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**Attn: Docket No. CDC-2022-0024**

Dear Dr. Jones:

We thank you for the opportunity to provide feedback on the 2022 Centers for Disease Control and Prevention’s Proposed Clinical Practice Guideline for Prescribing Opioids. The **National Pain Advocacy Center (NPAC)** is a 501(c)(3) nonprofit alliance of clinicians, scientists, public health experts, and people with lived experience of pain or addiction, working together to advance the health and human rights of people with pain. We take no pharmaceutical or industry funding and are currently funded by grants from Open Societies Foundation, the Ford Foundation, and individual donations.

NPAC shares the CDC’s goal of encouraging *appropriate* opioid prescribing: patients who require the use of opioid medication should not face barriers in obtaining that care, while those who can benefit from alternative therapies should have ready and affordable access to them.

But there are no short cuts to achieving that objective, a point illustrated by developments in the US since the CDC issued its 2016 Guideline. Opioid prescribing on a per capita basis has fallen to levels last seen in 1993, according to a 2021 Food and Drug Administration (FDA) presentation.1 In the 6 years since the CDC released the 2016 Guideline, total drug poisoning deaths have reached all-time highs, driven in large part by polysubstance use and a dangerous illicit street supply.2 And patients who require opioid medications, including those with cancer at the end of life,3 have faced mounting barriers getting medication and proper care.4 Recent research shows that roughly one-half of US primary care practices have shut their doors to any patient on prescription opioids,5 an unacceptable compromise of both safety and care for several million Americans, many with disabilities and chronic significant illnesses.

NPAC thus strongly endorses the CDC’s directive that pain care must be individualized, given the great variety in pain severity and type (inflammatory, neuropathic, etc.), and in the underlying conditions that give rise to it. To have practical effect, however, this imperative of an individualized, patient-centered approach to care *must* be integrated throughout the document. Currently, there exists a fundamental tension in the Guideline between generally-applicable recommendations and individualized care.

We further endorse the CDC’s warning that its Guideline should not be used as a basis of policy or applied as inflexible standards across patients or systems. However, a similar disclaimer was offered in the 2016 Guideline,6 without practical effect. Consequently, in 2019, the CDC was compelled to declare that its 2016 Guideline had been widely misapplied by policymakers in ways that harmed patients with pain.7 In light of this history, we strongly urge the Agency to draft its final Guideline with the full knowledge that policymakers *will* adopt, implement, and enforce the new Guideline strictly. Anticipating the potential pitfalls of future applications is essential, because this Guideline—with its vastly expanded scope—could well become a national mandate for the clinical management of virtually all pain.

NPAC’s feedback is summarized in brief, and then laid out in detail. In brief:

**We endorse**:

* The omission of arbitrary day and dosage thresholds from the 12 recommendations.
* The directive that pain care must always be individualized and patient-centered. This imperative should be affirmed in the implementation bullet points for *each recommendation*.

**We do not endorse**:

* A widely expanded “clinical practice” guideline developed with insufficient input from *practicing clinicians* that covers virtually all pain, but lacks a clinical discussion of pain, tools for its assessment and management, and a framework for weighing benefits and risks of treatments.
* Repeated reliance on MME thresholds throughout the text, which invites future misapplication.
* The exclusion of key studies on tapering risks, which include a three to fivefold increased risk of suicide or overdose, and the counsel not to reverse a taper once initiated.
* Treatment recommendations based solely on pain’s duration.
* Sweeping recommendations rooted in low quality evidence, selective omission of evidence, and poor transparency about evidence limitations.

Our comments address, in turn, Areas of Agreement with the proposed update; Our Top 5 Concerns; Additional Issues; the Urgent Need for Stakeholder Engagement; and Implementation.

1. *Areas of Agreement with the Proposed Guideline*

*1. Omission of supply and dose thresholds from the 12 recommendations*

**Recommendation**: **Any final Guideline should not contain arbitrary dose and duration thresholds, and the CDC should state clearly that the 2016 Guideline is no longer in effect**.

**Discussion**: When the 2016 Guideline was under development, many warned that its thresholds would be interpreted as mandates. These concerns proved correct: insurers, benefit plans, pharmacies, licensing boards, and law enforcement authorities widely adopted or applied supply or dose (Morphine Milligram Equivalent, or MME) thresholds as ceilings, or as the basis for criminal referral of clinicians to law enforcement.8,9 Moreover, 37 states passed laws applying these thresholds to at least one population.10

As a result, patients faced formidable hurdles in accessing care. Too many were subjected to dangerous opioid tapering or cessation practices that studies now show increase their risk of death,11 suffering, and mental health crisis.12-16 These forced dose reductions were often implemented because dose thresholds and dose reduction were wrongly seen as an easy path to patient safety.

