Overview

The Stakeholder Review Group (SRG) represents a broad group of interested parties responsible for reviewing the full draft of the CDC Guideline and providing comments to improve the specificity, applicability, and implementability of the recommendations. In this group, there is representation from professional organizations that represent specialties by which opioids are commonly prescribed (e.g., obstetrics and gynecology, geriatrics, pain medicine, physical medicine and rehabilitation, and pediatrics). The group also includes representation from community stakeholders and advocacy organizations (e.g., pain management societies, societies representing patients with chronic pain, societies focused on responsible opioid prescribing).

Over the course of approximately two weeks, SRG members reviewed and submitted over 300 comments on the Guideline. CDC subject matter experts carefully reviewed each SRG comment individually and considered modifications to the guideline in response. Comments were then categorized into themes. Presented below is a summary of SRG comments, grouped by theme, with example comment excerpts listed to illustrate the theme. This summary captures the larger constructive themes of the SRG’s written comments, and is not inclusive of all the SRG comments received. Similarly, this summary captures the more substantive edits made to the guideline in response to stakeholder review and is not inclusive of all the edits made. The summary reflects edits made after all SRG comments were reviewed and feedback from CDC clearance reviewers on the revision was received. CDC thanks the members of the SRG for providing constructive comments that will improve the quality, credibility, and implementability of the recommendations for opioid prescribing.

Comments about Specific Recommendations

Determining when to initiate or continue opioids for chronic pain outside end-of-life care

1. Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider adding opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks.

Theme 1a: Reduced access
Questions about whether this will limit or reduce access to opioids for people for whom they are needed and effective, especially for those with specific conditions.

- This statement could be misinterpreted or misused in the context of patients with moderate to severe chronic pain not relieved by non-opioid treatments. This could include, for example, patients with sickle cell disease or blood cancers, both of which are treated by hematologists .... We suggest that statement 1 exclude these patient populations and refer to existing guidelines.
- We agree with the premise of this recommendation outside of end-of-life care, but believe that the management of cancer pain or other serious illnesses requiring palliative care (but not involving end-of-life care) should be distinguished.
- As presented, this recommendation may be interpreted as requiring a “fail first” approach. We ask that the CDC clarify that this is not the intent, especially for serious illnesses and conditions.

Theme 1b: Add interventional therapy
Recommendation should include interventional therapy for chronic pain.
Non-pharmacologic therapy and non-opioid pharmacologic therapy are alternatives for chronic pain, [organization] believes and evidence supports that Interventional Pain Medicine...should be included as an alternative to opioid therapy.

Interventional therapies for pain management may also provide another good alternative for non-pharmacologic pain management. However, interventional treatments are not mentioned in recommendation. We recommend inclusion of interventional therapies as a non-pharmacologic treatment for chronic pain.

Theme 1c: Limitations to non-pharmacologic/non-opioid pharmacologic therapy
Addresses barriers to non-pharmacologic therapy (e.g., cost, reimbursement, and access) or limitations and risks of non-opioid pharmacologic therapy (e.g., NSAID side effects).

- While it is true that nonsteroidal anti-inflammatory drugs (NSAIDs) can be helpful for mild-moderate musculoskeletal pain, the risks associated with both the acute and chronic use of these drugs should not be minimized. Much attention has been devoted to limiting the use of NSAIDs to the lowest dose for the shortest duration of time.
- Of concern is the harms of NSAID therapies which are well known, particularly serious GI bleed, perforation and obstruction. We recommend a careful assessment of harms of individual alternative treatments that might alter the risk/benefit ratio and thus decision making on the use of opioids in some patients.
- Cognitive behavioral therapy (CBT) is not always available, is time consuming and may not be appropriate for all chronic pain patients.
- Many non-pharmacological therapies, are not reimbursed by Medicaid, Medicare or third party payors. Support for such therapies in the guidelines might be useful for implementation of this recommendation.
- The evidence presented for the effectiveness of non-pharmacologic approaches focuses on cognitive behavioral therapy (CBT), exercise therapy, and integrative multimodal therapies. While some modest short terms effects are apparent, none of these studies are sufficient to conclude that such approaches can be widely implemented and are effective for long term use.
- I would agree with this recommendation, but the problem is that many of the health care providers have never been trained to apply therapies other than opioids or procedures for people with pain. It is the lack of education that has been partly responsible for this dilemma.

CDC Response
- CDC clarified that this guideline is intended to apply to patients aged ≥ 18 years with chronic pain outside of active cancer treatment, palliative care, and end-of-life care. In addition, given the challenges of management of painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute’s Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease. CDC added that additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking.
- CDC edited the rationale for the recommendation to indicate that interventional approaches such as arthrocentesis and intraarticular glucocorticoid injection for pain associated with rheumatoid arthritis or osteoarthritis and subacromial corticosteroid injection for rotator cuff disease can provide short-term improvement in pain and in function and can facilitate exercise therapy.
- CDC added that multimodal therapies and multidisciplinary biopsychosocial rehabilitation combining approaches (e.g., relaxation approaches with CBT or exercise) can improve long-term pain and disability compared with usual care and compared with physical treatments (e.g., exercise) alone. CDC also acknowledged barriers associated with alternative treatments, such as insurance coverage
for cognitive behavioral therapy or multimodal therapy, and recommended that combinations of therapies should be tailored depending on patient needs, cost, and convenience.

- CDC added information about the risks associated with non-opioid pharmacologic therapies (e.g., NSAIDs), particularly for older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease to the contextual evidence review and the recommendation rationale statement. CDC recommended that non-opioid pharmacologic therapies should be used only after assessment and determination that expected benefits outweigh the risks.

2. Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

Theme 2a: Details on meaningful improvement and risk
Requests additional details on meaningful improvement and risks/benefits.

