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Thomas Frieden, MD, MPH
National Center for Injury Prevention and Control
Centers for Disease Control and Prevention
4770 Buford Highway NE.
Mailstop F-63
Atlanta, GA 30341

Re: Docket No. CDC-2015-0112; Proposed 2016 Guideline for Prescribing Opioids for Chronic Pain

Dear Dr. Frieden,

The American Academy of Pain Medicine (AAPM) is an interdisciplinary society of pain medicine. AAPM is committed to ensuring the safety, efficacy, and cost-effectiveness of patient care through evidence-based care, patient-centered research, public and professional education, and science-based policy. AAPM appreciates this opportunity to provide further input to the revised CDC draft guidelines regarding prescribing opioids for chronic noncancer pain. We acknowledge the many changes that have been made since the prior draft, reflecting active debate about a variety of concerns raised during review of the initial and revised draft guidelines. We continue, however, to support ongoing efforts to address persistent shortcomings in the current revised draft document. Towards that end, we now provide further general comments as well as specific recommendations regarding the language of the CDC guideline document.

General Comments:

In AAPM's initial correspondence regarding the guidelines (see italicized text below) we highlighted several areas of major concern. The first general concern is that in essence, the CDC guidelines appear to be focused upon societal risk mitigation in response to an epidemic of opioid misuse and abuse. They are not an evidence-based clinical practice guideline in the conventional sense, in which the clinical trial literature addressing a particular question is reviewed thoroughly and systematically to guide practice recommendations. Such an approach, relying upon the "best available evidence" was employed earlier by Dr. Chou, Dr. Ballantyne, and a distinguished group of clinicians and scientists in their 2009 systematic review of the same topic, sponsored by the American Academy of Pain Medicine and the American Pain Society.

Now, as a result of setting the threshold duration of clinical observations for efficacy and effectiveness so high that no studies met inclusion criteria for review in the current document, these same and other advisors have introduced negative bias that could lead to recommendations that adversely impact patient care. We are disappointed that despite our and others' raising this fundamental concern, no substantive changes have been made in the methodology that remedies the biases of the current draft guideline. We emphasize that a number of unbiased authoritative entities (e.g., Cochrane Collaboration, US Food and Drug Administration, International Conference on Harmonization) as well as the peer-reviewed medical literature have accepted evidence addressing the efficacy and effectiveness of opioid therapy based upon clinical trials lasting one year or less. Obviously, the practical and ethical difficulties surrounding prospective randomized trials of greater than a year's duration are such that none have been published. Our earlier comments (italicized below) remain relevant:

EVIDENCE REVIEW

There are very significant concerns regarding the methodology of the evidence review. This is highlighted by the fact that, without major changes in available peer reviewed high quality studies, the conclusions of this review are far different than a major review published in 2009 (Chou et al). Indeed the literature has evolved some; however it is felt that the political climate and attitudes of the lay press and other interests have significantly changed and in part influenced the methodology of this work. Raising the bar for study inclusion to one year for outcome reporting excluded a significant number of scientific studies. As detailed on page 3 of the manuscript, the scope of the guidelines are for treatment of pain lasting longer than three months. Eliminating data regarding efficacy between 3 months and 1 year then creates a very significant bias and constitutes a methodological flaw. This could be addressed by including literature in the evidence review reporting outcomes at three months or more, or revising the guideline scope to address opioid prescribing in patients with chronic pain of one year duration or more.

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. This is an important point in that, with publication of these guidelines, a new prescribing standard will be set. It will be set based upon indirect evidence and opinion. In general, the opinions seem sensible and consistent with quality health care delivery, however proper evidence based outcome studies across the spectrum of chronic pain conditions need to be developed and the future direction of any guideline should support and facilitate such an endeavor.

The current draft guidelines seek to reduce the public health risks related to opioid overdose and abuse; they are prepared by the Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control. AAPM fully concurs with the vital importance of reducing

public health risks related to opioid prescriptions; however, these guidelines must be appropriately balanced to ensure that the needs of patients in pain can be met. Chronic pain is a national healthcare crisis as well. Population-based epidemiologic investigations are not necessarily intended, nor are they sensitive, to detect subgroups for whom the benefit-to-harm ratio may differ from the population at large. In the current era of personalized, “precision” medicine, we should be mindful that some patients do well on chronic opioid therapy for noncancer pain, and conduct evidence reviews that seek to identify such subgroups.

In order to be more transparent about the methodological limitations of the guidelines we strongly recommend changes be made to language in the first “Summary” paragraph of the document. The paragraph currently reads:

“CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and recommendations are made on the basis of a systematic review of the scientific evidence while considering benefits and harms, values and preferences, and resource allocation.”

