. Harm resulting from de-prescribing may indicate a hidden population of patients who benefit from opioid medication but are not represented in other literature. Peer-reviewed studies increasingly show rapid and/or inappropriate nonconsensual opioid taper associated with overdose and death. Yet AHRQ's list of risk factors ignores this factor: Oliva Elizabeth M, Bowe Thomas, Manhapra Ajay, Kertesz Stefan, Hah Jennifer M, Henderson Patricia et al. Associations between stopping prescriptions for opioids, length of opioid treatment, and overdose or suicide deaths in US veterans: observational evaluation BMJ 2020; 368 :m283 doi: https://doi.org/10.1136/bmj.m283 James, J.R., Scott, J.M., Klein, J.W. et al. Mortality after discontinuation of primary care-based chronic opioid therapy for pain: a retrospective cohort study. J GEN INTERN MED	As per the guiding questions, the finding do, as you suggest, focus on opioid-related harms. We did not review the effects (benefits) of opioids, per se. but instead focused on situations where the harms outweigh the benefits (which assumes that there are benefits in appropriate situations). We have added further research recommendations regarding deprescribing of opioids (to avoid harms).

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		(2019) 34: 2749. https://doi.org/10.1007/s11606-019-05301-2 Glanz JM, Binswanger IA, Shetterly SM, Narwaney KJ, Xu S. Association Between Opioid Dose Variability and Opioid Overdose Among Adults Prescribed Long-term Opioid Therapy. JAMA Netw Open. 2019;2(4):e192613. doi:10.1001/jamanetworkopen.2019.2613 Fenton, J., Agnoli, A., Xing, G., et al., Trends and Rapidity of Dose Tapering among Patients Prescribed Long-Term Opioid Therapy, 2008-2017. JAMA Netw Open. 2019;2(11):e1916271. doi:https://doi.org/10.1001/jamanetworkopen.2019.16271 Perez, H., M. Buonora, C., Cunningham, M. et al., Opioid Taper Is Associated with Subsequent Termination of Care: A Retrospective Cohort Study, J Gen Intern Med (Aug 19 2019). DOI: 10.1007/s11606-019-05227-9 Demidenko MI, et al. Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users, Gen Hosp Psychiatry. 2017 Jul;47:29-35. doi: 10.1016/j.genhosppsych.2017.04.011. Epub 2017 Apr 27.	

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 5: Anonymous	g. Next Steps	In suggesting future research needs, one is missing: AHRQ should encourage studies that specifically include older patients who benefit from long-term opioid therapy, to determine what factors they have in common (hint: they came to long-term opioid therapy as a last resort) with the goal of ensuring such therapy remains accessible in an increasingly hostile regulatory environment.	In the section "Research Needs Specific to Comparative Effectiveness of Opioids and Nonopiids in Older Adults", we have added the following: "Therefore, in addition to understanding the comparative effectiveness of opioids and nonopioids in older adults, research is necessary to both identify subgroups of older adults for whom long-term opioid may be the only viable option and how to best ensure that system-wide interventions do not mistakenly attempt to replace their opioid therapy with non-viable non-opioid therapies."

Public Reviewer 5: Anonymous	g. Next Steps	In general, AHRQ evidence reviews tend to zoom in on the weeds of variable types, confidence intervals, strong/weak associations, etc. AHRQ could do better by the citizens it serves, by reconsidering which questions are asked in the first place. If the question is “what harms are associated with opioid prescribing?” the Guiding Questions should also include “what harms are associated with mandatory system-wide tapering?” and “what harms are associated with fewer physicians accepting patients on long-term opioid therapy?” Reliable evidence shows older adults with chronic pain are losing access to care. This evidence could have been included in AHRQ’s review: Lagisetty PA, Healy N, Garpestad C, Jannausch M, Tipirneni R, Bohnert ASB. Access to Primary Care Clinics for Patients With Chronic Pain Receiving Opioids. JAMA Netw Open. 2019;2(7):e196928. doi:https://doi.org/10.1001/jamanetworkopen.2019.6928 Quest Diagnostics and Center for Addiction, HealthTrends, Drug Misuse in America: Physician Perspectives and Diagnostic Insights on the Evolving Drug Crisis (2019) [https://questdiagnostics.com/home/physicians/health-trends/trends/pdm-health-trends.html], accessed 11/20/19. Through lived experience, many older Americans can testify that long-term opioid therapy is helpful and necessary. When the scope of an evidence review is framed to mostly ignore such reports, the result is unintentional exclusion of people with disabilities.	It is not possible to address all questions in one report. HHS has released guidance on tapering that addresses these issues and therefore this report did not attempt to re-address them. We did include the concept of effects of mandatory system-wide tapering of opioids (as a potential intervention of interest). Access to care among older adults is beyond the scope of this Technical Brief.

