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Oversight on Revision of US CDC Opioid Guidelines: A Process Pre-Destined to Fail

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ABSTRACT

In December 2019, the US Centers for Disease Control and Prevention (CDC) announced their intention to review and revise their 2016 Guideline on Prescription of Opioids to Adults. As part of this revision, CDC solicited nominations for an advisory "Opioid Workgroup" to report to the Board of Scientific Counselors of the National Center for Injury Prevention and Control.

This paper offers a critical review of concerns identified in the final Workgroup report of July 2021, as contrasted against the revised and expanded guidelines published 16 months later in November 2022. The author finds that although the Workgroup was tasked to identify substantive issues, its input to the CDC was largely marginalized or ignored in the revised guidelines. The workgroup also failed to reach consensus on central issues of methodology, which should disqualify the CDC guidelines as a de factor standard of clinical practice. Arguably, the CDC should be removed from all further participation in development of public policy for the treatment of severe pain.

Keywords

Guidelines, Opioid, Workgroup.

Introduction

In March 2016, the US Centers for Disease Control and Prevention (CDC) published guidelines for prescription of opioid pain relievers to adults with severe chronic pain [1]. These guidelines almost immediately became controversial as they were taken up by multiple States as a de facto mandatory standard of clinical care, prompting legislation restricting patient access or limiting dose and duration of opioid pain relievers [2].

Some clinicians immediately spoke out against the guidelines, deeming them "neat, plausible, and generally wrong" [3,4]. Also of great concern was the non-consensual tapering of legacy patients to ineffective dose levels below the 50 Morphine Milligram Equivalent Daily Dose threshold declared by the guidelines [5].

In early 2019, the high volume of this criticism finally forced US CDC to release a disclaimer, advising that their prescribing guidelines were never intended to become an inflexible "practice standard" made mandatory under State laws [6,7]. On December 4-5, 2019, CDC announced its intention to revise and reissue the guidelines. They likewise announced formation of an advisory "Opioid Workgroup" that would independently evaluate proposed changes to the guidelines. Clinical professionals and others were invited to nominate themselves by February 22, 2020 [8]. However, it is unclear who within CDC validated their credentials or what selection biases may have operated in the confirmation process.

As originally conceived, the revision process was expected to last only one year. However, publication of Workgroup terms of reference did not occur until July 6, 2020 [9]. Both the revisions and the Workgroup review dragged on into 2021.

In minutes of the February 2021 meeting of the Workgroup and the Board of Scientific Advisors (BSC) of the National Center for Injury Prevention and Control (NCIPC), two members of the Workgroup – Dr Elizabeth B Habermann and Dr Frank Floyd -- wrote to express several concerns [10]:

- As of February 2021, the Workgroup had met only three times and future meetings were scheduled quarterly. It was felt that the volume of work needed should justify at least monthly meetings.
- The CDC work plan as of February 2021 would have delayed publication of proposed updates to the guidelines until 2022. As noted in their letter [10].

"This is an unacceptable time period for the millions of patients who suffer long-term, chronic, and high-impact pain. Millions of these patients, who benefit from long-term opioid therapy, have been immensely harmed by the misapplication of the Guidelines and disruption of their care…"

"Last, we object to the manner in which the public comment period was conducted. Most attendees who waited patiently throughout the day-long meeting to give their comments were unable to do so due to technical difficulties and/or lack of instructions regarding the methods required to unmute and give comment. In addition, multiple members of the Workgroup appeared uninterested, unengaged, or absent from the public comment period."

Dr. Floyd and Dr. Habermann requested that the Workgroup take several actions:

- Restructure the review schedule for monthly meetings.
- Practice transparency and provide regular updates to the public and health care professionals regarding both scope and evidence for the revised Guideline.
- Schedule an open public comment period no shorter than one hour to allow all those who had registered or requested to give comments.

Some of these concerns were at least partially addressed. The Workgroup met more often and generated a summary of its findings on July 2, 2021, to support a public meeting of the NCIPC Board of Scientific Counselors on July 16, 2021 [11]. 1016 pages of minutes of this meeting were published in November 2021 [12]. Many respondents expressed dissatisfaction with the content of the then-draft CDC guidelines and the technical difficulties that led to many of those registered for the meeting being unable to speak.

Fair disclosure

The author was among those who protested the process and content of the Workgroup meeting in its minutes. He submitted three substantive papers totaling 38 pages and ~40 references:

1. A review of highlights of the meeting itself (5600 words, 18 references)
2. First-round comments on AHRQ Comparative Outcomes Review 240, "Treatments for Acute Pain [13,14]".
3. Second-round comments on COR 240, titled: "Methodological Errors in "Treatments for Acute Pain – A Systematic Review (AHRQ)" [14,15]. The comments were directed as a multiple-author letter to the Director of AHRQ, calling into question "the scientific and ethical integrity of multiple AHRQ reports in which Dr Roger Chou has been the principal author. The issues involved include unacknowledged bias, technical and methodological errors, cherry-picking of data and over-generalization of findings, and failures of public transparency in AHRQ internal review processes" [15].

Insofar as a reading of the November 2022 CDC opioid guidelines can reveal, none of the material noted immediately above was considered pertinent by CDC guideline writers – if it was read at all. The methodological errors identified to AHRQ were not addressed in the published guidelines. On February 10, 2022, CDC announced a three month public review and comment period for draft guidelines in the Federal Register. About 5500 comments were received. CDC characterized the review in the following terms.

