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Director
Centers for Disease Control and Prevention
1600 Clifton Road
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Dear Dr. Frieden:

On behalf of our physician and medical student members, the American Medical Association (AMA), the largest physician organization in the United States, appreciates the opportunity as a designated stakeholder to review and comment on the Centers for Disease Control and Prevention's (CDC) *Draft Guidelines for the Use of Opioids in Chronic Pain.* The AMA shares with CDC the goal of reducing the burden of harm from controlled substances, including opioid analgesics. The individual and family tragedies and societal costs attributable to opioid-related overdose, emergency department visits, deaths, and addiction are deeply concerning. To make meaningful progress in addressing these problems, a broad-based public health approach is required. This approach must balance the needs of pain patients with efforts to promote appropriate prescribing, reduce diversion and misuse, promote an understanding that substance use disorders are chronic conditions that respond to treatment, and expand access to treatment for individuals with substance use disorders.

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, 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). The HHS initiative is designed to work in a collaborative fashion with multiple stakeholders in the medical community including the AMA, American Dental Association, and American Osteopathic Association, as well as other medical specialty societies and state medical associations. Most recently, and in an effort to engage the physician community more directly in seeking solutions to opioid misuse and harm, we formed a Task Force of medical specialty society and state medical association partners to promote appropriate pain care, reduce opioid misuse and harm, expand the use of naloxone, and reduce the stigma commonly experienced by patients with chronic pain or substance use disorders. (www.ama-assn.org/go/endopioidabuse)

We offer general comments and concerns about the process for developing the guidelines, as well as specific comments on the recommendations, including suggested modifications. While the AMA broadly supports many of the recommendations, some are problematic. Our comments have been informed by internal review of the guidelines and accompanying evidence reviews, as well as comments and concerns that have been shared with us by AMA Task Force Members, patient groups, and individual patients following the CDC's public engagement webinar.

Review Process

The AMA 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. This sentiment is based on the very limited time allowed for public comment and the decisions to avoid answering questions or post the actual text of the draft recommendations for follow-up review. This approach is disappointing given the stature of the CDC as a public agency, the serious nature of the problem, and likely impact of specific guidance that may be released. While we understand the urgency of the situation and agree that the status quo is unacceptable, we recommend that additional opportunities for review and comment be offered.

The methodology description notes that the evidence for this process was built on systematic reviews conducted in 2009 and 2014, with an update to the 2014 review. What is not explained is that the inclusion criteria for efficacy studies was changed from a "best evidence" approach in 2009 to a requirement for a study duration of one year for the 2014 review, thereby eliminating virtually all of the controlled, opioid-based, efficacy studies. Given that chronic pain is defined as pain persisting for at least three months or beyond the expected time of tissue healing, this approach may introduce a selection bias regarding adverse events and harms.

Core Expert Panel

The AMA has great respect for the core mission and activities of the CDC that are designed to protect the health of the public. Individuals from a variety of disciplines and settings with specific expertise were chosen for the expert panel, a reflection of the challenges faced in trying to address this complex public health issue in a balanced fashion. The expert panel was charged with the most significant assignment in this process. It appears that only a limited number of clinicians who are actively managing chronic pain patients were included. While it is necessary to integrate various disciplines because of the complex nature of prescription drug misuse and addiction, the process may have been better served by constructing a more balanced panel that included clinicians from various medical specialty and practice settings representing a diverse set of views and experiences in treating chronic pain and limiting participation of individuals aligned with public policies that may have a predictable effect on the recommendations. This type of approach is even more important when the evidence-base is limited, thereby requiring a consensus-type approach and the use of "expert opinion."

The Target Audience

We generally agree that the target physician audience should be primary care, and that the guidelines should focus on chronic pain in patients 18 years of age and older. Several constituents believe that, in addition to chronic pain outside end-of-life care, the guidelines should not be applicable to patients with cancer pain and other patients with serious illnesses receiving palliative care. Many such patients suffer increased burdens of chronic pain (i.e., pain lasting longer than three months), but are not experiencing end-of-life care. The undertreatment of cancer pain was recognized more than 20 years ago with the development of a federal practice guideline by the Agency for Healthcare Research and Quality, formerly known as the Agency for Health Care Policy and Research (Management of cancer pain. Clinical guideline No. 9. *AHCPR Publication No. 94-0592*. Rockville, 1994). Opioids are recognized as drugs of

choice for moderate-to-severe cancer pain, and undertreatment of cancer pain is still prevalent (Greco MT et al. *J Clin Oncol.* 2014 Dec 20;32(36):4149-54).