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 5: Anonymous	a. General Comments	I can understand the problem and the evidence; however, the problem is only partially stated and the evidence is incomplete. I could, but some policymakers may read an unintended message into the results and conclusions. In the Introduction, AHRQ notes that "[a]ppropriate use of opioids under clinicians' supervision may provide many older adults with necessary pain relief, allowing them to remain active, independent... and able to maintain a higher quality of life" AHRQ waits until the ending Summary to conclude: "the outcome long-term opioid use does not address whether the harms associated with use outweigh the benefits. Long-term use may be a poor proxy for potential harms or problematic opioid use and may simply be an indicator of greater need for long-term use to manage chronic pain." Given recent evidence of harm from systematic de-prescribing, both of these conclusions could be included in the Evidence Summary and more prominently featured throughout the report.	We have better described throughout that long-term opioid use is not, per se, problematic, and may indicate inadequate management of an underlying condition (or ongoing, chronic pain).
Public Reviewer 6: [Reviewer's name redacted due to inclusion of personal medical information]	a. General Comments	Out of high school I trained as a US Navy Hospital Corpsman, licensed as an RN in 1973 and certified as a nurse practitioner in 1977. As a corpsman, RN and Nurse Practitioner I provided outpatient and inpatient services as well as emergency and primary care in rural and urban	Thank you for sharing your experience. We are very sorry to hear that you are in pain and sincerely hope your doctors can assist you in finding relief. Inadequately treated pain is a significant problem which needs to be addressed by research and policy.

		settings. None of my patients who are over 50 were at risk for an opioid adverse event or abuse of the opioids that they needed to control the pain that they were living with for decades. There was only one event that occurred to a 63 year old patient of mine. She suffered from advanced rheumatoid arthritis and needed her pain medication refilled. When I opened the locked cabinet that contained the controlled substances I found that one of my younger staff had stolen the medication. It was a rural setting and it took two days for the central pharmacy to ship the medication to me. She was a lovely lady who was forced to live in agony because some kid thought he needed the morphine. After 9 years of developing primary care clinics and providing primary care services I was hired as a Consultant at the California Department of Health Services. In that position I had oversight responsibilities for the community clinics in California, wrote policies, protocols and procedures for the State clinics and testified before administrative law judges and as an expert witness for the Office of the California Attorneys General and in both criminal and civil proceedings. At no time did any of my patients over the age of 50 at the 40 plus clinics abuse or misuse the medications that were derived from opiates and prescribed for them by a licensed clinician who is registered with the DEA. I was then recruited by the California Department of Forestry and Fire Protection to create a comprehensive medical services program for CDF firefighters. So that I could provide direct emergency and clinical services in the field, I trained as a wildland firefighter, hired two additional nurse practitioners and built a mobile urgent care service on wheels. It was a fully stocked with supplies that we needed at major fires and disasters throughout the State.	

