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CDC Guidelines on Prescription of Opioids – More and Less Than Meets the Eye

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ABSTRACT

On February 10, 2022, the US Centers For Disease Control and Prevention (National Center for Injury Prevention and Control) circulated a draft revised and expanded "2022 CDC Clinical Practice Guideline for Prescribing Opioids". This proposal incorporates major expansions of scope and revisions of recommendations in the earlier 2016 CDC Guideline on prescription of opioids to adults with chronic non-cancer pain.

Mainstream press articles have described the 2022 Guideline as a major improvement over the 2016 predecessor document in that it emphasizes the need for clinicians to exercise their own judgment on behalf of patients and to tailor treatment to individuals. However, deeper reading of the proposed 2022 Guideline calls the impressions of press reporters into serious question. In the opinion of the author and many others, the 2016 CDC Guideline has already wrecked the practice of pain medicine in the US, and proposed 2022 "revisions" may continue the destruction.

The only ethically sound courses of action now open to the CDC are either to repudiate and withdraw both 2016 and draft 2022 guidelines without replacement, or to burn them to the ground and start over with condensation and correction of gross errors and policy mis-directions under a new, unbiased and clinically qualified writers group.

Background

In March 2016, the US CDC issued a Guideline for prescription of opioids in the treatment of chronic non-cancer pain [1]. This guideline was almost immediately taken up by more than 35 State governments in legislation to limit prescription opioid doses and duration for treatment of chronic pain. Partially in response to widespread opposition by clinicians [2,3], CDC issued a disclaimer suggesting that their Guideline was never intended to serve as a legally binding practice standard and had been "misapplied" [4].

However, public controversy continued as law enforcement and State Medical Boards continued to challenge and sanction clinicians' use of long term opioid therapy in the management of severe chronic pain. In December 2019, CDC announced that their Guideline would be revised; nominations were requested of medical and public health professionals to staff a temporary "Opioid Workgroup" to provide oversight to the Board of Scientific Counselors of the National Center for Injury Prevention and Control [5]. Draft revised CDC recommendations and Workgroup comments were briefed at a public meeting of the NCIPC BSC in July 2021 [6]. A 216-page draft guideline revision was circulated for public comment in the Federal Register from February to April 2022. [7]. Over 26,000 comments were received, with 5,300 posted to the Federal Register as of May 24, 2022 [8].

Highlights of 2022 Proposed Revised CDC Guideline

The draft circulated for public comment in February 2022 represents a substantial expansion of the document published in March 2016. Like the original, treatment of sickle cell disease, cancer pain, palliative, and end-of-life care are excluded. Guidance is focused specifically on out-patient care.

Originally phrased as guidance primarily for general practitioners, the new Guideline is expanded to address "other" practitioners,

presumably including specialists in pain medicine. The 2022 draft is widened to address acute, sub-acute, and chronic pain treatment employing either prescription opioids or non-opioid therapies.

According to CDC documents [9], a peer review group was to meet "in parallel" with public comments, to evaluate the draft guidelines. It is unclear whether this review group was tasked to evaluate comments appearing in the Federal Register. Publication of the final guideline is anticipated in late 2022.

What Did the Press Read?

From laudatory comments registered in much of the US national press, it appears that many reporters may have begun and ended their investigation of the draft Guideline with the following boxed highlights on the second page of the document:

"This clinical practice guideline is

• A clinical tool to improve communication between clinicians and patients and empower them to make informed, person-centered decisions related to pain care together…
• Intended for primary care clinicians and other clinicians providing pain care for outpatients…
• Intended to be flexible to enable person-centered care-centered decision-making, taking into account an individual's expected health outcomes and well-being."

"This clinical practice guideline is not

• A replacement for clinical judgment or individualized, person-centered care
• Intended to be applied as inflexible standards of care across patients, and/or patient populations by healthcare professionals, health systems, pharmacies, third-party payers, or governmental jurisdictions or to lead to the rapid tapering or discontinuation of opioids for patients
• A law, regulation, and/or policy that dictates clinical practice or a substitute for FDA-approved labeling."

