

Draft CDC Guideline for Prescribing Opioids for Chronic Pain, 2016: Summary of Peer Review Comments and CDC Response

Overview

Three peer reviewers were responsible for reviewing the full draft of the CDC Guideline and providing comments. Reviewers were asked to address the reasonableness of the recommendations, and the strength of the recommendations, based on evidence and expert opinion; the clarity with which scientific uncertainties are identified; and the rationale, importance, clarity, and ease of implementation of the recommendations. Peer reviewers were selected based on expertise and diversity of scientific viewpoints, while addressing conflict of interest concerns and ensuring independence from the guideline development process. Peer reviewers were selected who have high scientific standing; appropriate academic training and relevant experience; and proven scientific excellence in opioid prescribing, addiction, substance use disorder treatment, and pain management.

CDC reviewed all peer reviewer comments in their entirety. What is presented below is a summary of peer reviewer comments, grouped by topic, with comments listed for each. CDC also provides a response to reviewer comments; these responses were completed after all peer reviewer comments were reviewed and feedback from CDC clearance reviewers on the revision was received. Minor editorial suggestions made by peer reviewers are not reflected. Note that reviewers also mentioned general points of agreement on the clinical questions addressed, recommendation statements, ratings of quality of evidence and strength of the recommendation, the supporting rational statements, and potential for translation/dissemination materials. While these positive and reflective impressions are appreciated, the comments are not reflected in the summary below. CDC thanks the peer reviewers for providing constructive comments that will improve the quality, credibility, and implementability of the recommendations for opioid prescribing.

Overview, definitions, and framing

- Reviewers # 1, # 2, and # 3 made several suggestions for providing definitions and clearly framing the guideline (e.g., defining the scope of “outside of end-of-life care”; clarifying when recommendations applied outside of active cancer treatment; defining opioid use disorder early in the document; clarifying terms that could be considered jargon such as cost efficiency, grey literature; removing potentially stigmatizing terms).
 - CDC made edits to the document in several places within the rationale, scope, and recommendation statements clarifying that the recommendations do not apply to palliative care, end-of-life care, and patients in active cancer treatment. CDC also made edits to the document to clarify jargon and removing potentially stigmatizing terms.
- Reviewer # 2 requested clarity on the statistic presented about opioids being commonly prescribed, and whether the statistic reflected acute or chronic pain.
 - CDC clarified that an estimated 20% of patients presenting to physician offices with non-cancer pain symptoms or pain-related diagnoses (including acute and chronic pain) receive an opioid prescription; data are not available from the cited study on the percentage of patients presenting with acute pain compared to chronic pain that received opioid prescriptions.
- Reviewer # 2 requested clarity on how short-term efficacy of opioids for pain was measured in the cited studies.
 - CDC clarified that short-term efficacy was measured by improvements in both pain and function.

- Reviewer # 2 requested an indication of when prescribers might know that when they start prescribing for acute pain that it will become chronic pain.
 - CDC clarified 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 opioids for painful conditions that can or have become chronic.

Guideline development methods and evidence review

- Reviewer # 3 requested clarification on how low and high dose were defined in a cited study.
 - CDC clarified the definitions of low and high dose in the study cited.
- Reviewer # 3 requested clarification of how quality of evidence was characterized (e.g., differences between low and very low quality of evidence), and felt a stronger note of caution was needed that the recommendations are based on low quality evidence.
 - CDC clarified 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:
 - Type 1 evidence: randomized controlled trials, or over-whelming evidence from observational studies; equivalent to “high” quality evidence;
 - 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 clarified that the guideline provides recommendations that are based on the best available evidence and informed by expert opinion, and that the clinical scientific evidence informing the recommendations is low in quality (primarily type 3 and type 4 evidence).
- Reviewer # 3 requested clarification of terms used in tables, such as imprecision, inconsistency, limitations, etc., and when a study might have “no limitations”.
 - CDC refers to other GRADE publications for specific information for detailed definitions and methodological details of the approach. The full GRADE methodology is too extensive to completely summarize within the CDC guideline (a description of the approach has been described in multiple part journal series). CDC notes that ratings of imprecision, inconsistency, limitations, etc. in the GRADE table are based on GRADE quality assessment criteria, and that “no limitations”, for example, indicates that limitations assessed through the GRADE method were not identified.
- Reviewer # 2 wondered about the ability to address whether the overprescribing of opioids for acute pain can lead a patient’s acute pain to transition to chronic pain.
 - CDC did not identify specific evidence for the overprescribing of opioids for acute pain causing a transition to chronic pain.
- Reviewer # 2 requested clarification on the reasons for shifts from use of prescription opioids to heroin, such as availability and cost.
 - CDC clarified the findings of the cited study that there were other reasons identified by participants for switching beyond ease of use that includes cost and availability.