- Little mention is made regarding how the above “outcomes” (pain and function) will be defined and who determines what and when the observed or measured changes are meaningful.
- While we agree with the concept of this recommendation, the CDC does not propose any method for monitoring and/or auditing if there is clinically meaningful improvement in pain and function. We highly recommend the development of measures to help enhance this recommendation.
- It is important to have a discussion with the patient to determine what is clinically meaningful improvement. In reality, there may always be some level of pain and the person with pain needs to understand this. It is important to engage that patient in determining a realistic sense of treatment goals and function as measuring success.
- If a patient is receiving clinically meaningful benefit from opioid therapy (say improved physical function) clinicians don’t have the tools to weigh formally this benefit versus the risk of harm that may accrue. It is important to translate the recommendation into something that is actionable for clinicians.

Theme 2b: Emphasis on pain and function
Function may not improve, so relief of pain may be sufficient in some cases.

- Many people with chronic pain have conditions that will not permit meaningful improvement in functioning. For those individuals, maintenance of functioning with improvement in pain is a valid clinical goal. Further, some patients may see a decline in function as their underlying condition progresses; here again, improvement in pain alone is an appropriate clinical goal. Throughout the guideline, an effort must be made to “decouple” pain from function, because they are not directly correlated with each other in all cases. There is concern that opioids need to improve both pain AND function in order to justify their use. Certainly this would be the goal. However in challenging chronic pain cases this may not be possible. If the benefits, whatever they may be, outweigh the risks then seemingly their use is justified. We recommend removing the word BOTH from the recommendation and changing the AND to an OR.

Theme 2c: Address barriers
Stresses need to address barriers to assessing meaningful improvement and cost-benefit.

- ...[C]linicians may not know how to operationalize the 2nd recommendation. If a patient is receiving clinically meaningful benefit from opioid therapy (say improved physical function) clinicians don’t
have the tools to weigh formally this benefit versus the risk of harm that may accrue. It is important to translate the recommendation into something that is actionable for clinicians.

- Unless you are in a pain clinic the doctor does not have enough time to do this in a practice setting. Often they will give printed info but this does not allow for questions. We must figure a way to compensate for this time.

**CDC response**

- CDC clarified that experts thought that goals should include improvement in both pain and function (and therefore in quality of life). However, there are some clinical circumstances under which improvement in pain without improvement in function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma.
- CDC is dedicated to developing translation documents and evidence-based tools that will be disseminated after guideline publication and available on the Injury Center website.

3. **Before starting and periodically during opioid therapy, providers should discuss with patients risks and realistic benefits of opioid therapy and patient and provider responsibilities for managing therapy.**

**Theme 3a: Address barriers**
Comments highlight importance of communication between provider/patient and realities of barriers that currently exist.

- Communication is the key to developing a good relationship with one’s health care provider. While I agree with the recommendation, I wonder how we are going to be able to provide the necessary time for the provider to have these conversations and still be reimbursed for their time.
- Unless you are in a pain clinic the doctor does not have enough time to do this in a practice setting. Often they will give printed info but this does not allow for questions. We must figure a way to compensate for this time.

**Theme 3b: Patient-centered approach**
Comments highlight importance of addressing individual patient’s treatment goals.

- We support this recommendation, but caution that the points of emphasis for implementing this recommendation must be done in a patient-centered way, on an individual basis, and in a manner that does not promote stigma or adversely affect the patient-physician relationship.
- Consider review of family history of substance use problems and opioid use/efficacy history.

**CDC Response**

- CDC edited the document to highlight barriers and added that policy initiatives that address barriers, such as reimbursable time for patient counseling, might likewise demonstrate efficacy in enhancing implementation of recommended practices.

**Opioid selection, dosage, duration, follow-up, and discontinuation**

4. **When starting opioid therapy, providers should prescribe short-acting opioids instead of extended-release/long-acting opioids.**

**Theme 4a: Patient-centered approach**
Comments stress importance of provider flexibility in decision-making for individual patient situations.

- Individual patient response due to polymorphism variability to opioid types.
• “Experts agreed that providers should not initiate opioid treatment with ER/LA opioids…” “ER/LA opioids should be reserved for severe, continuous pain.” This combination of statements leaves us wondering what a provider is to do if a patient presents for an initial visit with severe, continuous pain.
• When starting opioids therapy it is important to administer in the setting of a balanced approach that ensures use of other pain management strategies. This should be emphasized in this recommendation.

Theme 4b: Clarify co-prescribing issues
Comments request further clarity of issues arising from co-prescribing short-acting and extended-release/long-acting opioids.
• While [organization] supports this major change in current practice, this statement may create significant unintended risk for providers. In particular, there are cases where popular acetaminophen-containing short-acting opioid tablets are “maxed out,” thus the primary physician initiates a low dose ER/LA agents to allow for a perceived improvement in analgesia with a potential for reduction in the short acting agent, all the meanwhile daily MME is increasing as is tolerance, risk, dependence, etc. If left in the guidelines, the statement should be further reinforced with the rationale behind it, specifically, a reiteration of the increased risk and diminishing returns of such an approach in chronic, non-malignant pain. Stating such instances warrant heightened monitoring of risk and continued functional benefit may codify the intention of and rationale for this recommendation.
• Though we agree that in general the concomitant use of short acting opiates and ER/LA opiates should be avoided, this statement may create significant unintended risk for providers, and further evidence for this statement should be provided.

Theme 4c: Against short-acting opioids
Comments regarding efficacy of short-acting or similar/greater risks of extended-release/long-acting.
• We disagree with this recommendation. While we believe it to generally be true that initiation of opioid therapy with short-acting medication that permits dose titration is a good policy, it is not always safer, nor is it always appropriate. Patients with continuous, unremitting pain should not be forced to take more medication every 3-4 hours all day and night, when it is apparent that their pain will still be there when the previous dose wears off.
• “The clinical evidence review did not find evidence that continuous….” This statement cuts both ways. Clearly, if the evidence review found that using ER/LA opioids in this context was LESS effective or LESS safe, or that it INCREASED risk of misuse or addiction, the review would have stated this. As it is, with evidence that finds no difference, there is no support here for the recommendation.