Members of NPAC’s Community Leadership Council of people with lived experience of serious pain have directly endured these harms, as have the patients we hear from every day. These harms are ongoing; they continue to damage the lives and care of people with pain.

We thus appreciate the CDC’s recognition of these harms and strongly support the Agency’s decision to remove the two provisions that were most widely misapplied in the 2016 Guideline:

* + Day and/or supply limits
  + Dosage (MME) thresholds

If the Agency finalizes its proposal, it should rescind the 2016 Guideline and take additional steps to redress ongoing harm, as we discuss in part E., below.

*2. Importance of individualized, patient-centered care*

**Recommendation: The CDC’s directive that its recommendations should be applied in an individualized manner should be integrated into the implementation bullet points for *each recommendation*.**

**Discussion**: We strongly endorse the CDC’s directive that care must be individualized and patient-centered. The greatly expanded reach of the 2022 update to cover virtually all pain care makes this especially important. We endorse the CDC’s adoption of two bedrock principles of humane care. Namely:

* providers should rely on their clinical judgment and not on fixed directives, and
* providers should tailor care to the unique concerns presented by the patient in front of them.

It is vital, however, that this mandate be integrated across the Guideline and implementation instructions for *each recommendation*, because of the inherent conflict between generally-applicable recommendations and individualization.

1. *Our Top Five Concerns*
2. *Dramatic expansion of scope, absent relevant stakeholder input*

**Recommendation: Given the dramatically expanded scope of the proposed 2022 Guideline, the CDC must engage a much broader range of experts and solicit input from clinicians and patients likely to be most affected by its update.**

**Discussion**: In contrast to the 2016 Guideline’s focus on chronic pain and primary care clinicians, the 2022 draft revision covers acute, subacute and chronic pain, and declares itself a “clinical practice” guideline applicable to virtually all clinicians. The update is no longer, as its name suggests, simply about prescribing opioids. While the proposed Guideline adopts a binary opioid versus non-opioid approach, it surveys and recommends a wide range of treatments. For these reasons, the 2022 proposal sets itself up as a national blueprint for the clinical management of nearly all types of pain and painful conditions.

Given its reach and likely impact, we have two substantial concerns.

First, the Guideline catalogues a variety of treatments, but critically lacks both a discussion of the condition(s) being treated and a framework for clinical decision-making. This omission makes it anomalous among clinical practice guidelines. The draft fails adequately to define pain, or to outline appropriate standards for its assessment, or to suggest goals for its management. It counsels clinicians to weigh risks and benefits of treatments, without offering a framework for doing just that.

Perhaps because of its injury prevention focus, the document emphasizes risks – indeed, “risk” appears first in virtually all recommendations. But what of benefits? Both benefits and risks matter in the provision of medical treatment. Accordingly, how should each be measured? If improved function were to indicate benefit, which metrics should be used? On this matter, the draft Guideline offers no counsel whatsoever.

Second, this update defines itself as a “*clinical practice*” guideline, but it was not authored by *practicing clinicians* nor developed with significant input from them. The Guideline’s treatment of multimodal care illustrates the consequences of their absence. Aside from a brief paragraph, the Guideline suggests trying one treatment modality and then another, *i.e*., sequentially. But treating pain often involves a multimodal approach tailored to the patient. Another glaring omission is the lack of a framework for managing pain in the large population of Americans with disabilities and co-occurring conditions.

We respectfully question whether the CDC’s Injury Center possesses the requisite expertise to create a clinical practice guideline for the treatment of all pain. Moreover, we are troubled by the Agency’s zeal for expansion—at a time when the well-acknowledged harms of its previous effort have yet to be remediated, and especially when those harmed continue to suffer now, in real time.

While we strongly support redaction of the day and supply limits from the 2016 Guideline, NPAC cannot endorse the proposed 2022 update.

The best course of action, in our view, is for the CDC to issue a simple redaction of the day and dose limits from the 2016 Guideline’s topline recommendations for opioid treatment of chronic pain, while initiating a reassessment with input from a *much broader* array of relevant stakeholders, as we address in greater detail in part D., below.