		After over 20 years of experiencing transient neurological symptoms I was diagnosed with multiple sclerosis (MS) in 2001. Because my MS symptoms were debilitating enough to interfere with my work I was forced to retire at the age of 51. In addition to my MS, I have struggled with an immune deficiency since early childhood. In 2015 I had a full genome sequencing done. It revealed markers for alpha1 antitrypsin deficiency (A1AT) and Ehlers Danlos Syndrome. One of the more difficult symptoms that patients who have been diagnosed with either MS and/or Ehlers Danlos Syndrome is a severe form of pain that emanates from almost every part of our bodies. In addition, I have been diagnosed with peripheral neuropathies, a deep and unrelenting pain in my shoulders, chest and runs down both arms. That particular pain is caused by spinal disks that are collapsing and crushing the nerves at the level of my C-6 C-7 vertebra and a generalized, intractable and grinding pain caused by both my MS and Ehlers Danlos Syndrome. To blunt the pain when I was in my 20s, I began taking large doses of aspirin and later ibuprophen (Advil) every day. I was aware that I could ask my physician to prescribe an opiate so that I could control my pain but I did not want to experience the humiliation of having to eventually beg for a pain medication when I could use an NSAID. In my mid 50s my lab work showed that the aspirin and ibuprophen I took for most of my adult life had caused extensive kidney damage. I am now at Stage II Renal Failure. I was told to stop taking any kind of aspirin or ibuprophen and referred to pain management specialists. It was a spine surgeon who recommended that I wait five years until the use of stem cells to regrow disks is approved. That was over eight years ago. He had no reservations about prescribing Tylenol with codeine but because the acetaminophen would	

		cause further damage to my liver (A1AT) I could only take a limited amount of the acetaminophen. Over time my pain became intolerable. The second pain specialist was a physiatrist. She sent me to a physical therapists (PT) and ordered a broad range of palliative treatments that included exercise, stretching, cold laser treatments, trigger point therapy, heat and cold applications, massage, etc. Nothing the PT did helped. The physiatrist also renewed my prescription for codeine. When the codeine failed to stop any of my pain I was given a prescription for morphine. After two weeks taking morphine it became clear that I am non-responsive to opiates. Despite taking the highest recommended dose, neither the codeine nor the morphine did anything to mitigate the unrelenting, deep grinding pain I experience every day and every night. I spent years in a sleep deprived state and it was horrible. Over the years I have been given medications such as gabapentin, Lyrica, Toroidal, Cymbalta and concoctions like low dose naltrexone. Most of the medications increased my MS symptoms. None of them helped me to control my pain. It was not until I was given a relatively new drug called Nucynta that I experienced a decrease in my pain. Nucynta is classified as a C-II narcotic but it has no extrapyramidal effects. What that means is that the side effects that opiates are known for (heroin, codeine, morphine, Fentanyl, etc.) are not experienced when I take Nucynta. Nucynta blunts my pain enough to allow me to fall sleep before midnight and sleep for six to seven hours. What makes this medication unique is the manufacturer has removed the part of pain medications that cause people to experience things like euphoria, reduced anxiety and whatever else others often associate with	

		opiates. Because it has no side effects that would entice people to abuse the drug there is no reason to classify it as a C-II drug. It is the only pain medication I can take yet I am treated like a street junkie and the pharmacy technicians look down their nose at me when I pick up my refill of Nucynta. Without Nucynta my pain is so severe that I cannot take a nap during the day. My physicians were forced to go through repeated denials and challenges from my insurance company just so I could have the luxury of sleeping more than two hours at a time, be awake enough during the day so that I can live something akin to a normal life and, though I am 71, create a life for myself. It has been four years since I began taking Nucynta. I have not experienced any untoward side effects but obtaining refills is a problem. Almost every time I need a refill the pharmacies have to order a supply of Nucynta. In May of this year it took the pharmacy two weeks to provide me with a refill. I am mentioning this information because I was told that Nucynta is addictive. Almost every month I have to wait for at least a week to obtain a refill of Nucynta. During that time I do not experience any withdrawal symptoms. None. It may be due to my non-responsiveness to opiates but there is no reason to stop my use of Nucynta because someone thinks that I might experience withdrawal symptoms. I do not and will not experience withdrawal symptoms because I do not intend on stopping my use of Nucynta and because it is the only medication that can help to at least blunt my pain. I have spent at least a decade in a sleep deprived state. Sleep deprivation can cause neurological damage, can aggravate my MS symptoms, cause hypertension and increase the rate that cardiovascular disease develops, cause injuries from inattentiveness and a host of other	