Theme 4d: Provider education
Comments emphasize the need for education and tools for providers to minimize risk of implementing this recommendation, especially around certain types of opioids.
• Concerned about lack of education to providers who would qualify to provide this treatment. Will this not limit access to care? Again, education is needed for providers.
• In this recommendation I strongly recommend including an opioid dose conversion chart. Many opiates are prescribed in morphine dose equivalents that may cause toxicity in patients.
• We also note that this section raises considerable concern about the use of transdermal fentanyl. This may be an opportunity for the CDC to work with the FDA and others to help promote education for clinicians about fentanyl.
CDC Response

- CDC added information consistent with FDA guidance on use of ER/LA opioids. In particular, the FDA has noted that some ER/LA opioids are only appropriate for opioid-tolerant patients, defined as patients who have received certain dosages of opioids (e.g., 60 mg daily of oral morphine, 30 mg daily of oral oxycodone, or equianalgesic dosages of other opioids) for at least one week. ER/LA opioids should be reserved for severe, continuous pain and should only be considered for patients who have received immediate-release opioids daily for at least one week. When changing to an ER/LA opioid in a patient previously receiving a different short-acting opioid, providers should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance. CDC also clarified that while there might be situations in which clinicians need to prescribe short-acting and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to short-acting opioids by temporarily using lower dosages of both), in general, it is preferable to avoid use of short-acting opioids in combination with ER/LA opioids given potentially increased risk and diminishing returns of such an approach for chronic pain outside of end-of-life care. CDC also added information consistent with FDA guidance on abuse-deterrent formulations.

- CDC is dedicated to developing translation documents and evidence-based tools that will be disseminated after guideline publication and available on the Injury Center website (e.g., an MME calculator).

5. **When opioids are started, providers should prescribe the lowest possible effective dosage. Providers should implement additional precautions when increasing dosage to ≥ 50 MME/day and should avoid increasing dosages to ≥ 90 MME/day.**

Theme 5a: Comments specific to specific dosages referenced

Comments raised with regard to specific dosages and/or processes for deriving them.

- There are concerns that the numbers of 50 MME and 90 MME are arbitrary and not specifically supported by scientific evidence. The rationale for the recommendations states that these numbers came from contextual review and, primarily, expert opinion. Though we agree that in general these are good principles, however, precise dosing MME equivalencies may vary considerably among individual patients with divergent medical conditions, perhaps the language should be softened a bit.

- This is an extremely important recommendation. Common sense and a growing body of evidence shows that the harms of opioids are dose-dependent. A recent study not cited in your review observed that 3.8% of men and 2.2% of women receiving opioids at > 200 MME / day died of opioid-related causes (http://www.plosone.org/article/related/info:doi/10.1371/journal.pone.0134550).

- The reliance on expert opinion throughout this section, the existing multitude of state MME thresholds, and the absence of MME thresholds from the current product labeling for opioid analgesics coupled with a high degree of variability in patient responsiveness to opioids and uncertainty in morphine equivalent calculators, argue against establishing a bright line for clinical decision making based solely on this variable.

- We urge that this recommendation either be reconsidered in its entirety, or that the focus be redirected to encouraging use of the lowest possible effective dose, with any dose escalation based on clinical response and the existence of continued improvement in pain and function.

- We suggest that more oversight and follow up, or referral to a specialist, be used in the situations that exceed the 90 MME/day suggested in these guidelines, and recommend that the wording be restated as: “prescribers should be aware that risk of opioid-associated harm is greater with higher dose opioid therapy and should, therefore, carefully justify a decision to titration opioids beyond 90 MME/day”. However, it is important to point out that even this wording suggests that a “risk
“threshold” suggests at a particular dose. ... Careful justification of a decision to titrate up opioids should begin with 1mg MME (as with virtually all other drugs in medicine).

**CDC Response**
- CDC has clarified that providers should use caution when prescribing opioids at any dosage. Providers should implement additional precautions when increasing dosage to 50 mg/day or greater in morphine equivalents (MME), and should *generally avoid* increasing dosage to 90 MME per day or greater.

6. **Long-term opioid use often begins with treatment of acute pain.** When opioids are used for acute pain, providers should prescribe the lowest effective dose of short-acting opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery.

**Theme 6a: Comments on duration**

Comments specific to the reference of three or fewer days as usually sufficient for non-traumatic pain
- The short-term use of opioids for postsurgical pain is variable, not only depending upon the surgery, but the level of tolerance exhibited by the patient, i.e. whether they are opioid tolerant or currently utilizing chronic opioid therapy. In these cases, very often up to 7-10 days is acceptable.
- We agree generally with this recommendation although it is somewhat peripheral to the expressed purpose of the guideline — chronic pain.
- This recommendation seems to be primarily drawn from emergency department prescribing guidelines for non-traumatic non-surgical pain. There are numerous painful conditions that are non-traumatic and non-surgical that have more protracted courses (such as pancreatitis, renal colic, and sickle cell disease) that may often require longer duration treatment. Additionally, though specifically stated in the recommendation that the three day or less rule applies to non-traumatic and non-surgical pain, there is concern that physicians may misinterpret the guideline and inappropriately generalize the recommendation to all acute pain conditions.
- Excellent recommendation on danger of using ER/LA opioids for acute pain. Consider specifically stating the opioids so as to drive this point home...may want to state something specific about the dangers of such a practice related to specific ER/LA opioids and comment specifically regarding use of methadone as well. The re-evaluation recommendations will be hard for providers to accept as is due to resources, availability, etc...consider adding statement regarding follow-up meaning a variety of options (e.g. telemedicine, phone contacts, AP or nursing follow-up).
- Putting a timeframe of 3 days or fewer will greatly restrict highly trained professionals’ autonomy to make decisions that are best for some of their patients. We recommend taking out the 3 days or less and put in place a monitoring mechanism with measures that will then inform a standard of how many days should be appropriate for opioid use. Our reviewers are unclear what the evidence base is to recommend providing patients with 3 days of opioid therapy for acute pain. We recommend amending this to state that for the subset of patients who continue to manifest severe pain after 3 days that reassessment of the patient and consideration of extending the course of strong pain medication be considered.