"CDC carefully catalogued, reviewed, and qualitatively analyzed all comments submitted by members of the public. All public comments were carefully reviewed and considered when revising the Clinical Practice Guideline. Public comments included patient, family, friend, and caregiver experiences; considerations for recommendation statements; concerns about implementation and misapplication of the 2016 Guideline; suggestions for implementation of the 2022 Clinical Practice Guideline; concerns about access and barriers to pain care; and suggestions for scientific articles about acute and chronic pain management" [12]. Still to be determined,
however, is whether CDC guideline writers substantively embraced the feedback they got from these multiple sources, in their final publication of November 2022. There are strong indications that they did not.

Discussion

In its July 2021 summary of findings [11], the BSC Opioid Workgroup identified significant issues in the then-current draft updated guidelines. Members of the Workgroup were not unanimous concerning the impact of these findings. Thus, we often read phrases like "many workgroup members were" or "some workgroup members felt".

Overarching general themes sounded in the Workgroup report included the following:

"Overall, many workgroup members felt that much of the supporting text of the guideline was not balanced and was missing key studies. Many workgroup members felt that the guideline focused heavily on the risks or potential harms of opioids, while less attention was focused on the potential benefits of opioids, or the risk of not taking opioids or undertreating pain. In addition, some workgroup members felt that the language of the recommendation statements or supporting text conveyed more certainty or was more absolute than warranted by the evidence."

Author's Observation

This lack of balance was carried into the November 2022 revised guidelines. The term "risk" appears nearly 500 times in the revised document, while "benefit" appears 195 times [16].

Again **from the Workgroup:**
"Much of the discussion of the recommendations centered around the concern for misapplication of the guideline. Because of the consequences of misapplication of the 2016 guideline, many workgroup members were concerned about how the recommendation could be misapplied, leading to potential harm to patients. The workgroup discussion thus focused on how best to mitigate against this valid concern while preserving the benefits of the guideline. However, some were concerned that the workgroup may have been over-correcting and so much concern about future misapplication could potentially be detrimental to the greater good."

Author's Observation
In light of the damage done by the CDC guidelines of 2016 – and acknowledged in the revised guidelines of 2022 – it is hard to underestimate the potential for further damage created by the update [17-20].

Again from the Workgroup:
"Many workgroup members were cautious about including specific opioid dose thresholds in the recommendations. Workgroup members acknowledged the importance of having benchmarks, but many felt that specific opioid doses would be misapplied as absolute cutoffs or thresholds for policies or practices. Many workgroup members felt the specific opioid dose thresholds belonged in the supporting text where the discussion could be more nuanced. In addition, there is no single standard formula for calculating MMEs"

Author's Observation
Placement of MME thresholds in supporting text rather than in summary level recommendations is a distinction without a difference, still intended to discourage high-dose prescribing. As published, the revised CDC guidelines refer to "50 MMED" 24 times, and to "90 MMED" 4 times, primarily in a context of asserting that there is a threshold of "diminishing returns" for opioid dose levels. However, such thresholds are directly contradicted by multiple sources in clinical literature [21-25].

From the Workgroup:
"Many workgroup members felt that the recommendation category A [recommendations deemed applicable to all patients] was overutilized (11 of the 12 statements had recommendation category A). Members felt that this type of grading likely contributed to the misapplication of the 2016 guideline."

Author's Observation
The number of Category A recommendations was reduced from 11 to 7 in the revised guidelines. However recommendations to which Category A was applied included a naïve preference for non-opioid therapies – reinforcing the overall anti-opioid bias of the document [26,27]. The Workgroup also identified issues for each of the twelve guideline recommendations (short-form summary titles are provided by the author in brackets).

Recommendation #1 [non-opioid therapies preferred in acute pain)]

From the Workgroup:
"There was particular concern about limited access to non-opioid pain management modalities, in part due to lack of availability or lack of coverage by payers. Improving access to non-opioid pain management modalities should be a priority."

Author's Observation
Issues involved are significantly larger than "availability" -- a point that the Workgroup seems to have missed or deemphasized in its report. CDC writers and reviewers ignored fundamental realities in the medical trials literature. A careful reading of AHRQ Outcomes Review 220 reveals that its abstract is not supported by data documented in its appendices and tables [26,27].

1. No published trials were found that directly compared outcomes of opioid therapy against outcomes from use of "alternative" or "non-invasive" therapies like massage, acupuncture, cognitive behavior therapy or other forms of counseling.
2. Improvements in pain documented by the AHRQ Outcomes Review were limited and temporary –on the order of 2 points or less on a visual analog scale of 1 to10.
3. Trials uniformly failed to establish details of "usual and customary treatments" to which non-invasive therapies were added in the collected trials. From nearly 5,000 trials identified in the literature only 218 passed quality review. In more than half of those 218, AHRQ evaluated strength of evidence as "weak".

Recommendation #2: [Non-opioid therapies preferred for sub-acute and chronic pain]

From the Workgroup:
"Some workgroup members felt the language in this recommendation is somewhat too strong, given problems with some of the cited evidence. Words like "are preferred" might be softened to "may be preferred" or "may be effective". Although the harms of opioids are very well-defined, the benefits (especially long-term) are not well understood and difficult to study."