We recognize, however, that the Agency is likely to proceed with the proposed document, and thus offer the following specific comments on it.

1. *Continued over-reliance on MMEs and dose thresholds*

**Recommendation: Rather than focus on specific dose thresholds that are likely to be interpreted as mandatory ceilings, the Guideline should explain that risks rise with increased prescription dosage, with the caveat that patients’ individual needs and circumstances are paramount.**

**Discussion**:While we strongly appreciate the CDC’s removal of dose thresholds from its topline recommendations, we remain troubled by the Agency’s over-reliance on Morphine Milligram Equivalents (MMEs), and its repeated references to concrete thresholds throughout the document.

A threshold of 50 MME appears in bold text and far more frequently in this draft than it did in the 2016 Guideline. Repeatedly specifying a particular threshold invites misapplication. Patients now reasonably to fear that, by lowering the key reference point from 90 to 50 MME, the 2022 update will cause new problems by forcing all patients below 50 MME, regardless of clinical indications, outcomes or prior dose history.

Evidence supports the Agency’s counsel to go slowly when elevating dosage and its conclusion that risks can rise at higher doses.17-19 But evidence from large studies does *not* support over-reliance on a single inflection point in dose,20,21 or even an emphasis on prescription dose as the main risk factor for drug poisoning.22 Crucially, most drug poisoning deaths among prescription recipients occur with a low prescribed dose, or after prescription stoppage.20,23 Further, the absolute risk of overdose in adherent patients remains low.21

As troubling, the validity and reliability of MMEs as a measure were described as poor in a 2021 Food and Drug Administration (FDA) Workshop,24 in part because MME calculations fail to account for well-established genetic variability in opioid metabolism,25 and in part because methods of dose computation produce widely variable results.26 Depending on the denominator, the same medication given at the same interval can have a daily MME that falls far above or below the 50 MME threshold, with significant implications for oversight and care.

In light of recognized harms associated with concrete dose thresholds, and severe limitations to the metric’s validity and reliability, we urge the Agency to abandon its reliance on MME thresholds.

1. *Exclusion of key evidence on tapering risks resulting in unsafe recommendations about tapering and its reversal*

**Recommendation: Box 1 of the Guideline should refer not simply to risks of “abrupt tapering” but to “any incentives by which payers, health care organizations, quality metric agencies, or other authorities reward or require discontinuation or tapering of opioids.”**

**Additionally, the CDC’s advice that a taper “should not be reversed” must be removed, as no evidence supports this proposition.**

**Discussion**: In a Guideline that focuses at length on opioid-related risks, most of the emerging literature on risks of opioid dose reduction is omitted, and when cited, is cited incorrectly.

To date, there are at least 11 studies finding adverse outcomes after opioid stoppage, dose reduction or dose variation. The outcomes include death by suicide and overdose,15,16,27 suicidal ideation,28 nonfatal overdose,12,29 mental health or substance-related crises,12,30 turning to illicit substances,31,32 and termination of care relationships.33 When studies show as much as a three to fivefold increased risk of suicide16 or overdose,29 or death,15 incorporating such evidence is both relevant and urgent.

Moreover, the draft Guideline implies that the risks of opioid reduction are limited to situations of abrupt reduction. Among the 11 studies cited above, different rates of dose reductions were associated with harm in at least three.12,16,29

Equally troubling is the CDC’s suggestion that it is improper to reverse tapers once initiated. To our knowledge, this proposition has never been subject to scientific study. Advising clinicians to ignore signs of harm or decline in their patients when risks include death is reckless and at odds with standard medical practice. Language should be modified to suggest that some adjustment time is often required before patients who may see benefits experience them. When patients suffer harm, reversal should be considered.

Finally, in the current draft, the CDC recommends transition to buprenorphine if tapering fails, referencing a sublingual dose, which is only possible with products formally approved by the FDA for the treatment of addiction. Because payors typically decline to cover off-label use of sublingual buprenorphine, this change to care will encourage imposition of false diagnoses and further breakdowns in care relationships.