This sentence could be misleading, making it appear that recommendations were made on abundant good scientific information – which was not the case. Disappointingly, when multiple reviewers pointed out this discordance, the draft was revised such that its language became even more opaque, by substituting a numerical evidence rating scale for the previous clear wording.

The present summary paragraph of the draft document does not reflect 1) that data from studies less than one year outcome were not considered, 2) that the recommendations are made on weak or no scientific evidence, and 3) that the majority of the recommendations are simply recommendations from the core panel of experts assessing indirect “contextual evidence”. For clarity and transparency we would suggest adding language to this effect:

It should be noted that the scientific evidence for this review, in contrast to the 2009 systematic review of the same topic, excluded the entire clinical trial literature on efficacy and effectiveness because no such study assessed such outcomes for over one year of treatment. Thus, the quality of evidence informing the present recommendations is generally low. Consequently, the CDC guidelines process relied heavily on clinical opinion and judgment of a small group of panelists whose remit was to address public health issues related to opioid overutilization.

We strongly recommend that, as is customary for other systematic reviews, a sensitivity analysis be conducted and reported as part of the literature review to assess how the findings on efficacy and effectiveness would be altered by including literature describing clinical trials of varied durations.

Additional specific recommendations for revising the current draft guidelines follow.

Recommendation #5 currently reads

When opioids are started, providers should prescribe the lowest effective dosage. Providers should use caution when prescribing opioids at any dosage, should implement additional precautions when increasing dosage to ≥ 50 morphine milligram equivalents (MME)/day, and should generally avoid increasing dosage to ≥ 90 MME/ day (recommendation category: A, evidence type: 3).

Recommended change:

When opioids are started, providers should prescribe the lowest effective dosage. Providers should use caution when prescribing opioids at any dosage, and should implement additional precautions and monitoring when considering dose increases (recommendation category: A, evidence type: 3).

Then, in the nonbolded text following this specific recommendation, the draft guidelines could give examples (as it now does) of dosage thresholds proposed as demarcating lower from higher doses in this context, e.g., 90 MME/day. The current text in the draft guidelines in fact appropriately takes this approach to reviewing evidence for such thresholds and corresponding clinical decision-making.

Rationale:

We believe it is wrong to quote an arbitrary dose despite scientific evidence documenting individual genetic and environmental factors that produce variability of individual responses to opioid medications. This was the same conclusion reached by the US Food and Drug Administration (FDA) in its 2013 response to the Citizens' Petition requesting limits on routine opioid daily dose and duration of treatment. The detailed literature review and scientific analysis underlying that refusal were provided in detail in that FDA document.

Recommendation #6 currently reads

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 immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three or fewer days usually will be sufficient for most nontraumatic pain not related to major surgery (recommendation category: A, evidence type: 4).

Recommended change:

Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, providers should prescribe the lowest generally effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. The duration of severe pain varies depending on the individual's medical conditions but the need for

opioids rarely exceeds one to two weeks for most nontraumatic or nonsurgical pain (recommendation category: A, evidence type: 4).

Rationale:

The relatively brief time when an acute pain episode may require opioids is not adequate to undertake an “N-of-1” dose response titration to determine the minimally effective dose, particularly if level of pain intensity is fluctuating. For those patients who require an opioid for longer than three days, the additional copays and cost of returning to a physician for a follow up prescription would be burdensome. Other practical difficulties for many seeking to return to a physician's office include scheduling logistics or continuing acute pain. In our initial correspondence we made the following recommendation (see italicized text below) but it does not appear to have been taken into consideration. We continue to strongly recommend removing the last sentence of the recommendation "Three or fewer days will usually be sufficient for non-traumatic pain not related to surgery".

In our initial response we noted the following:

There is agreement that it is important not to over-prescribe opioids for acute pain. However there is substantial concern that the stated recommendation of “three or fewer days will usually be sufficient” is not accurate. 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 nontraumatic and nonsurgical 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. We recommend removing the last sentence of the recommendation ("Three or fewer days will usually be sufficient for non-traumatic pain not related to surgery").

In conclusion, we would like to reiterate our support for the CDC's goal to reduce unnecessary morbidity and mortality associated with the misuse and diversion of opioid analgesics. We note that nonopioid prescription and over-the-counter analgesics such as NSAIDs likewise have a substantial associated morbidity and mortality. While the proposed guidelines may in theory have a positive impact on some of the public health issues regarding opioid abuse, addiction, and overdose, there is also an obligation to protect the ability of physicians to meet the legitimate needs of their patients. There are concerns that other Federal institutions such as the FDA are not aligned with the guiding principles of this draft document. As part of the Federal Partner Engagement Process we would urge the CDC to strengthen its communication with the FDA if these draft guidelines move forward. We sincerely hope that the information provided will be used constructively to inform additional necessary revisions to the CDC document.