Recommendation 1

- Reviewer # 2 noted challenges of messaging potential harms of opioids to patients when short-term benefits might be achieved.
 - CDC will further address communication with patients within translation materials that accompany the guideline.
- Reviewer # 1 requested inclusion of patients with gastrointestinal disorders (such as inflammatory bowel disease, recurrent gastric or duodenal ulcers) in the list of patients potentially at increased risk associated with non-opioid pharmacologic therapies.
 - CDC included patients with gastrointestinal disorders as patients potentially at increased risk related to non-opioid pharmacologic therapies.

Recommendation 2

- Reviewer # 3 requested clarity on “meaningful improvements in pain and function” and circumstances when pain may improve yet function remains the same and treatment goals may not be realistically met.
 - CDC clarified that experts thought that goals should include improvement in both pain and function; 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).
- Reviewer # 3 reflected that there should be a stronger mention of inter-individual variability in treatment response.

- CDC clarified the evidence on what is known about treatment response; that is, based on systematic review, there is weak evidence for clinically significant improvement in chronic non-cancer pain among patients who do not discontinue opioids because of adverse effects or insufficient benefit.
- Reviewers # 2 and # 3 requested an acknowledgement that opioids are effective for some patients, with an understanding by Reviewer # 2 that it is challenging to identify who will benefit.
 - CDC clarified that some patients do experience clinically meaningful improvement from opioid therapy.
- Reviewer # 2 reflected on the reasonableness of the recommendation, indicating that it is challenging for providers to recognize when they are starting long-term opioid therapy for chronic pain (rather than opioid therapy for acute pain that might be continued if pain becomes chronic).
 - CDC highlighted in the recommendation rationale 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.
- Reviewer # 2 suggested inclusion of return to work as being limited by opioid therapy.
 - CDC is aware of studies showing an association between opioid therapy and decreased likelihood of return to work; however it was unclear how to modify the recommendation based on such studies. In the rationale statement, CDC noted that monitoring progress toward functional goals such as return to work can contribute to the assessment of functional improvement.

Recommendation 3

- Reviewer # 2 questioned whether use of opioid treatment agreements with a structured format would help clinicians have a more standard discussion.
 - CDC and the core expert group was concerned that making a strong recommendation to formalize documentation of the discussion might burden providers and be counter-productive, emphasizing completion of documents and signatures rather than meaningful discussions between providers and patients. Structured tools that providers can opt to use can be considered as part of implementation, however.
- Reviewer # 2 reflected on the implementability of the recommendation, given that some percentage of patients may desire continuation of therapy regardless of whether the therapy is working.
 - CDC believes that most patients will be able to fully participate in assessment of benefits and risks and decisions about continuing, changing, or stopping opioids; thus it is important that providers have meaningful conversations with their patients about benefits and risks.
- Reviewer # 1 suggested explaining that conditions such as headache, fibromyalgia, and non-specific low back pain are not improved and can be worsened when opioids are used.
 - The evidence review found limited or insufficient evidence for effectiveness of long-term opioid therapy for chronic pain, including for the conditions noted by the peer reviewer. It is now noted in

recommendation #1 that evidence is limited or insufficient for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain, headache, and fibromyalgia.

- Reviewer # 1 suggested adding consultation with pain specialists when there is uncertainty as to whether opioid therapy is appropriate.
 - Recommendation #3 is focused on communication with patients about the benefits and risks of opioid therapy rather than making a decision about whether to start opioid therapy; thus, no change was made. Consultation with pain specialists is noted within other recommendations when appropriate.
- Reviewer # 1 suggested referring to recommendation 8 (possible role of emergency naloxone) when discussing risks and managing opioid therapy with patients.
 - CDC included discussing naloxone use for overdose prevention, with a reference to recommendation #8, in the list of items that providers should discuss with patients.
- Reviewer # 3 requested including information about disposal of opioids.
 - CDC added a statement emphasizing the importance discussing with patients the storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids in the rationale supporting recommendation #3.