Author's Observation
The Workgroup acknowledged "problems with some of the cited evidence" but did not address the outright factual errors in several reports generated by the Agency for Healthcare Research and Quality. The author was among those pointing out these errors in detailed analysis presented to AHRQ in September 2021 and again in January 2022 [14,15]. However, the author finds no evidence in the November 2022 published CDC guidelines that either AHRQ or the CDC writers ever reexamined the protocols or assumptions of the AHRQ outcomes reviews referenced in the guidelines.

Recommendation #3 [when initiating opioid therapy, immediate release opioids are preferred over extended-release/ long acting opioids]

From the Workgroup:
"Several workgroup members appreciated the support text discussion regarding abuse-deterrent formulations."

Author's Observation
Several sources in medical literature provide reason to reconsider the roles of immediate release versus extended release opioids [22,23]. Extended release opioids offer the advantage of better support for restful sleep and perhaps less patient susceptibility to accidental double-dosing [24,25].

Recommendation #4: [prescription of lowest effective opioid dose and clinician caution when increasing dose above thresholds of "diminishing returns"]

From the Workgroup:
"Many workgroup members voiced concern about the dose thresholds written into the recommendation. Many were concerned that this recommendation would lead to forced tapers or other potentially harmful consequences. Though workgroup members recognized the need to have thresholds as benchmarks, many felt that including these thresholds in the supporting text could serve to de-emphasize them as absolute thresholds, and thus recommended removing the specific MME range from the recommendation. In addition, these thresholds are felt to be arbitrary to some degree and could be calculated differently based on different conversion formulas, but when they appear in the statement, they appear to be authoritative."

Author's Observations
Specific dose and duration limitations were removed in the November 2022 revised CDC guidelines, in favor of language asserting a "threshold of diminishing returns" in opioid dose – a term that appears six times. However, the guidelines as published do not identify specific sources from which this assertion was derived.

Recommendation #5 [review and tapering of opioid dosing for legacy patients if anticipated benefits do not outweigh risks]

From the Workgroup:
"Similar to the observations noted for recommendation #4, many workgroup members felt that the threshold dose should be removed from the statement and included in the supporting text.

"Several workgroup members noted that the framing of this recommendation is not balanced – that it does not include the risk/benefit calculation of continuing opioids. For example, a more balanced approach is to have one sentence about continuing opioids and one sentence about tapering opioids in terms of risk/benefit analyses. Also, not fully acknowledged is that continuing opioids and not tapering opioids avoids risks of poor analgesia, worsening functioning, and suffering, and potentially illicit opioid use."

"Many workgroup members appreciated the supporting text. However, there were some specific issues that were noted as concerning by some members, these included: never going back up in dosage during opioid tapering; lack of inclusion of observational studies showing potential dangers of tapering; minimal discussion about risk of tapering; role of patient-centeredness approach; representing the role of buprenorphine as established rather than emerging; an explicit discussion of goals of tapers is needed, particularly related to public health versus individual patient outcomes; there seems to be an underlying assumption that the goal is to get to zero MME, but perhaps it should be to get to a safer dose or better symptoms or function; a section on iatrogenic harms of tapering may be warranted."

Author's Observations
As in Recommendation #4, CDC writers relocated and rephrased references to MMED to the supporting comments for Recommendation #5, phrasing them in terms of thresholds of "diminishing returns" that are not specifically traceable to published medical literature. A complicating factor in both recommendations is that iatrogenic opioid addiction is often confused with physiological dependency. No less an authority than the Director of the National Institute on Drug Abuse informed us as early as March 2016 that neither outcome of treatment is "a predictable consequence of prescribing" and that there was no current consensus on the incidence of iatrogenic addiction at the time [28].

Multiple published sources likewise inform us that the factors that most influence incidence of opioid overdose, suicidality or dependence in medical patients have very little to do with prescribed opioid dose or duration during ongoing pain management [16,29-31]. The factors that most influence risk for bad outcomes from treatment with opioids primarily relate to a history of psychiatric disorders, previous hospitalizations, diagnoses of opioid use disorder or alcoholism [30]. The factor that most influences incidence of prolonged prescribing in post-surgical patients treated with opioid pain relievers is the type of surgery, not opioid type, dose, or duration [3]. Incidence of iatrogenic opioid overdose or misuse in post-surgical patients is estimated at much less than 2% -- in a range where the accuracy of the diagnosis itself is doubtful [32].

Recommendation #6 [Initial prescribing limited to no more than 7 days in acute pain]

From the Workgroup:
"Several workgroup members were concerned about the potential application of this recommendation. Some felt that removing the last sentence would reduce risk of misapplication and questioned the evidence supporting the statement (evidence type = 4). The challenges of defining acute pain were noted again (see observations for statement #1 - e.g., it is not a diagnosis, it does not reflect pathophysiology), and some workgroup members felt many potential exceptions may require more than 3 days of opioids (and that "rarely" doesn't seem accurate). However, others felt differently, and did not want to water down this statement so much that it doesn't help improve excess opioid prescribing that exists."

Author's Observations
Although the CDC writers removed mention of expected durations of initial prescribing, the wording of Workgroup comments reveals

a lack of consensus on the issue of "over-prescribing". Publications noted in the author's observations for Recommendation #5 (above) call into question whether "over-prescribing" actually exists at a level that can be reliably measured.

If clinical exposure to prescription opioids is a major factor in iatrogenic opioid addiction, then we should expect to see significantly elevated incidence of opioid misuse in previously opioid-naive surgical patients who are prescribed opioids for post-surgical pain control. However, multiple large scale retrospective studies of patient electronic health records do not demonstrate such elevated incidence [29-31].