**CDC Response**
- CDC clarified that three or fewer days will usually be sufficient for *most* non-traumatic pain not related to major surgery. CDC clarified that several guidelines on opioid prescribing for acute pain from the Emergency Department and other settings have recommended prescribing ≤ 3 days of opioids in most cases, while others have recommended <7 or <14 days.
CDC clarified that experts thought based on clinical experience regarding anticipated duration of pain severe enough to require an opioid that in most cases of acute pain not related to major surgery or trauma, three or fewer days' supply of opioids will be sufficient. For example, in one study of the prognostic course of acute low back pain (not associated with malignancies, infections, spondylarthropathies, fractures, or neurological signs) in a primary care setting, there was a large decrease in pain until the fourth day after treatment with paracetamol, with smaller decreases thereafter. Providers should consider a default of three or fewer days of opioids for acute pain and adjust the duration based on the circumstances of the pain syndrome.

7. Providers should evaluate patients within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation to assess benefits and harms of continued opioid therapy. Providers should evaluate patients receiving long-term opioid therapy every 3 months or more frequently for benefits and harms of continued opioid therapy. If benefits do not outweigh harms of continued opioid therapy, providers should work with patients to reduce opioid dosage and to discontinue opioids when possible.

Theme 7a: Patient-centered approach
Comments highlight the need to ensure consideration of individual patient needs and specific conditions.
- We have concerns about who and how pain and function will be defined and the natural history of function during disease progression or aging. Outcomes for pain and function should be tailored and patient-centered. They should not be solely based on population studies (i.e., 30% decrease in pain and 30% improvement of function) and should instead reflect what the patient and provider define as “clinically meaningful” improvements in these variables.
- We agree with the need to closely monitor patients during the onset of long term therapy or after dosage escalation, but defer to the various medical specialty societies in the stakeholder review panel to address the specific timeframes that comprise this recommendation.

Theme 7b: Resources on tapering
Provide resources on tapering therapy and more information on discontinuing opioids.
- When treatment benefits do not outweigh harms, it is sensible to alter treatment approaches. The consideration for tapering opioids needs to be done in the context of offering other strategies that may be useful to managing pain and reducing suffering. What is missing from this recommendation are other aspects of a balanced approach to pain management.
- Why is the use of buprenorphine to facilitate tapering—especially from higher doses—not even mentioned in this section. This is a glaring omission.
- Suggest including referral to detoxification specialist and/or clinic and evaluation for chemical dependency and opioid/substance use disorder in case of overdose coupled with signs of opioid use disorder or identification of certain other risk factors.

CDC Response
- CDC clarified that providers should maximize pain treatment with non-pharmacologic and non-opioid pharmacologic treatments as appropriate (see Recommendation 1), and consider pain specialty consultation as needed to assist with pain management.
- CDC edited the document in response to individual, specific SRG requests not reflected in the themes above. For example, CDC removed the phrase “when possible” after indicating that providers should work with patients to reduce opioid dosage, and clarified that at reassessment providers should identify if there are signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use).
8. **Before starting and periodically during continuation of opioid therapy, providers should evaluate risk factors for opioid-related harms. Providers should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid-related harms are present.**

**Theme 8a: Strengthen naloxone recommendation**

Strengthen recommendation of providing naloxone to mitigate risk for opioid-related harm.

- I am hoping that the word “consider” naloxone is changed to strongly recommend. It can save lives due to unintentional overdose and more.
- Should consider offering naloxone is a theme throughout these recommendations. I hope it become more than a consideration!
- We agree with this statement, although we believe you should consider extending the offer of naloxone to all patients prescribed opioids.

**Theme 8b: Address implementation**

Requests for the recommendation to address cost, reimbursement, and physician training.

- We agree with this recommendation. However, we would like to see specific guidance with regard to a number of issues relevant to implementation of this recommendation including insurance coverage, costs of training patients and caregivers, and reimbursement to providers who spend time educating and teaching patients and caregivers about naloxone.
- Given that these treatment recommendations are designed for use by primary care physicians we strongly recommend that further emphasis be placed on consulting substance use disorder specialists and pain specialists in individuals with active or recent past history of substance abuse.
- We strongly agree with the language presented in recommendation #8 as a prudent clinical approach, as well as the guidance offered on expanding the use of naloxone. Because the evidence review concludes that primary care physicians are not well equipped to assign risk profiles, commonly recommended screening instruments do not work, and physicians already have heightened concerns and misgivings about managing patients with chronic pain and prescribing opioid analgesics, additional clarity about implementing this recommendation is needed.

**Theme 8c: Consideration for special populations**

Provide additional guidance in this recommendation for special populations (e.g., older adults, children and adolescents, pregnant women).

- Patients over age 65 are at increased risk of both over treatment pain and under treatment of pain. The under treatment of pain in this population has been documented, and must be evaluated in the risk/benefit equation related to harms.
- Suggest comment related to lactation/nursing mothers and referral to lactation specialist with experience in opioid use during lactation. Comment that certain opioids have increased risks (codeine, etc.) whereas others are fine during breastfeeding (e.g. buprenorphine).
- We recommend adding another paragraph under Recommendation #8: “Children and Adolescents.” Young children are susceptible to unintentional ingestion, and adolescents commonly initiate nonmedical use of prescription opioids via family member or peer’s prescription, or their own prescription leftovers. Patients receiving opioid prescriptions should be instructed about secure storage to prevent theft and accidental ingestion, dissuaded from stockpiling old prescriptions, and directed to FDA and local resources for proper disposal of unused medicines.
- Although these recommendations are intended to focus on opioid therapy for pain management, their across-the-board statements discourage appropriate prescribing of opioids for pregnant women, limiting pregnant women’s access to care. Most notably, the statement that, “Providers should avoid initiating opioid therapy in pregnant women whenever possible given that opioid
therapy during pregnancy has been associated with stillbirth, poor fetal growth, neonatal abstinence syndrome, and birth defects,” is misleading and based on a contextual evidence review that misinterprets and miscommunicates the risks of appropriate opioid therapy during pregnancy.