The Patient

The guidelines and supporting discussion are devoid of a patient-centered view and any real acknowledgement or empathy of the problems chronic pain patients may face. Although population level data may be relied on to help construct clinical guidance, pain is an intensely personal and conscious experience influenced by emotion, cognition, memory, interpersonal and social context, and other factors. Patient-reported intensity of pain may not correlate with the magnitude or identifiable source of injury. Because objective tests for pain intensity (or even the presence or absence of pain) are still at a rudimentary stage of development, the best clinical approach in most circumstances is to assume that the patient is reporting a true experience. Accepting a patient's complaint of pain as valid does not require clinical identification of a physical cause, or demand the initiation of a specific treatment. It does, however, provide a foundation for assessment and the basis for developing an effective patient-physician dialogue and an approach to individualized, patient-centered treatment. Health disparities in pain management and legitimate access to opioid analgesics for acute pain remain evident, and clinically relevant differences in pain expression and responsiveness based on sex, race/ethnicity, and genetic constitution also exist.

Based on feedback from patient groups, patients suffering from chronic pain increasingly view themselves as collateral damage in efforts to restrict opioid prescribing decisions via state-based regulations and legislative mandates, and are fearful of the potential effect these guidelines may have on access for patients with legitimate medical needs. It is important that this not be an unintended consequence of this process.

Specific comments

As requested, specific comments have been embedded in the Excel Spreadsheet and submitted to CDC. They are reproduced here for the sake of clarity.

Recommendation #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.

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. Furthermore, broad-based, effective implementation would require large scale changes in the public and private payer communities and better evidence to inform the most effective non-pharmacologic approach for various chronic pain conditions. To say that "cost is an important consideration" is an understatement; payers currently do not adequately cover non-pharmacologic therapy. In addition, 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.

The evidence review concludes that "several non-pharmacologic and non-opioid pharmacological treatments have been shown to be effective in managing chronic pain." 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 term 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. It is not clear how many primary care clinicians are proficient in offering important non-pharmacologic approaches including mindfulness, focused imagery, biofeedback, relaxation, or CBT, which at its most comprehensive implementation requires a multidisciplinary approach performed by various experts. As previously noted, access to these treatments and reimbursement for them are inadequate, especially for multidisciplinary care (http://www.painmed.org/files/minimum-insurance-benefits-for-patients-with-chronic-pain.pdf). 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 (Alliance for Rational Use of NSAIDs; http://nsaidalliance.com). It also is not clear from the discussion whether the efficacy standard for the non-pharmacologic and non-opioid pharmacological treatments also required a one-year duration. If not, then this limitation should be noted in the discussion.

Therefore, we recommend the following revisions to Recommendation #1.

Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Providers should only consider ~~adding~~ using opioid therapy if expected benefits for both pain and function are anticipated to outweigh risks. In order to achieve this goal, public and private payer policies must be fundamentally altered and aligned in support. In addition, more evidence must be developed to inform clinical decision-making on the use of non-pharmacologic approaches, and more clinicians need to be trained in their effective use.

Recommendation #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.

While we generally support this recommendation, some situations exist where patients may have intractable pain and sufficient disability that functional improvement is not possible, and relief of pain and suffering is a supportable primary goal.

Recommendation #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.

We support this recommendation, but note 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.

Recommendation #4

When starting opioid therapy, providers should prescribe short-acting opioids instead of extended release/long-acting (ER/LA) opioids.

We support this recommendation. 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. The AMA stands ready to promote such education.

Recommendation #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.

This recommendation is in direct conflict with approved product labeling for the clinical use of opioid analgesics and the findings of the recent review by the Food and Drug Administration on this issue. A variety of prescriber behaviors, patient/user behaviors and characteristics, and environmental and systemic determinants exist that contribute to opioid overdose mortality. These factors may operate independently but interact in complex ways according to geography and population (King NB et al. *Am J Public Health*. 2014 Aug;104(8):e32-42). Accordingly, preventing additional opioid-related mortality will require interventions that address multiple determinants that are tailored to specific locations and populations.

While several states have enacted laws or regulations designed to modify clinical decision-making based on MMEs, analysis of the actual efficacy of these approaches and their effect on reducing overdose and pain management is lacking, including whether they may have unintended consequences (Ziegler SJ. *Pain Medicine*, 2015). In states that have adopted MME thresholds, prescribers appear to modify behavior to avoid specific sanctions and/or the need for additional action steps. The effects on patients have not been quantified. New data from Ohio, which has an 80 mg MME threshold, demonstrates that fewer high dose prescriptions were issued and the number of prescriptions was reduced overall, but death rates due to opioids, and in particular heroin, continued to rise. 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. This could be accomplished by revising recommendation #2 to read as follows:

Before starting long-term opioid therapy, providers should establish treatment goals with all patients, including realistic goals for pain and function. Providers should initiate opioid therapy with the lowest effective dose. Continued opioid therapy and/or dose escalation should occur only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.