US CDC has been on record for at least 10 years with claims that the US "opioid crisis" is or was driven by clinicians over-prescribing to their patients. However, recent statistical analysis of opioid prescribing versus hospitalizations for opioid toxicity and/or mortality where prescription opioids are a factor reveals no such relationship since at least as far back as 2010 [33].

Recommendation #7 [frequency of reviews for patient benefit versus risk, for patients with subacute or chronic pain]

From the Workgroup:
"Overall, many workgroup members felt ok with the statement in general and the recommendation category. They noted that there is little evidence to support it, particularly the specific time frames of 1-4 weeks and 3 months; however, it was reasonable and reflects common practice.

"As mentioned in overall themes, several group members observed that the use of "risks" and "harms" in this recommendation is inconsistent and recommend more careful and consistent consideration of these terms. Several members felt that using the term risk would be more appropriate than harms, as harms are typically not currently present.

Author's Observations
Discussion of the implementation of Recommendation 7 is lengthy in the revised CDC guidelines of November 2022. However, both the Workgroup and the CDC writers failed to understand and address a fundamental distinction. Benefits of opioid therapy are reported by patients in present tense. However, "risks" represent the judgments of clinicians about the likelihood of future bad outcomes from treatment. It is unclear how clinicians are expected to respond to a generalized "risk" in terms meaningful to specific treatment. As earlier noted, we are informed by the Director of the National Institute on Drug Abuse that opioid addiction is "not a predictable outcome" of clinician prescribing [28]. Moreover, clinicians depend upon drug testing to detect indications that a patient may be "abusing" prescription medication or taking additional non-prescription narcotics [34]. Under increasing regulatory pressure by State Medical Boards and the US Drug Enforcement Administration [35], it is inevitable that some doctors will err on the side of *their own* safety rather than that of their patients.

Also pertinent in this discussion is the concept of "expectation bias" [36,37]. Succinctly phrased, time-stressed clinicians have considerable difficulty "seeing" patterns of patient behavior that are unreported or that they do not expect. This effect in clinical science has strong parallels in failures of military intelligence interpretation in threat assessment. Succinctly, we very often see what we expect to see, whether it is there or not.

Recommendation #8 [ongoing patient risk evaluation and strategies to mitigate risks]

From the Workgroup:
"Several workgroup members noted concern about naming specific conditions that increase risk; it suggests a parity among them. There is concern that listing these conditions implies that they carry equal risk, and that other conditions that are not listed carry less risk. In addition, specifying the 50 MME dose threshold is concerning, and conveys similar risk as the other conditions. The dose threshold is arbitrary and inconsistent with other sections of the guideline (50 vs. 90 MME). As noted in overarching themes, many members recommended that these specific conditions be removed from the recommendation.

"Many workgroup members noted that the supporting text was not balanced, and a full discussion of risks and benefits are needed – that address risk/benefits of prescribing opioids and of not prescribing or limiting opioids. For example, the discussion about older adults focuses on risks of opioids, but there is no discussion about risks of untreated or undertreated pain in this population (e.g., potential worsening of blood pressure, mood, cognition). A similar point was made regarding individuals with psychiatric conditions, and the possibility of destabilization with untreated or undertreated pain. Likewise, the discussion about people with substance use disorders was unbalanced, with little discussion regarding the challenges of pain management (and buprenorphine's analgesic effect was missing). This issue of an unbalanced discussion in the supporting text is noted as an overall theme throughout the guideline.

Author's Observations
Specific MME levels are removed from Recommendation #8 in the November 2022 published guidelines. But they remain in supporting rationale and discussion. Likewise guideline discussion continues to emphasize undefined strategies for reduction of (future) "risks" of opioid prescribing while advocating for treatment of co-morbid depression employing means other than Benzodiazepine drugs. Missing in this discussion is any acknowledgement of the underlying reality that "risk" of opioid abuse in clinically managed patients may be too low for poorly trained and time-stressed clinicians to accurately assess.

Recommendation #9 [initial and periodic review of prescription drug monitoring programs]

From the Workgroup:
"Several workgroup members felt that the word "dangerous"

may be too strong and too binary. Some felt "high-risk" may be more appropriate, noting that there are nuances to deciding whether specific combinations of medications put individuals at risk. In addition, some workgroup members noted that it would be important to check the PDMP for risks that are broader than overdose.

"There were conflicting opinions regarding checking the PDMP for acute pain. Some workgroup members felt that prior to prescribing opioids for a small number of days, checking the PDMP may not be warranted or feasible, and therefore, the word "acute" should be removed or a qualifying term like "when possible" should be added. Others disagreed and felt acute pain should remain in the recommendation statement. "Some workgroup members expressed caution regarding potential harms of the PDMP, particularly when algorithms are used to create risk scores that lack evidence without qualifications. Some mentioned the cost to the patient-provider relationship; however, others discussed that when protocols are standardized, there is less risk to negatively impacting the patient-provider relationship and less risk of bias."

Author's Observations

As published in November 2022, the revised CDC guidelines state Recommendation #9 as follows:

"When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose (recommendation category: B; evidence type: 4)." Thus, the recommendation of the Workgroup was followed in replacement of the term "dangerous" with "high risk". However, ignored in this process was the reality that the jury remains out concerning whether use of PDMP data actually reduces accidental opioid overdose mortality [38]. Demographic studies of medical records of all patients in the State of North Carolina who were prescribed opioid pain relievers in a period of one year confirm that mortality rates are relatively higher among people who are treated with both Opioids and Benzodiazepines. However, the absolute incidence was estimated between 0.7 per 10,000 person-years and 7.0 per 10,000 person years [39].