1. *Focus on pain duration as the sole metric for recommended treatments (Recommendations 1 & 2)*

**Recommendation: The CDC should redraft Recommendation 1 to state, “nonopioids are effective for many common types of acute, subacute, and chronic pain,” and amend Recommendation 2 to advise that clinicians should discuss risks and benefits of opioids with patients *any* *time* they are initiated.**

**Discussion**: Recommendations 1 & 2 do essentially the same thing: both recommend use of nonopioid therapies. The problem is that they impose different standards based solely on pain duration.Equally problematic, only Recommendation 2, which currently addresses subacute and chronic pain, includes language counseling communication regarding risks and treatment goals with patients when opioids are prescribed. There is no such guidance for acute pain. This makes little sense, since opioid prescribing often begins with acute pain, and risks apply with use for acute pain.

Another problem is that Recommendation 1 focuses on the “effectiveness” of treatment, whereas Recommendation 2 deems nonopioids “preferred.”

Using payer terminology (“preferred”) is likely to result in the failure to cover of opioids (as “nonpreferred treatment”) even when the medication is indicated. Moreover, “preferred” is a statement of value – but of whose values?

We suggest instead that the Guideline apply “effectiveness” to all pain types. The CDC might also consider the approach taken in FDA labeling practice. For example, the FDA label for oxycodone states that the medication is for "management of pain severe enough to require an opioid analgesic and for which alternative treatments are *inadequate*."

The ideal guidance for clinicians who will be tasked with applying this Guideline and considering information in the FDA label is for the CDC to apply a primary standard of “effectiveness” to pain of all duration. The CDC should also direct clinicians to weigh treatments for their adequacy in addressing individual patient needs.

We also agree with the CDC’s appointed Opioid Work Group (OWG) 2021 that Recommendation 2 is too sweeping.34A category A designation is problematic because it suggests application across all patients, regardless of pain severity or underlying condition. In their publicly-available report, OWG members suggested both qualifying the recommendation and designating it category B, given the low evidence quality supporting it. Curiously, the CDC declined to accept the OWG recommendations and changed the evidence grade from a 3 to a 2, thus strengthening it, even in the absence of new evidence.

1. *Evidence omission and poor characterization of limitations*

**Recommendation: The Guideline should include a broader range of relevant evidence. It should be transparent about the limitations of evidence it relied upon: randomized controlled trials (RTCs) that typically include participants with one type of pain and few comorbidities.**

**Discussion**: The CDC’s decision not to include most of the studies on tapering risks, which we addressed above, reflects an overall pattern of selective evidence omission.

Among the studies it did survey, the CDC fails to outline the limitations of the evidence it presents. This omission is striking as such limitations are plainly stated in the Agency for Healthcare Research and Quality (AHRQ) reviews. Critically, the AHRQ reviews found ***no evidence of long-term efficacy for any intervention for treating pain*** of any kind. Yet, the Guideline only highlights such inefficacy regarding long-term opioid therapy.

Indeed, given the sparsity of evidence related to pain treatments and limited findings of efficacy across many treatment modalities, the Agency’s persistence in drawing an arbitrary line of over one year when assessing long-term efficacy of opioids—but no other treatment modality—

is highly problematic. Instead, it should lay out the evidence that exists and then identify that there are in the few trials lasting more than one year. The Agency should also be transparent about the reasons few such trials exist, which include the shorter durations of testing required for FDA drug approval, and the practical and ethical difficulties involved in long-term placebo-controlled RTCs with real, suffering people.35

Importantly, with most treatment modalities lacking long-term studies, the CDC should not imply that opioids are ineffective. Instead, it should provide an evidence-based framework through which practicing clinicians can effectively evaluate the benefits and risks of all treatments for their patients.

Yet, as in 2016, this update makes sweeping recommendations founded on limited evidence. Only one recommendation is supported by high-quality evidence.

Finally, the CDC should note the obvious limitations of most trials in the AHRQ reviews: the trials reflect patients with common conditions who consented to randomization. Persons with rare or severe diseases or concurrent morbidities were poorly represented in the trials, even though such individuals appear commonly in care and will disproportionately bear the costs of rigid Guideline application.

1. *Other Issues*
2. *Exemptions and exceptionalism*

**Recommendation: The CDC must draft its final Guideline with the understanding that its recommendations will, in fact, be applied to the patients it seeks to exempt.**

**Discussion**: The CDC’s 2016 Guideline exempted of patients with cancer, sickle cell disease and those in palliative and end-of-life care, but as the Agency acknowledged in 2019,7 the 2016 Guideline was applied equally to people with cancer and sickle cell disease. A major decline in use of prescribed opioids in cancer care was confirmed following the 2016 Guideline.3 If “bright line disease” categories have not been effectively exempted, then the CDC’s language exempting “palliative care,” which means different things to different parties, is likely to be meaningless as well.