		diseases that can emerge over time. The fact is that sleep deprivation can cause us to also develop life threatening diseases and disorders. Day to day, year to year sleep deprivation leaves me cognitively impaired and it severely aggravates the neurological symptoms that go along with having MS. Sleep deprivation has made it very difficult for me to do even the basic chores that are commonly associated with living as a normal adult. There have been times that I could not fill out a shopping list or fix a simple meal for myself. In the past three years I have been able to sleep enough so that I can function at a level that I need to survive. Because I am now able to at least blunt my pain, I can get to sleep and stay asleep long enough that I no longer wander aimlessly through my life. I now have purpose, can make plans for the future and can manage my day to day affairs. I am no longer a target of greedy relatives or the criminals that I may cross paths with and can walk and move with little to no impairment from the pain that has been a part of my life for almost 50 years. When I have an appointment to see my pain management specialist, I am required to fill out a battery of questionnaires, provide a urine sample and be reevaluated each time. This month I was told that I have to see my pain management specialist two times every month. I was given no reason, but now I am being given only half of the pain medications I need. It is a humiliating experience for me to be treated like a street junkie but I cannot go back to living with the severe pain that I have had to endure for my entire adult life. And, if it is not yet clear, the only pain medication I can take is Nucynta. I would like to propose that if the DEA continues to pursue this misguided effort to prevent the insurance industry losses due to an imaginary rush to drug rehab facilities that the DEA develop	

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		a waiver system that will allow us to obtain the medications we need without having to be monitored for some imaginary misuse of the medications. A true waiver program should allow those of us who really need to take opiates or their relatives to at least blunt our pain. Please take a minute to think about the people over 50 who have pain related to genetic conditions or injuries that are incurred while serving in our military. Because of my background I am able to document my need for a medication that can help me control my pain but there are many others who have just as much pain as I do but they are less able to write an effective letter. Those of us who are over 50 and have a clear need for an opiate medication should be allowed to participate in a waiver program that will allow us to obtain the medications we need to control or at least blunt our pain without a DEA agent harassing the physicians who know us. Thank you for your time and consideration in this matter. Please note that I fully support of the Herculean level of work that Dr. “Red” Lawhern has dedicated himself to and also the content and the comments he has published over the years.	

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Public Reviewer 7: [Reviewer's name redacted due to inclusion of personal medical information]	a. General Comments	9 surg since 12. If denying pain meds was ever done to me it would and at present time is causing irreparable physical mental and financial harm. First drs hand out pain meds like candy. Then they deny to paitents w ddd disease and other connective tissue diseases. While at the same time under diagnosing and undertreating painfully debilitating diseases. Also pilling on worthless amd harmful treatments. May God Help save us from gready corporate interests denying payment for pain meds through propaganda easily traced back to these insurance companies. While corporate immunity from jail needs to stop.	We are hopeful that our work, and that of our colleagues will help reduce the burden of poorly-controlled pain.
Public Reviewer 7: [Redacted]]	a. General Comments	All bullshit propaganda. If Institutions were interested genuinely peventing and curing illnesses we would be discussing laps in diagnosis of Spondolytis type diseases 3 times more prevalent than rheumatoid arthritis and treatable if detected early. Now the average is 7 years to diagnosis. Oh and one day u will pay.	We did not exclude any specific disease.

Public Reviewer 8: David Becker	a. General Comments	The AHRQ vice epistemology is on display as is their cartoon thin evidentialism and lack of regard for responsibilism. YOu're not data wranglers- you used data dredging to try to justify your data torturing marching orders to limit use of opioids as much as possible for elderly and fatally damage their claim to full moral status to make their own individual decisions on their care. It is clear AHRQ's epistocratic and discursive imperialism is designed to destroy the works of Beauchamp and Childress and institutionalize testimonial epistemic injustice and hermeneneutic injustice in pain care. Debate me on that- and dont forget to bring your p enhanced multilevel quasi markov model and stochastic gradient descent- youll need that and some morals to debate with or convince yours truly. Youve falsely framed the issue regarding pain care. It is a terrible thing to see and have no vision, as Helen Keller wrote what is your health justice model- is it necessitarian, sufficientarianism? You dont say- gee i wonder why. It is really a thinly veiled form of ersatz expected utility model you embrace- but you lack the honesty to state clearly what your end goals are. and no doubt, you have no regard for the capabilities model. No wide reflective equilibrium- just dirty data dredging- no surprise coming from DHHS who will stop at nothing to destroy principlism in pain care and do as much dignitarian harm to people in pain as they possibly can. Debate me in public on that hotshot It was a foregone conclusion that AHRQ would engage in cherrry picking to justify their surveillance and disaster algocratic, epistocratic imperialism in pain care. The total lack of care and relational ethics makes the moraly midgetry of AHRQ unobscured. The implications of the report are clear- to, In Orwellian fashion to destroy preferentism and	Thank you for your comments.