Such low incidence of mortality associated with prescription opioids once again reinforces the observation of Volkow and McClellan [28] that opioid use disorder is not a predictable outcome of opioid prescribing. Thus holding clinicians responsible for performing individual "risk-versus-benefits" analysis in effect demands the impossible and encourages patient desertion. The most that a reasonable person would expect is that clinicians will be sensitive to patient history that alerts them to a need for closer or more frequent monitoring of treatment outcomes. Refusal to treat pain because of an amorphous "risk" of future bad outcomes is not an acceptable clinical or ethical practice.

Recommendation #10 [Drug testing before starting opioid therapy and periodically thereafter]

From the Workgroup:

"Interpretation of urine drug tests results can be complicated, and many providers lack this knowledge, which can lead to inappropriate negative consequences. In addition, because most urine drug tests are screening tests, false positive or false negative tests are not uncommon. Such inaccurate tests could lead to punitive action. Confirmatory testing is important but can also lead to financial issues for patients. Several workgroup members felt these potential harms are not fully addressed in the supporting text. In addition, the concept of a screening test should be included (e.g. with false positives and negatives).

"As mentioned in the overall themes, there are biases and disparities in which patients have urine drug tests. Several workgroup members felt that this issue should be more centrally addressed, as the recommendation statement could have substantial disproportionately negative consequences among Black and Latinx patients."

Author's Observations

The revised CDC guidelines appear responsive to many of the concerns voiced by Workgroup members. However, one implementation consideration in the revised guidelines is startling for what it reveals [40]:

"Predicting risk is challenging, and available tools do not allow clinicians to reliably identify patients who are at low risk for substance use or substance use disorders. Clinicians should consider toxicology screening results as potentially useful data, in the context of other clinical information, for all patients and consider toxicology screening whenever its potential limitations can be addressed."

Predicting individual risk is more than "challenging" for clinicians who manage their patients' pain by means of opioid analgesics. In point of fact, this CDC observation confirms the conceptual impossibility of conducting definitive future risk analysis for any individual patient. The most that a clinician can do is to identify conditions in the medical history of the individual that may warrant closer clinician monitoring or referral for ancillary support by a specialist in addiction medicine.

Recommendation #11 [avoid concurrent opioid and benzodiazepine prescribing]

From the Workgroup:

"Several workgroup members felt the words "avoid," and "whenever possible" are problematic as they can be interpreted as "never". Some proposed that a more appropriate phrase may be to use extreme caution. In specific situations, benzodiazepines can be beneficial, and stopping benzodiazepines can be destabilizing. Additionally, benzodiazepines may serve as a marker for risk of overdose due to underlying conditions. It's also important to differentiate between chronic stable prescribed use versus erratic

unpredictable non-prescribed use. Some workgroup members felt including an entire class of medications (central nervous system depressants) was far-reaching and could lead to unintended negative consequences.

Author's Observations

The revised CDC guidelines of November 2022 employ the phrase "clinicians should use particular caution" rather than "avoid". However, it is doubtful that this distinction makes a useful difference in clinical practice. Doctors are still being told that co-prescription of benzodiazepine drugs can get them into trouble. Moreover, it is well known that clinical depression is a serious factor in patient medical collapse and suicide [25]. Thus, the revised guidelines confront doctors with an impossible dilemma. If they do not treat for depression and anxiety, then their patients may be harmed. But if they do treat with a highly effective class of medications, they may be prosecuted by the US Drug Enforcement Administration for prescribing "outside the bounds of accepted medical practice."

Recommendation #12 offering or arranging for concurrent medication assisted therapy in patients with opioid use disorder]

From the Workgroup:

"New regulations regarding buprenorphine prescribing should be included in the supporting text.

"Several workgroup members noted that the supporting text should better distinguish opioid agonist versus opioid antagonist treatment and questioned the framing as the medications being equal options. Opioid agonist treatment has stronger evidence for better outcomes, doesn't require abstinence, has less challenges with inductions, and is much more widely utilized. "Some workgroup members noted a conflation regarding management of problematic opioid use versus OUD in the supporting text. Reassessing pain is important prior to deciding whether to taper or discontinue opioids. "Several specific details about OUD treatment were felt to be inaccurate in the supporting text, and additional review by an OUD expert is warranted.

Author's Observations

Recommendations of the Workgroup were wide-ranging, though largely focused on only one modality of addiction treatment (medication assisted therapy employing agents such as Methadone and Buprenorphine). Prominent in the November 2022 revised guidelines are detailed subsidiary recommendations, including:

"Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria.

"For patients meeting criteria for opioid use disorder, particularly if moderate or severe, clinicians should offer or arrange for patients to receive evidence-based treatment with medications for opioid use disorder. "Clinicians should not dismiss patients from their practice because of opioid use disorder because this can adversely affect patient safety.

These recommendations encounter serious obstacles in real-world clinical practice. First, very few clinicians are dual Board Certified in pain medicine and addiction medicine [41]. Relatively few clinicians have extensive training in the use of the DSM-5's eleven symptoms and three degrees of severity [42] in diagnosing substance use disorder. It is highly doubtful that this elaborate classification system has any particular relevance in clinician choices for a course of therapy for pain that also balances concerns for undesired outcomes in iatrogenic physiological dependency, tolerance or addiction [43]. Finally, due to the departure of thousands of clinicians from the practice of pain medicine [35], caseloads have risen to such a level that pain management clinicians may simply not be able to take on more patients who are suffering with opioid addiction.

