February 22, 2022

U.S. Centers for Disease Control and Prevention
National Center for Injury Prevention and Control
Division of Overdose Prevention

Re: Comment on CDC's Draft Clinical Practice Guideline for Prescribing Opioids
Document Number: 2022-02802
Docket Number: CDC-2022-0024

To Whom it May Concern:

My name is Jeffrey A. Singer. I am a Senior Fellow in Health Policy Studies at the Cato Institute. I am also a medical doctor specializing in general surgery and have been practicing that specialty in Phoenix, Arizona for over 35 years. The Cato Institute is a 501(c)(3) non-partisan, non-profit, tax-exempt educational foundation dedicated to the principles of individual liberty, limited government, free markets, and peace. Cato scholars conduct independent research on a wide range of policy issues. To maintain its independence, the Cato Institute accepts no government funding. Cato receives approximately 80 percent of its funding through tax-deductible contributions from individuals. The remainder of its support comes from foundations, corporations, and the sale of books and other publications. The Cato Institute does not take positions on legislation.

I would like to thank the CDC for providing me the opportunity to comment on the proposed revision to the 2016 Guideline for Prescribing Opioids. I appreciate this opportunity to provide my perspective, as a health care practitioner and policy analyst.

The CDC correctly issued an Advisory in 2019, urging health care practitioner to avoid misinterpreting and misapplying the 2016 guideline, correctly stating that the 2016 guideline never intended for practitioners to impose hard limits on the dose and number of opioids prescribed to pain patients and that it was never intended for practitioners to abruptly taper patients whose chronic pain had been well controlled with opioids. The Advisory was issued after 36 states codified hard limits on opioid prescribing inspired by the 2016 Guideline, and a plethora of patients subsequently being abruptly cut off from or denied pain medication, many of whom resumed a life of despair. It was also issued around the same time that the American Medical Association released a similar statement.

The draft revision of the CDC guideline opens by emphatically making the same point, stating "The voluntary clinical practice guideline provides recommendations only and is intended to be flexible to support, not supplant, clinical judgment and individualized, patient-centered decision-making." The draft emphasizes, "This clinical practice guideline should not be applied as inflexible standards of care across patient populations by healthcare professionals, health systems, pharmacies, third-party payers or state, local, and federal organizations or entities."

Cato Institute • 1000 Massachusetts Ave., N.W., Washington, D.C. 20001 • (202) 842-0200
Fax: (202) 842-3490 • www.cato.org

This disclaimer is good as far as it goes. The realities are that when the CDC issues guidelines, they become **de facto edicts**. As occurred after the CDC released the 2016 Guideline, lawmakers, pharmacies, third-party payers, and state and local organizations or entities will interpret the Guideline as the "official" standard of care. Therefore, while the disclaimer is laudable, it will not have the intended effect. The only effect it will have is to assure the CDC is not held responsible for misapplication of the revised guideline.

Furthermore, it is inappropriate for a government agency such as the Centers for Disease Control and Prevention, which is subjected to special interest pleading and political pressures, to establish "standard or care" or "best practices" guidelines. That has always been a principal function of medical specialty organizations, such as the American College of Physicians, American College of Surgeons, American Academy of Pediatrics, etc. These organizations are non-profit, non-governmental bodies that were created specifically to evaluate the evidence and provide education and practice guidance to practitioners in their specialty. To do so, they establish working committees of active clinicians, many of whom are also educators and researchers, and all of whom are aware of the nuances of clinical medicine and the variability of clinical circumstances. Such committees are better able to adjudicate pronouncements and assertions by various participants in the field.

Notwithstanding the well-intentioned exhortations and disclaimer in the draft 2022 opioid prescribing guideline, the recommendations change very little from those put forth in 2016.

For example, the guidelines still rely on Morphine Milligram Equivalent (MME) dose recommendations, even though there is no pharmacologic or biochemical basis for relying on equianalgesic conversion factors.

As Fudin et al point out in a 2017 White Paper:

> Unfortunately, these equianalgesic conversion tables rely on a few assumptions that commonly are ignored by prescribers, dispensers, policymakers, and payers. Among these assumptions are that: 1) all the analgesic effect derived from a given medication is due to its action on the mu opioid receptor; and 2) all patients respond identically to all opioid medications. One group of opioids with multiple mechanisms of action, often referred to as "atypical opioids," illustrates the dangers that can result from erroneously accepting these assumptions. Using common equianalgesic conversion tables to determine doses of these atypical opioids is fraught with danger, and potentially can result in patients unintentionally being under-dosed or over-dosed.

Patients vary genetically in how they metabolize various opioids. Drug interactions also effect the enzymes that metabolize various opioids. Renal function, blood volume, and body mass index also play a role, as dose route of administration. Finally, opioids differ in their bioavailability and half-life. Biochemist Jonathan Bloom, PhD, Director of Pharmaceutical and Chemical Science at the American Council on Science and Health states:

> The CDC MME chart, in fact, the entire concept of morphine milligram equivalents may be convenient for bureaucrats but because of differences in the absorption of different

> drugs into the bloodstream, half-life of different drugs, the impact of one or more other drugs on opioid levels, and large differences of the rate of metabolism caused by genetic factors, is not only devoid of scientific utility, but actually causes far more harm than help by creating "guidelines" that are based upon a false premise. When a policy is based on deeply flawed science, the policy itself will automatically be fatally flawed. It cannot be any other way.

Complicating the pharmacologic futility of attempting to establish equianalgesic conversion tables is the fact that, as Professor Nabarun Dasgupta has recently shown, there is no standardized way to calculate Morphine Milligram Equivalents. And, as I recently co-wrote, building upon earlier work by several other scholars, the MME conversion table adopted by the CDC is based upon research that is cobbled together from a number of small, clinically insignificant studies dating back over 60 years. These studies never even compared the doses of the various opioids that cause respiratory depression and death. The types of trials that went into the table would never be conducted today. Some would call this junk science.

Both the 2016 and the proposed 2022 revised guideline mistakenly conflate dependency with addiction. As Drs. Nora Volkow and Thomas McLellan of the National Institute on Drug Abuse pointed out in the New England Journal of Medicine in 2016, dependency and tolerance refer to the physiologic adaptation to the presence of a drug such that abrupt tapering can lead to a withdrawal reaction. This is seen with many classes of drugs, including beta blockers, anti-epileptics, antidepressants, benzodiazepines, and opioids. But addiction is not the same as dependence. Addiction is defined as compulsive use despite negative consequences. It is a behavioral disorder in which the patient has preexisting vulnerabilities, and traumatic events during early developmental years play a major role. Addiction is not exclusively seen with substance use. It is also seen with certain activities, such as gambling addiction, shopping addiction, and sex addiction. Drs. Volkow and McLellan state in their article:

> 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.

Researchers reporting in the BMJ in 2018 reviewed 568,000 opioid-naïve postsurgical patients in the Aetna insurance database prescribed opioids from 2008 to 2016 and found a total misuse rate of 0.6 percent. Cochrane systematic reviews in 2010 and 2012 have shown addiction in chronic non-cancer pain patients to be very uncommon. Researchers from Albert Einstein College of Medicine followed 484 opioid-naïve patients who were prescribed opioids for acute pain in the emergency department. Reporting in the Annals of Emergency Medicine in 2019, they found 1 percent were still using opioids at six months, and four-fifths of them were still suffering from their painful condition at that time.

My colleagues and I surveyed data from the National Survey on Drug Use and Health and from the CDC and reported in the Journal of Pain Research in 2019 there was no evidence of any correlation between the opioid prescription rate per 100 persons and “past month nonmedical use of pain relievers among people aged 12 or older” or “pain reliever use

disorder in the past year among people aged 12 or older," during a period of time when the amount of opioids prescribed doubled.

Meanwhile, as prescription volume peaked in 2012 and has decreased roughly 60 percent since that time, overdose deaths have soared to record levels, and in the CDC's most recent report, 83 percent of opioid-related overdose deaths involved illicit fentanyl. Moreover, the overwhelming majority of overdose deaths involve multiple drugs, with the stimulants methamphetamine and cocaine each involved in roughly one quarter of overdose deaths. Yet prescription opioids have been a consistently small component of overdose deaths (roughly 13 percent) for several consecutive years.

And prescription volume has been brought down at the expense of acute and chronic pain patients, whose desperation has grown noticeable enough to prompt the CDC's 2019 Advisory and the current plan to revise the opioid prescribing guidelines.

As the Joint Economic Committee of Congress reported in 2019, overdose deaths from nonmedical drug use have been steadily increasing since 1959. And researchers at the University of Pittsburgh Graduate School of Public Health reported in 2018 that overdose deaths have been on an exponential growth trend since at least 1979, with the only differences over the decades being the drugs predominating among the causes of the overdose deaths.

The overdose crisis preceded the approval of OxyContin by the Food and Drug Administration and continues despite the dramatic curtailment of opioid prescribing since 2012. There is a growing population of nonmedical drug users, and drug prohibition makes that use much more dangerous than it would otherwise be. Cicero, et al reported that in 2015 more than 33 percent of heroin addicts admitted to rehab stated they *initiated* drug use with heroin, compared to roughly 9 percent who stated that ten years earlier.

The overdose crisis in the early part of this century largely involved prescription opioids. But this was not because doctors were producing people with drug addiction but because, as more opioids were prescribed, more were available for diversion into the black market for nonmedical users. The National Survey on Drug Use and Health consistently reports that less than 25 percent of nonmedical users of prescription opioids state they ever received their opioid from a prescriber.

In conclusion:

1-The Centers for Disease Control and Prevention should not be issuing opioid prescribing guidelines. Professional specialty organizations, overseen by practicing clinicians and clinical educators, are the institutions that should be issuing standard of care and best practices guidelines.

2-The CDC guideline will inevitably become interpreted and adopted as hard and fast rules by state and local governments, pharmacies, health plans, and third-party payers, despite guideline warnings against doing so.

3-The 2022 guideline very closely resembles the 2016 guideline and is based on weak evidence; in the case of Morphine Milligram Equivalent recommendations, the guideline is pharmacologically unsound, and the conversion tables are based largely on decades-old subjective studies that didn't even examine toxicologic effects such as respiratory depression rates.

4-The overdose crisis is largely caused by a growing population of nonmedical drug users intersecting with increasingly dangerous drugs being developed for the black market fueled by drug prohibition. Efforts to address the problem through reductions in opioid prescribing have only exacerbated the situation by driving nonmedical users to more dangerous drugs while depriving pain patients of necessary relief.

5-The Centers for Disease Control and Prevention should abandon its efforts to establish a prescribing guideline and defer to the professional institutions usually charged with establishing best practices.

Respectfully submitted,

Jeffrey A. Singer, MD, FACS
Senior Fellow
Department of Health Policy Studies
Cato Institute