Devils in the Details

Many aspects of the 12 recommendations of the CDC writers unfortunately diverge substantially from statements at the beginning of their guidelines. Seven of the guideline recommendations are identified as "Category A", defined as "most patients should receive the recommended course of action." The remaining five are "Category B," where "different choices will be appropriate for different patients, requiring clinicians to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations…"

To any reasonable reader – and to lawyers concerned with potential sanctions or prosecutions levied against doctors – it must be apparent that Category A recommendations can be read as a de facto mandatory practice standard. Likewise, the strong emphasis on risk throughout the draft guideline makes plain, without explicitly stating, that any US clinician who prescribes opioid pain relievers to any patient for any reason at any dose is "on their own" if challenged by the US Drug Enforcement Agency, other law enforcement agencies, a State Medical Board, or a health care provider organization.

The emphasis on risk in the draft guidelines must inevitably have an overshadowing effect on the willingness of clinicians to employ opioids in treating pain. How can Category A recommendations possibly be read as "flexible" or "patient centered?"

Likewise, how are clinicians to interpret a guideline in which the terms "risk" or "risks" appear 512 times compared to 167 mentions of "benefits" – often in a context of repeated admonitions to perform a "risk versus benefits" analysis every time the clinician considers an initial opioid prescription, periodically assesses patient progress, or increases opioid dose?

The guideline emphasis on risk is especially troublesome in light of an admission buried deeply in the January 2022 draft revision where few reporters will have read it:
"There is no validated, reliable way to predict which patients will suffer serious harm from opioid therapy and no reliable way to predict which patients will benefit from opioid therapy" [bold emphasis by the author]

Such a combination must seem to any reasonable reader to comprise a major oxymoron: clinicians must repeatedly perform a risk versus benefits analysis for every patient, but there are no validated profiling instruments for accomplishing this task. Thus the clinician is again placed at risk of prosecution – or perhaps more accurately "persecution" – by US DEA or State drug enforcement investigators.

Other terms or phrases also occur often enough in the draft guidelines to raise major concerns for patient welfare:
"Taper" or "Tapering" appear 200 times, indicating that patients who are prescribed opioids should be tapered if they do not show evidence of improvements in pain control or quality of life. Unmentioned is that tapering– whether voluntarily or involuntarily – is associated with significantly elevated risk of medical crisis and overdose [10]. Likewise, analytic review of the clinical literature indicates a relatively wide range (on the order of thirteen to one) in minimum effective opioid dose levels between individuals [11].

The 2016 CDC Guideline directed general practitioners to assess benefits and risks of opioid therapy for any patient receiving 50 Morphine Milligram Equivalent Daily Dose (MMEDD) or higher, and to refer patients prescribed over 90 MMEDD to a pain management specialist. Clinicians were also advised to limit initial prescriptions to seven days or less. Both 90 MMEDD and 7-day limits are removed from the 2022 revised and expanded guidelines. However, "50 MMED" continues to appear at least 20 times as a threshold of presumed increased risk. This threshold is also asserted to be a "point of diminishing returns," above which benefits of opioids are progressively marginalized. A dose of 90 MMEDD is mentioned three times and invoked as the definition of "high dose" treatment.

Since February 2022, patient reports have appeared in social media groups indicating that some clinical practices are already limiting all of their remaining pain patients to no more than 50 MMEDD, anticipating that this dose will become a hard limit in the revised CDC Guideline or in State laws.

Also of concern are repeated mentions in the 2022 CDC guidelines that mortality risk increases with opioid dose – without also noting that absolute risk for doses up to 100 MMED is on the order of 0.25% per year, increasing to 0.5% per year over 100 MMED [op cit, 11]. Similar levels of mortality risk are common for several other medications, notably blood thinners used to prevent stroke in patients with atrial fibrillation. It seems unlikely that chronic pain patients will find a mortality risk of 0.5% unacceptable, in light of the horrendous alternative in severe pain.

Glaring Omissions and Junk Science

It has been known for years that genetic polymorphisms play a significant role in mediating the metabolism of medications broken down in the liver [12]. The natural consequence of CYD6P2 pharmacogenics is to create two sub-groups of pain patients. "Average metabolizers" may do well on a 20-100 MMEDD regimen for severe chronic pain. However, "poor metabolizers" and "hyper" metabolizers may require significantly higher dosage to moderate their pain [13]. There are case reports of small numbers of patients whose pain is well managed on opioid doses exceeding 2,000 MMEDD, with minimal side effects [14].

Unfortunately, none of these known effects are acknowledged or explored in the 2022 CDC draft Guidelines. "Genetics" appears only once in the document and then peripherally without discussion.

Even more glaring is a CDC failure to acknowledge that MMEDD itself is at best a highly approximate metric with limited value only for gross estimation of prescription doses when initiating or switching between opioids. Multiple models for MMEDD produce different estimates of dose equivalence. None of these models is grounded upon validated data [15]. Thus it may not be going too far to suggest that MMEDD is simply "junk science" and should be totally removed as a criterion in clinical practice guidelines for pain. Such removal would parallel the approach of the US Federation of State Medical Boards in their 2017 published guideline [16].

A significant conflation is also present throughout the 2016 and 2022 Guidelines. The CDC authors repeatedly suggest that there is insufficient medical evidence to demonstrate that prescription opioids are effective as long-term therapy for pain. However, they link this suggestion to the absence of long-term double-blind trials for opioids versus placebo in medical literature. While it is true that the literature contains only one long-term double-blind trial of opioids (involving patients with mild to moderate pain) [17], the reason for the paucity of trials of long-term treatment is the high dropout rate of patients in moderate to severe pain treated with placebo [18] -- not the ineffectiveness of prescription opioids as such. Enriched enrollment trials appear to offer a promising methodology [19]. Likewise, this conclusion ignores the lived experience of millions of seniors and others who have been successfully maintained on prescription opioids for years.

Weak Medical Evidence and Inappropriate Recommendations

The CDC Guidelines characterize strength of medical evidence at four levels. Of these, Type 3 and Type 4 are scientifically weakest. Evidence said to support seven of the 12 CDC recommendations is Type 4: "clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations." Several of these seven are Category A – essentially mandatory standards. Three other recommendations are of Type 3: "observational studies or randomized clinical trials with notable limitations". Close reading of the guidelines fails to fully identify just "whose" experience and observations have been incorporated in Type 4 evidence.

Possibly the most controversial recommendation of both 2016 and 2022 Guidelines is the following:
"Recommendation 2: Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient..."

A key reference offered as support for this recommendation was published by the US Agency for Healthcare Research and Quality under tasking from US CDC. AHRQ Comparative Effectiveness Review 227 is titled "Noninvasive, Nonpharmacological Treatment for Chronic Pain" (initially published in 2019, expanded and updated April 2020). It is referenced 13 times in the 2022 draft guidelines.

This source identifies no published trials that directly compare opioids and alternative non-drug therapies on an "either/or" basis. Moreover, the state of methodological rigor in the medical literature for alternative therapies is arguably so poor that we really don't know if most work any better than placebos [20]. Degree of pain improvement in trials reported by this source is generally a maximum of two levels on a Visual Analog Scale of ten. AHRQ analysts were forced to "assume" that alternative therapies were applied as adjuncts to "usual and customary treatment," because trial protocols almost universally failed to document what customary treatment actually comprised.

Among 7,700 trials of ten types of non-pharmacological therapy for five broad categories of pain, only 247 trials survived AHRQ quality review. This was in part because relatively few trials followed patients for at least 30 days after treatment to assess lasting pain improvement (an objective of the Outcomes Review). Many trials noted no improvement or minor temporary improvement in pain, and a majority were graded as "medical evidence weak".

After a deep reading, the details in this reference reveal that non-opioid therapies cannot possibly be regarded as "preferable" to opioids. At best, therapies like massage, acupuncture, or Cognitive Behavioral Therapy might be regarded as adjuncts to treatments employing various analgesics – helpful for some patients, some of

the time, but not replacements for drug therapy.

Characterizing Opioid Addiction Mortality Versus Chronic Pain Demographics

Much is made in popular literature and news of the idea that America's opioid overdose crisis was created by evil pharmaceutical companies seeking profits, and by doctors "over-prescribing" opioids to people in pain. In the author's view, this narrative is hugely false. Demographic data provide strong contradictions to the conclusions of the CDC guidelines.

Addiction is widely understood to be a complex, multi-factorial condition strongly influenced by social determinants of health, rather than growing only from exposure to legal or illegal opioids. The "typical" addict (if there is such an entity) is a young adult male with limited education and a history of unemployment, involvement with the criminal justice system, and mental health problems. This is a medically underserved population.

By contrast, clinicians who treat pain tell us that their patients are most likely to be women in their 40s or older. If a woman's life is stable enough to see a doctor regularly for pain treatment, such a patient is rarely an addict.

Rates of medical opioid prescribing are higher among seniors over age 62 than in young adults, due to the accumulation of chronic medical conditions with age. By contrast, rates of opioid overdose related mortality are currently four times higher in young adults age 25-34 than in seniors age 65 and older (Figure 1).

Recently published re-analysis of CDC published data also reveals that since 2010, there has been no cause-and-effect relationship between rates of opioid prescribing versus either hospital admissions for opioid toxicity or overdose-related mortality [21]. Though there was a relationship in 2000-2009, this relationship appears to have been driven to some degree by pill mills operated by a small minority of clinicians and pharmacists.

Data portrayed in Figure 1 were downloaded in the Fall of 2021 from the US National Cause of Death database indexed by CDC-Wonder. Each data point is an aggregation of all narcotics-related intentional or accidental mortality (Codes X42 and X62 of the International Classification of Diseases (ICD-10) system), with six codes for contributing causes of death:

T40.0: Poisoning by Opium
T40.1: Poisoning by Heroin
T40.2: Poisoning by Other Opioids
T40.3: Poisoning by Methadone
T40.4: Poisoning by Other Synthetic Narcotics
T40.6: Poisoning by Other and Unspecified Narcotics [18]

Several general characteristics of opioid overdose related mortality stand out in the Figure.

1. Mortality rises significantly over 20 years in adults age 35 to 64, while remaining low and relatively stable in youth under age 25 and seniors 65 and older. Youth are prescribed opioids least often of all age cohorts and seniors most often.
2. Overdose mortality for adults ages 35 to 54 somewhat levels off during 2006 to 2012, and then rises from 2013 onward.
3. The most persistent rise in overdose mortality occurs among the generation who were aged 55 to 64 in year 2000 and thereafter. Perhaps coincidentally, this group includes the generation in which hundreds of thousands of young soldiers fought in Southeast Asia and were exposed to cheap, highly concentrated heroin. Many of those soldiers have "aged out" of 2020 overdose statistics, replaced by younger people who never saw service in Vietnam.

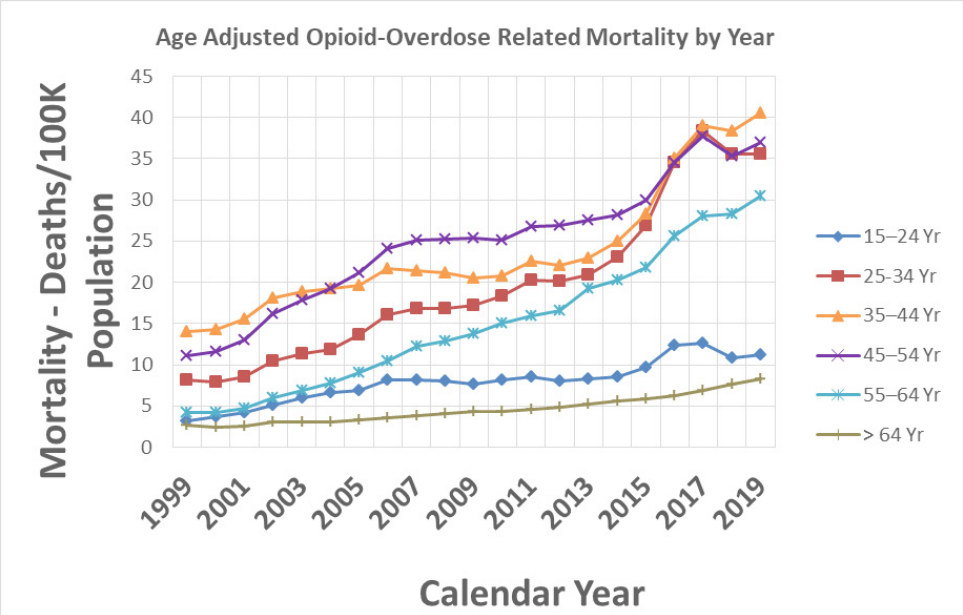

Figure 1: Demographics of Opioid Overdose Related Mortality.

We cannot reliably assign cause and effect to these statistics, standing alone. However, we should recognize that multiple external events may have influenced the shapes of these curves to varying degrees. Such events include

- the financial crash of 2008, with subsequent automation and outsourcing of many US labor-intensive jobs and hollowing-out of Rust Belt and rural communities;
- rapid expansion of pill mills in the 2000-2012 epoch, (particularly in the State of Florida), which flooded the American market with "legal" prescription opioids. This expansion was almost certainly aided by major drug distribution companies, which failed to honor their responsibilities for auditing drug allotment, and the DEA, which failed to meet its legal responsibility to monitor these companies.
- 2010 FDA-mandated reformulation of Oxycontin in abuse-deterrent form, with an associated tripling of heroin mortality and rapid emergence of illegal fentanyl as a contaminant in counterfeit street drugs misrepresented as pharmaceutical opioids.
- 2010-2012 legislative action by 12 states to regulate pill mills, coupled with major expansion of prescription drug monitoring plans, ultimately to 49 states, which served to shine a bright light on pill mill operations. Failure of states to anticipate the consequences of these actions, which eventuated in a ready market for heroin and fentanyl and demand rapidly met by Mexican and Chinese entrepreneurs.
- The particular deadliness of fentanyl, which is 50 times as potent as heroin.

Conclusions and Recommendations

Deep reading of the 2022 draft CDC opioid guidelines reveals many nuances that appear to have been missed by mainstream press reporters in their rush to publish on a 24-hour news cycle. Journalists saw several new statements to the effect that guidelines are not intended as hard limits on prescribing and that doctors should emphasize patient-centered and evidence based treatment of patients as individuals. But these new statements are overshadowed by continuing anti-opioid bias, cherry-picked and misinterpreted research, junk science and false narratives concerning risks of over-prescribing [23,24].

Likewise, CDC offers no patient profiling tools to enable clinicians to actually perform the comparisons of risk versus benefits that the guidelines demand. Thus, if published in their draft form, the 2022 Guideline will predictably expose the few remaining practitioners of pain medicine to unjustifiable sanctions and prosecution by law enforcement agencies intent on suppressing patient access to opioids, regardless of potential harms to patients.

A compelling argument can be made for outright public repudiation of both the 2016 and draft 2022 CDC opioid guidelines, formal withdrawal without replacement, and active steps to repair the widespread damage CDC has already done to clinicians and their patients. Development of consensus standards of practice should be left to medical specialty academies and societies whose members are clinicians practicing medicine in communities – not public health "experts" whose concerns are policy-centered rather than patient-centered, and whose bias has been publicly exposed.

Failing a complete withdrawal of the 2022 draft Guidelines, in the opinion of the author, it should be (figuratively) burned to the ground and CDC should start afresh. New writers should be drawn from a consensus committee led by practicing clinicians and supported by patient advocates and patients themselves, as voting members. A third-round effort to develop standards might start from observations of the 2018-2019 US Health and Human Services Inter-Agency Task Force on Best Practices in Pain Management: there is no one-size-fits-all patient or therapy program [25].

As a last resort, it may be time for clinicians and their professional organizations to stand up and be counted. Proponents might circulate an invitation to multiple professional groups, establish an independently audited National Legal Defense Fund, hire a law firm, and seek injunctions against CDC to force retraction or major revision of the 2016 and 2022 guidelines. Grounds for such action arguably comprise public malfeasance, fraudulent misrepresentation, collusion between CDC insiders and anti-opioid zealots [26], and extensive violations of the Americans with Disabilities Act.

Author Note

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