A Central and Disabling Issue in Revised CDC Guidelines and Findings of the Workgroup

From the Opioid Workgroup Guiding Principles (Appendix):

"PRINCIPLE 2: SCIENTIFIC INTEGRITY

"Review evidence to support MME classifications and other latent factors that could distort outcomes for primary opioid science (genetics and CYP enzymes, drug metabolism, and variability in bioavailability)."

This is the only occurrence of the term "genetics" in findings of the Workgroup. The term likewise appears only once in the November 2022 CDC guidelines, in footnotes to the Table on "Morphine milligram equivalent doses for commonly prescribed opioids for pain management" (Page 31). In the view of the author, this omission must disqualify not only the revised CDC prescribing guidelines, but of much of the literature on safety and effectiveness of prescription opioid therapy.

There is a well-established 20-year- clinical literature on effects of genetic polymorphism in the expression of CYP-450 enzymes that moderate opioid metabolism in the human liver [44,45]. The practical outcome of polymorphism is that some patients are poor metabolizers of opioids, some are average metabolizers, and some are "hyper" metabolizers who break down opioids into metabolic byproducts that cross the blood-brain barrier in minutes rather than hours. This natural variation in metabolism is associated with an estimated 15-to-1 range in minimum effective opioid dose between individuals [25].

Unacknowledged genetic variation in opioid metabolism may explain the relative rarity of both short term and long-term trials for opioid effectiveness in clinical practice. Long-term double-blind randomized trials of opioids fail because of high dropout rates among the placebo arm. But the 2016 CDC guidelines conflated the absence of long term trials with an absence of opioid effectiveness [46]. It appears that the same conflation is made in the 2022 revision, with greater subtlety. Enriched Enrollment Randomized Gradual Withdrawal designs have been proposed as a needed correction of methodology, but are not yet reflected in

clinical literature [47]. Arguably, almost the entire trials literature for effectiveness of pain relieving therapies needs to be burned to the ground and started over. Protocols must address greatly expanded patient cohorts, base-lining of patient genomics, and gradual up-titration of individual patients to effective dose levels.

Follow-up on Findings of the July 2021 Opioid Workgroup

The Opioid Workgroup was disbanded after publishing its findings in July 2021. The minutes of its July meeting were published in November of that year. The 1063 pages of those minutes reveal very sharp criticism of the draft guidelines on multiple grounds.

Of particular import were suggestions that MMED thresholds should be entirely removed from the document, and effects of genetically mediated opioid metabolism should be addressed. Also noted (by the present author among others) were systemic errors in methodologies applied by the Agency for Healthcare Research and Quality in their updated outcomes reviews. Careful reading of the voluminous November 2022 revised CDC guidelines reveals that few if any of these substantive issues were addressed.

Conclusions

Critical review of Opioid Workgroup findings in July 2021 versus revised CDC guidelines released in November 2022 reveals a process in the Workgroup that seems calculated to create an appearance of independence and scientific rigor, but without the substance of any deep impact on the guidelines themselves. Many findings and concerns of the Workgroup were consistently marginalized or ignored in the published Guideline revision.

In two critical areas, both the Workgroup and the Guideline writers failed to recognize major failings of methodology that effectively disqualify the Guidelines even as advisory public health policy:

- Guideline writers and Workgroup participants failed to understand the asymmetry between perceived demographic "risks" of opioid prescribing versus individual patient "benefits" thereof. "Risk" is applicable only in large populations, but without reliability for any individual patient. The term implies an ability to assess the likelihood that prescription of opioids will lead to iatrogenic opioid addiction in individual clinical patients. Lacking an accepted consensus on the relationship between prescribing and iatrogenic opioid addiction, this concept is not supported in the medical literature.

- Both the Guideline writers and the Workgroup were aware of a long-existing medical literature addressing genetic polymorphism in expression of six key enzymes that mediate opioid metabolism in the human liver. However, both groups failed to address the implications of this literature. The consequence of polymorphism is a wide range in minimum effective opioid doses and sensitivity to side effects between individuals treated with prescription opioids. None of the present trials literature reflects this phenomenon in protocols assessing the effectiveness of opioid analgesics in management of pain. Likewise none of this literature reflects the manner in which opioid analgesics are actually used in clinical practice.

"Golden rules" of pain treatment employing prescription opioids can be traced back 40 years to the World Health Organization "Ladder of Pain Management". In chronic pain, clinicians should start with low doses of non-opioids or weaker opioid medications, and titrate up to effective dose for the individual patient, while monitoring for and managing side effects. If disabling side effects are encountered, then taper down previous therapies while titrating up other analgesics or combinations involving different biological mechanisms.

Non-analgesic therapies may be useful adjunct treatments for some patients, some of the time. But they cannot replace opioid therapy and are not "preferable" thereto. Involuntary tapering of legacy patients solely to meet arbitrary MMED thresholds is never ethically or clinically appropriate. Denial of patient access to opioid therapy has no prospect of addressing America's "opioid crisis" and may amount to patient desertion. The failure of revised CDC guidelines to address these "golden rules" may constitute grounds for legislative removal of the CDC from all future roles in development of public health policy for pain medicine.