While such exemptions have failed to protect patients, they also do real harm to how practitioners understand pain, insofar as exemptions send a signal to clinicians of whose pain is serious and whose is not. But just as one patient might have mild pain from skin cancer, another could suffer severe pain from a noncancer condition like multiple sclerosis. Guideline-declared exemptions foster exceptionalism and imply a hierarchy of deservingness.

1. *Lack of coverage for recommended therapies*

**Recommendation: The CDC must state prominently that patients should never be denied treatment when the therapies recommended by the Guideline are effectively unavailable to them**.

**Discussion**: We appreciate the CDC’s recognition that some of the non-opioid and non-pharmacologic treatments it recommends are poorly covered by payers. Still, by recommending modalities that are not available under some payers or in some areas of the country, the Guideline will only exacerbate existing disparities in pain care. While we strongly support broader coverage of a range of pain treatments, a practice shift takes time.

1. *Unwieldy format*

**Recommendation: The CDC should move its Box summarizing Recommendations to the beginning of the document, immediately following Box 1. Wherever possible, the CDC should deliver critical information in bulleted summations, early and up front.**

**Discussion**:The 200+ page format of the update renders the document unusable by frontline clinicians, who are likely to skim the recommendations and miss the often-buried information on how to apply those recommendations responsibly.

1. *The Urgent Need for Stakeholder Input*

**Recommendation: The CDC should solicit input from the full range of clinicians targeted by its updated Guideline. It should engage patients whose care will be affected, and re-activate its OWG to assist as it finalizes this draft and develops training modules and implementation tools.**

**Discussion**: For reasons outlined in our discussion of Guideline’s expanded scope, we urge the CDC to solicit much broader input from the full range of clinical professionals whose practices will be covered by its proposed update. This includes, among others, pain management specialists, emergency room providers and surgeons or hospitalists who prescribe for home use following discharge, primary care professionals, dentists, pharmacists, and, because exemptions are unlikely to be honored, oncologists, hematologists and palliative and hospice care providers, and the various medical and specialty societies that represent them. We do not regard the open register as fulfilling this obligation. Moreover, the CDC’s technical advisors and peer reviewers should be diverse, representative of all implicated health conditions and disciplines, and publicly disclosed. Information on conflict of interests for technical advisors and peer reviewers should also be publicly available.

While we appreciate the CDC’s effort to assemble its OWG, the OWG was only tasked with reviewing a preliminary draft of the published proposal, and was sunsetted long before its work was done. It should be reactivated and consulted as the Agency finalizes the Guideline and prepares implementation tools.

Once the Guideline is finalized, its impact as a lengthy document will likely come down to how the CDC summarizes its contents, and what the Agency includes in its communication efforts, training modules, and other implementation endeavors. Eliciting a variety of perspectives on the resulting documents and modules is an important safeguard against major misapplications going forward.

1. *Implementation and Undoing Harm*

**Recommendation: The CDC should take active steps in its implementation efforts to undo harms from its 2016 Guideline.**

**Discussion**: While we appreciate the Agency’s recognition of harms from the 2016 Guideline, acknowledgment alone is insufficient. The CDC acknowledged these harms in 2019, yet patients continue to experience them. Likewise, admonishing clinicians not to abandon their patients will do little unless the reasons for abandonment remain unaddressed.

The CDC should take affirmative steps to undo past harms in its implementation efforts. It should underscore in unmistakable terms to clinicians, health systems, insurance companies, and government entities that individualized pain care is paramount. In addition, it should meet with lawmakers, federal agencies such as the Drug Enforcement Agency, the Center for Medicare and Medicaid Services and others to make abundantly clear its decision to abandon thresholds because of the harms that resulted when policymakers embraced them–and to pointedly discourage the imposition of any blanket or one-size-fits-all prescribing thresholds or practices.

**In conclusion, we urge the CDC to recognize that simply measuring success in terms of gross reductions in overall opioid prescribing, without considering outcomes, has proven problematic. Known outcomes matter. These include increased pain and suffering, mounting barriers to care, and escalating drug overdose deaths. We also urge the CDC to recognize that pain and its management are complex. Given the real harms perpetrated in the wake of the Agency’s 2016 Guideline, preventing future misapplication of this far more ambitious revision will require several corrective steps with which we are ready to assist.**

We thank you for your consideration,

Kate M. Nicholson

Kate M. Nicholson, JD

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