CDC Response

- CDC clarified that providers and patients should together carefully weigh risks and benefits when making decisions about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, providers should discuss family planning and how chronic opioid use might affect any future pregnancy. For pregnant women already receiving opioids, providers should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (see Recommendation 12). Providers caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat NAS. Neonatal toxicity and death have been reported in breast-feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible in mothers who are breast feeding and if used, should be limited to the lowest possible dose and to a 4-day supply.
- CDC clarified that when providers ask patients about their drug and alcohol use, they can use simple questions. For example, the question “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?” (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview.
- CDC clarified that given that pain management in patients with substance use disorder can be complex, providers should consider consulting substance use disorder specialists and pain specialists regarding pain management for individuals with active or recent past history of substance abuse.
- CDC added that resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org/.

9. **Providers should review the patient’s history of controlled substance prescriptions using state PDMP data to determine whether the patient is receiving excessive opioid dosages or dangerous combinations that put him/her at high risk for overdose. Providers should review PDMP data when starting opioid therapy and periodically during long-term opioid therapy (ranging from every prescription to every 3 months).**

**Theme 9a: Support of PDMP Policy**

Recommendation should support national facilitation of state PDMPs (e.g., data sharing, national PDMP).
- PDMP data is felt to be extremely useful and across state line communication should be facilitated by a national task force and regulations that are conducive to appropriate controlled drug monitoring.
- There are some states with incredibly easy access (and mandated) to PDMP (e.g. New York). I think this paragraph overstates that sometimes the system is a bit burdensome. We need to fix the system and have a national PDMP that is readily accessible, quick and mandated (provider friendly like NY).

**Theme 9b: Emphasize other uses of PDMPs**

- Emphasize that the PDMP’s purpose is not solely to detect diversion or abuse/misuse.
- PDMP are effective in transitions of care – and this should be emphasized
**CDC Response**

- CDC has clarified ways in which PDMP data can be helpful beyond identification of risk. For example, PDMP data can be helpful when patient medication history is not otherwise available (e.g., patients from other locales) and when patients transition care to a new provider. CDC also added that policy initiatives that address barriers to implementation of the guidelines, such as accessibility of PDMP data, might likewise demonstrate efficacy in enhancing implementation of the recommended practices.

10. **Providers should use urine drug testing before starting opioids for chronic pain and consider urine drug testing at least annually in all patients on long-term opioid therapy to assess for prescribed medications as well as other controlled substances and illicit drugs.**

**Theme 10a: Frequency based on risk**

Revise recommendation to clarify that frequency of urine drug testing should be based on risk (e.g., increased risk=increased frequency/lower risk=lower frequency).

- Urine testing for high MME should be more frequent.
- The recommended frequency of at least annual urine testing seems very low compared to the intensity of many of the other recommendations especially given that urine drug testing is one of the only objective measures (aside from PDMP perhaps) of adherence to the medication being prescribed or risk for other use. Consider increasing the recommended frequency of testing to something more along the lines of frequency of visits.
- Urine testing can stigmatize patients unnecessarily. Recommend fewer tests in patients with 2-3 compliant urine tests.

**Theme 10b: Address barriers**

Comments address barriers to urine drug testing (e.g., cost, transportation, provider education).

- Agree with the routine UDT resulting in decrease stigma. No other area of medicine would we risk patient safety by overlooking as important a screening tool as the UDT. At the same time providers using these medication should be adequately educated in the interpretation of UDTing.
- We strongly agree that urine drug testing is a risk mitigation strategy that should be employed when designing treatment and monitoring strategies for patients on chronic opioid therapy. As previously mentioned, significant knowledge gaps exist regarding the use and interpretation of urine drug tests in primary care, as well as payment and reimbursement barriers.
- Providers frequently do not understand how to best use UDT; they often fail to understand the meaning of test reports they receive; they do not base their frequency of testing on risk stratification; and a very few engage in egregious over-testing for financial reasons. Meanwhile, patients are left holding the bag financially, because coverage for UDT in this setting is notoriously poor. Further, this recommendation treats UDT as an entity distinct from other risk mitigation strategies.

**CDC Response**

- CDC clarified that previous guidelines have recommended more frequent urine drug testing in patients thought to be at higher risk for substance use disorder. However, experts thought that predicting risk prior to urine drug testing is challenging and that currently available tools do not allow clinicians to reliably identify patients who are at low risk for substance use disorder.
- CDC highlighted barriers to urine drug testing and added that policy initiatives that address insurance coverage and appropriate urine drug testing might demonstrate efficacy in enhancing implementation of the recommended practices.
11. Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible.

**Theme 11a: Other drug classes**
Recommendation should include other classes of drugs, as well as alcohol, that increase risk when combined with opioids.

- We recommend that the wording be changed to be more inclusive of other CNS depressants. This is a critical recommendation, but it could be more strongly worded - specifically, that the co-prescribing of opioids and benzodiazepines is contraindicated. There are very good data to indicate that benzodiazepines increase the risk of respiratory depression and death from opioids, and they are often found together on postmortem toxicology. This recommendation should perhaps extend to other CNS depressants as well and should be made explicit (for example, mentioning “muscle relaxants”, gabapentin etc.). Finally, given its ubiquity, prescribers should explicitly inform patients of the risks of (and discourage use of) alcohol in patients receiving opioids.
- This recommendation should probably also apply to benzodiazepine receptor agonists such as barbiturates and carisoprodol. Text should be added to this effect.

**Theme 11b: Patient-centered approach**
Comments highlight the need to consider individual patient needs and specific conditions.

- We would favor adding an additional sentence to the recommendation, to the effect that, in cases where benzodiazepines are being considered for treatment of people taking opioids, a consultation and potential co-management with a mental health professional is recommended.
- We generally support this recommendation, however we prefer that the language be framed in a way that recognizes the clinical-decision making authority of the clinician, to read as follows: “Providers should avoid prescribing of opioid medication and benzodiazepines concurrently whenever possible, unless it is clinically indicated and required for optimal patient management.”