		principlism in pain care and to egregiously conflate your vice epistemology, ecological fallacy, McNamara fallacy as intellectual virtue and to relegate people in pain to civil and moral vagabondage with your narcissistic sociopathic neofeudalism and merciless marching order to eliminate the use of opioids as much as possible and use neutralization theory to justify your heartless fascism. Same ol stuff we have seen from the CDC- your cut and paste job is apparent. AHRQ is lacking in moral and social values, not to mention vision and moral magnificience. You wouldnt last 5 minutes debating me on the issue. You lack the intellectual virtues of open mindedness, thoroughgoingness, and humility. You belong in Orwells 1984 as you believe Americans are free to think what they want about pain care- as long as they obey AHRQ. You would force pain care to be like Kafka's The Trial where anyone seeeking opioids is seen as guilty and undergo theater of the absurd/suffering to add to the precarity and troubledness of their condition. Youve got your heartless resume builders and you wish to promote disaster and surveillance capitalism in pain careyoure despicable. This report is trash. It reflects the mercenary efforts of the iron trianle of government, academia, and industry to expand their sphere of influence and profits at the expense of democracy. As Bentham wrote- sinister interests are hostile to all suitors- especially those who have need to be. It is clear you dont believe individuals have the discursive capacity or moral status to make their own decisions for pain care. Your malignant narcissism and lack of caritas and humilitas is on display. The words principlism, dignity, and mercy are not in your vocabulary. Youre robopathic borgs who conflate your mcdonaldized vice epistemology as	

Section	Commentator & Affiliation	Comment	Response
		important. You make me and Americans sick of our government and inflame the trust deficit in health care. Yes. Your infrahumanization is on display with your obscure and ungainly draft. I guess thats what happens when you consume too many rubber chicken dinners. But i am no boiled frog so i wont ddrink your kool aid and whistle dixie. We know you will stop at nothing to limit the publics access to opioids. So much for your responsibilism and total lack of mercy. How you like them apples you heartless epoistocratic imperialist dogs.	

Public Reviewer 9: Anonymous	a. General Comments	The evidence is biased in that it relies solely on the premise that opioids are bad. Patient quality of life should be included in any research regarding medication. This research also fails to separate chronic pain patients from drug addiction disorder. It blankets both issues into one inferring that the pain patients are suspect because he/ she uses opioid medication. The morality police tone clearly evident here Very biased. Opioids contribute to quality of life and are the only option for some people for some quality of life. You should focus on research based on outcomes of patients using opioid therapy vs. non opioid therapy. People are dependent on many medications to have more quality of life. Not just opioids. This research would be ridiculous if instead of opioids the subject was high blood pressure medications Again methods focus on bias premise that opioids are bad and should be avoided at all costs when in reality they can be life saving medications for chronic pain patients. Why not include patient outcomes. Why else do this research if not focused on patient outcomes? Everything else is just to prove an agenda. Not valid research when you already have an agenda. None of the findings support patient outcomes. Just bias opioid policing and restrictions as the goal for this research. What are the implications for this research? Policing chronic pain patients? Intrude on their human right to adequate pain management? The implications of this tone in this research suggest bias and not real science. Bias against the use of opioids as medicine. No focus on patient outcomes. A paper written for draconian policing of essential medications for millions who would live in torment if not for these medications.	We agree that patient-centered outcomes, including quality of life and function are very important, especially for older adults. . We recommend more research on such outcomes. Several of the noted research needs emphasize the importance of conducting research to generate more evidence about patient-centered outcomes. The report includes a range of outcomes, including patient outcomes, such as quality of life and pain, but also harms.

Section	Commentator & Affiliation	Comment	Response
		Opioids used as medicine are not a problem. They are life saving drugs. Drug addiction and medicinal use of opioids are two separate issues Moderately. What is clear is the biased tone against opioid medication. They are unclear.	