Recommendation #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.

The three-day limit imposed by this recommendation seems to be arbitrary. If this recommendation is targeting post-surgical prescriptions, then an effort should be made to provide the supporting evidence base. The referenced clinical practice guidelines focus almost entirely on emergency department protocols or "bridge" prescriptions intended to allow the patient sufficient time to follow-up with their primary care provider, and not as a clinical recommendation based on anticipated healing time or duration of pain sufficient to require an opioid analgesic. However, we do strongly support messaging about the need to conservatively tailor the number of pills per prescription for acute pain. We believe this can be accomplished by modifying this recommendation to read as follows:

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~~ in a quantity ~~than~~ needed for the expected duration of pain severe enough to require opioids, and not based on prescriber or patient convenience. ~~Three or fewer days will usually be sufficient for non-traumatic pain not related to major surgery.~~

Recommendation #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.

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. We repeat our concern about using an MME threshold of ≥50 mg as a sole factor in triggering something as clinically significant as a tapering episode.

Recommendation #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.

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. The supporting text identifies patients with sleep-disordered breathing, pregnant women, and patients with renal or hepatic insufficiency, patients aged over 65 years, patients with mental health conditions and those receiving benzodiazepines, and patients with substance use disorder. Otherwise, providers are: 1) directed to ask patients about drug and alcohol use, use Prescription Drug Monitoring Program (PDMP) data and drug testing as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and/or overdose; 2) advised to counsel patients on increased risks of overdose when opioids are combined with other drugs or alcohol; and 3) directed to ensure that patients receive effective treatment for substance use disorders when needed. Significant knowledge gaps exist regarding the use and interpretation of urine testing, as well as payment barriers. It may be helpful to identify specific questions (or line of questioning) that would comprise adequate history taking for alcohol and drug use.

Recommendation #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.

We strongly agree with the need for physicians and other prescribers to register for and access their state-based PDMP when clinically appropriate. This is a primary goal of the AMA Task Force. We defer to the medical specialty society stakeholders to comment on the appropriate triggers for how often a PDMP should be consulted.

We appreciate that CDC recognizes the sometimes significant barriers to PDMPs being more widely used by physicians exist. The AMA has long advocated for reauthorization and full funding of The National All Schedules Prescription Electronic Reporting Act (NASPER), and we work regularly with state medical societies to advocate for stable funding streams for state PDMPs. Furthermore, we are pleased to see that CDC also recognizes that some patients may suffer unintended consequences by being discharged. Specifically, the AMA notes that CDC and several states have publicized decreases in the incidence of individuals who would qualify as "doctor shoppers." Data are lacking about the characteristics of these patients and concerns remain about what happens to them after they are identified. For example, some may be receiving multiple controlled substances from multiple providers because of fragmented care in need of coordination (e.g., Medicare Part D beneficiaries). Some are in need of treatment for an opioid use disorder, and some may be promptly discharged from the practice and be at risk for seeking illicit substances. While PDMPs can help identify patients receiving multiple prescriptions from multiple prescribers or dispensers, and this behavior is a risk factor for unintentional overdose, we believe the steps to be taken after identifying such individuals are much more complex and

require further research and attention. While it is an important variable to quantify, one should not be satisfied with concluding that PDMP data were used to reduce "doctor shopping."

Recommendation #10

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

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.

Recommendation #11

Providers should avoid prescribing of opioid pain medication and benzodiazepines concurrently whenever possible.

We generally support this recommendation; however, we would 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.

Recommendation #12

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

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. Accordingly, we urge that this recommendation be revised to read as follows:

Providers should offer or arrange evidence-based treatment (usually opioid agonist treatment in combination with behavioral therapies) for patients with opioid use disorder. In order to achieve this goal, more clinicians need to be trained in providing direct patient care for individuals with opioid use disorder, and government funding, as well as public and private payer policies, must be fundamentally altered and aligned in support of expanded access to treatment. In addition, efforts should be directed at reducing the stigma associated with substance use disorders and raising awareness that addiction is a chronic brain disease.

The AMA appreciates the opportunity to review and comment on this important issue. We sincerely hope that CDC will seize the opportunity to align itself with other ongoing efforts designed to foster a balanced, public health-based approach to improving pain management practices while minimizing the diversion of controlled substances, reducing unintentional overdoses and deaths from opioid analgesics, and supporting improved access to treatment for patients with substance use disorders.

Sincerely,

James L. Madara, MD

cc: Deborah Dowell, MD, MPH