Recommendation 4

- Reviewer # 2 asked about inclusion of abuse-deterrent formulations and associated FDA requirements and guidance.
 - CDC clarified the evidence around abuse-deterrent formulations and associated FDA guidance.

Recommendation 5

- Reviewer # 3 recommended that providers should “generally” avoid ≥ 90 MME/day.
 - CDC edited the recommendation to specify that providers should implement 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.
- Reviewer # 1 recommended including FDA guidance on ER/LA opioids.
 - CDC added guidance consistent with FDA REMS to the rationale for recommendation #4.
- Reviewer # 1 recommended including guidance for providers who are seeing new patients that have already been prescribed long-term opioid therapy (e.g., how to have discussions about benefits and risks and tapering protocols).
 - CDC added guidance for providers who are seeing new patients that have already been prescribed long-term opioid therapy (e.g., patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages; providers should empathically review benefits and risks of continued opioid therapy and offer to work with the patient to taper opioids to safer dosages). CDC also includes information about this issue in the rationale for recommendation #7, and cross-references the discussion for readers.

Recommendation 6

- Reviewer # 2 reflected on the reasonableness of the recommendation, indicating that although it may be feasible in the emergency department and primary care, provider and patients may be frustrated with refill needs.
 - CDC and the core expert group acknowledges the barriers for implementation of this recommendation, however determined that the recommendation is reasonable. CDC clarified that providers should consider a default of three or fewer days, and adjust the duration based on the circumstances of the pain syndrome.
- Reviewer # 1 reflected agreement with prescribing as few doses as possible, but that the guidelines references are often emergency department guidelines, and the 3-day benchmark may not be a sufficient or practical interval due to concerns about access to pain care from lack of clinic appointment slots, weekends and holidays, limited transportation, travel after a non-traumatic pain condition, etc., and suggested that the recommendation be changed to 3-7 days.
 - CDC clarified the scope of the guidelines on acute pain and added the number of days recommended by other guidelines, with references. CDC also qualified that the recommendation applies to “most” non-traumatic pain not related to major surgery, and that providers should consider a default of three or fewer days, and adjust the duration based on the circumstances of the pain syndrome.
- Reviewer # 3 indicated a need for additional, separate acute pain guidelines.
 - CDC acknowledges the need for additional, separate acute pain guidelines.

Recommendation 7

- Reviewer # 3 suggested that more information be provided about how primary care providers could pragmatically conduct an assessment of the risks and benefits of opioid therapy and whether a tool is available.
 - CDC outlined the expert recommendations on how to assess risks and benefits in the supporting text of Recommendation 7, including specific circumstances warranting consideration of tapering/discontinuing opioids; however, unfortunately there is not a tool available that covers the full process of assessing risks and benefits that can be recommended within the guideline.
- Reviewer # 2 questioned reasonableness and barriers associated with frequent follow-up, such as reimbursement.
 - CDC recognizes the barriers of follow-up in the rationale supporting this recommendation; however the time frames recommended for follow-up were considered appropriate by CDC and the expert panel.

Recommendation 8

- Reviewer # 2 reflected that prescribing naloxone may be difficult to implement and questioned when it would be appropriate to prescribe – initially, or when risk factors present themselves, or when misuse develops.
 - Because risks for opioid-related harms, including development of misuse, might change over time and patients can benefit from risk mitigation strategies, CDC recommends that naloxone be offered when prescribing opioids to patients when factors become present that increase the risk of overdose (e.g., patients with a history of overdose or substance use disorder, patients taking

benzodiazepines with opioids, patients on higher dosages of opioids, and patients at risk for returning to a high dose to which they are no longer tolerant).

- Reviewer # 1 suggested including use of instruments to assess anxiety, depression, and PTSD given that psychological distress frequently interferes with improvement of pain and function.
 - CDC added that because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or anxiety might help providers improve overall pain treatment outcomes.