**CDC Response**

- CDC clarified that experts agreed that while there are circumstances when it might be appropriate to prescribe opioids to a patient receiving benzodiazepines (e.g., severe acute pain in a patient on long-term, stable low-dose benzodiazepine therapy), providers should avoid prescribing opioids for patients receiving benzodiazepines whenever possible. Because of greater risks of benzodiazepine withdrawal relative to opioid withdrawal, and because tapering opioids can be associated with anxiety, when patients require tapering of benzodiazepines and/or opioids to reduce risk of fatal respiratory depression, it might be safer and more practical to taper opioids first (see Recommendation 7). Providers should taper benzodiazepines gradually if discontinued because abrupt withdrawal can be associated with rebound anxiety, hallucinations, seizures, delirium tremens, and in rare cases, death (contextual evidence review). A commonly used tapering schedule that has been used safely and with moderate success is a reduction of the benzodiazepine dose by 25% every one to two weeks. CBT increases tapering success rates and might be particularly helpful for patients struggling with a benzodiazepine taper. If benzodiazepines prescribed for anxiety are tapered or discontinued, or if patients receiving opioids require treatment for anxiety, evidence-based psychotherapies (e.g., CBT) and/or specific anti-depressants or other non-benzodiazepine medications approved for anxiety should be offered.

12. Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder.

**Theme 12a: Address barriers**
Comments highlight the need to address barriers to treatment (e.g., access, cost, lack of primary care provider knowledge about treatment).

- Given that these treatment recommendations are designed for use by primary care physicians we strongly recommend that further emphasis be placed on consulting substance use disorder specialists and pain specialists regarding the treatment of individuals with active or recent past history of substance abuse.
- We support this recommendation. However, the ability of primary care physicians to “ensure that patients get treatment for opioid use disorder when needed” is severely constrained by a lack of access to treatment and numerous public and private payer policies that are based on a lack of understanding that addiction is a chronic brain disease.

Theme 12b: Clarify relevance
Clarify this recommendation as it relates to pain treatment.

- We also ask CDC to clarify if this recommendation is truly needed as it seems to relate more to directing people to the correct form of treatment for opioid use disorder than it does to the prescription of opioids for chronic pain.
- We find this recommendation difficult to understand. We believe it is trying to say that people with opioid use disorder should be referred for medication assisted treatment. If that is what it is trying to say, we agree. However, we also note that there is no reference whatsoever to the presence of pain in the patients being considered here. Thus, it is not clear if this is meant to refer to people with both pain and an opioid use disorder (OUD), or if it refers only to people with an OUD.

CDC Response

- CDC clarified that while identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Providers should continue to use non-pharmacologic and non-opioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider pain specialty consultation as needed to provide optimal pain management.

General Comments

13. Guidelines methods and evidence
Theme 13a: Evidence review and data
Comments about the scientific evidence and review process used to develop recommendations and potential limitations.

- The method of adjudicating both the clinical and contextual evidence is not clear. Our reviewers recommend more transparency in how the committee reviewed both sets of evidence.
- While clearly RCTs are the gold standard for medication efficacy studies, well-done, observational studies can provide needed longitudinal data in this area. The document seems to apply the GRADE approach to say that observational studies just by their methodology are low quality studies, potentially not discriminating between methodologically robust longitudinal studies and those that clearly are of low quality.
- There are also significant concerns regarding the quality of evidence upon which the 12 specific recommendations are made. In 5 cases recommendations are made in the setting of low quality of evidence and the remaining 7 recommendations are made in the setting of very low quality of evidence. Thus the “contextual evidence” and expert opinion really form the basis of these entire guidelines rather than scientific data. This unfortunately is the status of the literature and our scientific knowledge and it is certainly not the CDC’s fault that this data is lacking. However, it
should be recognized that interpretation of the “contextual evidence” is prone to bias as is the input of experts, (including our own).

- It also is not clear from the discussion whether the same efficacy standard for opioids (controlled trial of one-year duration) was required for evaluating the efficacy of non-pharmacologic and non-opioid pharmacological treatments. If not, then this significant limitation should be noted in the discussion.
- I wondered why the literature search did not look at some of the data for the period of time when we had the gold standard of multidisciplinary pain programs that actually allowed people to regain control of their pain and their life. We have lost the components of pain management that actually made a significant difference in individual lives as well as their families.
- There is concern that given the lack of scientific evidence for this review that there is an over reliance on the “contextual evidence”. There are not clear distinctions between patients with opioid use disorder and patients diverting drugs, from the compliant patients. Many of the conclusions from the “contextual evidence” in regard to morbidity and mortality at a societal level may be much less applicable to the compliant patient. Thus, the “contextual evidence” introduces a bias against the compliant patient with few medical or behavioral co-morbidities.

**Theme 13b: Reconciliation with other federal efforts**
Comments about how recommendations align with other federal agencies’ work.

- There are concerns that other federal institutions such as the FDA are not aligned with the guiding principles of this document—to provide appropriate pain care to patients while minimizing the use of opioids due to their inherent risks and seeming lack of efficacy for chronic pain. While the FDA mandate for abuse deterrent formulations is a positive step for patient safely, the real question regarding efficacy in various chronic pain conditions still remains unaddressed. Despite the "lack" of long-term evidence and mounting public health concerns, there have been more FDA approvals for opioids in the past five years than in the previous two decades. As part of the Federal Partner Engagement Process we would urge the CDC to communicate to the FDA that drug approval rates are outpacing the ability to demonstrate long-term efficacy and a disease-specific approach to opioid use will much better serve both public health and patient care.
- We recommend that the CDC’s efforts in this area be aligned with those of other federal partners, including the Office of National Drug Control Policy (ONDCP), the Interagency Pain Research Coordinating Committee and its National Pain Strategy, the National Institute on Drug Abuse, the Substance Abuse and Mental Health Services Administration, and the forthcoming initiative of the Department of Health and Human Services (HHS).

**Theme 13c: Comments about external review process**
Comments about scientific process used to engage partners and constituents.