About the Author

The author writes as a non-clinician subject matter expert in public policy for regulation of prescription opioid analgesics and of doctors who employ these therapies in managing acute, sub-acute, and chronic pain. He has authored or co-authored over 200 papers, articles, and interviews in this field, in a mixture of peer-reviewed medical literature and popular media.

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References

1. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain United States. March 18 2016. Morbidity and Mortality Weekly Report. 2016.
2. Lieberman A, Davis C. Laws Limiting the Prescribing or Dispensing of Opioids The Network for Public Health Law. May 11 2021. https://www.networkforphl.org/resources/laws-limiting-the-prescribing-or-dispensing-of-opioids/
3. Martin SA, Poteet RA, Lazris A. Neat Plausible and Generally Wrong A Response to the CDC Recommendations for Chronic

Opioid Use. Medium. 2016. https://medium.com/@stmartin/neat-plausible-and-generally-wrong-a-response-to-the-cdc-recommendations-for-chronic-opioid-use-5c9d9d319f71#.wzchd1kkl

4. Satel S. The Myth of What's Driving the Opioid Crisis. Politico Magazine. 2018. https://www.politico.com/magazine/story/2018/02/21/the-myth-of-the-roots-of-the-opioid-crisis-217034/
5. Beth D Darnall, David Juurlink, Robert D Kerns, et al. International Stakeholder Community of Pain Experts and Leaders Call for an Urgent Action on Forced Opioid Tapering. Pain Medicine. 2019; 429-433.
6. Dowell D, Haegerich T, Chou R. No Shortcuts to Safer Opioid Prescribing. New England Journal of Medicine. 2019. https://www.nejm.org/doi/full/10.1056/NEJMp1904190
7. Centers for Disease Control and Prevention. CDC Advises Against Misapplication of the Guideline for Prescribing Opioids for Chronic Pain. 2019. https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html
8. Curtis CR. Request for Formation of Opioid Workgroup. 2019. https://www.cdc.gov/injury/pdfs/bsc/Request_for_OWG_BSC_NCIPC_Final_120419-508-1.pdf
9. Opioid Workgroup Board of Scientific Counselors. National Center for Injury Prevention and Control Centers for Disease Control and Prevention. Terms of Reference. 2020. https://www.cdc.gov/injury/pdfs/bsc/OWG_Terms-of-Ref_FINAL-7-6-2020-r.pdf
10. US CDC NCIPC Board of Scientific Counselors. Open to the Public. 2021. https://www.cdc.gov/injury/pdfs/bsc/BSC_NCIPC_Meeting_Minutes_7_16_2021_Final.pdf
11. Cunningham C. Observations of the Opioid Workgroup of the Board of Scientific Counselors of the National Center for Injury Prevention and Control on the Updated CDC Guideline for Prescribing Opioids. 2021. https://www.cdc.gov/injury/pdfs/bsc/OWG-Report-of-Recs-1-12-06.30.21-FINAL-508.pdf
12. US CDC. CDC Response to Public Comments on the Draft 2022 Clinical Practice Guideline for Prescribing Opioids for Pain. 2022. https://www.regulations.gov/document/CDC-2022-0024-5549
13. Lawhern R. The Agency for Healthcare Research and Quality Labors Mightily to Produce a Mouse September. Correspondence from Richard Lawhern PhD to the acting Director, Agency for Healthcare Research and Quality. 2020. https://www.cdc.gov/injury/pdfs/bsc/BSC_NCIPC_Meeting_Minutes_7_16_2021_Final.pdf
14. Lawhern R. Methodological Errors in Treatments for Acute Pain A Systematic Review. AHRQ. 2021. https://www.cdc.gov/injury/pdfs/bsc/BSC_NCIPC_Meeting_Minutes_7_16_2021_Final.pdf
15. Lawhern RA, Rose M, Tennant F, et al. Correspondence to David Meyers Acting Director Agency for Healthcare Research and Quality re AHRQ Comparative Effectiveness Review 240 Treatments for Acute Pain Must Be Immediately Withdrawn. 2021.
16. Lawhern R. United States Opioid Prescribing Guidelines 2022 A Critical Policy Review. The Medical Research Archives. 2023. https://esmed.org/MRA/mra/article/view/4379/99193547246
17. Ghey N. The Other Opioid Crisis How False Narratives Are Hurting Patients. Discourse. 2022. https://www.discoursemagazine.com/culture-and-society/2022/07/18/how-false-narratives-about-opioids-are-hurting-patients/
18. Szalavitz M. Entire Body is Shaking Why Americans with Chronic Pain are Dying. New York Times Opinion. 2023. https://www.nytimes.com/2023/01/03/opinion/chronic-pain-suicides.html
19. Zoellick L. Chronic Pain and Suicide. National Pain Report. 2022. https://nationalpainreport.com/chronic-pain-and-suicide-8835351
20. ACP Internist Stopping opioid treatment linked to increased risk of death from overdose or suicide in veterans. 2022. https://acpinternist.org/weekly/archives/2020/03/17/2.htm?fbclid=IwAR0mttCKBkyx2-QOZ2u1JrCv_hHpsQ0mmhsa29-Chn1I9XvgUZftb9CgPpY
21. Tennant F. Opioid Ten Year Longevity Survey Final Report. Practical Pain Management. 2010; 10. https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/opioid-treatment-10-year-longevity-survey-final-report
22. Tennant F, Porcelli M, Costello L, et al. Justification of Morphine Equivalent Opioid Dosage Above 90 mg. Pract Pain Manag. 2017; https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/justification-morphine-equivalent-opioid-dosage-above-90-mg
23. Schneider J, Anderson A, Tennant F. Patients Who Require Ultra-high Opioid Doses. Pract Pain Manag. 2009; 9. https://www.practicalpainmanagement.com/treatments/pharmacological/opioids/patients-who-require-ultra-high-opioid-doses
24. Schneider JP. A Practical Introduction to the Use of Opioids for Chronic Pain. Practical Pain Management. 2009. https://www.practicalpainmanagement.com/author/2460/schneider
25. Nadeau SE, Wu JK, Lawhern RA. Opioids and Chronic Pain An Analytical Review of the Clinical Evidence. Frontiers in Pain Research. 2021. https://www.frontiersin.org/articles/10.3389/fpain.2021.721357/full
26. Andrea C. Skelly, Roger Chou, Joseph R. Dettori, et al. Noninvasive nonpharmacological treatment for chronic pain a systematic review. AHRQ Comparative Effectiveness Reviews. 2020.
27. Lawhern RA, Nadeau SE. Understanding the Limitations of Non-Opioid Therapies in Chronic Pain. invited editorial for the October 2017 print edition, in Practical Pain Management. 2017. https://www.practicalpainmanagement.com/resources/practice-management/behind-ahrq-report