Recommendation 9

- Reviewer # 1 Suggested that review of PDMPs occur when embarking on long-term opioid therapy (not necessarily with initial prescription), and by all patients presenting to emergency rooms, urgent care clinics, and whenever admitted for in-patient hospital care; and that frequency should be based on measured risk.
 - CDC clarified that PDMP checks are recommended when prescribing opioid therapy for chronic pain, specifically. CDC does not recommend that PDMP checks are conducted based on patient risk because CDC and the core expert group judged that based on evidence, there are not reliable methods to predict individual patient risk.
- Reviewer # 1 reflected on the challenges of access to PDMPs across states and within the EHR.
 - CDC agrees there are challenges with access. CDC had indicated these challenges in the rationale supporting recommendation #9 and indicated that PDMP data be reviewed before every opioid prescription in all states with well-functioning PDMPs and where PDMP access policies make this practicable (e.g., provider and delegate access permitted). CDC recognized that such a practice is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), providers' ease of access in reviewing PDMP data is expected to improve. In the conclusions and future directions section, CDC added a statement indicating that policy initiatives that address barriers to implementation of the guidelines, such as accessibility of PDMP data, might demonstrate efficacy in enhancing implementation of the recommended practices.
- Reviewer # 1 suggested including information about when the PDMP information may be incorrect (e.g., if pharmacist entered in wrong name or birthdate, or patient uses nickname or maiden name, or provider misspells name on query).
 - CDC clarified examples of when the PDMP information may be incorrect as suggested by the reviewer.

Recommendation 10

- Reviewer # 3 mentioned barriers to implementation, such as insurance coverage for urine drug testing.
 - CDC edited the rationale statement for recommendation #10 to expand the discussion of barriers of urine drug testing, including insurance coverage. CDC has also mentioned in the conclusions and future directions that policy initiatives that address insurance coverage for appropriate urine drug testing could demonstrate efficacy in enhancing implementation.

- Reviewer # 3 asked whether evidence was available on provider confidence in using urine drug testing and rates of misinterpretation.
 - In the contextual evidence review, CDC added information about the proportion of providers using urine drug testing who could correctly answer questions about test results in research studies and included associated references.
- Reviewer # 2 questioned whether random urine drug testing would improve sensitivity for misuse and diversion. Reviewer #1 noted that some clinics obtain a urine specimen every visit, but only send it for testing on a random schedule.
 - CDC added that while random drug testing might destigmatize urine drug testing, experts thought that truly random testing was not feasible in clinical practice. CDC added that some clinics obtain a urine specimen every visit, but only send it for testing on a random schedule.
- Reviewer # 1 suggested consideration of drug testing based on measured risk or adherence to treatment, begun at or before 90 days of regular use, and with every refill for high risk or following any aberrancy.
 - CDC clarified that previous guidelines have recommended more frequent 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.
- Reviewer # 1 suggested adding other sedatives and alcohol as substances that can increase risk of overdose
 - There is insufficient evidence to add other sedatives, and the role of urine drug testing for alcohol is unclear; based on evidence and expert opinion, CDC did not include sedatives and alcohol as substances that can increase risk of overdose within the context of this recommendation focused on urine drug testing.
- Reviewer # 1 recommended adding information about costs of confirmatory urine drug testing that can provide a financial burden on patients, and clarifying that if unexpected results are found a conversation with the patient may yield a candid admission of why a substance is present, that would obviate need for expensive confirmatory testing.
 - CDC added that discussion with patients prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit.

Recommendation 11

- Reviewer # 1 suggested including a statement that opioids reduce lower esophageal sphincter pressure, and so increases risk of aspiration.
 - CDC did not include such a statement as it is unclear what weight this would be given as harm, and how it would affect the recommendation that providers should avoid prescribing opioid pain medication for patients receiving benzodiazepines.
- Reviewer # 1 recommended inclusion of delirium tremens as being associated with withdrawal from benzodiazepines.
 - CDC added delirium tremens as being associated with withdrawal from benzodiazepines.
- Reviewer # 1 suggested including a note that tapering of opioids provokes anxiety, so maintaining benzodiazepines at a stable dose during the opioid taper may facilitate the opioid taper.

- CDC added that 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.

Recommendation 12

- Reviewer # 1 recommended inclusion of methadone and buprenorphine in the top line recommendation statement to clarify evidence-based treatment.
 - CDC clarified that providers should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder.