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REVIEW ARTICLE

US Opioid Guidelines 2022 - More and Less Than Meets the Eye

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ABSTRACT

The United States is currently embroiled in a contentious and multi-dimensional public conversation about addiction-related mortality, chronic pain, and government regulation of clinicians who employ opioid analgesic pain relievers in treating pain. The US Centers for Disease Control and Prevention (CDC) have published and updated guidelines to clinicians concerning appropriate practices for managing severe chronic pain by means of opioid analgesic pain relievers.

This Critical Policy Review briefly outlines the history of US public health policy on regulation of prescription opioid pain relievers. The author then compares recommendations and data sources of the updated November 2022 CDC guidelines against findings from a wide range of pertinent clinical literature. He finds that the most recent effort by CDC is fatally flawed by weak evidence and methodologically unsound research, disproportionate emphasis on risk, and failure to address genetically mediated variability in minimum effective opioid dose between individuals. Compounding these difficulties are indications of professional conflicts of interest and persistent anti-opioid bias on the part authors of the most recently released CDC guidelines.

Introduction

This critical policy review is expanded from an invited presentation given at the July 2022 annual conference of the Florida Society for Interventional Physicians and the Florida Society of Physical Medicine and Rehabilitation. [1] The Florida review addressed policy issues embedded in a then-circulating draft update to the 2016 CDC guidelines for prescription of opioids to adults with chronic pain. The present paper addresses the published November 2022 US CDC guidelines on prescription of opioid pain relievers. [2] Hereafter, 2016 and 2022 CDC guidelines are referred to as CDC-2016 and CDC-2022.

The author is a non-physician healthcare writer and subject matter expert on US public health policy for regulation of prescription opioid pain relievers and of clinicians who manage them. He has authored or co-authored over 200 papers in this subject area, in a mix of peer reviewed journals and mass media [3], [4].

Current medical literature and popular media reveal an ongoing and highly contentious public health policy debate concerning the origins and possible remedies for a so-called “opioid crisis” in the United States. A dominant theme in these

sources is an asserted causal relationship between clinicians prescribing to their patients, versus addiction, hospitalizations, and mortality involving opioid overdose. However, increasing concern is also emerging for the impact of restrictive US regulatory policies on patients, their families and pain management clinicians [5], [6]. Patients are dying in pain in hospital, having been denied effective pain care by clinicians afraid of being sanctioned if they treat pain with prescription opioids [7]. At least hundreds if not thousands of suicides have been documented among out-patients in crisis, unable to find a doctor who will continue their long-term opioid therapy or a pharmacy that will dispense their medications. [8], [9], [10]

Methods

A critical analytic review was performed on the November 2022 CDC updated practice guidelines for prescription of opioids (CDC-2022). Related medical literature was reviewed and summarized as it applies to twelve recommendations of these guidelines. Keyword search was employed to characterize the emphasis placed on several themes, as noted in Table 1.

Table 1: Keyword Search – CDC-2022

Keyword	# Occurrences
- risk	[488]
- acute	[247]
- chronic	[214]
- taper	[209]
- benefit	[195]
- effectiv (effective or effectiveness)	[119]
- nonpharmaco (nonpharmacogenic, non-pharmacologic)	[72]
- NSAID	[63]
- trial or trials	[27]
- 50 MME	[24]
- diminish (diminished)	[10]
- Incidence	[5]
- 90 MME (90 Morphine Milligram Effective Dose)	[4]
- genetics	[1]

Discussion

HISTORICAL BACKGROUND

America’s “opioid crisis” is not new. It can be traced at least as far back as the wide-spread use of Laudanum to manage the pain of wounded Civil War veterans. In the 1890s, German pharmaceutical company Bayer marketed heroin as a morphine substitute and cough suppressant.

Bayer promoted heroin for use in children suffering from coughs and colds. [11]

Highlights of the subsequent development of US public health policy include the Harrison Act of 1914, alcohol prohibition from 1920 to 1933 under the 18th Amendment to the US Constitution (repealed by the 21st Amendment) and the Controlled Substances Act of 1970 which created the US Drug Enforcement Administration (DEA) and

established a “scheduling” hierarchy for oversight and control of drugs regulated by the US government [12], [13], [14].

Just as America’s opioid crisis is not new, neither is America’s crisis in under-treated pain.

“In 2001, as part of a national effort to address the widespread problem of underassessment and under-treatment of pain, The Joint Commission (formerly called The Joint Commission on the Accreditation of Healthcare Organizations, or JCAHO) introduced standards for organizations to improve their care for patients with pain”. [15]

The report of the Joint Commission led to a general easing of restrictions on opioid prescribing in 2001 to 2011, with prescriptions dispensed by retail pharmacies expanding by 56% [ibid]. The American Pain Society and pharmaceutical companies promoted this expansion with a publicity campaign using the slogan “Pain As the Fifth Vital Sign” [16]. However, initially lacking effective local or Federal oversight, some unscrupulous doctors and pharmacists generated enormous profits by running pill mills that dumped large volumes of pharmaceutical-grade opioid analgesics into street reseller markets. [17]

The business model that allowed such abuses was largely interrupted in 2010-2012 by six key States that passed legislation creating Prescription Drug Monitoring Programs and requiring clinicians to report controlled substance prescriptions to these centralized databases [18]. The spread of PDMPs to all 50 States has effectively closed the door on pill mills. However, although prescribing dropped precipitately from 2011 onward, it is still unclear whether PDMPs had any direct effect on mortalities associated with legitimate prescribing [19].

CONTROVERSIES SURROUNDING CDC-2016

After at least a decade of increasing discomfort among public health officials and some doctors over perceived risks of prescription opioids, the US National Center for Injury Prevention and Control in the US CDC assembled a team of external consultants to develop guidelines for prescription of opioids to adults with chronic pain. The process was initially highly secret, involving key participants with ties to “Physicians for Responsible Opioid Prescribing (PROP)”, an organization with a declared mission of limiting availability of prescription opioids in clinical practice.

Following a letter from the Washington Legal Foundation to the US House Congressional

Oversight and Accountability Committee, CDC was directed in December 2015 to open the guidelines process to public input. [20] Thousands of comments were received in the United States Federal Register. However, the author has been unable to locate any published record of specific actions taken by the CDC to adjudicate these comments.

Public reaction to CDC-2016 guidelines was widespread, sustained and often highly critical. Among representative titles from authoritative writers were the following:

“Opioid Abuse in Chronic Pain -- Misconceptions and Mitigation Strategies” [21]

“Neat, Plausible, and Generally Wrong: A Response to the CDC Recommendations for Chronic Opioid Use” [22]

“Are Prescription Opioids Driving the Opioid Crisis? Assumptions vs Facts” [23]

“The Myth of What’s Driving The Opioid Crisis” [24]

“Not Allowed to Be Compassionate – Chronic Pain, the Opioid Crisis, and Unintended Harms in the US” [25]

Despite such concerns, CDC-2016 was rapidly adopted as a standard of practice in the laws of multiple US States. CDC was forced in 2019 to issue cautionary notices that their guidelines were never intended to be applied as inflexible standards, and did not justify rapid involuntary tapers of legacy patients [26], [27], [28].

An extract from one of the papers above (authored by Dr Nora Volkow, Director of the US National Institute on Drug Abuse, and A Thomas McMillan) seems pertinent for the present critical policy review:

“Unlike tolerance and physical dependence, addiction is not a predictable result of opioid prescribing. Addiction occurs in only a small percentage of persons who are exposed to opioids — even among those with preexisting vulnerabilities... Older medical texts and several versions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) either overemphasized the role of tolerance and physical dependence in the definition of addiction or equated these processes (DSM-III and DSM-IV). However, more recent studies have shown that the molecular mechanisms underlying addiction are distinct from those responsible for tolerance and physical dependence, in that they evolve

much more slowly, last much longer, and disrupt multiple brain processes.” [op cit 21].

A central assertion of CDC-2016 was that effectiveness of opioid analgesics is unsupported by long-term randomized double-blind trials. That assertion, as far as it went, was generally true. However, CDC failed to explain the reasons behind this outcome in their 2016 narrative. They continue their silence on the subject in CDC-2022.

- Long term randomized double-blind trials predictably fail because of high drop-out rates among patients placed in the placebo arm, due to breakthrough pain.
- A second and possibly dominant factor is that past randomized trials fail to design for significant variability in minimum effective opioid dose between individuals, following from genetic polymorphism in expression of CYP450 liver enzymes that mediate opioid metabolism [29], [30]. One recent estimate of the natural range of this variability is on the order of 15-to-1 [Op Cit 17].
- Available opioid trials also fail to address the manner in which opioids are actually used in clinical practice. Prolonged dose titration may be required to establish an effective opioid dose that is not accompanied by unacceptable side effects. Patient response in pain control also varies between weak and strong opioids. Thus, single-encounter trials of opioid medications administered for acute pain cannot be generalized to estimate effectiveness of all opioids for acute and chronic pain.

Addressing these research issues may require the use of much larger trials cohorts, longer trials periods, and different protocols, notably Enriched Enrollment Randomized Gradual Withdrawal (EERGW) designs [31]. Meanwhile, the entire trials literature investigating effectiveness and risks of opioid pain relievers must be recognized as methodologically weak and possibly inconclusive.

2022 UPDATED CDC OPIOID GUIDELINES – HIGHLIGHTS

Like its predecessor, CDC-2022 addresses prescription of opioids for chronic pain in adults, excluding treatment for sickle cell disease, cancer, or patients receiving palliative or end-of-life care. The guideline is significantly expanded to address not only chronic pain lasting over 90 days, but also sub-acute pain lasting 30-90 days and acute pain lasting up to 30 days.

As central elements of its 2022 update, CDC funded the Agency for Healthcare Research and

Quality (AHRQ) to conduct systematic reviews of the scientific evidence in five areas: 1) noninvasive nonpharmacologic treatments for chronic pain, 2) nonopioid pharmacologic treatments for chronic pain, 3) opioid treatments for chronic pain, 4) treatments for acute pain, and 5) acute treatments for episodic migraine [32], [33], [34], [35], [36].

CDC-2022 is organized around 12 recommendations, each of which is graded for strength of evidence and identified as either expected of all clinicians in treating all patients (Category A) or tailored on an individual patient basis (Category B).

“Category A recommendations typically apply to all persons in the group addressed in the recommendation and indicate a course of action that can be followed in most circumstances... For category B recommendations, clinicians must help patients arrive at a decision consistent with patient values and preferences and specific clinical situations (shared decision-making).”

Eight of 12 recommendations are identified as category A and four as category B. It is thus not difficult to understand why some clinicians might view CDC-2022 guidelines as a potentially legally actionable standard of practice, despite multiple declarations of support for individualized patient care.

Four “Types” of evidence are identified and aligned to the research grading system of AHRQ. Ten out of twelve recommendations are graded as Type 3 or Type 4, with relatively low strength of evidence. While such evidence might reasonably prompt further research, it is highly concerning that CDC-2016 and CDC-2020 have applied it as a basis for major changes in US National practice guidelines for management of pain.

Type 1 - Randomized clinical trials or overwhelming evidence from observational studies; (equivalent to AHRQ high strength of evidence) [1 recommendation].

Type 2 - Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies; (equivalent to AHRQ moderate strength of evidence) [1 recommendation].

Type 3 - Observational studies, or randomized clinical trials with notable limitations; equivalent to most AHRQ low strength of evidence ratings) [3 recommendations].

Type 4 - Clinical experience and observations, observational studies with

important limitations, or randomized clinical trials with several major limitations. [7 recommendations].

Both CDC-2022 and other CDC publications summarize what the guidelines “are” versus what they “are not” [29]. Wording directed to patients and clinicians seems conciliatory. However, CDC-2022 continues to advocate for maximum thresholds on opioid dose, beyond which CDC asserts that benefits are overshadowed by risks.

Reading of the CDC-2022 reference list reveals a centrally important source for assertions of a point of diminishing returns: a comparative outcomes review on opioid versus non-opioid treatment in acute pain [35] conducted by AHRQ. Independent analysis of this source reveals significant errors of methodology and assumptions, among the most notable of which was inappropriate application of meta-analysis to multiple small trials with non-comparable patient cohorts [37].

This AHRQ review was headed by Dr Roger Chou, who later became one of the principal writers of both CDC-2016 and CDC-2022. The role of Dr Chou has been prominent and problematic from the inception of the CDC guidelines effort. He headed or participated in several of the AHRQ outcomes reviews cited by CDC. He then became one of the authors of both CDC guidelines and also served on the Board of Scientific Counselors of the National Center for Injury Prevention and Control (NCIPC-BSC), which provided oversight on the guideline update process. He briefed the Opioid Workgroup tasked by the BSC to evaluate the interim draft of the revised CDC-2022. [38] Thus, Dr Chou was in a position to advocate for the acceptance of his own work as a de facto National standard for opioid prescribing practice. Moreover, there are indications that Dr Chou had significant and unacknowledged professional conflicts of interest that CDC management ignored when selecting him to the writing teams for both versions of the guideline [39] [40], [41].

Also prominent in CDC-2022 are advisory comments on tapering opioid analgesics. Table 1 above identifies 209 uses of the word. This emphasis may be related to deep concerns that arose after publication of CDC-2016 regarding forced tapers of legacy patients to meet arbitrary MME thresholds [42]. [43]. There is also concern that patients are still being force-tapered or refused treatment by community clinics across the US. [44] These outcomes are directly related to unwillingness of community clinics to take on new patients for pain management due to

overshadowing effects of CDC-2016 and CDC-2022 [45].

Other CDC-2022 Issues

1. INAPPROPRIATE EMPHASIS ON RISK

As noted in Table 1, both CDC-2016 and CDC-2022 use the term “risk” hundreds of times, and the term “incidence” hardly at all. It is important to distinguish between the two.

“Incidence” relates to the number of times a defined event occurs in a defined population. However, “risk” implies a knowable cause-and-effect relationship pertaining to “bad things”, whereby if “A” happens, then “B” will also occur with some knowable likelihood. Incidence is essentially “value-free”, whereas risk pertains primarily to bad outcomes. For example, clinicians would almost never write about the “risks” of live births among a population of healthy women who choose to become pregnant. But “risk” is frequently used in analyzing factors that contribute to still births [46].

A second and related issue is misuse of odds ratios. It is sometimes written that the “odds” of some defined condition (let us say “opioid use disorder”) occurring in a defined population (for instance, people who are prescribed opioids) are “X” times greater than in some other population (patients not prescribed opioids). However, if the outcome of concern occurs in a very small number of people in the first place, then clinicians may not see enough cases in practice to have confidence in what they are observing or how they should act to avoid undesired outcomes. For a clinician, odds ratios are meaningless in practice unless accompanied by absolute incidence. In small cohorts, the ability to measure outcomes of concern may also be compromised by multiple unacknowledged confounds in data collection protocols [47].

None of these issues is addressed in CDC-2022

2. CORRELATION IS NOT CAUSE

Anyone trained in science or technology will be familiar with the dictum “correlation is not cause”. Simply because observed outcome “A” occurs before or frequently at the same time as outcome “B”, does not mean that A caused B or even that the two are necessarily related. However, this principle has an additional dimension: without correlation, there can be no cause-and-effect relationship between observed events.

There is conclusive evidence from multiple sources that clinicians’ prescribing of opioids has no statistically significant correlation to either hospitalizations for opioid toxicity or mortality in

which a prescription opioid is implicated as a factor.

In 2018, Hawre Jalal, Jeanne M Buchanich and their colleagues [48] analyzed records of 599,255 deaths from 1979 through 2016 from the National Vital Statistics System in which accidental drug poisoning was identified as the main cause of death. By examining all available

data on accidental poisoning deaths back to 1979 and showing that the overall 38-year curve is exponential, they provided “evidence that the current wave of opioid overdose deaths (due to prescription opioids, heroin, and fentanyl) may just be the latest manifestation of a more fundamental longer-term process.” Mortality data that they analyzed are summarized in Figure 1 below, from the original paper.

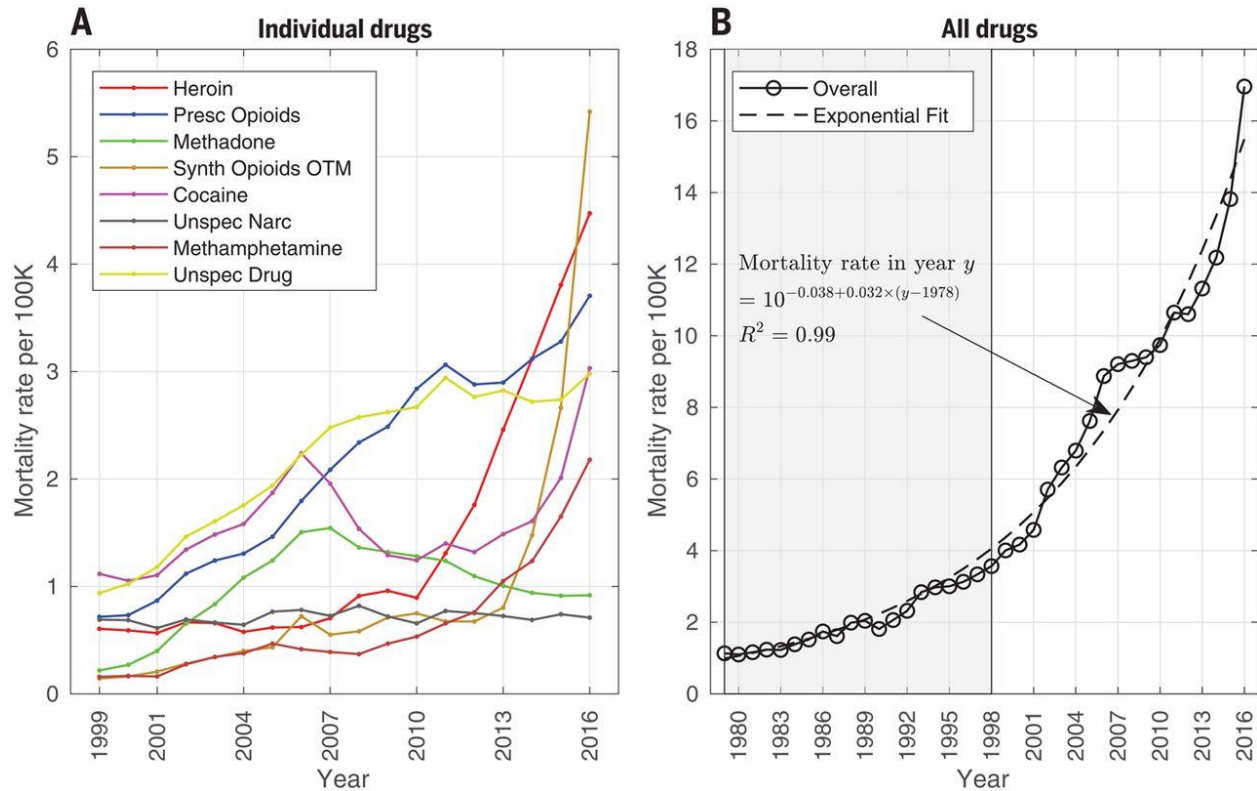


Figure 1: Mortality Rate from Drug Overdoses

This report is also important for confirming that the US “opioid epidemic” has not been uniform across the United States or over the past 40 years. Accidental deaths from various contributors varied significantly over time and between areas of the US. (See also [51]). Overall, it is clear that although prescription opioids contributed to accidental drug overdose mortality prior to 2012, such drugs are only one among seven specific factors -- and likely were never the dominant factor even during the pill mill era. Illicitly imported street Fentanyl now dominates drug overdose mortality.

A second landmark analysis in August 2022 by Larry Aubry and B Thomas Carr [49] confirms and extends details of Jalal et al. As noted in their report;

“The analyses revealed that the direct correlations (i.e., significant, positive slopes) reported by the CDC based on data from 1999 to 2010 no longer exist. Based on data from 2010 to 2019, the relationships either have reversed (i.e., significant, negative slopes) or are non-existent (i.e., no significant model).”

Aubry and Carr downloaded data of the National Institute on Drug Abuse, for volumes of opioid prescribing characterized by prescription opioid sales in Morphine Milligram Equivalents per Capita, and mortality rates in which one or more prescription opioids were identified as factors in accidental death. They also compared year-by-year opioid treatment admissions to opioid sales. Their results are summarized in Figure 2 below, used by permission.

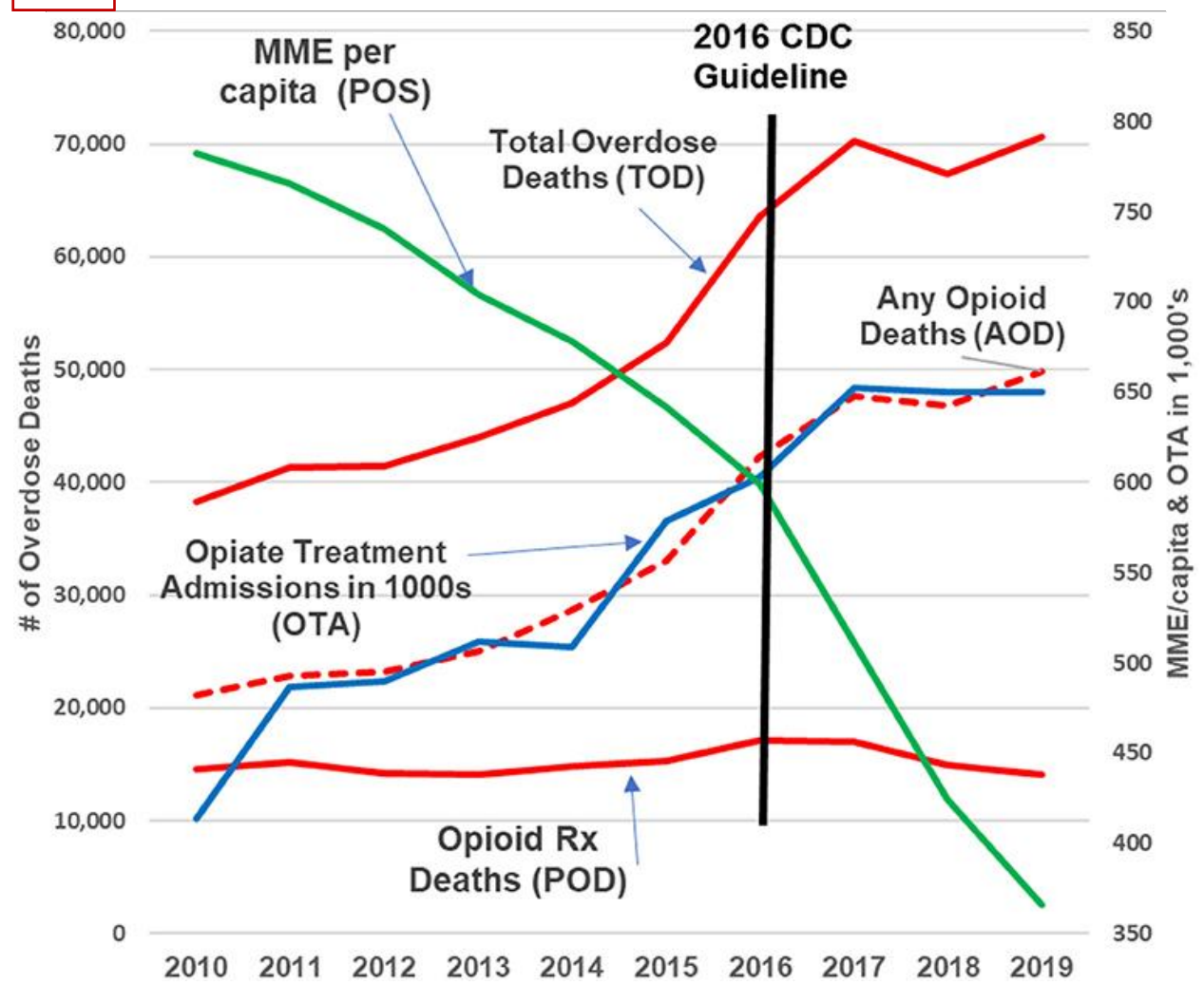


Figure 2: US Overdose Deaths and MME Per Capita Vs Time

From 2010 to 2019, volume of opioid prescribing in the US dropped by 55%. Reported hospital admissions for treatment of opioid toxicity rose 58% from 410,000 to 650,000. Accidental deaths attributed to prescription opioids remained nearly constant at 14,000 to 16,000 per year, while deaths involving other opioids rose from 10,000 to about 48,000 per year. Mortality due to opioid overdose has since continued to rise.

involving prescription opioids. The share of opioid-related deaths involving “synthetic opioids other than methadone” rose from 14% in 2010 to 60% in 2017. According to the Drug Enforcement Administration, that category consists almost entirely of illicitly produced fentanyl and fentanyl analogs, manufactured in Asia or Mexico and smuggled into the United States, often via mail or private courier.”

Findings reported by Aubry and Carr reinforce those of an earlier 2019 paper by Jeffrey Singer, Jake Z Sullum, and Michael E Schatman [50]. Noting that “today’s nonmedical opioid users are not yesterday’s patients”, these authors explored the emergence of illegal fentanyl as the most important driving factor behind rising drug overdose mortality. From their report:

“The actual components of the opioid-related death toll are as alarming as they are revealing. Since 2010, deaths involving heroin and fentanyl have risen much more dramatically than those

3. ARE “NONPHARMACOGENIC” THERAPIES ACTUALLY “PREFERRED” FOR SUBACUTE AND CHRONIC PAIN?

The second recommendation of CDC-2022 reads as follows:

“Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and

function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A; evidence type: 2)."

This recommendation and its characterization of the strength of evidence are fundamentally in error. Some pain patients do benefit from use of non-drug therapies (physical therapy, massage, psychological counseling, cognitive behavior therapy, others). However, deep reading of AHRQ references provided in CDC-2022 [33], [34], reveals that improvements in pain and quality of life are temporary and very limited in scope.

The quality of medical trials literature for this class of therapies is candidly abysmal. Among 4996 initially recovered trials, AHRQ identified only 218 that passed rigorous quality review – and none directly compared non-pharmacological therapies with opioids [52]. Quality of medical evidence was assessed as “weak” in over 150 of these 218. Even trials that passed quality review failed to describe the nature of “usual and customary” treatments against which trials outcomes were nominally compared.

Given the weakness of medical evidence, “nonpharmacogenic” therapies cannot be viewed as “preferred” replacements to drug treatments. They are at most useful adjunct treatments to be administered in coordination with a program of opioid or non-opioid analgesic therapy. EERGW trials designs offer a ready means of testing the ability of such ancillary therapies to enable reduction of opioid dosage and to determine the duration of their effects.

NSAIDs like Ibuprofen (Advil, Motrin IB, others), Naproxen Sodium (Aleve, Anaprox DS, others), Diclofenac Sodium and Celecoxib (Celebrex) have been shown to reliably and consistently reduce pain. However, absolute magnitudes of effects are very modest. NSAIDs also have safety concerns that render them contraindicated in significant numbers of patients with severe pain. [53], [54]. High sustained doses of Tylenol (acetaminophen) are associated with thousands of US hospital admissions for gastrointestinal bleeds each year. There is evidence that reduction of

exposure to Tylenol actually improves patient safety [55].

4. HOW VALID ARE MMED THRESHOLDS AS GUIDES TO CLINICAL PRACTICE?

As noted in Table 1, CDC-2022 (like CDC-2016) continues to advocate for use of MMED thresholds in assessing risks versus benefits and managing chronic pain in adults. However, it has long been known that the MMED concept itself lacks rigorous trials data or even consistent definition [56]. Compounded by a failure to address genetic effects on opioid metabolism or to acknowledge the relative rarity of opioid addiction as an outgrowth of clinical therapy, this emphasis may reasonably be viewed as disqualifying of CDC-2022.

In May 2022, during the review cycle for the prepublication draft of CDC-2022, the American Medical Association recommended as follows;

“To build on the Proposed Guideline’s strengths, we ask the CDC to join the AMA in urging all relevant state, national and federal stakeholders, including legislatures, regulators, health plans, pharmacy chains, and pharmacy benefit management companies (PBMs) to remove all vestiges of inflexible numeric thresholds based on the 2016 Guideline. The revised guideline, when published, should have a disclaimer on every page that the CDC’s recommendations should not be used or interpreted as an inflexible law or policy, and that any reference to specific prescribing or treatment decisions are for illustrative purposes only and should not be deemed a standard of care or inflexible threshold. The AMA encourages CDC to go further with its disclaimer by saying that the CDC opposes the use of its recommendations to justify any law or policy with a specific threshold.” [57]

Also notable from this source was the acknowledgement that “we know patients on opioid therapy are functional on a wide range of opioid therapy dosage and quantity.”

Although CDC-2022 incorporates conciliatory assurances that the guidelines should not be used as an inflexible standard of care, the document stops well short of the standard of professionalism advocated by the AMA.

5. HOW COMMON IS ADDICTION IN PATIENTS TREATED WITH OPIOIDS?

CDC-2022 asserts that

“Clinical evidence reviews found observational evidence that opioid use for acute pain is associated with long-term opioid use and that a greater amount of early opioid exposure is associated with greater likelihood of long-term use, noting recent evidence for a dose- and duration-dependent effects (.63,75,141,244,251, 252).” [2].

The CDC writers appear to have misread or ignored several implications of the work of Brat, et al, which they cited [58].

Brat et al conducted a retrospective cohort study of “surgical claims from a linked medical and pharmacy administrative database” for over 37 million commercially insured patients between 2008 and 2016. They identified just over a million “opioid-naïve” patients undergoing surgery during that period. Of these, 568,612 (56.0%) patients received postoperative opioids. They defined “misuse” as the occurrence of a medical record code for opioid dependence, abuse, or overdose. One or more of these codes was subsequently identified for 5906 patients from the million-plus who underwent surgery (0.6%).

Patients were defined as “opioid-naïve” if their total opioid use in the 60 days before surgery was seven days or less. Postsurgical opioid use was measured if the member filled a prescription for an included opioid within 30 days of discharge. Use was considered to have stopped when either 30 days elapsed without a filled opioid prescription or a misuse diagnosis was observed.

Several issues arise in this source and the interpretation of its results in CDC-2022. First, opioid “dependence” is not addiction [21]. It is unclear why Brat et al combined these codes under the single term “misuse”, used nearly 100 times in their paper. Long-term prescription use also does not equate to opioid use disorder or misuse. Post-surgical prescriptions may also occur among patients for whom a surgical procedure has failed and pain has transitioned from acute to chronic. This reality is confirmed in data reported by these authors for different types of surgery.

Even including dependence, the reported rate of “misuse” signaled by post-surgical medical record entries was only weakly sensitive to daily dose below 150 MME, varying from 0.13% to about 0.35% as dose per day varied from less than 20 MME to over 150 MME. There was no clear threshold of increased “risk” of bad outcomes in this range, and certainly not at 90 MMED as asserted by CDC-2022. The aggregate incidence

of undesired outcomes was also reported for a heterogeneous population: 44% of the million-plus opioid-naïve post-operative patients were not prescribed opioids, versus 56% who were so prescribed.

Finally, a recommendation of Brat and his colleagues was overlooked in CDC-2022:

“Our findings suggest that opioid naïve patients who receive low to moderately high doses of analgesics for short durations have small associated increases in overall rates of misuse. Many studies have shown that pain is often poorly managed after surgery... Higher doses within standards of moderation may better saturate μ receptors, whereas under-treatment of acute pain increases the risk of pseudoaddiction, chronic pain, and, potentially, overdose. These findings suggest a more nuanced understanding of the relation between duration and dosage, with a focus on early appropriate treatment of pain (including higher doses) for a limited time. Such findings imply that optimal postoperative prescribing, which maximizes analgesia and minimizes the risk of misuse, may be achieved with moderate to high opioid dosages at shorter durations, a combination that merits further investigation in population based and clinical studies.”

The findings of Brat et al are thus consistent with those of Volkow and McMillan [21]. Opioid dependence and addiction are not predictable outcomes of clinical prescribing and are relatively rare. An incidence rate 0.6% in reports of patient addiction or overdose is at least arguably too low to justify one-size-fits-all limitations on opioid prescribing at an arbitrary threshold of 90 MMED.

A second large-cohort analysis of prescribing versus opioid use [59] is also pertinent in this critical policy review. Although the work of Eric C Sun, Baker L C Mackey et al is referenced in CDC-2022, implications of that work are not explored.

Sun et al sought to “characterize the risk of chronic opioid use among opioid-naïve patients following 1 of 11 surgical procedures compared with nonsurgical patients.” The study included 641,941 opioid-naïve surgical patients and 18,011,137 opioid-naïve nonsurgical patients.

“...Retrospective analysis of administrative health claims to determine the association between chronic opioid use

and surgery among privately insured patients between January 1, 2001, and December 31, 2013. The data included 11 surgical procedures (total knee arthroplasty [TKA], total hip arthroplasty, laparoscopic cholecystectomy, open cholecystectomy, laparoscopic appendectomy, open appendectomy, cesarean delivery, functional endoscopic sinus surgery [FESS], cataract surgery, transurethral prostate resection [TURP], and simple mastectomy)..."

Chronic opioid use was defined as "having filled 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days. For nonsurgical patients, chronic opioid use was defined as having filled 10 or more prescriptions or more than 120 days' supply following a randomly assigned "surgery date.""

Sun et al found that;

"...among the surgical patients, the incidence of chronic opioid use in the first preoperative year ranged from 0.119% for Cesarean delivery (95% CI, 0.104%-0.134%) to 1.41% for TKA (95% CI, 1.29%-1.53%). The baseline incidence of chronic opioid use among the nonsurgical patients was 0.136% (95% CI, 0.134% - 0.137%)."

"Except for cataract surgery, laparoscopic appendectomy, FESS, and TURP, all of the surgical procedures were associated with an increased risk of chronic opioid use, with odds ratios ranging from 1.28 (95% CI, 1.12-1.46) for cesarean delivery to 5.10 (95% CI, 4.67-5.58) for TKA. Male sex, age older than 50 years, and preoperative history of drug abuse, alcohol abuse, depression, benzodiazepine use, or antidepressant use were associated with chronic opioid use among surgical patients."

Thus, four of eleven procedures showed no elevated incidence of persistent opioid prescribing following surgery. The highest odds ratio for ongoing chronic use of prescription opioids was found for Total Knee Arthroplasty -- a procedure well known to be associated with higher surgical failure rates. Incidence of protracted prescribing was actually lower in patients who underwent Caesarean Section (all female) relative to those who did not undergo surgery (male and female).

These results directly contradict the widely prevalent perception that all patients treated with opioids are rapidly at risk for opioid dependence or addiction. It is indeed plausible that continuing prescription of opioids following initial post-surgical treatment is at least as much related to procedure failure and emergence of chronic pain as it may be a result of any inherent addictive influence of prescription opioids per se.

Finally, a third large-cohort analysis [60] provides insight into factors in patient background that may flag nominally "opioid-naïve" individuals for enhanced clinical oversight when they are treated with opioid pain relievers.

In a Veterans Administration population of 1,135,601 patients, a multivariate mixed effects logistical regression model was developed to predict any FY2011 drug overdose, suicide-related events (ideation or attempt), or death on the basis of FY2010 data on patients with an outpatient opioid prescription. In FY 2011, the total incidence of such events was 2.1%.

In the final model, the area under the receiver operator characteristic curve (true positive rate (sensitivity) plotted against false positive rate (1-specificity) was 0.83, suggesting that the model was highly predictive. Among the 1,000 patients identified as being at highest risk, the predicted 2011 overdose/suicide-related event rate was 57.9% and the actual rate was 53.7%.

Among factors associated with higher risk, all but one of had nothing to do with clinician treatment of pain:

- Prior overdose/suicide event, odds ratio (OR) 23.1,
- detoxification 18.5,
- inpatient mental health treatment 16.1,
- diagnosis of sedative use disorder 11.2,
- OUD 8.2, or other substance use disorder 8.0,
- number of classes of other sedating medications 6.1,
- cannabis/hallucinogen use disorder 5.9,
- bipolar disorder 5.8,
- other mental health disorder 5.7,
- alcohol use disorder 5.3, and
- major depressive disorder 4.8.

For opioid therapies of various types, relative to tramadol, the Odds Ratio (OR) for negative outcomes in FY2011 was 1.1-1.5. Each additional MMED increased risk by 0.3% (e.g., a dosage of 333 MMED would have doubled total risk).

Notably, the retrospective study design precluded entering adequacy of control of physical pain into the analysis, although the high OR associated with OUD raises the possibility that inadequately treated pain may have been an important factor. Moreover, if higher opioid doses are associated with more complex and treatment-resistant medical conditions – an assessment that was not made in the paper – then one would expect higher natural mortality due to underlying medical conditions in higher-dose patients, rather than due to opioid overdose per se.

Conclusions

A critical policy review has been conducted for the updated US CDC 2022 Clinical Practice Guideline for Prescribing Opioids for Pain, comparing recommended policies of the guideline with other pertinent medical literature.

This review confirms that there are good reasons for clinicians to exercise prudent oversight when initially evaluating patients in pain or when prescribing opioid analgesics for them over the long term. However, multiple instances were found where CDC authors appear to have over-generalized or misinterpreted from very weak medical evidence. Despite repeated assertions

that patient care must be individualized, a one-size-fits-all framework was constructed of proposed restrictions on prescribing, based on Morphine Milligram Equivalent Dose thresholds. There are also indications of preexisting and unacknowledged professional conflict of interest on the part of at least one of the writers.

Overall, the most significant – and methodologically fatal – error of CDC-2022 may be its failure to address genetics of opioid metabolism. Genetic polymorphism in expression of CYP450 liver enzymes introduces a wide range in opioid minimum effective dose and sensitivity to side effects between individuals. None of the outcome's reviews referenced in CDC-2022 even acknowledged such variations, rendering their findings of very limited value, if not outright biased. Of secondary import are persistent over-emphasis on “risk” and a naïve over-generalization of the supposed benefits of non-opioid or non-invasive modalities of therapy as substitutions for opioid analgesics.

Taken in combination, these factors may warrant the repudiation of both CDC-2016 and CDC-2022, and withdrawal of CDC from policy making roles in the practice of pain medicine.

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