- We have concerns that the attempts to solicit public input on the draft guidelines were cursory and did not allow adequate opportunity for thoughtful responses. While a public webinar was held to discuss the recommended guidelines, it was not well advertised and many interested parties were denied access because the webinar lacked sufficient capacity. Further, only a brief summary of each of the recommendations was shared, with no supporting documentation to provide evidence, context, or insight into the process. The public had 48 hours to comment, a rather abbreviated time period when compared to typical 30-90 day comment periods for similarly impactful proposed policies by the administration.
- “Development of clinical practice guidelines with public funding decreases the likelihood of conflicts of interest that can result in commercial influence and bias.” This is not necessarily true. The truth of this statement depends on who is selected to develop the guidelines, not the source of payment. Perhaps you should indicate that this was the INTENT of using public funding.
• [Organization] strongly supports opening up a formal public period to extend the same opportunity for review to other key stakeholders (including many state and specialty medical societies) that has been afforded to us and other designated stakeholder reviewers. The review process used to date by CDC, especially the public engagement webinars, has generated concern about lack of transparency.

• Given the limited and low-quality evidence on which the guidelines were based, the individual opinions of the Core Expert Group have the potential to significantly impact the nature of the guidelines. Broad stakeholder representation and robust conflict of interest protection, in theory, could mitigate biases in this group, or at the very least make them transparent. CDC indicates that it undertook an effort to discern conflicts of interest, but it is not clear that CDC fully accounted for intellectual and professional activities and relationships or developed an explicit strategy to mitigate biases.

• The distinct roles of CDC staff members and the Core Expert Group have not been made clear. According to the draft recommendation document, the Core Expert Group was not actually involved in writing the draft guideline; rather it was CDC staff who authored the draft. The Core Expert Group commented on the CDC-drafted recommendations, and no information was provided about whether and how the Core Expert Group’s input resulted in changes to the recommendations.

CDC Response

• CDC edited the document to further clarify that the core expert group reviewed written summaries of the scientific evidence (both the clinical and contextual evidence reviews conducted for this guideline) as well as the final guideline, and CDC reviewed the group members’ written comments and incorporated changes within the guideline document. CDC clarified that the federal partners provided written comments on the full guideline and CDC reviewed comments and incorporated changes within the guideline. CDC clarified that two webinars were hosted on September 16 and September 17, 2015 to provide information about the methodology for developing the guideline and present the key recommendations, that a fact sheet was posted on the CDC Injury Center website summarizing the guideline development process and clinical areas addressed in the guideline, with instruction on how to submit comments via email, and that CDC solicited comments during the webinar and for 2 days following the webinar, considered all comments submitted individually and carefully, and considered them when revising the guideline.

• CDC provided references to FDA guidance that relates to specific recommendations throughout the document (e.g., related to ER/LA opioids).

• CDC clarified the selection criteria for systematic reviews of the effectiveness of non-opioid pharmacologic and non-pharmacologic therapy and the duration of studies examining effectiveness.

• CDC added information about findings on the short-term effectiveness of opioids for pain from a 2009 evidence review.

• CDC edited the document to further explain the GRADE approach, and revised terminology to be consistent with other CDC efforts; specifically, terminology used within recommendations issued by the Advisory Committee for Immunization Practices (ACIP). ACIP uses the GRADE approach, with terms that better organize the level of evidence and strength of recommendations.

• In this guideline, using the ACIP GRADE approach, CDC clarified that the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence had in the effect of a clinical action on health outcomes. The categories include the following types of evidence:
  o Type 1 evidence: randomized controlled trials, or over-whelming evidence from observational studies; equivalent to “high” quality evidence;
  o Type 2 evidence: randomized controlled trials with important limitations, or exceptionally strong evidence from observational studies; equivalent to “moderate” quality evidence;
Type 3 evidence: observational studies, or randomized controlled trials with notable limitations; equivalent to “low” quality evidence; and

Type 4 evidence: clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations; equivalent to “very low” quality evidence.

The ACIP GRADE approach used in this guideline likewise presents recommendations in the following two categories:

- Category A recommendations: apply to all persons in a specified group and indicate that most patients should receive the recommended course of action (equivalent to a “strong” recommendation); and
- Category B recommendations: indicate that there should be individual decision making; different choices will be appropriate for different patients, such that providers must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (equivalent to a “weak” recommendation).

CDC clarified that Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs.

CDC also added that this guideline provides recommendations that are based on the best available evidence and informed by expert opinion. The clinical scientific evidence informing the recommendations is low in quality (primarily type 3 and type 4 evidence).

14. Implementation and dissemination

Theme 14a: Develop translation documents and evidence-based tools

Providers need practical tools to adopt guidelines, and practical guidance on when precautions should be taken (e.g., transition from acute to chronic pain).

- Very useful information for clinicians - ideally would be easily searchable by key clinical topic (e.g., location of type of pain, side effect) by clinicians to be used in real time to discuss with individual patients at point of care
- It is essential to provide guidance for operationalizing “before starting long-term opioid treatment” so that primary care clinic policies can be developed to monitor compliance with guideline recommendations. If left entirely to clinical judgment, research suggests that recommended precautions will often not be taken until patients have been using opioids for many months, if at all. We recommend supplementing the CDC guideline definition of initiation of long-term use (when the expected duration of acute treatment is exceeded) with specific guidance regarding when precautions should be completed, to guide clinic efforts to monitor quality of care. This does not obviate the need for precautions that need to be taken every time opioids are prescribed (e.g. checking the PDMP and advising patients of risks of overdose and addiction). We recommend “within 30 days of the initial opioid prescription” for purposes of monitoring quality of care.

Theme 14b: Reimbursement

Comments highlight need to address barriers to implementation, i.e. reimbursement deficiencies.