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 10: Robert Rust	a. General Comments	When faced with clinical decision making in older patients, the clinical information regarding the effects of planned changes in medication available to the practictioner that acquired by his original education, ongoing education, and clinical experience, including consultation when appropriate. NO ONE else is in this unique position. Not any person. agency, or insurance company. CDC in its lack of wisdom developed guidelines which were misinterpreted and feared by providers. This has produced new providers who are fearful that their clinical decision making will be chastised, condemmed, or punished. The result has been new providers are fearful of treating pain, which new patients present with 40% of the time, especially to their primary care providers. Despite letters pointing out the misguided guidelines, by Dr. Heury and later the agency itself, recently trained providers are refusing to treat pain, referring to pain specialists, and under treating common pain issues out of fear. Agencies exist such as Boards of Medicine and other disciplinary bodies such as hospital staffs and physician employers to monitor and control physician behaviour regarding their opiate and other prescription habits. Allowing insurance agencies, especially Medicaid, to interfere with physician decision making on the basis of various “guidelines” is interfering with good patient care and harming patients. If AHRQ wishes to address issues regarding patient care, they should do so by utilizing educational opportunities, not by creating mandates that interfere with clinical decision making by providers of medical care, who best understand the needs of each patient. Would be happy to provide examples on request.	The goal of this report is to summarize the state of the evidence and to spur future research that will be of value to people in pain (who may need opioid treatment). AHRQ does not create any type of mandate for clinical practice or even recommendation (except regarding future research).

Public Reviewer 11: Anonymous	a. General Comments	am 65 years old I was put on "opioids since 1993 that is almost half my life! I was diagnosed with a incurable disease after three failed surgeries with the fourth surgery breaking before I was able to leave hospital, and the pain is unbearable! YET! the medical system had no care in the irreparable HARM done to me cutting my dosage in half after 28 years of taking exactly what I was prescribed three times a day for 365 days, for 28 years! at the most vulnerable time of this disease last phase! I have had to live my life in debilitating pain! for three years ABANDONED BY the medical system , my doctor of 32 years EVERYTHING! and YES! a weaker woman would have killed herself! OPIOID USE DISORDER - WHAT A INSULT!!! TO YOU AND THE WHOLE MEDICAL SYSTEM – THERE WAS NO "DISORDER" when I was prescribed this medicine, from a licensed doctor , a smiling pharmaceutical cashier, I never once ran out too soon, lost it , OR abused it.... in any way in the 28 years of taking it!! TO HAVE IT cut in half forcing my body into extreme pain for three years THAT IS ABUSE!!! I AM STILL GOING THRU ABUSE!! EXCEPT NOW MY DISEASE HAS SPREAD FURTHER DOWN MY SPINE AND ITS ATTACKING MY HEART _ YOU ALL SHOULD BE CHARGED WITH MURDER THE WAY YOU HAVE TREATED THE OLDER AGED PATIENTS IN THIS COUNTRY! ALL OF YOU PEOPLES METHODS TO THIS SADISTIC MADNESS IS SHAMEFUL, what kind of money and greed makes people do such horrid things to your own elders !!! May you all rest in hell with incurable painful diseases - with nothing and no help- from the very people you should be able to trust!! YOU say you have not enough patients to learn from as you turn a blind eye to all this suffering you have caused and	Thank you for your story. We are saddened that your pain and other issues have not been well-addressed. We are hopeful that the future research this report suggests can help people in your situation or situations that are like yours. As we suggest in the report, opioids should not be deprescribed without explicit consent from the patient, and any decision to reduce the dose of opioids or stop opioids should be made with the patient.