28. Volkow N, McMcClellen AT. Opioid Abuse in Chronic Pain Misconceptions and Mitigation Strategies. N Engl J Med. 2016. http://www.nejm.org/doi/full/10.1056/NEJMra1507771

29. Oliva EM, Bowe T, Tavakoli A, et al. Development and Applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation STORM to Improve Opioid Safety and Prevent Overdose and Suicide. Department of Veterans Affairs. Psychological Services. 2017; 14: 34-49. https://psycnet.apa.org/doiLanding?doi=10.1037%2Fser0000099

30. Bohnert ASB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011; 305: 1315-1321.

31. Sun EC, Darnall BD, Baker LC, et al. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. JAMA Intern Med. 2016; 176: 1286-1293. https://doi.org/10.1001/jamainternmed.2016.3298 PMID:27400458

32. Brat GA, Agniel D, Beam A, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse retrospective cohort study. BMJ. 2018; 360: j5790. https://doi.org/10.1136/bmj.j5790 PMID:29343479

33. Aubry L, Carr BT. Overdose opioid treatment admissions and prescription opioid pain reliever relationships United States. 2010-2019. Frontiers in Pain Medicine. 2022. https://www.frontiersin.org/articles/10.3389/fpain.2022.884674/full

34. Dydyk AM, Sizemore DC, Haddad LM, et al. NP Safe Prescribing of Controlled Substances While Avoiding Drug Diversion. Stat Pearls Publishing. 2023. https://www.ncbi.nlm.nih.gov/books/NBK564518/

35. London C. DOJ Overreach The Criminalization of Physicians. Journal of Legal Medicine. 2023; 41: 191-203. https://doi.org/10.1080/01947648.2022.2147366|

36. Lang TA, Stroup DF. Who knew The misleading specificity of double blind and what to do about it. 2020.

37. Hillary FG, Medaglia JD. What the replication crisis means for intervention science. Editorial. Int J Psychophysiol. 2020; 154: 3-5.

38. Liang D, Shi Y. Prescription drug monitoring programs and drug overdose deaths involving benzodiazepines and prescription opioids. Drug Alcohol Rev. 2019; 38: 494-502.

39. Nabarun Dasgupta, Michele Jonsson Funk, Scott Proescholdbell, et al. Cohort Study of the Impact of High-dose Opioid Analgesics on Overdose Mortality. Journal of Pain Medicine. 2016; 17: 85-98. https://pubmed.ncbi.nlm.nih.gov/26333030/

40. Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report, Recommendations and Reports. 2022; 71: 50.

41. Lawhern RA. CDC Guidelines on Prescription of Opioids More and Less Than Meets The Eye. Yearly conference of the Florida Society for Interventional Pain Physicians. Tampa Florida. 2022.

42. American Society of Addiction Medicine. DSM-5 Criteria for Diagnosis of Opioid Use Disorder. 2023. https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf

43. Lawhern RA, Nadeau SE. Understanding the Limitations of Non-Opioid Therapies in Chronic Pain. invited editorial for the October 2017 print edition in Practical Pain Management. 2017. https://www.practicalpainmanagement.com/resources/practice-management/behind-ahrq-report

44. Deepty Agrawal, Mercy A. Udoji, Andrea Trescot. Genetic Testing for Opioid Pain Management A Primer Pain Therapy. 2017. https://pubmed.ncbi.nlm.nih.gov/28409480/

45. Carsten Skarke. Genetic Predictors of the Clinical Response to Opioid Analgesics. Clinical Pharmacokinetics. 2004. https://www.academia.edu/28334503/Genetic_Predictors_of_the_Clinical_Response_to_Opioid_Analgesics

46. Martin SA, Poteet RA, Lazris A. Neat Plausible and Generally Wrong A Response to the CDC Recommendations for Chronic Opioid Use Medium. 2016. https://medium.com/@stmartin/neat-plausible-and-generally-wrong-a-response-to-the-cdc-recommendations-for-chronic-opioid-use-5c9d9d319f71#.wzchd1kkl

47. Nadeau SE, DelRocco N, Wu SS. Opioid trials time for a new approach. Enriched enrollment randomized gradual withdrawal designs. 2022. https://doi.org/10.2217/pmt-2021-0112