- First line of rationale should also say something about the amount of non-reimbursable time the PCP is expected to spend to accomplish many of the recommendations outlined. Without some changes in reimbursement the success of this would be limited to Pain clinic patients.
- Lack of evidence that payers will pay for alternative pain therapies when recommended.
- Acknowledge the potential need for additional copays by patients who initially receive a 3 day prescription then need to refill it. Consider adding talking points for providers to address this if patients request a larger number of pills, and consider mentioning how copay policies could help to address this.
CDC Response:

- CDC is dedicated to developing translation documents and evidence-based tools that will be disseminated after guideline publication and available on the Injury Center website.
- CDC edited the document to acknowledge that the transition from use of opioid therapy for acute pain to chronic pain is hard to predict and identify; however the guideline is intended to inform providers who are considering prescribing opioids for painful conditions that can become chronic. CDC clarified that because the line between acute pain and initial chronic pain is not always clear, it might be difficult for providers to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be significantly shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of initiation of opioid therapy for chronic pain. Providers often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for > 30 days are likely to represent initiation or continuation of long-term opioid therapy. Prior to writing an opioid prescription for > 30 days, providers should establish treatment goals with patients.
- In several places, CDC edited the document to highlight barriers as they relate to specific recommendations (e.g., reimbursement for non-pharmacologic therapies, urine drug testing), and added that policy initiatives that address barriers to implementation of the guidelines, such as accessibility of PDMP data, insurance coverage for non-pharmacologic treatments and appropriate urine drug testing, and reimbursable time for patient counseling might likewise demonstrate efficacy in enhancing implementation of the recommended practices.

15. Considerations for clinical decision-making and clinical care
Theme 15a: Patient-centered care
Take a patient-centered approach and consider specific medical conditions (e.g., cancer, sickle cell disease, rare pain disorders) and treatment disparities (e.g., race).

- Our reviewers appreciate the clarity in stating that the guidelines are not meant for providers delivering end-of-life care. What is not clear in the current document is where patients with advanced chronic illness fall, e.g., those who might benefit from or are currently receiving palliative care. Our reviewers recommend mentioning this as a limitation, as the risks and benefits of opioid use in this target population lie somewhere between end of life care patients and those seen in primary care.
- Patients who have cancer with chronic pain should be excluded from the guidelines (page 3, under scope and audience).
- Adequate management of pain associated with sickle cell disease (SCD), both acute and chronic, is an ongoing challenge for patients with SCD and for the clinicians that are responsible for their care. ...suggests that the exclusion of SCD patients be made more explicit, and not limited to acute pain from vaso-occlusive crisis.
- For each person the necessary combination of therapies and interventions will be different, based on individual need. Unlike traditional medicine where the “patient” is a passive participant, living a full life with pain requires that we take an active role in the recovery process.
- Our reviewers want to point out that aging and particularly those over age 75 may often present exceptions to the recommendations in this document. ... But there is little evidence presented by the CDC that patients in this age group, treated for “non-end of life”, chronic pain have experienced the high prevalence of opioid related deaths or substance use disorder compared to younger populations. The CDC analyses have added little evidence to identify or characterize lower risk individuals or populations for which the risk/benefit ratio might be different.
• The document needs to point out the possibility of inequitable chronic pain management based on race. There is some literature that suggests acute pain management has not been equitable.
• Whereas this document addresses patients who are 18 years and older, we recommend developing specific guidance to pediatricians and family practitioners who care for children with chronic pain.

CDC Response
• CDC clarified the scope of the guideline to indicate that this guideline is intended to apply to patients aged > 18 years with chronic pain outside of active cancer treatment, palliative care, and end-of-life care. In addition, given the challenges of management of painful complications of sickle cell disease, readers are referred to the NIH National Heart, Lung, and Blood Institute’s Evidence Based Management of Sickle Cell Disease Expert Panel Report for management of sickle cell disease. CDC added that additional research can inform the development of future guidelines for special populations that could not be adequately addressed in this guideline, such as children and adolescents, where evidence and guidance is needed but currently lacking.
• CDC clarified that the guideline offers recommendations rather than prescriptive standards; providers should consider the circumstances and unique needs of each patient.

16. Suggested content
   Theme 16a: Additional resources, data, and citations
   Suggested research studies, guidelines, and evidence for consideration.
   • Add links to additional resources, or to another report that describes other modalities for pain treatment such as Physical Therapy, ergonomic adjustments, icing, application of heat, to be used by clinicians in discussion with patients
   • It would also be helpful to have background or epidemiologic data on the scope of chronic pain in the US and the issue of inadequately treated pain.
   • Data on renal function decline with aging is old. These studies by Rowe and others have not been repeated since the 1980’s. Our reviewers recommend addressing this in the discussion as an area where additional research is needed.
   • ASAM white paper is a consensus tool available for review [re: urine drug screening]

   Theme 16b: Scope of guidelines should be expanded
   Suggestion that guidelines not be limited to primary care providers
   • Consider broadening the scope to any prescriber of opioids for chronic, non-end-of-life pain.
   • The scope of the targeted patient population is described as including those with current or past cancer diagnoses. Given that the focus of the guideline is to primary care providers, there seems to be a disconnect between target patient and provider populations. Patients with current cancer diagnoses typically do not receive prescription opioids from PCPs, so why does the guideline not extend to oncologists, surgeons, or pain management specialists? In addition, with overly broad diagnostic targets there is a significant risk that the disparities inadequate pain treatment that was well documented in the 1980’s and early 1990’s may recur. Finally, given that the pathology related to most cancer-associated pain is different from that of chronic non-cancer pain, it seems that combining approaches to all of these is mixing apples and oranges.
   • Expand the audience by changing the words 'primary care' to 'providers for patients who will be in an ambulatory setting' so that the broader audience of 'providers' suggested in the subsequent paragraphs is engaged in reading this important set of documents (for example, need to include certain medical and surgical specialties, trainees, urgent care providers, advanced practitioners who do not do primary care).

CDC Response
• CDC considered additional resources and references provided by stakeholders.
CDC clarified that some of the recommendations might be relevant for acute care settings or by other specialties, but use in these settings or by other specialists is not the focus of this guideline.

**Stakeholder Review Group**

American Academy of Neurology  
American Academy of Pain Management  
American Academy of Pain Medicine  
American Academy of Pediatrics  
American Academy of Physical Medicine and Rehabilitation  
American Cancer Society Cancer Action Network  
American Chronic Pain Association  
American College of Medical Toxicology  
American College of Obstetrics and Gynecology  
American Geriatrics Society  
American Hospital Association  
American Medical Association  
American Pain Society  
American Society of Addiction Medicine  
American Society of Anesthesiologists  
American Society of Hematology  
American Society of Interventional Pain Physicians  
Physicians for Responsible Opioid Prescribing