		still causing I was forced off of medicine that prevented my disease from getting worse! BUT DOCTORS do not want to risk their livelihoods by doing the right thing and deny being my doctor. I am abandoned by all doctors and left with NO HELP – I am being HARMED by the medical system that I trusted my life to ! AND No ONE will do anything to help me!! To deny morphine as a pain medication that helped, after having tried every known pain medication at the time, it worked without causing bad side effects after having a negative reaction to synthetic chemicals of other pain medications, without harming my liver and kidneys. BUT that is just why you created this crisis YOU WERE NOT MAKING ENOUGH MONEY FROM OLDER PEOPLE, FROM THEIR PAIN AND SUFFERING - THERE WERE NO SIDE EFFECTS YOU CAN MAKE MONEY OFF OF!!! Imagine living with a rare genetic bone disease that has no cure, the type of bone disease that turns your bones black, after eating away all the cartilage and cushions between them, Imagine having bones that grind against each other, causing excruciating and debilitating pain.Â Then Imagine the prescribed pain medication that effectively alleviated that pain for 28 years is abruptly cut down to a dosage that does nothing to stop the pain. Older adults deserve better than to be treated with such cold evil actions as to deny them the very medicines you got them dependent on, medicines that gave them the quality of life they deserve!! !! WHY..... because their kids stole it out their medicine cabinets and decided to misuse them!! YES VERY DIFFICULT - the horrible dis-information,and lies is very difficult to bear!	

Section	Commentator & Affiliation	Comment	Response
		THE ONLY CONCLUSION IS THIS COUNTRY CARES NOTHING FOR ITS ELDERLY AND ITS DISABLED PEOPLE! THE GREED THAT KEEPS YOU GOING WITH THESE REPORTS- IS BECAUSE "OPIOIDS" HAVE THE LEAST SIDE EFFECTS THAN OF EVERY OTHER SYNTHETIC NASTY PAIN MEDICINE YOU SELL- SO THEREFORE, YOU CAN'T MAKE ANY EXTRA MONEY OFF OF THE PAIN AND SUFFERING OF ELDERLY PEOPLE! IT IS ALWAYS ABOUT THE MONEY!!! GOD WILL MAKE YOU PAY AND NOT WITH THE MONEY YOU CARE SO MUCH ABOUT- ABOVE THE HEALTH OF OTHER HUMAN BEINGS! SHAME ON YOU ALL!!	

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 12: [Reviewer's name redacted due to inclusion of personal medical information]	a. General Comments	I am 72 years old and have been using pain meds, both Morphine and Oxycodone for 20 some years for pain. I have been on the same daily amount all that time and never have had to ask for more and my doctors are always asking me how I do so when all their other patients want to raise the amounts the take. The reason is, I never take it as an automatic dose, every 4 to 6 hours and only take it when the pain gets my attention. My pain levels depend on how many times I must transfer to and from my wheelchair so on quiet days, I don't need as much	Thank you for your story. You provide an excellent example of the fact that opioids can be used safely and (we hope, for your sake at least) effectively, even over the long-term. We have added the following statements to the "" section of the report in response to your story: "Related to goal-setting and shared decisionmaking is the need to identify how to best measure the outcomes of pain management that are of utmost importance to older adults. In particular, research on outcome measures that relate to older adults' goals of pain treatment could help to optimize opioid use and pain treatments more broadly. Some older adults have more severe pain at times when they must be more active or mobile (e.g., when they must transfer into or out of a wheelchair), yet few studies have examined outcomes like transfers or the ability to perform activities of daily living without pain. Such outcomes are essential for understanding when opioids might provide benefits that outweigh harms, and are important to older adults. More research is also necessary to understand the effectiveness of dosing strategies that maximize patient-centered outcomes; for example, research to understand the comparative effectiveness of taking opioids at times when more mobility or activity is necessary versus taking opioids at scheduled times regardless of activities of daily living or other activities that might increase the presence or severity of pain."

Section	Commentator & Affiliation	Comment	Response
Public Reviewer 13: Steve Ariens	a. General Comments	The treatment of all subjective diseases cannot be properly treated using some sort of "cookbook or checklist" type of therapy. There are so many variables to come to a final plan of treatment.. starting with BMI, CYP-450 enzyme opiate metabolism rate, single or multiple sites that is the genesis of the pt's pain and the condition itself can be a multiplying factor in the pt's pain level experience. While pain is a constant in these pts, the intensity of their pain can vary dramatically hour to hour .. day to day. Since studies indicated that 98%+ of chronic pain pts WILL NOT BECOME ADDICTED - this whole exercise is looking for and trying to solve a problem that does not exist	We agree. Research is needed to better be able to distinguish the majority who can safely treat their pain with opioids from the important minority who may suffer harms that negate or far outweigh any benefits.